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Synthesis and characterization of biodegradable pH-sensitive hydrogel based on poly(ε-caprolactone), methacrylic acid, and Pluronic (L35) ☆

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ABSTRACT

A series of biodegradable and pH-sensitive hydrogels based on poly(ε-caprolactone) (PCL), Pluronic, and methylacrylic acid (MAA) were successfully prepared by UV-initiated free radical polymerization, which were further characterized by ^{1}H NMR and FTIR. Swelling behavior in different aqueous media and pH-responsibility of the hydrogels were studied in detail. With increase in pH value of aqueous media from 1.2 to 7.2, swelling ratio of the hydrogels increased accordingly. The hydrolytic degradation behavior of these hydrogels was also investigated in detail. The biodegradable pH-sensitive hydrogel obtained in this work might have great potential application in drug delivery system.

1. Introduction

Hydrogels are three-dimensionally cross-linked hydrophilic polymer networks that are capable of absorbing a large amount of water in the swollen state in presence of chemical or physical cross-links (AmEnde & Peppas, 1996; Elliott, Macdonald, Nie, & Bowman, 2004; Huang, Yu, & Xiao, 2007). In the last decades, great attention has been focused on environmentally sensitive hydrogels due to their special properties and potential applications in biomedical fields (Bajpai & Singh, 2006; Chao et al., 2006, 2008; Cruise, Scharp, & Hubbell, 1998; Iza, Stoianovici, Viora, Grossiord, & Couarraze, 1998; Liu et al., 2007; Singh, Chauhan, Kumar, & Chauhan, 2007; Xu, Kang, & Neoh, 2006; Zhang, Tang, Bowyer, Eisenthal, & Hubble, 2005). These environment-sensitive hydrogels were also called "smart" or "intelligent" hydrogels, which might have great potential applications in targeting drug delivery system due to their biocompatibility and resemblance to biological tissues (Bell & Peppas, 1996; Chiellini, Petricco, Ranucci, & Solaro, 2002; Kumar, Lahiri, & Singh, 2006; Shang, Zhang, Du, & Venkatraman, 2008).

Currently, therapeutic proteins or peptide drugs were mainly administrated by intramuscular or intravenous injections, due to their delicate physicochemical characteristics in aqueous solutions and susceptibility to be degraded in acidic gastric fluid and biological fluids where there were many kinds of proteolytic enzymes (Gümüşderelioğlu & Kesgin, 2005). Unfortunately, parenteral administration of proteins or peptides drug is limited by rapid elimination, whereas oral administration is generally not successful owing to degradation in the gastro-intestinal tract. For this reason, pH-sensitive hydrogels are designed to solve the injection problem and widely used in the area of site-specific drug delivery to specific regions of the gastro-intestinal tract. In acidic gastric environment (pH 1.2), the drug is sustained in the hydrogel, whereas in intestinal region (pH 7.2), the drug can be released (Dergunov & Mun, 2009; Gao, Liu, Chen, Jin, & Chen, 2009; George & Abraham, 2007; He et al., 2009; Lee, Chung, & Kurisawa, 2009).

Various pH-sensitive hydrogels had been investigated widely as site-specific drug delivery carriers to specific regions of the gastro-intestinal tract because of their adjustable swelling behavior in aqueous medium, which can control the drug release rates in a mild manner (Huang et al., 2007). These pH-sensitive hydrogels bearing weak acidic pendant groups would exhibit pH sensitivity owing to the alternation of $COOH/COO^-$ upon pH changes. In order to change the biodegradation of these hydrogels, the objective of current studies was to investigate a novel biodegradable and

