Fluorocarbon-Containing Hydrophobically Modified Poly(acrylic acid) Gels as Drug Release System

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ABSTRACT: Hydrophobically modified acrylic acid (AA) hydrogels containing fluorocarbon hydrophobic group and hydrocarbon-modified gels using 2-(*N*-ethylperfluorooctanesulfoamido) ethyl methacrylate (FMA), and lauryl acrylate (LA) respectively, 2-(*N*-ethylperfluorooctanesulfoamido) ethyl methacrylate (FMA), were synthesized. Acetaminophen, with analgesic and antipyretic property, acted as the model drug. Swelling, rheological, and mechanical properties of the gels were investigated. Fluorocarbon-modified gels show the stronger hydrophobicity than do the hydrocarbon-modified gels, which affected the gel's drug-releasing behavior. The drug release behavior depends on pH of the solution medium, the type of hydrophobic modification and the amount of hydrophobes. Hydrophobically modified PAA gels have higher storage modulus E' than the unmodified PAA gels. © 2007 Wiley Periodicals, Inc. J Appl Polym Sci 106: 2075–2082, 2007

Key words: hydrogel; hydrophobic association; drug release; storage modulus

INTRODUCTION

Hydrogel-type delivery systems for bioactive compounds have received significant attention due to their acceptable biocompatibility and controllable permeability.[1–3] However, few systems[4–6] are available to control model drugs according to long-term first-/zero-order sustained release kinetics and/or complex dosage regiments. These unconventional delivery strategies are proposed to maximize drug efficiency and minimize side effects and tolerance development.[7,8] Introducing a small fraction of hydrophobic groups to a hydrophilic network, ''intelligent'' hydrogel[9–12] can be obtained, which is capable of both specifically interacting with and responding to the immediate chemical environment. Within intelligent hydrogel, hydrophobic groups aggregate with each other and form hydrophobic micelle-like microdomains,[13] which reversibly change with environmental stimuli, such as temperature, pH, electric field, light, ionic strength.[14,15]

In previous works,[15–17] the rheological properties, the interactions with various surfactants, and fluorescence of hydrophobically modified water-soluble polymers (HMWSP) were studied. It has been shown that fluorocarbon hydrophobes exhibit much stronger associations than the hydrogenated counterparts due to their low cohesive energy density and surface energy,[14] which prompted us to further investigate hydrophobic association of hydrophobically modified gel systems used in drug release. In this paper, hydrophobically modified poly(acrylic acid) (P(HMAA)) gels containing fluorocarbon hydrophobic side groups were prepared, and the analgesic and antipyretic acetaminophen has been chosen as the model drug, and the release kinetics have been studied. The swelling, the rheological, the mechanical properties of the gels were investigated to estimate drug release pattern and rate.

EXPERIMENTAL

Materials

2-(*N*-Ethylperfluorooctane-sulfoamido)ethyl methacrylate (FMA), which was supplied by 3M, was recrystallized from methanol twice and dried in vacuum drying oven at 40°C for 2–3 h before use. Lauryl acrylate (LA) and ethylene glycol dimethacrylate (EGDMA) were from Aldrich. Acrylic acid (AA) was distilled under the reduced atmosphere pressure by water flow pump before use. Azobisisobutyronitrile (AIBN) was purified by recrystallization in methanol. 4-Hydroxyacetanilide (acetaminophen), obtained from Sigma Chemical, was used as a model drug. The chemical structures of these hydrophobic comonomers were depicted in Scheme 1.

Syntheses of hydrogels

The macroscopic hydrogels were prepared in *tert*-butanol by free radical copolymerization of acrylic

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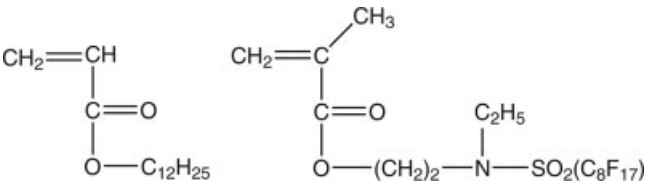

Scheme 1 Molecular structure of hydrophobic comonomers.

acid (AA) with/without a certain amount of hydrophobic comonomer (FMA, LA, respectively). The fraction of the hydrophobic comonomer varied from 0.1 to 2.5 mol % (relative to AA concentration), while the concentration of AA remained constant at 2.2 mol/L. In all cases, AIBN (as initiator) was kept at 0.001 mol/L and EGDMA (as crosslinker) was kept at 0.02 mol/L. The reaction was conducted in a sealed cylindrical glass tube (inner diameter = 10 mm) equipped with a nitrogen inlet tube at 60 ± 0.5°C for 24 h.

