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Preparation and Application in Drug Controlled Delivery of pH-Sensitive P(CE-*co*-DMAEMA-*co*-MEG) Hydrogel

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ABSTRACT: A pH-sensitive hydrogel [P(CE-*co*-DMAEMA-*co*-MEG)] was synthesized by the free-radical crosslinking polymerization of *N*,*N*-dimethylaminoethyl methacrylate (DMAEMA), poly(ethylene glycol) methyl ether methacrylate(MPEG-Mac) and methoxyl poly(ethylene glycol)-poly(caprolactone)-methacryloyl methchloride (PCE-Mac). The effects of pH and monomer content on swelling property, swelling and deswelling kinetics of the hydrogels were examined and hydrogel microstructures were investigated by SEM. Sodium salicylate was chosen as a model drug and the controlled-release properties of hydrogels were pilot studied. The results indicated that the swelling ratios of the gels in stimulated gastric fluids (SGF, pH = 1.4) were higher than those in stimulated intestinal fluids (SIF, pH = 7.4), and followed a non-Fickian and a Fickian diffusion mechanism, respectively. *In vitro* release studies showed that its release rate depends on different swelling of the network as a function of the environmental pH and DMAEMA content. SEM micrographs showed homogenous pore structure of the hydrogel with open pores at pH 1.4. © 2014 Wiley Periodicals, Inc. J. Appl. Polym. Sci. **2014**, *131*, 40737.

KEYWORDS: applications; crosslinking; drug delivery systems; kinetics; swelling

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INTRODUCTION

In the past decades, environmental stimuli-responsive hydrogels have been extensively investigated for their smart response to environmental stimulus, such as temperature, pH, electric field, solvent, light, ions, etc.[1,2] Environment-sensitive hydrogels have great potential in targeted drug delivery system, protein–ligand recognition, on–off switches for modulated drug delivery or artificial organs, and immobilization of enzyme.[3] In all of their applications, the controlled drug delivery is the most prominent area. A fatal shortcoming of traditional hydrogel is the slow response speed, therefore, in recent years much more attention has been directed to improve the response rate of intelligent gels.

Poly(ethylene glycol) methyl ether (MPEG) and polycaprolactone (PCL) have been widely investigated in materials science and biotechnology because of its stability, biocompatibility, nontoxicity, rapid clearance from the body.[4–8] In recent years, much more attention has been directed to PDMAEMA hydrogels that undergo controllable volume changes in response to small variations of pH and temperature changes in solution condition for use in a variety of novel applications including controlled drug delivery.[9–12]

In this study, a pH-sensitive P(CE-*co*-DMAEMA-*co*-MEG) hydrogel, which have shorter adsorption equilibrium time and has been found to respond rapidly to changes in the external pH, was successfully prepared using DMAEMA, MPEG-Mac, and PCE-Mac as monomers. The swelling behavior of the hydrogels as a function of temperature, pH values, and DMAEMA content were investigated. Additionally, release profiles of a model drug (sodium salicylate) from test hydrogels were studied in simulated gastric and intestinal fluids.