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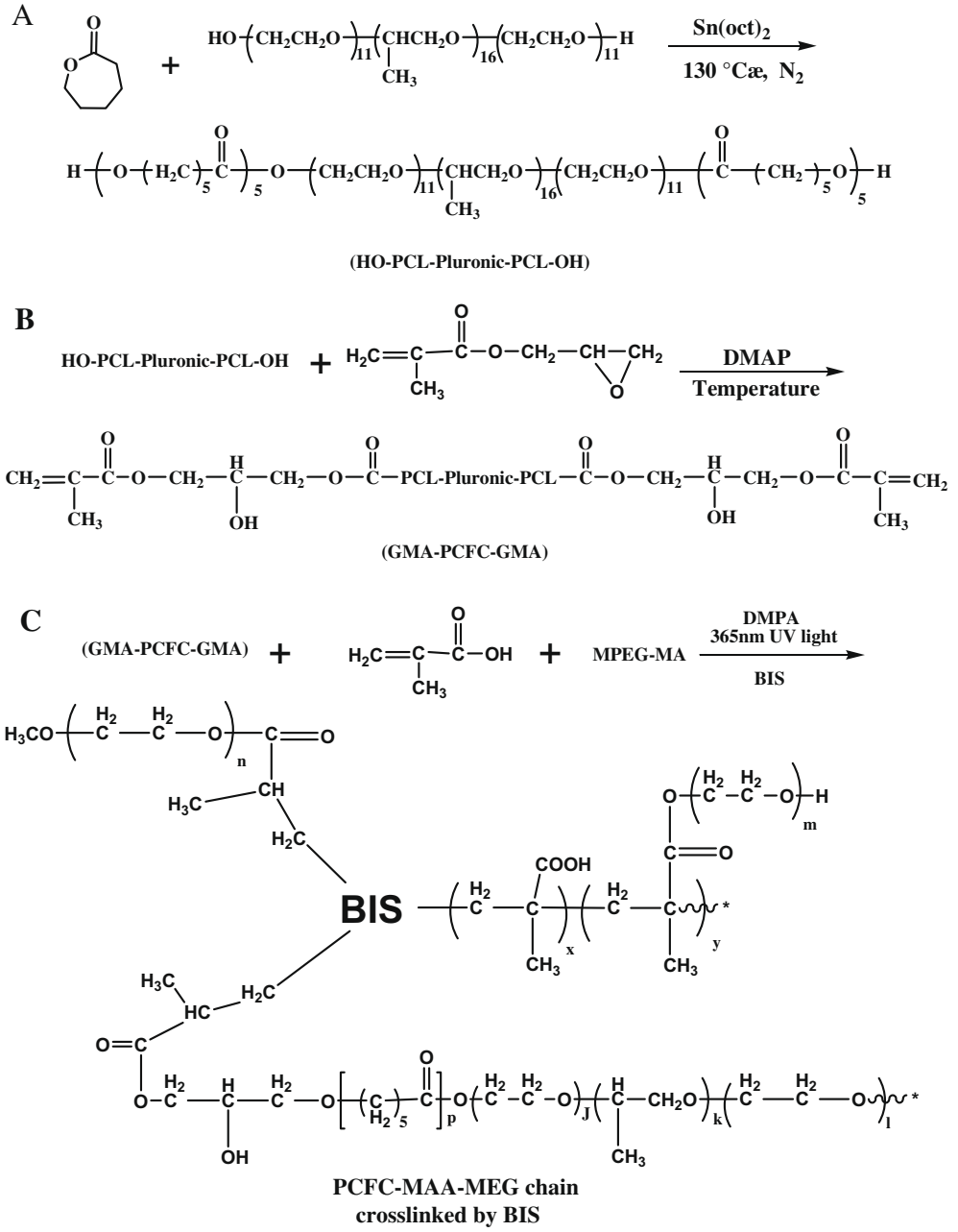
pH-sensitive hydrogels. During the last decade, biodegradable and pH-sensitive hydrogel has been extensively studied due to their great biodegradability, biocompatibility, and smart responsibility to the potential application of drug delivery system.