The resulting gels were removed and cut into 10-mm discs, and then soaked in a large amount of absolute ethanol, which was exchanged with fresh pure ethanol once every 2 days, to remove all unreacted components and sol fraction. After at least 1 week, the gels were dried in a vacuum drying oven at 40°C until reaching constant weight.

The *F* conversion was measured by element analysis (Model 1108 elemental analyzer, Carlo-Erba). Results indicate that most of FMA groups were incorporated into copolymer gels, as shown in Table I.

Gel characterization

Swelling measurement

The dry gel samples were immersed in excess pure water or buffer solution at different pH for at least 1 week to attain equilibrium. For the swelling capacity test, the gels were put into Britton–Robinson buffer solution at 20°C for 1 day. Then the gels were quickly removed, the surface water was carefully wiped off before weighing. Swelling ratio (SR) was measured gravimetrically as:

$$\mathrm{SR} = (M_t - M_0)/M_0 \quad (1)$$

where M_t and M_0 denote the weight of swollen gel and dry gel, respectively. All reported swelling ratios are averages of at least three trials.

Model drug loading

Copolymer dry hydrogels were preequilibrated in deionized water[20] and then immersed in a saturated aqueous model-drug solution, acetaminophen, at 5°C. After 6 days the hydrogels were removed from the solution. The amount of the drug loaded in the hydrogels was determined by measuring the drug concentration before and after soaking in these solutions using a spectrophotometer (Spectronic 1001, Bausch and Lomb, Rochester, NY, USA) at 243 nm.

Drug release

Drug releasing was carried out in 100-mL capped glass beaker, into which was added 50-mL PBS or distilled water. Each dried drug-loaded hydrogel was put into a separate beaker and stirred by a magnetic stirrer with 60 rpm at room temperature, and 0.5 mL of the solution was removed from the beakers periodically and the released drug was determined spectrophometrically. The volume of the release medium in the beakers was held constant by returning the sample back to the release medium after each sampling. The fractional release of the drug was calculated as a function of time. All the data are average value of three trials.

Rheological performance

The oscillation measurements were carried out by a Bohlin VOR rheometer with a plate–plate PP 15 measuring head geometry. The copolymers were swollen with pure water at room temperature to reach equilibrium. The frequency was initially fixed at 1 Hz, and the rheological parameters were measured as a function of the strain amplitude. This enabled one to obtain the linear region, where the complex modulus (E'') and the storage modulus (E') are independent of applied strain and frequency. The storage modulus (E') of the gels was measured at a fixed frequency (0.04 Hz), with strain in the range (0–0.1) at 20°C.

TABLE I
Characteristics of the Hydrogels With Different FMA Content[a]

Sample	HM*/AA ratio (mol %)		*F* conversion[b]	EWC (%)
	Feed	In polymer		
Unmodified PAA	0	0	0	600
P(FMA–0.5%-AA)	0.5	0.43	86.3	112
P(FMA–1.0%-AA)	1.0	0.81	81.5	40
P(FMA–2.0%-AA)	2.0	1.73	86.5	17
P(LA–1.0%-AA)	1.0	–	–	120

[a] In gel samples, the feed amounts of monomer AA, chemical crosslinker EGDMA, and initiator AIBN are 2.2, 0.022, and 0.0011 mol/L, respectively.
[b] The *F* conversion was measured by anion chromatography.

Theoretical estimation to drug release behavior

A useful approximation at early times of drug release from the hydrogel described by Fick's diffusion law[17] is used as follows:

$$M_t/M_\infty = kt^n \tag{2}$$

$$\log(M_t/M_\infty) = \log(k) + n\log(t) \tag{3}$$

where M_t and M_∞ are the fraction of drug release at t time and at equilibrium time, respectively, k is the release constant, and n is the release index which characterizes the mode of transport of the drug outside the matrix. For $n = 0.5$, the drug release is diffusion controlled and follows a Fickian mechanism. For $0.5 < n < 1$, an anomalous diffusion behavior is considered, and for $n = 1$, the drug release shows a zero-order profile.