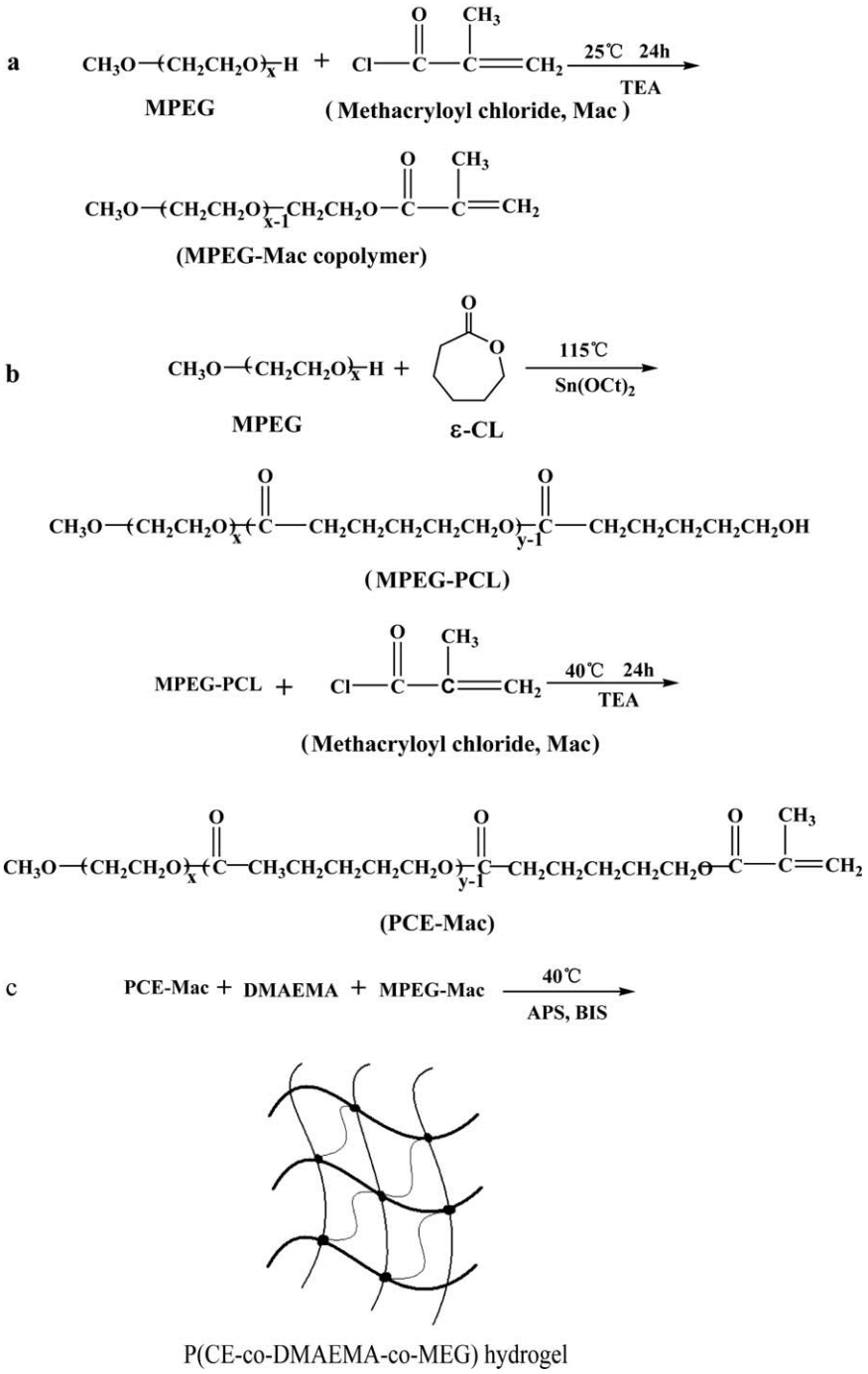
EXPERIMENTAL

Materials

Poly(ethylene glycol) methyl ether (MPEG, M_n = 1000), *N*,*N*-dimethylaminoethyl methacrylate (DMAEMA), tin (II) 2-etheylhexanoate [$Sn(OCt)_2$], ε-caprolactone (ε-CL) and sodium salicylate were purchased from Aladdin Chemical Co. Ltd.; Methacryloyl chloride, ammonium persulfate (APS) and *N*,*N*′-methylenebisacrylamide (BIS) purchased from Tianjin Kaixin Chemicals (China).

Synthesis of PCE-Mac

PCE-Mac was prepared according to Ref. [13]. A typical process as follows: ε-CL (50 mmol), $Sn(Oct)_2$ (0.5 mmol) and MPEG (5.0 mmol) were weighed into a round-bottomed, then, the reaction mixture was heated to 115°C and was kept at this temperature under a nitrogen atmosphere for 24 h. The purified



Scheme 1. Synthesis of MPEG-Mac (a), PCE-Mac polymer (b), and P(CE-*co*-DMAEMA-*co*-MEG) hydrogel (c).

polymer (MPEG-PCL) was first dissolved in dichloromethane, with a considerable amount of triethylamine, and reacted with methacryloyl chloride at 40°C, allowing reflux for 4 h according to Scheme 1(b) to acquire MPEG-PCL-Mac. In the following text, MPEG-PCL-Mac was denoted as PCE-Mac for simplification.

Synthesis of Hydrogels

The P(CE-*co*-DMAEMA-*co*-MEG) hydrogel was synthesized by free-radical polymerization of PCE-Mac, MPEG-Mac, and DMAEMA with APS as initiator and BIS as cross-linker. Stoichiometric monomers were dissolved in dimethyl sulfoxide (DMSO), and then BIS was added into the mixture with nitrogen for 30 min to remove the dissolved oxygen. Then, APS were added into the reaction mixture accompanied by rapid stirring at 40°C for 8 h. The just obtained P(CE-*co*-DMAEMA-*co*-MEG) hydrogel was immersed in distilled water for 7 d, and the water was refreshed everyday in order to remove residues of the unreacted monomers and crosslinking agents. The purified

Table I. Composition Feed of P(CE-*co*-DMAEMA-*co*-MEG) Hydrogels

Sample	DMAEMA (g)	MPEG-Mac (g)	PCE-Mac (g)	BIS (g)	APS (g)
DMP1	1.2	0.6	0.2	0.36	0.216
DMP2	2.4	0.6	0.2	0.34	0.204
DMP3	3.6	0.6	0.2	0.32	0.192

hydrogels were first dried at room temperature for 1 day, and then dried at 40°C under vacuum for 24 h. The obtained samples in this work were shown in Table I and the process is shown in Scheme 1(c).