Pluronic (Poloxamer) composed of poly(ethylene glycol)–poly(propylene glycol)–poly(ethylene glycol) (PEG–PPG–PEG) has been widely employed as a biomaterial for its great biocompatibility (Ha, Kim, & Lee, 1999; Lee & Yoo, 2008; Liu et al., 2007). Poly(ε-caprolactone) (PCL) is a biodegradable and biocompatible material with hydrophobic characteristics, which has been widely used in drug delivery systems and biomedical fields (Albertsson & Varma, 2003; Zhu, Xie, Tong, & Shen, 2007). Incorporation of PCL segments into PEG–PPG–PEG copolymer backbone could enhance the biodegradation of pH-sensitive hydrogels and result in distinct decrease in molecular weight after degradation and easier elimination from the body. In our previous work, we had synthesized P(CE–MAA–MEG) hydrogels and investigated the swelling behavior, hydrolytic degradation behavior of these hydrogels (Wang et al., 2009). But the degradation rate of P(CE–MAA–MEG) is relatively slow, even for those compositions containing high amounts of PEG. It made the application of drug delivery systems greatly limited. In order to overcome this shortcoming, and synthesized a new kind of pH-sensitive hydrogels, we will plan to use the Pluronic (poloxamer) for a new kind of hydrogels. In this study, a new kind of biodegradable and pH-sensitive P(CFC–MAA–MEG) hydrogel was successfully prepared from PCL, MAA, and Pluronic by an effective and mild photo-polymerization method. Compared with the P(CE–MAA–MEG) hydrogels prepared in our previous work, the accelerated hydrolysis will result in the formation of P(CFC–MAA–MEG) hydrogels with increased PCL contents. The swelling behavior, pH sensitivity, and degradation behavior of the hydrogels were studied in detail.



Scheme 1. Material synthesis: (A) synthesis of PCL–Pluronic–PCL; (B) synthesis of GMA–PCFC–GMA; (C) synthesis of P(CFC–MAA–MEG) hydrogel.

2. Materials and methods

2.1. Material

Pluronic (Mn = 1900, with 50 wt% of ethylene glycol. Aldrich, USA), ε-caprolactone (ε-CL), *N*,*N*′-Methylene-bis-acrylamide (BIS), methacrylic acid (MAA), poly(ethylene glycol) methyl ether methacrylate (MPEGMA, PEG), tin (II) 2-etheylhexanoate, glycidyl methacrylate (GMA), and 2,2-dimethoxy 2-phenyl acetophenone (DMPA) were all analytic grade, and purchased from Aldrich Company, USA. All the other reagents were also analytic grade and used as received.

2.2. Synthesis of GMA–PCFC–GMA macromonomer

At first, PCL–Pluronic–PCL copolymer (PCFC-diol) was synthesized by ring-opening copolymerization of ε-caprolactone (ε-CL, 0.2 mol) initiated by Pluronic (0.01 mol) at the presence of tin (II) 2-etheylhexanoate as a catalyst. Then the reaction system was kept at 130 °C for 6 h. After the mixture was degassed under vacuum for another 30 min, the resultant copolymer was cooled to room temperature. After polymerization, the obtained PCFC-diol was first dissolved in AR grade methylene chloride, and reacted with GMA for 48 h at 25 °C using DMAP as catalyst according to Scheme 1. And then the solution was precipitated in excessive petroleum ether and dried in vacuum at 25 °C.

2.3. Synthesis of P(CFC–MAA–MEG) hydrogel

The P(CFC–MAA–MEG) hydrogel was synthesized by UV-initiated free radial polymerization according to the method reported previously (Wang, Lu, Gruetzmacher, Currier, & Yaszemski, 2006; Zheng, Andreopoulos, Micic, Huo, & Pharm, 2001). DMPA was used for initiating the polymerization and BIS was employed as cross-linking agent. The typical P(CFC–MAA–MEG) (S-1) was prepared as following: the mixture of GMA–PCFC–GMA macromonomer (0.4 g), MAA (0.3 g), MPEGMA (0.3 g), BIS (0.06 g), and DMPA (3%w/w of the total monomers) was dissolved in *N*,*N*′-dimethylsulfoxide (DMSO) (6 ml), then the mixture was poured into a weighing bottle after bubbled with nitrogen for 5 min, and then the solution was irradiated by a 365 nm-long wave mercury UV lamp (500 W) for 30 min according to Scheme 1. And the samples prepared in this work were shown in Table 1.

