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Synthesis of pH-responsive hydrophobically-modified hydrogels of poly(methacrylic acid-*co*-diallylammonium salt) in aqueous solution

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Hydrophobically-modified hydrogels of poly(methacrylic acid) (P(CC16-MAA) were prepared by the free radical copolymerization of methacrylic acid (MAA) and diallyl methyl hexadecyl ammonium salts (CC16) in aqueous solution. The presence of hydrophobic segments could reduce or increase the degree of swelling significantly at low or high pH, respectively. DSC results indicated that crystalline behavior of poly(diallyl methyl hexadecyl ammonium) salts easily took place in the side chain. The gels showed swelling behaviors that were more sensitive to pH change than PMAA hydrogels and PMAA hydrogels hydrophobically-modified by poly(acrylic acid-2-ethylhexyl ester) (P(AAEHE-MAA)). These properties suggest that P(CC16-MAA) is a potential system suitable for drug delivery.

1 Introduction

Polyelectrolyte responsive hydrogels can conventionally undergo a volume change in response to environmental stimuli, including pH, temperature and ionic strength. These hydrogels offer many potential applications in controlled drug delivery, tissue engineering or the immobilization of enzymes, *etc*.[1–4] pH-sensitive polyelectrolyte hydrogels are particularly significant for drug release because their physiological pH range is from 1.2 to 7.4 and different body parts have a particular surrounding pH.[5] Most pH-sensitive hydrogels can be divided into two types. One is weak polybasic,[6–8] the other is weak polyacidic, for example poly(methacrylic acid).[9–11] These gels undergo a conformational transition from the collapsed state to the swollen state upon ionization in polar media. The main reason for such a transition is the osmotic pressure exerted by mobile counterions neutralizing the network charges. It is desirable to find a way to produce responsive gels with a predetermined pH value at the point of the swelling transition. One of the possible methods to control the pH responsive properties of the gels is to introduce a small fraction of hydrophobic repeating units into them. In this case, the hydrophobic groups can aggregate with each other when the gel is uncharged. These hydrophobic microdomains, acting as physical cross-links, interfere with the network swelling induced by ionization.[12] Hydrophobically-modified gels have been found to have the potential to act as carriers for medical controlled delivery. Generally speaking, the hydrophobic chains have been introduced into the gels by the copolymerization of main electrolyte monomers and alkyl acrylate monomers having a long side chain.[13–18] However, the reported polymerizations were always in organic solvents because the alkyl acrylate monomers were not soluble in water.

The discovery of the cyclopolymerization of *N*,*N*-diallyl quaternary ammonium salts by Butler *et al*.[19,20] led to the synthesis of an array of water-soluble cationic polyelectrolytes (CPEs)[19] of tremendous scientific and technological interest. These CPEs have found extensive industrial and commercial applications[21] as paper additives, de-emulsifiers of dispersed oil, paint thickeners, flocculants, and coagulant aids in portable water and waste water treatment. Poly(diallyl dimethyl ammonium salts) (DADMA) are water soluble. For diallyl ammonium monomers with long alkyl chains, their polymers are less soluble in water. By the copolymerization of this kind of monomer with DADMA, amphiphilic polymers containing a small proportion of hydrophobic groups incorporated in the hydrophilic polymer chains, known as associating water soluble polymers, can be obtained. Associating water soluble polymers have been the subject of extensive research during the past few decades because of their interesting rheological behaviors in aqueous solution.[22–25]

Benefiting from the concepts of "hydrophobically-modified gels" and "associating water-soluble polymers", we attempted the copolymerization of diallyl ammonium monomers possessing long alkyl chains with methacrylic acid in aqueous solution and succeeded in preparing hydrophobically-modified hydrogels with highly pH-sensitive properties. By using diallyl ammonium monomers instead of alkyl acrylate monomers, the polymerization could be performed in aqueous solution. Furthermore, the ammonium cations from the diallyl ammonium monomers brought new contributions to the association and pH-responsive properties of the hydrogels compared with when using alkyl acrylate monomers. In this Paper, we report the synthesis of such hydrogels in aqueous solution, their pH-sensitive properties and discuss the additional effects from the ammonium cations.