Study on the pH Sensitivity

A classical gravimetric method was used to study on the pH sensitivity. The dried hydrogels (W_d) were immersed in an excess amount of buffer solutions of 3–13 at 37°C. The wet weight of the samples (W_e) was determined after removing the surface water by blotting with filter paper. Taking the average value of three measurements for each sample, the equilibrium swelling ratio (Re) was calculated according to eq. (1):[14]

$$Re=(W_e-W_d)/W_d \quad (1)$$

Study on the Swelling Kinetics

For the swelling kinetics measurements, the hydrogels were immersed in SGF (pH = 1.4 buffer solution) and SIF (pH = 7.4 buffer solution) at 37°C. At a prescribed time interval, the hydrogels were taken out from the water and weighed after wiped off the surface of hydrogel. The swelling ratio (Rt) at each pH and temperature was calculated according to eq. (2):[15]

$$Rt=(W_t-W_d)/W_d \quad (2)$$

where W_d and W_t are the weights of dried and swollen hydrogels, respectively.

Study on the Deswelling Kinetics

The kinetics of deswelling of the hydrogels was also followed gravimetrically, in pH 7.4 buffer solution. The swollen hydrogels equilibrated first in SGF were transferred into SIF, the weight changes of the hydrogels were recorded during the course of deswelling at these time intervals. The normalized deswelling ratio (NDR) of the hydrogels was calculated according to eq. (3):[16]

$$NRD=\frac{W_t-W_d}{W_e-W_d} \quad (3)$$

where W_d and W_t are the weights of dry and swollen hydrogels, respectively. W_e denote the weight of the hydrogels at equilibrium swelling.

In Vitro Drug Delivery Study

The drug loaded and released properties were evaluated by using sodium salicylate as drug target. P(CE-*co*-DMAEMA-*co*-MEG) dried samples were immersed in the drug target aqueous solution (5 g/L) for 2 d at room temperature. The drug loaded hydrogels were rinsed with distilled water and dried till a constant weight under vacuum. After that, samples were submerged in 50 mL SGF and SIF release environment. The temperature was kept at 37°C and the stirring rate was maintained at 100 rpm using a thermostatic oscillator (WE-3, Tianjin, Ounuo, China). Aliquots from the dissolution medium were withdrawn periodically and analyzed using a UV–Vis spectrophotometer (Agilent 8453, Japan). The wavelength of maximal absorbance for sodium salicylate was set at (300 ± 1) nm. The concentration of sodium salicylate was obtained based on the standard curve eq. (4):[17]

$$c_t(g/L)=(A+0.0109/21.1737) \quad (4)$$

where A is the UV absorbance at (300 ± 1) nm. The cumulative drug release was calculated from the following relationship:

$$Cumulative\ release\,(\%)=c_tV_t/c_0V_0\times 100 \quad (5)$$

where c_t and V_t are the concentration and volume of drug released from hydrogels at time t, respectively. c_0 and V_0 are the concentration and volume of drug loaded into the hydrogels, respectively.

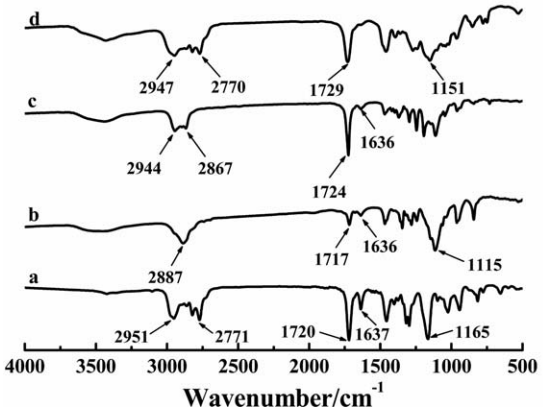


Figure 1. FT-IR spectra of DMAEMA (a), MPEG-Mac (b), PCE-Mac (c), and P(CE-*co*-DMAEMA-*co*-MEG) hydrogel (d).

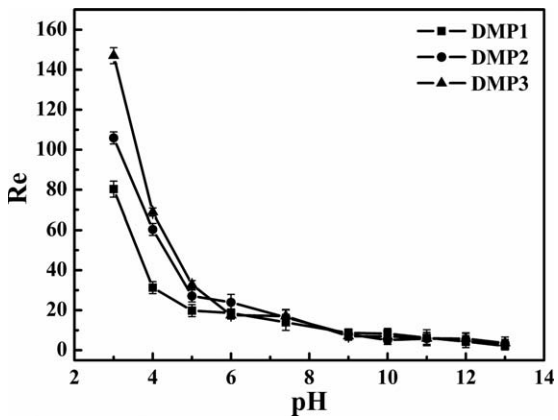


Figure 2. Equilibrium swelling ratios (Re) of various P(CE-*co*-DMAEMA-*co*-MEG) hydrogels samples as functions of solution pH values for various samples in buffer solution (mean ± S.D., n = 3).