Each release experiment was performed with gels loaded under the same conditions. The calculations were carried out using the mean curve of release for the drugs. The release indices n (Table III) were obtained by fitting the data of the mean curve with eq. (3).

RESULTS AND DISCUSSION

Swelling behavior of hydrogels

The swelling ratios of hydrogels in distilled water were studied kinetically and the results are shown in Figure 1. The swelling ratios of P(HM-AA) gels are lower than that of unmodified PAA gel. The higher the concentration, the slower the swelling and less the swelling degree in distilled water. In P(HM-AA) gels, the hydrophobic side chains tend to aggregate together and form hydrophobic micelles that act as physical crosslinking points and restrain the outer water from entering gel networks. As a result, the swelling ratios of P(HM-AA) gels decrease.

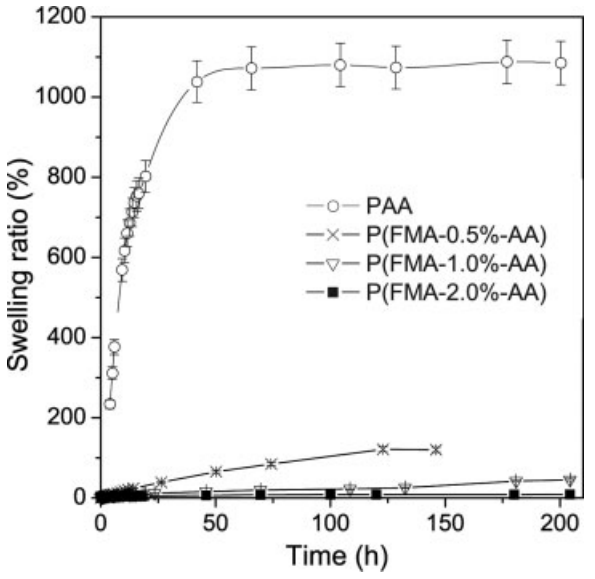

Figure 1 Effect of the degree of hydrophobic modification on the swelling dynamics of hydrogels.

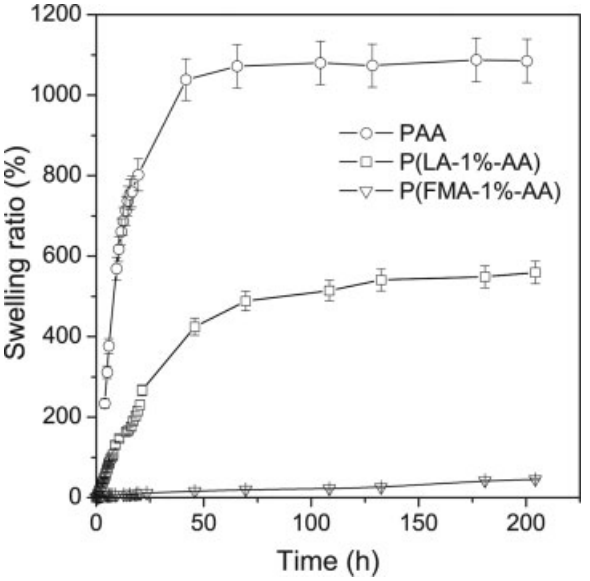

Figure 2 Swelling dynamics of hydrogels without modification and with different type of hydrophobic side groups.

The swelling ratios of the hydrogels with different hydrophobic side groups as a function of time are shown in Figure 2. With the same concentration, FMA-modified gels show the slower swelling ratios and lower degree of swelling than do LA-modified hydrogels, which proves that fluorocarbon groups have stronger hydrophobic association compared with hydrocarbon groups, due to the lower cohesive energy density[18] and surface energy[19] for fluorocarbon groups.