2.4. Purification of the P(CFC–MAA–MEG) hydrogel

The just obtained P(CFC–MAA–MEG) hydrogel was immersed in distilled water for 7 days, and the water was refreshed everyday. The purified hydrogels were first dried at room temperature for 1 day, and then dried at 50 °C under vacuum for another 6 days. The dried hydrogels were kept in airtight bags before use. The obtained samples in this work were shown in Table 1.

2.5. Fourier transforms infrared (FTIR) analysis

FTIR (KBr) spectra of the hydrogel sample and the macromonomers were recorded on NICOLET 200SXV spectrophotometer (Nicolet).

2.6. ^1H NMR

^1H NMR spectrum (in $CDCl_3$) was recorded on Varian 400 spectrometer (Varian, USA) at 400 MHz using tetramethysilane as internal standard.

2.7. Swelling study of the hydrogel

The hydrogel samples were immersed in aqueous media with different pH values (pH 1.2 and 7.2) at 37 °C for different periods. Then, they were taken out and the surplus surface water was removed by filter paper. The swelling ratio can be determined by the following equation:

$$\text{Swelling ratio (SR)} = W_t/W_0 \times 100\% \quad (1)$$

where W_0, being the initial dry weight and W_t the wet weight of the small molar hydrogel at time t, respectively.

In this article, the swelling ratio after immersed in aqueous solution for 120 h was defined as equilibrium-swelling ratio.

2.8. The dynamic swelling/deswelling study of the hydrogels

The dynamic swelling/deswelling experiment was conducted by measuring the humid weight of the hydrogels immersed in aqueous medium with different pH value (pH 1.2 and 7.2) at 37 °C.

The dried hydrogels about 0.1 g were first immersed in aqueous medium at pH 1.2 for 10 min, 20 min, 40 min, and 60 min, respectively. The surplus surface water was removed by filter paper, and the humid weight was then measured carefully. After the hydrogel was put in another aqueous medium at pH 7.2, and the swelling ratios at different time points were measured too. The pulsatile swelling/deswelling behavior was observed in aqueous medium with alternate pH value of 1.2 and 7.2 at 37 °C. The results were listed in Table 1.

In our previous article (Chao et al., 2008), we define a responsive index (RI), which was used to personification pH sensitivity of the hydrogel.

$$\text{RI} = \text{SR}_{(\text{pH 1.2}),\ t=60} - \text{SR}_{(\text{pH 7.2}),\ t=120} \quad (2)$$

where $\text{SR}_{(\text{pH 1.2}),\ t=60}$ and $\text{SR}_{(\text{pH 7.2}),\ t=120}$ is the swelling ratio at t = 60 min (pH 1.2) and t = 120 min (pH 7.2), respectively.

RI was defined as the difference between equilibrium swelling at pH 7.2 and pH 1.2. With increase in RI, the difference between equilibrium swelling at pH 7.2 and pH 1.2 enhanced, which indicated that pH sensitivity of the hydrogel increase accordingly.

Table 1
The hydrogels prepared in this paper.

Sample	CFC:MPEG:MAA (wt%)	PCL content (wt%)	Mn of Pluronic	BIS[a] (wt%)	Equilibrium swelling (pH 1.2)	Equilibrium swelling (pH 7.2)	RI (%)
S-1	40:30:30	15.2	1900	6	134.2	351.1	39.2
S-2	50:25:25	19.0	1900	6	151.3	319.4	38.8
S-3	30:35:35	11.4	1900	6	136.7	430.2	58.4
S-4	40:30:30	15.2	1900	9	150.4	359.9	36.6
S-5	40:30:30	15.2	1900	12	146.8	357.5	47.6

[a] Calculated from the Eq: BIS content = weight of BIS/weight of (CFC + MPEG + MPAA).