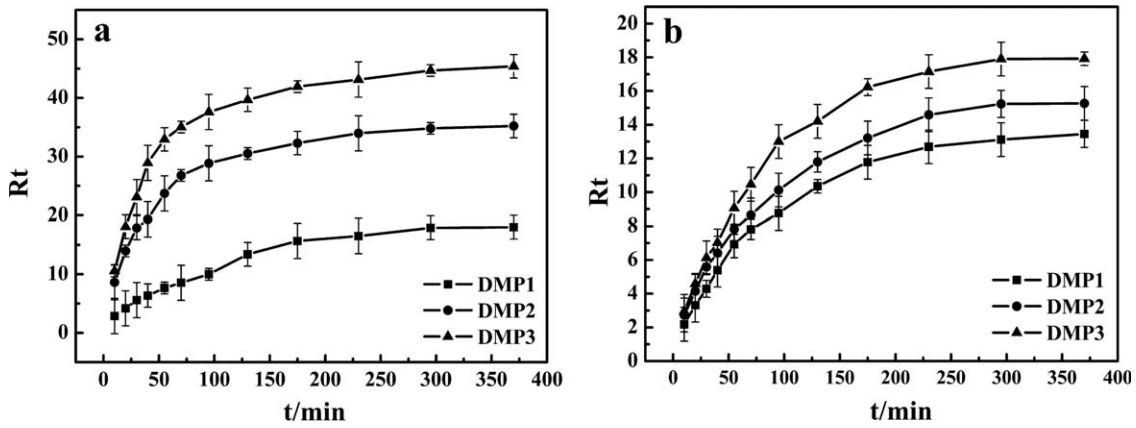


Figure 3. Influence of the composition of P(CE-*co*-DMAEMA-*co*-MEG) hydrogels on swelling ratios in SGF (a) and SIF (b) at 37°C (mean ± S.D., $n = 3$).

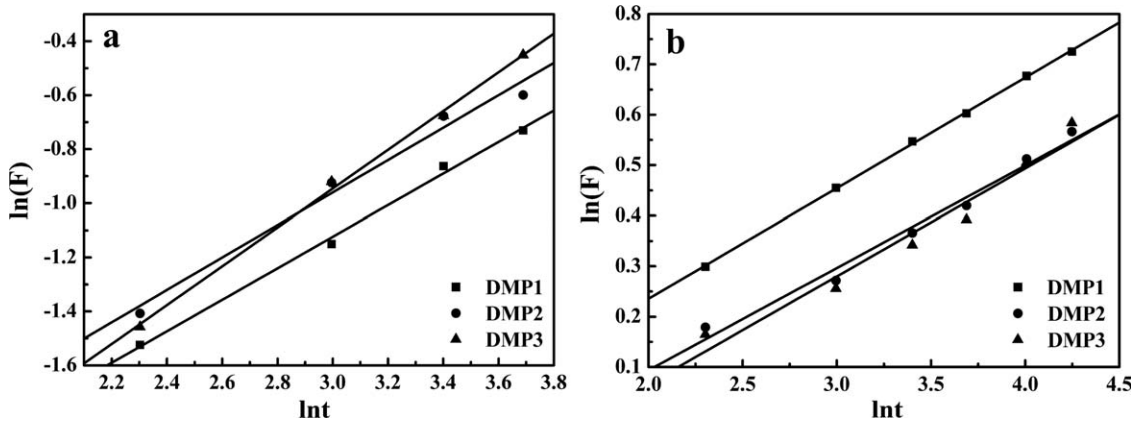


Figure 4. The ln F versus ln t curves of P(CE-*co*-DMAEMA-*co*-MEG) hydrogels in SGF (a) and SIF (b) at 37°C (mean ± S.D., $n = 3$).