The swelling behaviors with different hydrophobic side groups are investigated under the different pH medium (Fig. 3). The swelling ratios increase mainly due to the balance between electrostatic interactions and hydrophobic interactions. When the pH increases, the electrostatic force increases. These collapsed hydrophobic coils are diverted into highly expanded and hydrated ones. Compared with the LA-modified gel, the FMA-modified gel shows the maximum swelling ratio at a higher pH value. This indicates that stronger electrostatic force is required to disrupt the hydrophobic clusters. Figure 3 shows that the change of FMA-modified gels' swelling ratios with pH is less than that of LA-modified gels. The hydrophobic association of FMA groups is disrupted by electrostatic force with greater difficulty than that of LA groups.

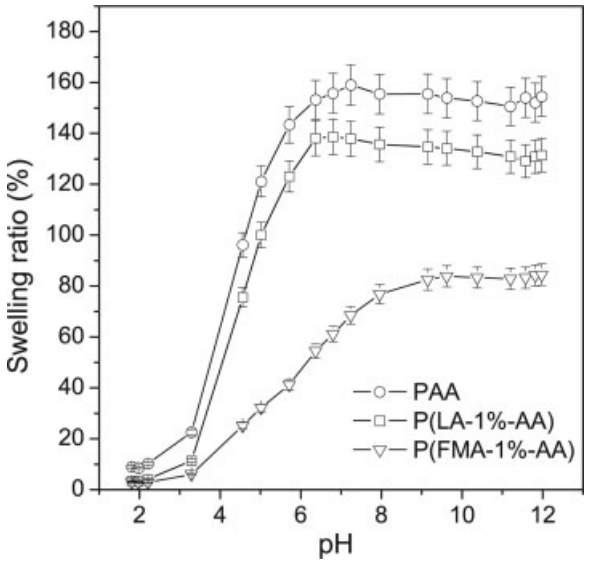

Figure 3 Effect of pH value on the swelling ability of hydrogels with different kinds of hydrophobic side groups.

Drug release behavior

Drug loading

The PAA, P(FMA–0.5%-AA) and P(FMA–1.0%-AA) gels, are immersed in solution with the fixed acetaminophen concentration to load the drug, respectively. The results are listed in Table II. In this case, because the total amount of acetaminophen in the outer medium is much larger than the equilibrium-loading amount of the drug, the penetration of the drug is dependent on the osmotic pressure arising from the drug concentration difference between the outer and the inner of the gels. Although the swelling capacity is affected directly by the loading amount of the drug and decreases with the content of FMA (Fig. 1), the gels with the higher content of FMA show a stronger absorbing ability for the drug (Table II). In addition, the ratio of the drug-releasing amount to the drug-loading amount (after 24 h) denotes the releasing efficiency, as listed in Table III. With increase in the content of FMA, the drug-releasing amount and the efficiency decreases and the partition coefficients of the drug between the bulk solution and gels increase. These results proved that the hydrophobic interaction between the drug and FMA side groups of gel network increases with the content of FMA.

As mentioned above, it will be expected that P(FMA-AA) can be used as candidates for delivery hydrophobic drugs, and drug release ratio from hydrogels can be controlled by the degree of hydrophobic modification. In this case, the model drug can act as a probe to determine hydrophobic association of hydrophobic side chains; that is, hydrophobic association can be investigated by controlling the drug releasing kinetics of hydrogels with different amounts of type of hydrophobic side chain.

Relevance of drug releasing to loading amount of drug

To study the relevance of the drug release pattern to the loading amount of the drug, the gels with different fractions of acetaminophen are immersed in deionized water and the release data of the gels were fitted according to the eq. (3).

Within the first stage, the data fit with the value of theory satisfactorily, all linear regressions being highly significant ($P < 0.001$). The regression parameters, n and k (given in Table III), testify the indistinguishable release behaviors of the same gel containing different fractions of the drug. However, when the n value of the gel releasing increases a little with the content of FMA, the releasing mode of drug changes little with the content of the drug.

As expected for gels with high swelling properties such as PAA (its swelling ratio is about 600), the release index n is close to 0.5; that is, the drug release from the hydrogel is controlled by diffusion. In these highly swollen hydrogels, the drugs lie in an environment close to a free solution. While for P(FMA-AA), the release indices (about 0.7) are above 0.5 obviously. This proves effectively that the interactions between the drug and the gel network lead to a deviation of the Fickian release.