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2 Experimental section

2.1 Materials

Methacrylic acid (MAA) was purchased from Tianjing chemical plant, China. *N*,*N*-Methylenebis(acrylamide) was purchased from Lancaster, UK (97%, Alfa Aesar). 2,2′-Azobis-(2-methylpropionamidine) dihydrochloride was obtained from Aohua chemical plant in Changzhou, China. All reagents were used without further purification.

Preparation. Diallyl methyl hexadecyl ammonium bromide was prepared from diallyl hexadecyl amine according to a reported method.[26] Diallyl hexadecyl ammonium chloride was prepared by the following procedure: Firstly, an excess of 1N HCl was added to diallyl hexadecyl amine, and then an excess of de-ionized water was added into the mixed system to give a precipitate. The precipitate was separated by centrifugation and dried in a vacuum oven. The product was purified by recrystallization from acetone to give a white powder.

Characterization

Diallyl methyl hexadecyl ammonium bromide (CC16). White powder. ^{1}H NMR ($CDCl_3$) δ (ppm): 0.846–0.910 (t, 3H), 1.255 (s, 26H), 1.760 (s, 2H), 3.307 (s, 3H), 3.237–3.403 (t, 2H), 4.222–4.417 (m, 4H), 5.723–5.899 (m, 4H), 5.927–6.091 (m, 2H). Element analysis (%): C: 66.31 (66.35), H: 11.39 (11.06), N: 3.13 (3.37).

Diallyl hexadecyl ammonium chloride (HC16). White powder. ^{1}H NMR ($CDCl_3$) δ (ppm): 0.845–0.910 (t, 3H), 1.253 (s, 26H), 1.878 (s, 2H), 2.885–2.994 (m, 2H), 3.603–3.551 (m, 4H), 5.451–5.595 (m, 4H), 6.074–6.245 (m, 2H). Element analysis (%): C: 73.84 (73.85), H: 12.03 (12.31), N: 3.85 (3.92).

2.2 Preparation of poly(diallyl methyl hexadecyl ammonium bromide–methacrylic acid) gels (P(CC16-MAA))

P(CC16-MAA) gels were prepared by the free radical copolymerization of diallylmethyl hexadecyl ammonium bromide and methacrylic acid in water. The fraction of diallyl methyl hexadecyl ammonium bromide in the monomer mixture was varied from 0 to 20.0 mol%. The copolymerization was performed at an overall monomer concentration of 2.10 mol L^{-1} with 2,2′-azobis(2-methylpropionamidine) dihydrochloride as the initiator and *N*,*N*-methylenebis(acrylamide) as the cross-linker. All the reagents were dissolved in water. 2 ml of the above solution was added into a glass ampoule in a vacuum line by using an injector. The solution was de-gassed by a freeze–thaw method. The ampoule was sealed under high vacuum and kept at 50 °C for 5 h to obtain a gel. The gel was cut into 2–3 mm circular disk samples. The samples were immersed in a mixture medium of ethanol–water (1 : 1 v/v). Exchange of the medium every 12 h removed the unreacted monomers, which were detected by a UV-vis spectrophotometer (Shimadzu, Japan). Finally, the samples were dried at room temperature for 1 d and further dried in a vacuum at 40 °C.

2.3 Preparation of poly(diallyl hexadecyl ammonium bromide–methacrylic acid) gels (P(HC16-MAA))

The preparation method was the same as discussed for P(CC16-MAA) gels.