RESULTS AND DISCUSSION

FT-IR

Figure 1 shows the FT-IR spectra of DMAEMA (a), MPEG-Mac (b), PCE-Mac (c), and P(CE-*co*-DMAEMA-*co*-MEG) hydrogel (d). Compared to the IR spectrum of DMAEMA, MPEG-Mac, PCE-Mac, the C═C stretching vibration peak at 1636 cm^{-1} and the out-of-plane bending band at 964 cm^{-1} for unsaturated C—H disappeared. The other characteristic peaks of the P(CE-*co*-DMAEMA-*co*-MEG) was observed at 1729 cm^{-1} for ester stretching peaks (C═O), the bands at 1151 cm^{-1} was assigned to the symmetric C—O—C stretching modes of the ester group, the bands at 2947 and 2770 cm^{-1} were assigned to the symmetric stretching modes of the $–CH_3$ and $–CH_2$. These provided evidence for the successful copolymerization of DMAEMA, MPEG-Mac, and PCE-Mac.

pH Dependence of Degree of Swelling

To investigate the influence of pH value of the medium on the equilibrium swelling ratios of the gels (Figure 2), the ionic strength of buffers is kept constant ($I = 0.2M$) by adding NaCl,

Table II. Swelling Kinetic Equations and Kinetic Parameters of P(CE-*co*-DMAEMA-*co*-MEG) Hydrogel Samples in SGF and SIF at 37°C (Mean ± S.D., $n = 3$)

Medium	Sample	Initial regression equation	R^2	n	ln k
SGF	DMP1	$\ln F_1 = 0.5837 \ln t - 2.8747$	0.9961	0.5837	−2.8747
	DMP2	$\ln F_2 = 0.6003 \ln t - 2.7611$	0.9927	0.6003	−2.7611
	DMP3	$\ln F_3 = 0.7184 \ln t - 3.1011$	0.9977	0.7184	−3.1011
SIF	DMP1	$\ln F_1 = 0.2191 \ln t - 0.2029$	0.9996	0.2191	−0.2029
	DMP2	$\ln F_2 = 0.2027 \ln t - 0.3115$	0.9814	0.2027	−0.3115
	DMP3	$\ln F_3 = 0.2134 \ln t - 0.3603$	0.9589	0.2134	−0.3603

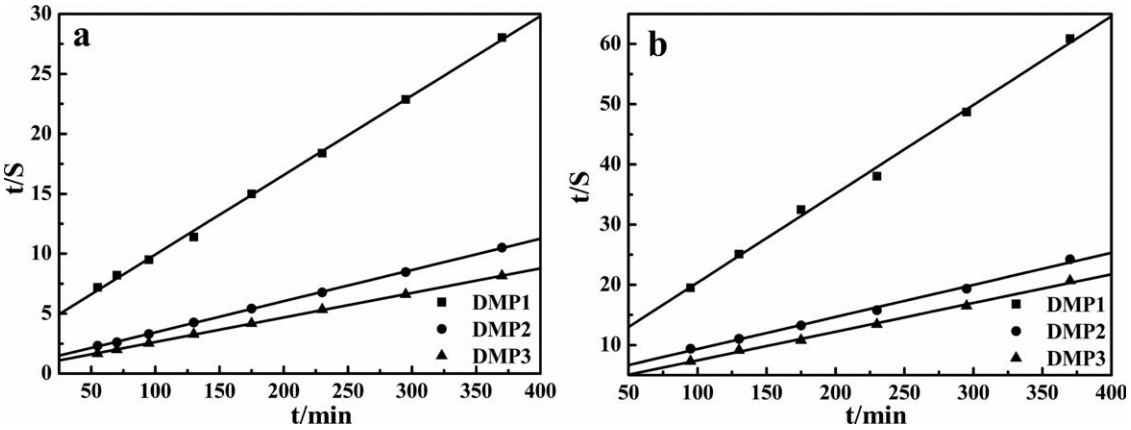


Figure 5. The t/S versus t curves of P(CE-*co*-DMAEMA-*co*-MEG) hydrogels in SGF (a) and SIF (b) at 37°C (mean ± S.D., $n = 3$).

Table III. Extensive Swelling Kinetic Equations, Initial Swelling Rates (r_0), and Maximum Theoretical Water Contents (S_∞) of P(CE-*co*-DMAEMA-*co*-MEG) Hydrogel Samples in SGF and SIF at 37°C (Mean ± S.D., $n = 3$)

Medium	Sample	Extensive regression equation	R^2	S_∞	r_0	k_s
SGF	DMP1	$(t/S)_1 = 0.0664t + 3.2962$	0.9988	15.0602	0.3034	0.0013
	DMP2	$(t/S)_2 = 0.0260t + 0.8414$	0.9998	38.4615	1.1895	0.0008
	DMP3	$(t/S)_3 = 0.0250t + 0.5749$	0.9999	48.7805	1.7394	0.0007
SIF	DMP1	$(t/S)_1 = 0.1475t + 5.6177$	0.9965	6.7797	0.1780	0.0039
	DMP2	$(t/S)_2 = 0.0533t + 4.0024$	0.9951	18.7617	0.2499	0.0007
	DMP3	$(t/S)_3 = 0.0477t + 2.6693$	0.9969	20.9644	0.3746	0.0009

the pH range is selected from 3.0 to 13.0 in this study. In the molecular structure of DMAEMA, there is an active tertiary amino group [–$N(CH_3)_2$)], and the protonation of the tertiary group could induce the swelling ratio to change with changing pH in aqueous solutions. By increasing the pH value, such ionization degree of tertiary amino group increases and as a result, the hydration degree reduced leading to the decrease in the swelling degree.