Relevance of drug delivery to hydrophobic modification

Release profiles of acetaminophen from gels (mean curves obtained from three replicates) with different FMA contents as a function of incubation time in the release medium (deionized water) are shown in Figure 4. The unmodified PAA gel with the largest swelling ratio shows the highest release rate. For P(FMA-AA), as the concentration of FMA increases from 0 to 1 mol %, the release rate of acetaminophen decreases, which is consistent with the results of the total releasing amount and the releasing efficiency

TABLE II
Drug Loading Capacity for the Hydrogels

Sample	Drug loading (mg/g)[a]	Partition coefficient
PAA	59.2	0.389
P(FMA–0.5%-AA)	189	4.923
P(FMA–1.0%-AA)	405	10.269

[a] The amount of drug loading was calculated by loaded drug weight/gel weight. The partition coefficient was measured as drug concentration between hydrogel and the medium for the loading process.

TABLE III
Characteristics of the Hydrogels Containing Different Acetaminophen Content

Sample	Drug loading (mg/g) ($Drug_{load}/M_{hydrogel}$)	Release index (n)	Release constant (k)	Releasing efficiency ($M_{24\ h}/Drug_{load}$)
PAA	59.2	0.552 (0.02)	0.4766	6.8
PAA	92.5	0.552 (0.03)	0.4801	6.9
P(FMA–0.5%-AA)	189	0.710 (0.02)	0.1549	3.2
P(FMA–0.5%-AA)	320	0.707 (0.02)	0.1575	3.2
P(FMA–1.0%-AA)	405	0.731 (0.02)	0.0735	1.3
P(FMA–1.0%-AA)	620	0.732 (0.03)	0.0743	1.3

(Table III). From these results, it can be proposed that hydrophobic modification plays an important role on the drug release kinetics of gels. The cross-linking density increases as a result of hydrophobic association with FMA groups, which induces the restrictive gel pore formation and reduces bulk diffusion. The mechanism of drug partitioning in hydrophobic domains of hydrogels will be studied further.

Furthermore, to evaluate the effect of fluorocarbon and hydrocarbon hydrophobic side groups on the release rate of drugs, the release of drug are carried out with hydrogels containing the same content of LA or FMA. Assuming the release behavior is close to a Fickian diffusion mechanism, a linear regression is used to fit the release data (Fig. 5) and results are shown in Figure 6. Because acetaminophen is loaded by solvent absorption that generally results in the surface loading of the gels, the release of superficially loaded drugs follows by slow pseudo-zero-order release because of a surface-localized burst effect. For instance, the amount of the drug release from surface burst decreases with the content of FMA (Fig. 4) by the order of PAA > P(LA–1%-AA) > P(FMA–1%-AA) (Fig. 5). Surface burst effects can be affected by the initial swelling of gels and the extent of surface layer incorporation of drug in the gels. Hence, the greater the hydrophobicity or heterogeneity of gels, the greater the amount of drug incorporated in the surface layer of the gel. In the zero-order kinetics release stage, the release rate of P(FMA–1%-AA) is lower than that of P(LA–1%-AA). The hydrophobic interaction between the polymer side chain and drug is proposed to play a significant role in such a release pattern.

As shown in Figure 6, during the early release, the linearity is quite good. The release index (n = 0.5791) of the LA-modified gel is similar to that (n = 0.5626) of unmodified PAA gel, but that (n = 0.7319) of the FMA-modified one is obviously higher. This confirms that the Fickian mechanism is not suitable to the fluoro-containing hydrogel, which

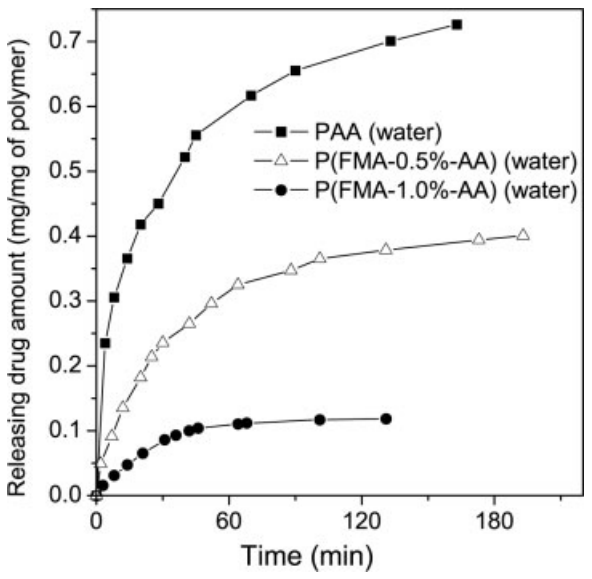

Figure 4 Drug release profile from hydrogels in aqueous media with different amounts of FMA.