2.4 Swelling measurements[5]

To investigate the swelling properties of the gels at different pHs, the dry gel samples were placed in a buffer solution at room temperature. Each buffer solution was adjusted to 0.1 M with a calculated amount of KCl. At regular time intervals, the gels were removed from the medium. The weight of the swollen hydrogels was determined after the removal of the surface water through blotting with filter paper. The equilibrium swelling ratio (SR) was calculated from the following equation:

$$\mathrm{SR} = (W_t - W_d)/W_d$$

where W_t is the mass of the sample swollen at time t and W_d is the mass of the dried gel sample. When the swollen hydrogels had reached a constant weight, the SR was considered to be in equilibrium. The following equation was used to determine the nature of the swelling process:[5]

$$M_t/M_\infty = kt^n$$

where M_t and M_∞ are the amounts of equilibrium water uptake at time t and the maximum water uptake, respectively, k is a proportional constant and exponent n describes the type of diffusion mechanism. A plot of ln M_t/M_∞ *vs.* ln t was used to calculate n and k from the slope and intercept. This equation is applicable to the initial stages of swelling and only yields straight lines up to nearly 60% of the maximum amount of absorbed water.

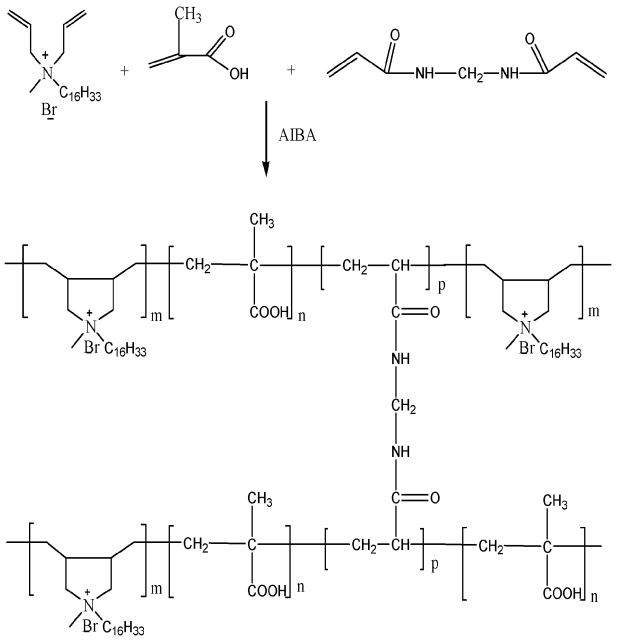
2.5 Differential scanning thermal calorimetry analysis

Samples were measured by a Q100 Differential Scanning Thermal Calorimetry instrument (USA Thermal Analysis Company). The samples were conducted in N_2 and heated from −25 °C to 150 °C at a scan rate of 10 °C min^{-1}, cooled from 150 °C to −25 °C at a scan rate of 20 °C min^{-1}. Then the curves were obtained when the samples were heated from −25 °C to 150 °C at a scan rate of 10 °C min^{-1} again.

3 Results and discussion

3.1 Preparation of P(CC16-MAA) gels

The reaction conditions for the preparation of P(CC16-MAA) gels (Scheme 1) were investigated with regard to the monomer ratio and concentration, reaction time, and temperature, *etc*. Hydrogels with high monomer conversion and without bubbles were obtained under conditions with the fraction of diallyl methyl hexadecyl ammonium bromide (CC16) in the monomer mixture ranging from 0 to 20.0 mol%, 2,2′-azobis(2-methylpropionamidine) dihydrochloride (AIBA) and *N*,*N*-methylenebis(acrylamide) concentrations of 2.0 mol%, an overall monomer concentration of 2.10 mol L^{-1}, and a polymerization time of 5 h at 50 °C.



Scheme 1 A schematic representation of the structure of P(CC16-MAA) gels.