2.9. Hydrolytic degradation study of the hydrogel

The aqueous solution with pH 1.2 and pH 7.2 were used as degradation medium. The detailed degradation process was shown as follows:

The dried hydrogels were put in aqueous medium with pH 1.2 and 7.2 at 37 °C, respectively, and the aqueous media were refreshed every week. The hydrogels were removed from the media at predetermined time, washed thoroughly with distilled water and then dried in vacuum for 6 days at 50 °C. Degree of degradation was calculated by weight loss according to following equation:

$$\text{Weight loss } (\%) = (W_0 - W_t)/W_0 \times 100 \quad (3)$$

where W_0 is the dry weight before degradation, W_t is the dry weight at time.

3. Results

3.1. Characterization of the macromonomer and the hydrogels

The PCFC–GMA macromonomer was characterized by ^{1}H NMR. And a typical ^{1}H NMR spectrum of macromonomer was presented in Fig. 1. The signals at 5.6 and 6.1 ppm correspond to protons of the carbon–carbon double bonds, and the signals at 1.6, 2.3, and 4.1 ppm correspond to the chain protons of PCL segments. The signals at 3.6 ppm correspond to the methylene protons of the end groups of the PCFC macromonomer. These results indicated that the terminal hydroxyl groups in the Pluronic precursor were converted to acrylate groups completely.

FTIR spectra of PCFC–GMA macromonomer and the hydrogel after UV-initiated free radical polymerization were shown in Fig. 2. The absorption bands at 1726 cm^{-1} and 1145 cm^{-1} presented in Fig. 2 were attributed to ester and ether stretching peaks respectively. The signals at 1626 cm^{-1} was attributed to C=C stretching of PCFC–GMA macromonomer, but it disappeared in S-1 hydrogel sample, which indicated that the end double bonds had been converted into carbon–carbon single bonds completely to form the main chain during the formation of hydrogel.

3.2. Water absorption behavior

The obtained hydrogels have the ability to respond to changes in their external environment. Water absorption was performed in order to indicate the influence factors of the network structures based on hydrophilic and hydrophobic segments. In this biodegradable pH-sensitive hydrogel, MAA and Pluronic segments were both hydrophilic, whereas the PCL segment was hydrophobic. The effect of PCFC and BIS content on swelling ratio at room temperature is illustrated in Table 1 and Fig. 3, and the equilibrium-swelling ratios of this hydrogel in pH 7.2 buffer solution are much higher than that in acidic solution (pH 1.2), which might be mainly contributed to hydrogen bond and electrostatic interaction (Bajpai & Singh, 2006; Chao et al., 2008).

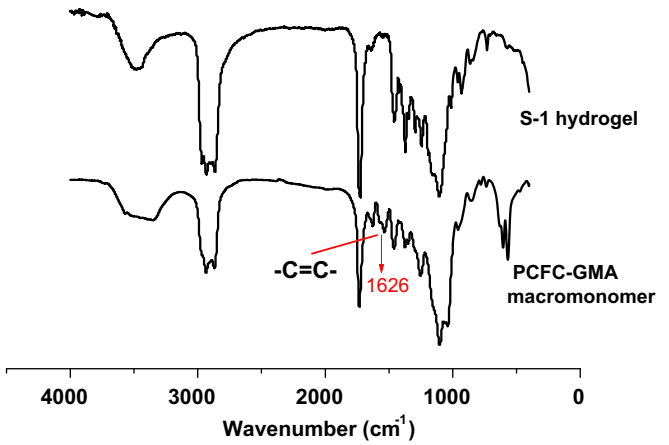


Fig. 2. FTIR spectra of PCL–Pluronic–PCL–GMA macromonomer and S-1 hydrogel sample.

3.3. The dynamic swelling/deswelling behavior (pH-sensitivity) of hydrogels

To evaluate the dynamic swelling/deswelling behavior (pH-sensitivity) of P(CFC–MAA–MEG) hydrogels, the equilibrium re-swelling behavior of the hydrogels was studied in this work, and the results were presented by the data in Fig. 4. Compared with the hydrogels synthesized in our previous work (Chao et al., 2008), these data displayed that the P(CFC–MAA–MEG) hydrogels have good re-swelling ability and maintain the high sensitivity to pH.