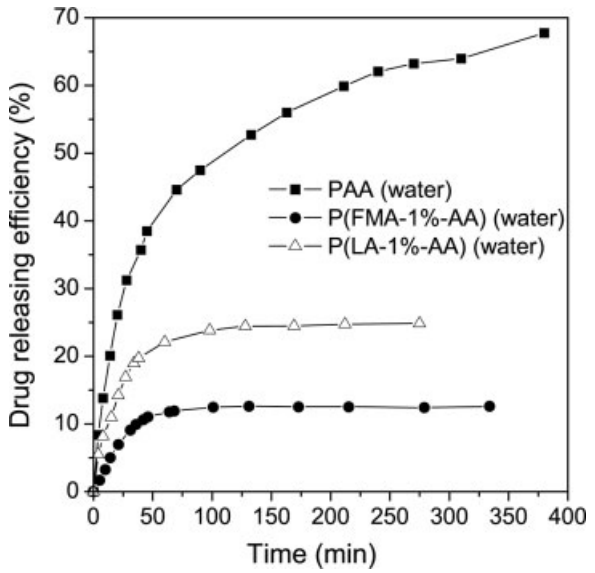

Figure 5 Release efficiency profile of acetaminophen from unmodified PAA, LA-modified and FMA-modified hydrogel.

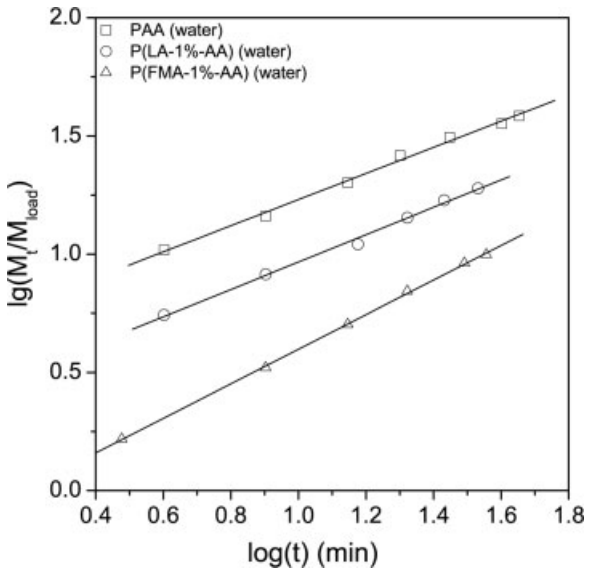

Figure 6 Plot of logarithmic slopes of release curves from unmodified PAA, LA-modified and FMA-modified hydrogel.

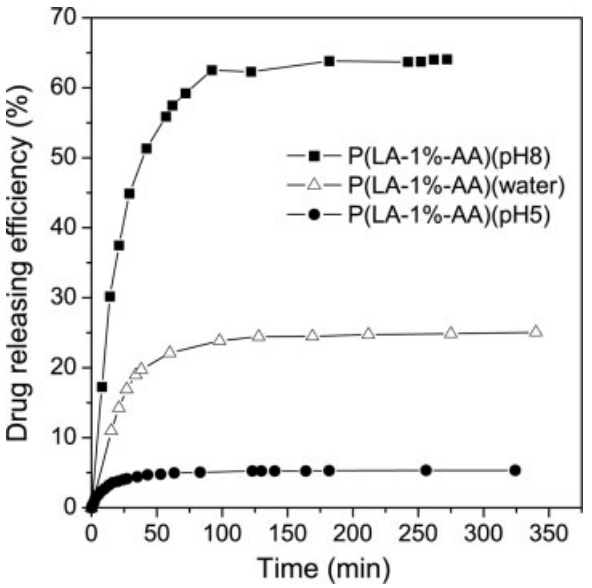

Figure 8 Dependence of acetaminophen release efficiency on time for LA-modified PAA hydrogel in media with different pHs.