3.2 Swelling behaviors of P(CC16-MAA) gels

Typical dependencies of the swelling degree of P(CC16-MAA) gels on the pH of the solution surrounding the gel sample is shown in Fig. 1. It can be seen that the gels shrink in acidic media and swell in alkaline media. This effect is related to gel ionization[15,27] and the molecular interactions of the polymer chains. Gel swelling upon ionization in polar media is known to be mainly due to the osmotic pressure exerted by mobile counterions.[15,28] On the other hand, the molecular interactions of the polymer chains tend to de-swell the gel. At pH values lower than 5, the protonated state (–COOH) of the gel dominates the system, which shows a shrunken state. At a pH value of 5.5, corresponding to the pK_a of PMAA,[27] the concentration of the ionized state of $–COO^-$ is equal to that of the protonated state and the swelling of the gel exhibits an abrupt change, which means the osmotic pressure exerted by the mobile counterions prevails over the molecular interactions of the polymer chains so as to destroy the compact structure of the gel. At pH values from 6 to 7.4, a new balance between the chemical cross-linking and the osmotic pressure from the ionized state is established, resulting in a flat change. At pH 8.0, all samples exhibited a decrease in swelling. This might be due to the fact that the ionization of the gel becomes slower than that when the pH is between 6 to 7.4.[15] At pHs from 8.0 to 9.0, the gel is in almost a complete ionized state, resulting in greater swelling.

With regard to the effect of gel hydrophobicity on the pH-responsive swelling behavior, it can be seen that at pH values lower than 5, the swelling of the gels decreases with increasing CC16 content. These phenomena are almost the same as the ones shown by the hydrophobically-modified gels of poly(methacrylic acid-*co*-alkyl acrylate).[5] There are possible two reasons for the results;[5,15,18] one is that the presence of hydrophobic CC16 units may shield the carboxylic acid groups and

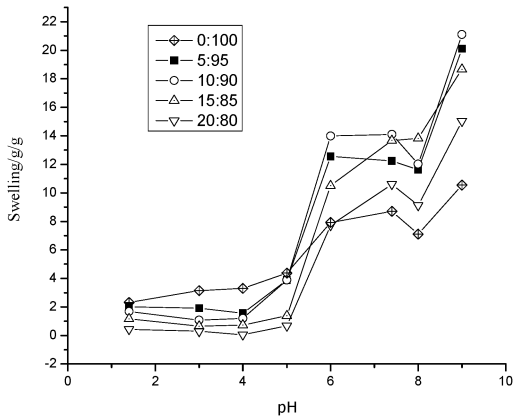


Fig. 1 Swelling ratios of the P(CC16-MAA) gels as a function of pH at room temperature $n_{CC16}:n_{MAA}$ = 0:100, 5:95, 10:90, 15:85 and 20:80 (molar ratios).

decrease the local dielectric constant close to the network chain. On the other hand, the hydrophobic groups from CC16 monomers interact with each other to form physical crosslinks. These make the hydrogels form a more compact structure. It was also found that swelling of all of the P(CC16-MAA) gels was higher than that of PMAA at pH values higher than 6. This means that the presence of the hydrophobic alkyl chains from CC16 can increase the swelling capacity of hydrogels at this pH. This suggests that P(CC16-MAA) gels exhibit a looser structure compared with PMAA.

In addition to the above two factors regarding the swelling properties of the gels (the ionization of the carboxylic acid groups and hydrophobic alkyl chain content), the ammonium ions in P(CC16-MAA) gels may also play an important role compared to reported poly(acrylic acid-2-ethylhexyl ester-*co*-methacrylic acid) (P(AAEHE-MAA)) gels.[5] In fact, by comparing the two systems, it can be seen that P(CC16-MAA) gels show two significant differences: (a) an earlier abrupt increase in swelling ratios at pH 6 and (b) at pH values from 6 to 9, the swelling ratios of all the P(CC16-MAA) gels were higher than that of PMAA, while for the P(AAEHE-MAA)) gels, this phenomenon was observed only at pH 9. These results suggest that the ammonium ions in P(CC16-MAA) gels play an important role, which is further confirmed in section 3.3.