3.4. Hydrolytic degradation behavior

In order to assess the effect of PCFC and BIS content on the hydrolytic degradation, specimens were degraded in pH 1.2 and pH 12 medium, respectively. The rate of hydrolytic degradation was increased with increase of PCFC content. According to Fig. 5(A), the networks were consistent with the characteristics

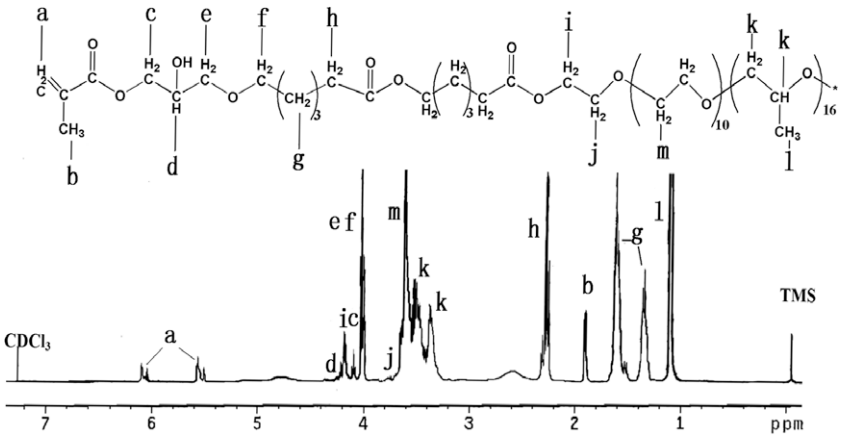


Fig. 1. ^{1}H NMR spectrum of PCL–Pluronic–PCL–GMA macromonomer (in $CDCl_3$).

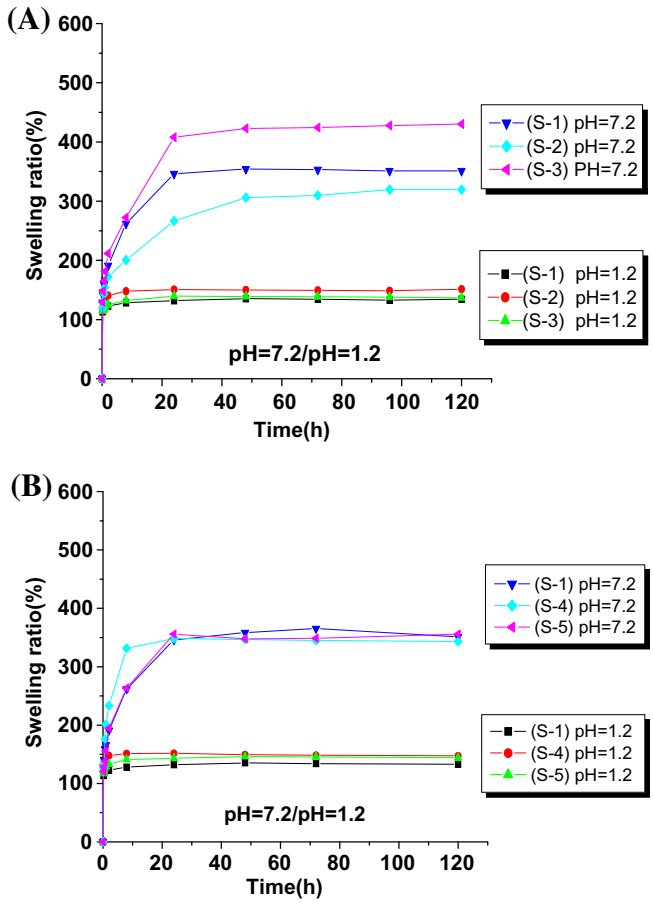


Fig. 3. Effect of PCFC and BIS content on swelling behavior of hydrogels in aqueous medium with pH 1.2 and pH 7.2 at 37 °C, respectively.