can be ascribed to the stronger hydrophobic association came from fluoro-containing groups.

pH effect on drug release

The three kinds of the gels containing drug, unmodified PAA, P(LA–1%-AA), and P(FMA–1%-AA), were cut into three pieces with the same volume and then immersed in the solutions of different pH values. The release kinetics of the gels exhibit a significant difference to the Fickian and the two-stage release patterns are shown in Figures 7–9. In different media, the efficiency and the release increase in the order: water > pH 8 > pH 5, pH 8 > water > pH5, and pH5 > water > pH8 for the gel PAA, P(LA–1%-AA), and P(FMA–1%-AA), respectively. This shows the dependence of swelling capacity of the hydrogels on pH. Generally, the amount and rate of

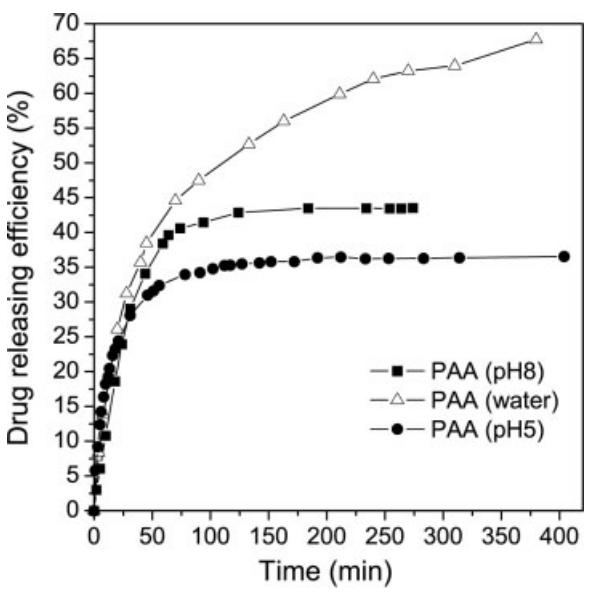

Figure 7 Dependence of acetaminophen release efficiency on time for unmodified PAA hydrogel in media with different pHs.

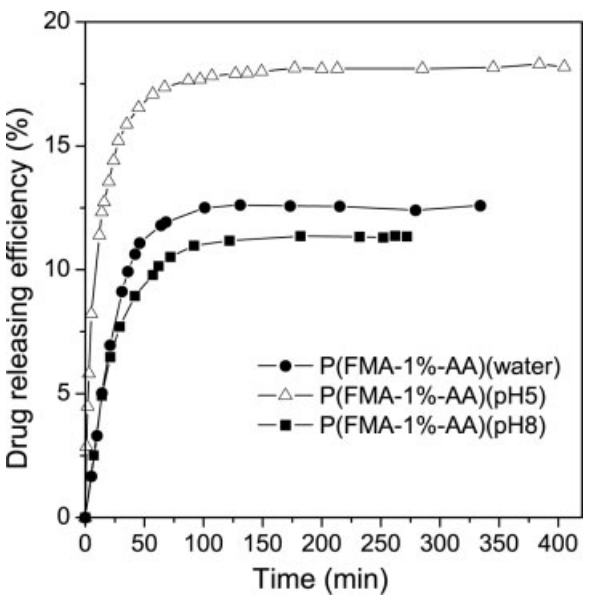

Figure 9 Dependence of acetaminophen release efficiency on time for FMA-modified PAA hydrogel in media with different pHs.

drug release shall increase with the pH value of the media, due to the higher swelling capacity of gels in neutral or basic media when COOH groups are ionized. After the gels load drugs in water, they are transferred into the medium with pH 5. This kind of medium change results in the decrease of electrostatic repulsive force in the gels. For the P(FMA–1%-AA) gel, the medium change induces gel shrinking and the entrapped drugs are mechanically squeezed out of the gel. For the unmodified PAA gel and P(LA–1%-AA) gel, this process of the drug squeezing is not so efficient after the process of loading drug because the gel networks are very loose. Instead, the medium change induces the formation of the gel ''skin'' layer, which prevents the flow of entrapped drug out of the gels. When the drug-containing hydrogels are transferred into the medium with the pH 8, the gels will swell continually due to the increase of electrostatic repulsive force. Among three kinds of the hydrogels mentioned here, the change of swelling ratio is the most obvious for the P(LA–1 mol%-AA) gel. Thus, it is possible to achieve highly efficient drug delivery under controllable condition by adjusting the type of hydrophobic modification.