3.3 The effect of ammonium ions on the swelling behavior

Diallyl hexadecyl ammonium salt (HC16) is different from diallyl methyl hexadecyl ammonium salt (CC16) in that it can be changed to a neutral, tri-valent amine at a high pHs by a neutralization reaction with OH^-. Accordingly, the ammonium ions in P(HC16-MAA) hydrogels, which can be prepared in the same way as P(CC16-MAA) hydrogels, can be changed to neutral, tri-valent amines at pHs higher than 6. Fig. 2 shows the swelling properties of P(CC16-MAA) and P(HC16-MAA) gels as a function of pH. At pHs lower than 4, there were no obvious differences between the two gels. However, at pHs higher than 5, swelling ratios of P(CC16-MAA) hydrogels were significant higher than those of P(HC16-MAA) hydrogels. These results further confirm that the ammonium ions in P(CC16-MAA) gels play an important role in the swelling

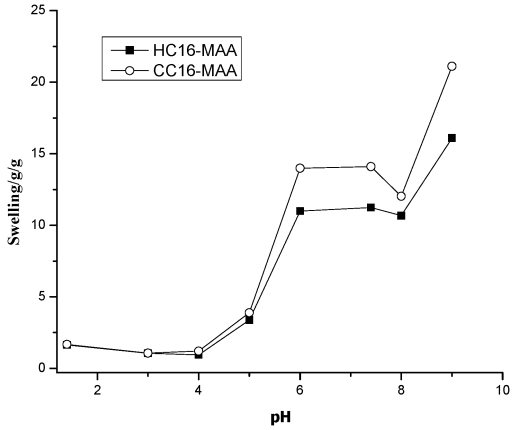


Fig. 2 Swelling ratios of PCC16-MAA and PHC16-MAA gels as a function of pH at room temperature $n_{CC16}:n_{MAA} = n_{HC16}:n_{MAA} = 10:90$ (molar ratio).

properties. The possible reason for this effect may be electrostatic repulsions of the ammonium ions.

3.4 The re-swelling behavior of P(CC16-MA) gels

In the application of these gels, the drug release from its dried loaded polymer matrix is closely related to the re-swelling kinetics of the matrix.[5] An investigation of the re-swelling kinetics of the P(CC16-MA) samples, as well as of PMAA, were conducted at pH 1.4 and 7.4, respectively.

Fig. 3 presents the re-swelling behaviors of the P(CC16-MAA) samples at pH 1.4. In the case of PMAA, the swelling equilibrium could be arrived at within 4–5 h. However, swelling equilibrium times for the P(CC16-MAA) samples at $n_{CC16}:n_{MAA} = 5:95$, 10 : 90, 15 : 85 and 20 : 80 were 11, 11, 13 and 14.5 h, respectively. These results mean that in the shrunken state of P(CC16-MAA) hydrogels, the presence of hydrophobic alkyl chains can markedly retard the swelling.

Fig. 4 shows the re-swelling behaviors of the hydrogels at pH 7.4. As seen from Fig. 4, the swelling kinetics of the hydrogels exhibited a significant difference. The required time to reach an equilibrium swelling state increased markedly with the increase in the hydrophobic CC16 content of the polymers. The swelling equilibrium times for PMAA ($n_{CC16}:n_{MAA} = 0:100$) and P(CC16-MAA) ($n_{CC16}:n_{MAA} = 5:95$, 10 : 90, 15 : 85 and 20 : 80) samples were 7, 7, 22 and 43 h, respectively.

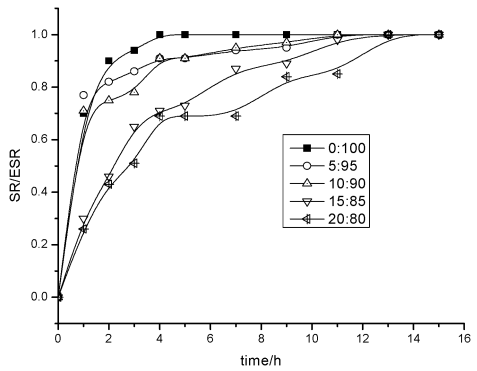


Fig. 3 Re-swelling behaviors of the P(CC16-MAA) samples at pH 1.4 at room temperature.