Swelling Kinetics in SGF and SIF

The swelling behaviors of hydrogels in SGF (a) and SIF (b) were shown in Figure 3. As shown in Figure 3, the equilibrium swelling ratios of this hydrogel in SGF are much higher than that in SIF, which might be mainly contributed to hydrogen bond and electrostatic interaction. In acidic solution (pH = 1.4), –$N(CH_3)_2$ groups can be integrated with H^+ ions into –$NH^+(CH_3)_2$ groups and the hydrogen bond broke owing to –$N(CH_3)_2$ groups becoming ionized. Meanwhile, electrostatic repulsion caused the network to expand, resulting in greater water uptake and producing a larger swelling ratio. When environmental pH value is set to 7.4, the amount of –$NH^+(CH_3)_2$ is gradually reduced inside the hydrogels, which leads to a decrease in osmotic pressure and makes the *Rt* of the hydrogels smaller.

It is clear that when hydrogel is bought into contact with water, water diffuses into the hydrogel, and the hydrogel swells. To investigate the diffusion mechanism in the hydrogels, the initial swelling data were fitted to eq. (6) for $S/S_\infty \leq 0.6$ as follows:[18]

$$F = S/S_\infty = kt^n \text{ or } ln(F) = lnk + nlnt \quad (6)$$

where F denotes the water fraction at time t, S and S_∞ represent the amount of water absorbed by the hydrogel at time t and at an equilibrium state, respectively; k is a characteristic constant of the hydrogel, and n is a characteristic exponent of the swelling which represents solvent diffusion modes inside hydrogels, and provides information about the mechanism of swelling kinetics. The constant n and k can be calculated from

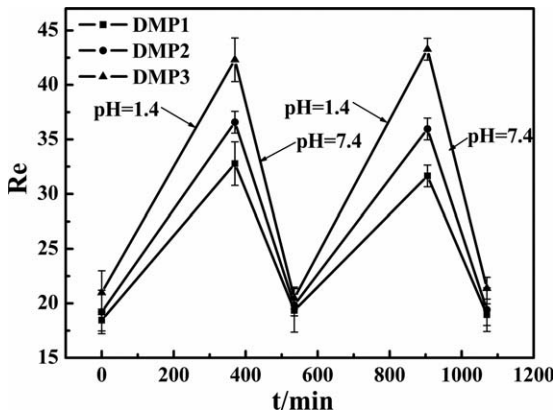


Figure 6. Reversible swelling of the P(CE-*co*-DMAEMA-*co*-MEG) in buffers solution with pH of 1.4 and 7.4 (37°C) (mean ± S.D., $n = 3$).

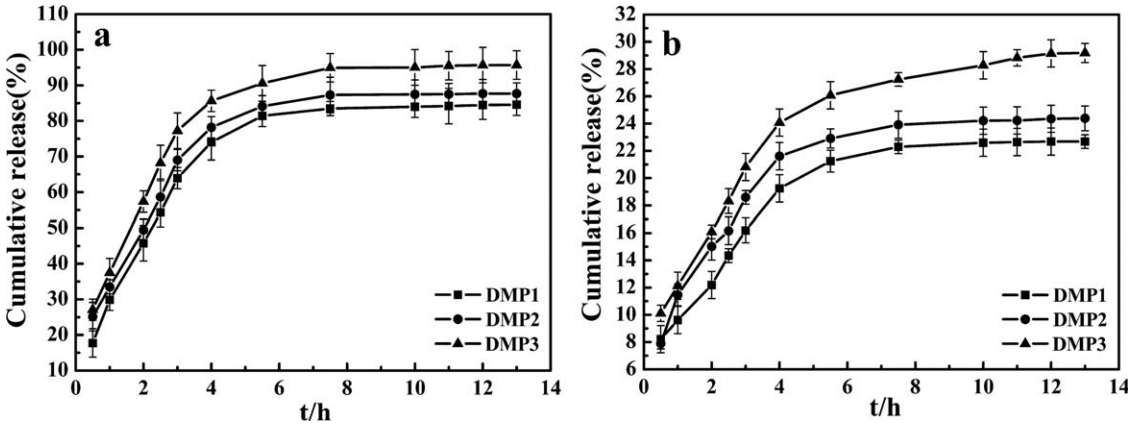


Figure 7. Sodium salicylate release profiles for synthesized P(CE-*co*-DMAEMA-*co*-MEG) hydrogels at 37°C in SGF (a) and in SIF (b) (mean ± S.D., $n = 3$).