Storage modulus of hydrogels

The storage modules E' of the hydrogels, swollen in pure water at 20°C, plotted against the strain are shown in Figures 10 and 11. The storage modules E' is independent of the frequency. The storage modulus of the unmodified PAA gel is on the order of 1 kPa, which is obviously lower than those of LA- and FMA-modified PAA gels whose modulus

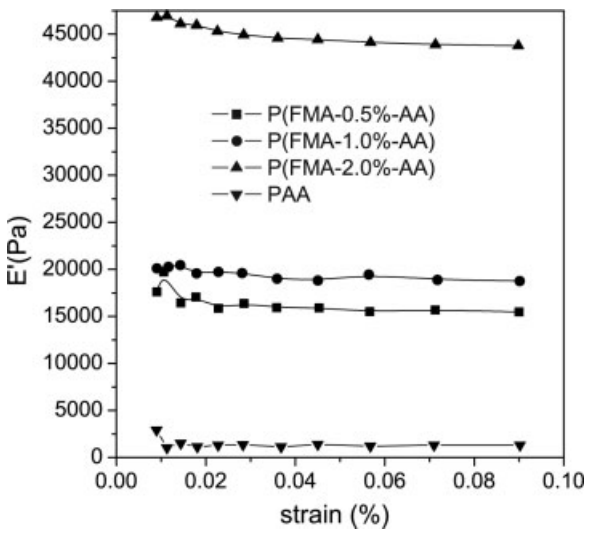

Figure 10 Storage modulus E' against strain for hydrogels with different amount of hydrophobic comonomer.

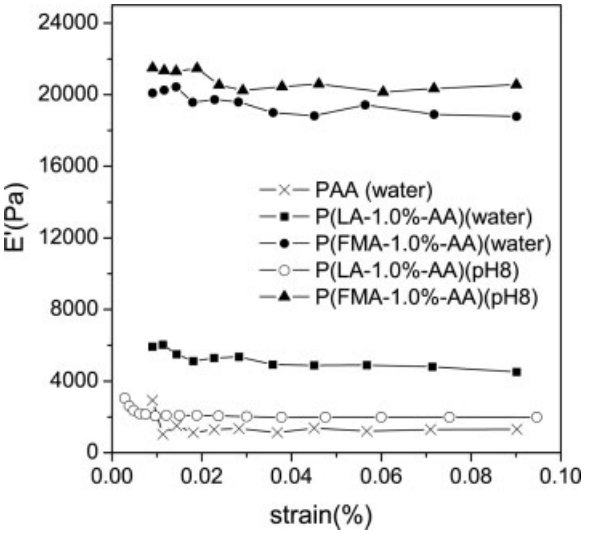

Figure 11 Storage modulus E' against strain for hydrogels with different hydrophobic type and in different media.

increase with the content of FMA. The difference can be ascribed to the association of the side chains. The E' of the P(LA–1%-AA) gel is 4.86 kPa in pure water and decreases to about 2.0 kPa when the gel is swollen in pH 8 medium. However, the storage modulus of the P(FMA–1%-AA) gel increases from about 19.2 kPa in water to about 20.1 kPa in pH 8 medium. These results indicate that LA-modified PAA gel combines the feature of polyelectrolyte and hydrophobically associating polymer. The high storage modulus results from the association of the hydrophobic side group, as well as the extension of the charged polymer chains.

CONCLUSIONS

The type and content of hydrophobe as well as the pH of the solution medium play an important role on the drug release pattern and rate of the gels. Compared with the hydrocarbon-modified gel, the fluorocarbon-modified gel has the stronger hydrophobicity, which affects gel's drug-releasing behavior. The storage modulus and the drug release show that P(LA–1%-AA) gels combine the feature of hydrophobically associating polymer and polyelectrolytes.

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