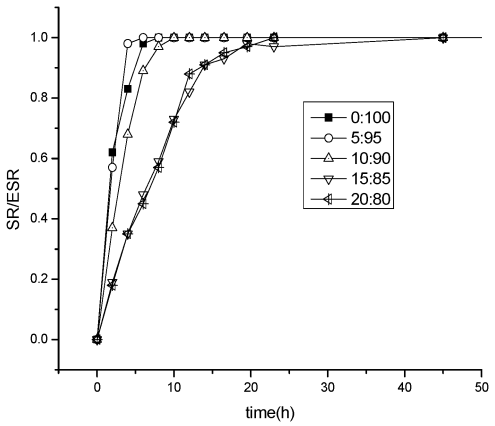


Fig. 4 Re-swelling behaviors of the P(CC16-MAA) samples at pH 7.4 at room temperature.

These results mean that the presence of hydrophobic CC16 units can also dramatically slow down the swelling rate of the hydrogels at pH 7.4.

These results are almost same as those reported for samples of P(AAEHE-MAA) gels.[5] However, differences between the two sample systems were also observed. Firstly, the times taken to reach the swelling equilibrium were shorter for the samples of P(CC16-MAA). Secondly, there was no slow swelling stage observed at the beginning for the samples of P(CC16-MAA). These results are accordant with the results for the swelling properties of the P(CC16-MAA) gels.

The results for the swelling and re-swelling properties of the P(CC16-MAA) gels suggest that they may have potential applications in drug release.

3.5 The water diffusion process at different pH values in buffer solutions

According to the semi-empirical equation $M_t/M_\infty = kt^n$, a plot of ln M_t/M_∞ *vs.* ln t can be used to calculate the values of n and k from the slope and intercept. The kinetics of swelling were therefore analyzed, and these values are listed in Table 1. The exponent n expresses the diffusion mechanism of water. When $n < 0.5$, the release is dominated by Fickian diffusion.[26] When $0.5 < n < 1$, the release follows non-Fickian diffusion. Finally, when $n = 1$, there is continuous zero-order release, where the system will be relaxation controlled.[29,30]

Table 1 shows the n values of the hydrogels at pH 1.4 and 7.4, respectively. As can clearly be seen, in contrast with the diffusion exponent of PMAA, the diffusion exponent of P(CC16-MAA) ($n_{CC16}:n_{MAA} = 5:95$, 10 : 90, 15 : 85 and 20 : 80) decreased at pH 1.4, indicating that the swelling extent is influenced by the content of the hydrophobic chain.

Table 1 Diffusion exponent n of the P(CC16-MAA) hydrogels

	n	
Sample	pH 1.4	pH 7.4
PMAA	0.22	0.37
$n_{CC16}:n_{MAA} = 5:95$	0.05	0.22
$n_{CC16}:n_{MAA} = 10:90$	0.08	0.76
$n_{CC16}:n_{MAA} = 15:85$	0.16	0.67
$n_{CC16}:n_{MAA} = 20:80$	0.11	0.70

However, the n values at pH 1.4 are still lower than 0.5 for all the samples, indicating a Fickian diffusion mechanism.

At pH 7.4, the n values for PMAA and P(CC16-MAA) ($n_{CC16}:n_{MAA}$ = 5:95) are lower than 0.5, but the n values for P(CC16-MAA) samples at $n_{CC16}:n_{MAA}$ = 10:90, 15:85 and 20:80, respectively, are higher than 0.5. The results indicate that the diffusion of water for samples of PMAA and P(CC16-MAA) of $n_{CC16}:n_{MAA}$ = 5:95 is dominated by Fickian diffusion; while for samples of P(CC16-MAA) at $n_{CC16}:n_{MA}$ = 10:90, 15:85 and 20:80, respectively, are dominated by non-Fickian diffusion. The n values for P(CC16-MAA) are non-linear. The diffusion exponent, n, is controlled by the degree of cross-linking, degree of branching, crystallinity, and so on.