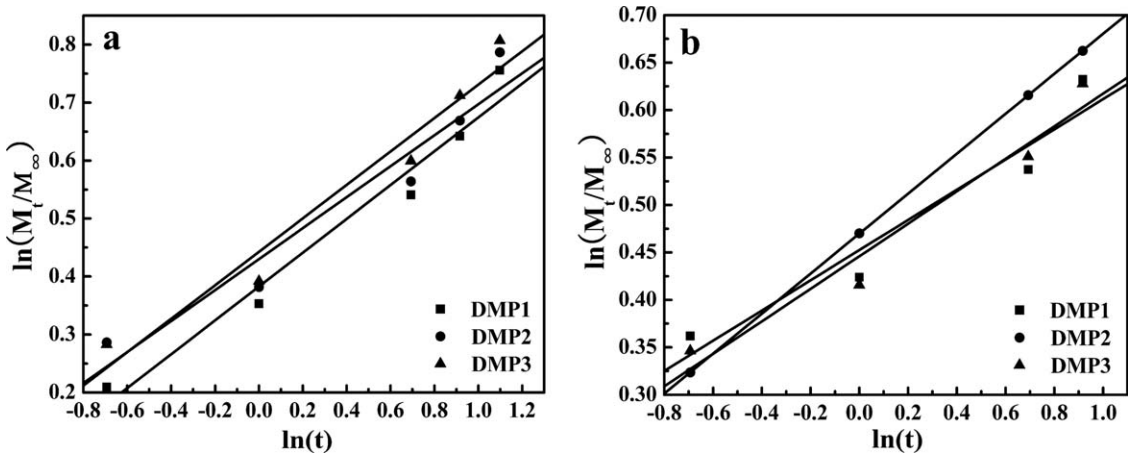


Figure 8. Linear regression curves of P(CE-*co*-DMAEMA-*co*-MEG) hydrogels at 37°C in SGF (a) and in SIF (b) (mean ± S.D., $n = 3$).

the slope and intercept of eq. (6). Figure 4 can be used to elucidate dependence of ln(F) on ln(t) for various hydrogel samples in SGF and SIF environments. After having been fitted, the kinetic parameters k and n as well as the correlation coefficient R^2 obtained are tabulated in Table II. In an acidic medium (SGF), the swelling index n values are evidently over 0.5, which represents a non-Fickian diffusion.[18] In the case of a more basic medium (SIF), the equivalent n values (an approximate 0.5 or below 0.5) for all the samples manifest that the diffusion behavior of water in these hydrogels follows the Fickian mechanism.

The extensive swelling process follows the Schott second-order dynamic equation [eq. (7)]:[2]

$$dS/dt = k_s(S_\infty - S)^2 \text{ or } t/S = A + Bt \quad (7)$$

The constants $B = 1/S_\infty$ and $A = 1/k_s S_\infty^2 = 1/(dS/dt)_0$ can be calculated from the slope and intercept of eq. (7). The function relations of t/S versus t are plotted in Figure 5. The swelling kinetic equations, k_s, r_0, and S_∞ values of hydrogel samples are tabulated in Table III. All the R^2 are greater than 0.99,

Table IV. Regression Equations and Kinetic Parameters Obtained from Fitting Drug Release Experimental Data to Ritger–Peppas Model

Medium	Sample	Regression equation	R^2	n	ln k
SGF	DMP1	$\ln(M_t/M_\infty) = 0.2916 \ln t + 0.3828$	0.9664	0.2916	0.3828
	DMP2	$\ln(M_t/M_\infty) = 0.2670 \ln t + 0.4130$	0.9361	0.2670	0.4130
	DMP3	$\ln(M_t/M_\infty) = 0.2883 \ln t + 0.4427$	0.9562	0.2883	0.4427
SIF	DMP1	$\ln(M_t/M_\infty) = 0.1590 \ln t + 0.4525$	0.9300	0.1590	0.4525
	DMP2	$\ln(M_t/M_\infty) = 0.2105 \ln t + 0.4698$	0.9999	0.2105	0.4698
	DMP3	$\ln(M_t/M_\infty) = 0.1713 \ln t + 0.4459$	0.9571	0.1713	0.4459

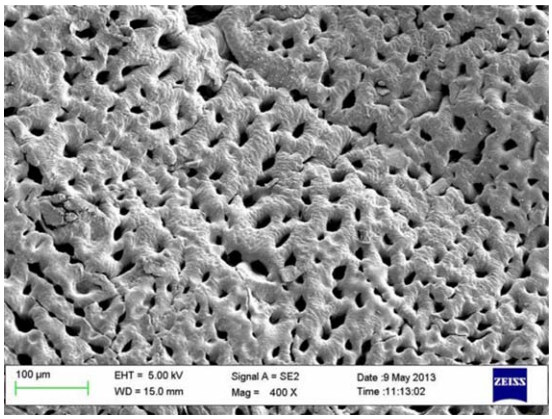


Figure 9. SEM picture of P(CE-*co*-DMAEMA-*co*-MEG) hydrogel at pH 1.4. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

indicating a small estimated standard error and a highly precise linear regression equation.