The n values at pH 1.4 indicate that the nature of hydrogel swelling is not influenced by CC16 segments in acidic media. The n values at pH 7.4 suggest that hydrogel swelling behavior is closely related to the CC16 content in the hydrogels. It indicates that the presence of CC16 in the hydrogels plays an important role in water diffusion.

This pH-dependent swelling behavior is schematically depicted in Fig. 5. At low pH 1.4, the hydrophobic units of the alkyl chains act as physical cross-links, forming stable hydrophobic domains and resulting in a low swelling ability for P(CC16-MAA) gels. As the environmental pH is increased, the ionization of the carboxylic acid groups occurs and their electrostatic repulsions cause the degree of hydrogel swelling to increase.[15,31,32] Meanwhile, the physical cross-link between the hydrophobic interactions is weakened and finally dissociated.

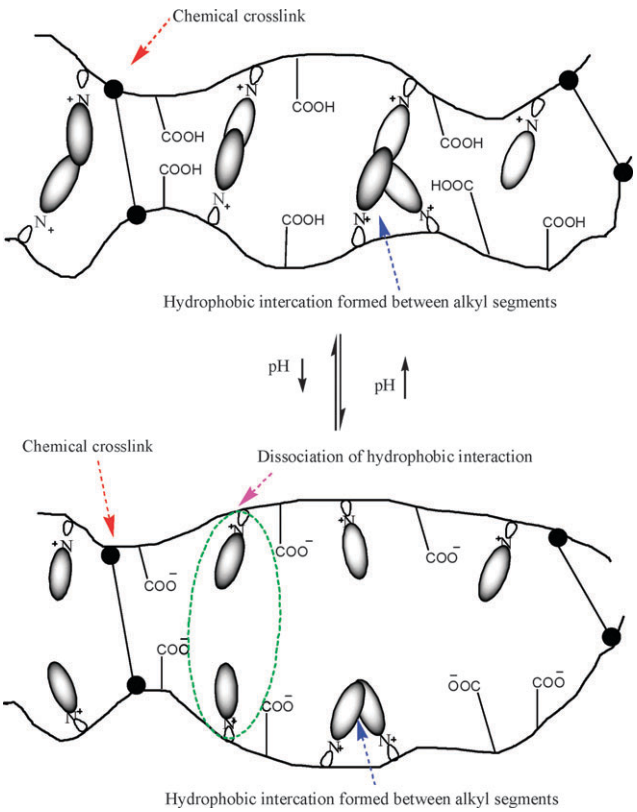


Fig. 5 A schematic illustration of the pH-dependence of the hydrogel swelling mechanism.

3.6 Investigation of the aggregation state of the gels by the DSC technique

Fig. 6 presents DSC curves of PMAA, poly(diallyl methyl hexadecyl ammonium bromide) (PCC16), poly(diallyl hexadecyl

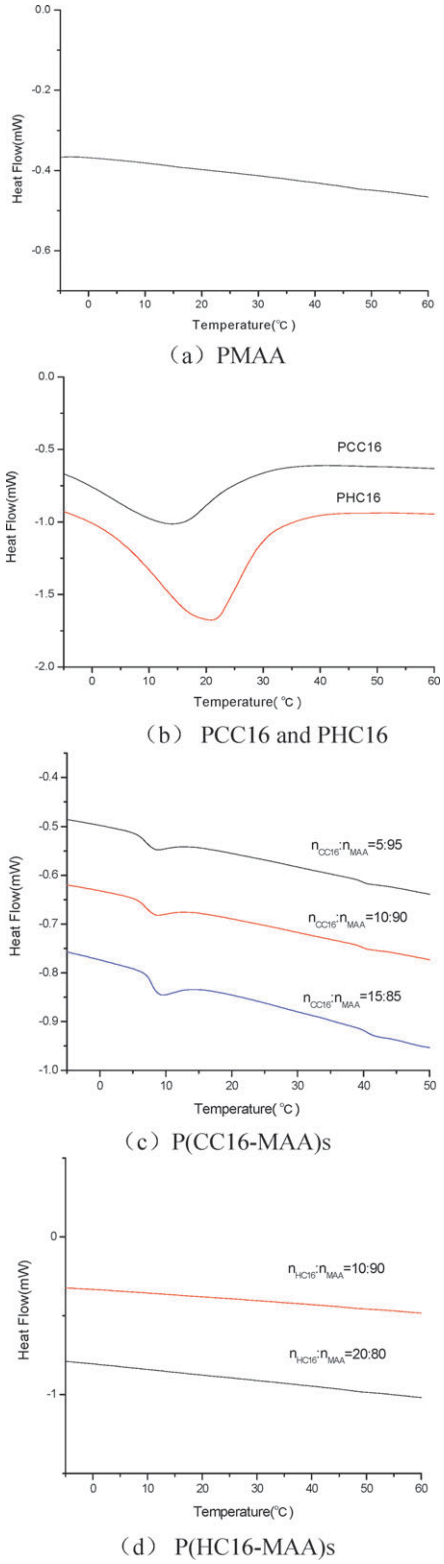


Fig. 6 DSC curves for (a) PMAA, (b) PCC16 and PHC16, (c) P(CC16-MAA)s, and (d) P(HC16-MAA)s.

ammonium chloride) (PHC16), P(CC16-MAA) and P(HC16-MAA). As seen clearly in Fig. 6(a) and (d), PMAA and P(HC16-MAA) gels gave no discernable DSC peak. In Fig. 6(b), there were endothermic peaks centered at 13.9 and 20.7 °C for PCC16 and PHC16, respectively. The calculated endothermic enthalpy values of PCC16 and PHC16 were 11.94 and 23.31 J g^{-1}, respectively. This indicates that PHC16 was much more regular than PCC16, possibly due to the hydrogen-bonding effect in PHC16.

All the P(CC16-MAA) gels exhibited two endothermic peaks below 10 °C (a big peak) and around 40 °C (a small peak), respectively (Fig. 6(c)). The first, bigger, peak may be associated with the crystallization effect of the long side alkyl chain and the second, smaller, peak to the glass translation temperature of the copolymers.

Accordingly, these results suggest that crystallization of the hexadecyl groups in the side chain of P(CC16-MAA) gels occurs,[33] and that their crystallization capacity was decreased by increasing the MAA segments. As for the P(HC16-MAA) gels, no crystallization peaks were observed, possibly due to the strong hydrogen bonding effect of the –COOH and $-^{+}NHR_3$ groups, which can prevent the local motion of the hexadecyl chains from aggregating them together.

4 Conclusion

Hydrophobically-modified hydrogels of poly(methacrylic acid) (P(CC16-MAA) were prepared by the free radical copolymerization of methacrylic acid (MAA) and diallyl methyl hexadecyl ammonium salts (CC16) in aqueous solution for first time. The gels showed swelling behaviors more sensitive to pH change than PMAA and the PMAA hydrogels hydrophobically-modified by poly(acrylic acid-2-ethylhexyl ester) (P(AAEHE-MAA)). As for the P(AAEHE-MAA) gels, the presence of hydrophobic segments from CC16 in P(CC16-MAA) gels could reduce and increase the swelling degree significantly at low and high pH, respectively. Moreover, the ammonium ions in P(CC16-MAA) gels also play an important role compared to P(AAEHE-MAA) gels. It was found that P(CC16-MAA) gels show two significant differences: (a) an earlier abrupt increase in the swelling ratio at pH 6 and (b) at pH values from 6 to 9, the swelling ratios of all of the P(CC16-MAA) gels were higher than that of PMAA, while for the P(AAEHE-MAA)) gels, this phenomenon was observed only at pH 9. These results suggest that P(CC16-MAA) gels may have potential applications in drug release systems.

Acknowledgements

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