Reversible Response of the Hydrogels in Different pH Solutions

A reversibility of the swelling and deswelling behavior was demonstrated by repeatedly cycling P(CE-*co*-DMAEMA-*co*-MEG) hydrogel samples in stimulated buffers of pH = 1.4 and pH = 7.4 in Figure 6. These experimental results hint that the hydrogels are provided with a relatively fast expansion rate in acidic surroundings, whereas they shrink as soon as they are immersed into alkalescent solutions. The phenomena can be explained by the formation and dissociation of protonation between $-NH^+(CH_3)_2$ groups. In low pH value (pH = 1.4), $-N(CH_3)_2$ began to protonate. Meanwhile, the osmotic pressure inside the hydrogels increased, and electrostatic repulsion caused the network to expand. In high pH value (pH = 7.4), most $-NH^+(CH_3)_2$ groups are in the form of $-N(CH_3)_2$, and large amounts of hydrogen bonds formed by DMAEMA chain corresponding with PEG chain. As show in Figure 6, hydrogels have good reversibility after multiple cycles, these data showed that the P(CE-*co*-DMAEMA-*co*-MEG) hydrogels have a good reswelling ability and maintain the high sensitivity to pH.

Drug Delivery Studies

The studies on the release of sodium salicylate from hydrogels were carried out by immersing the sodium salicylate-incorporated hydrogels in SGF or SIF. In order to examine the *in vitro* drug release well, cumulative release is simultaneously presented in Figure 7. As shown, in SIF, the released amount for all three test hydrogels were relatively low, only 22.7–29.4% of sodium salicylate released within 300 min. The relatively low amounts of sodium salicylate released were probably related to the comparatively low degrees of swelling of test hydrogels in SIF [Figure 3(b)]. In SGF, the released amounts increased significantly, 84.6–95.7% sodium salicylate released within 300 min. This is because the swelling of the test hydrogel network increased considerably due to protonate of $N(CH_3)_2$ groups on DMAEMA. With an increasing amount of DMAEMA used, the released amount of sodium salicylate increased.

To establish a relationship between the drug release rates and molecular transport parameters, we fitted the release data to the empirical equation [eq. (8)]:[19–21]

$$M_t/M_\infty = kt^n \text{ or } ln(M_t/M_\infty) = lnk + nlnt \quad (8)$$

M_t/M_∞ represents the fraction of drug released at time t. The relationship between $\ln(M_t/M_\infty)$ on $\ln(t)$ was made and the result is shown in Figure 8. After having been fitted, the kinetic parameters k and n as well as the correlation coefficient R^2 obtained are tabulated in Table IV and n values ranging from 0.1590 to 0.2916 for the present microspheres indicate a Fickian mode of drug transport. The preliminary kinetic model confirms that a new kind of intelligent hydrogel can be designed and created by a hydrophobically modified route. Therefore, the response of the hydrogels, the release rate of the mode drug in various media can be modulated by adjusting the proportion of hydrophobic domains.

SEM Observations

SEM was employed to investigate morphology of P(CE-*co*-DMAEMA-*co*-MEG) (DMP3) hydrogel. The hydrogel was immersed in pH = 1.4, and was frozen in liquid nitrogen and lyophilized for 24 h. Then, the hydrogel was sputtered with gold before observation. As shown in Figure 9, the pore structure is homogenous and the pores are open at this pH, as expected. As mentioned in the previous sections, large pores can probably lead to the high swelling ratios and high cumulative release (%) of drug.

CONCLUSIONS

A type responsive P(CE-*co*-DMAEMA-*co*-MEG) hydrogel was obtained from cross-linked DMAEMA, PCE-Mac, and MPEG-Mac. The swelling ratio was dependent on DMAEMA content and the environmental pH, being higher in simulated gastric fluid and lower in simulated intestinal fluid. The swelling ratio of the gels reaches a maximum at pH about 3.0 and the gel exhibits sensitive reversible response between pH 1.4 and pH 7.4. The *in vitro* cumulative release data were analyzed using an empirical equation to compute the diffusion exponent (n), whose values suggest a Fickian mode of transport. All results show that P(CE-*co*-DMAEMA-*co*-MEG) hydrogels were prepared would be a better application foreground in drug delivery systems.

ACKNOWLEDGMENTS

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