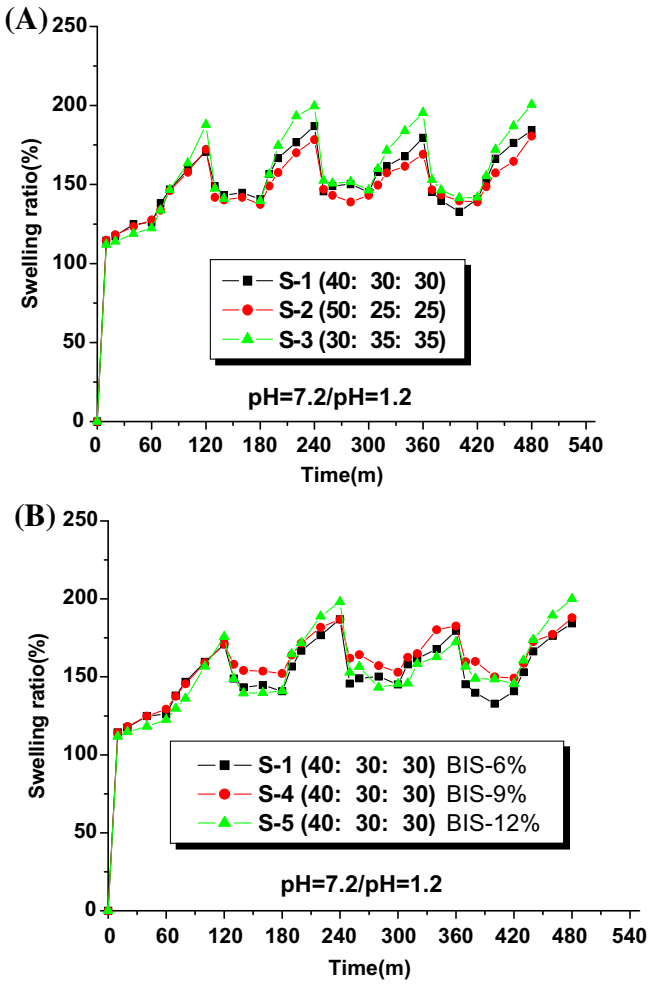


Fig. 4. Effect of PCFC and BIS content on the dynamic swelling/deswelling behavior of hydrogels in aqueous medium with pH 1.2 and pH 7.2 at an interval of 60 min, respectively (37 °C).

of PCFC. Meanwhile, effect of the content of BIS on degradation rate was investigated and shown in Fig. 5(B).

4. Discussion

The effect of pH value on the swelling ratio was determined in buffer media of varying pH, ranging from 1.2 to 7.2. The swelling ratios at various pH environments depend upon the available free volume of the expanded polymer matrix, polymer chain relaxation, and availability of ionizable functional groups such as –COOH able to form hydrogen bonds with water. At initial stage of hydrating when the pH value is 7.2, the hydrophilic segments of P(CFC–MAA–MEG) hydrogels such as carboxylic groups form hydrogen bonds with water molecules. These bonds act cooperatively to form a stable environment of hydration around the hydrophobic segments, resulting in greater water uptake and producing a larger swelling ratio (Bajpai & Singh, 2006). It is clear that the hydrogen bond broke with the ionization of carboxylic acid groups after the water molecular entered into the hydrogel network.

Swelling ratio was slightly influenced by BIS, which was used as cross-linking agent. The change of cross-linking density was dependent heavily on the content of BIS, and swelling ratio might be changed accordingly. According to Fig 3(B), the swelling ratio increased with decrease of BIS content.

A gradual increase in swelling ratios from pH 1.2 to pH 7.2 is obviously observed in Fig. 3. In acidic solution (pH 1.2), most carboxylic acid groups are in the form of COOH, and large amounts of hydrogen bonds formed by MAA chain corresponding with PEG chain. As shown in Scheme 2, the hydrogen bond broke owing to the environmental pH value raised up to 7.2, and carboxylic acid groups become ionized. Meanwhile, electrostatic repulsion caused the network to expand. The swelling ratio of hydrogel, observed in Fig. 3, increased obviously when pH value evaluated from 1.2 to 7.2. It might be mainly because increase of pH causes ionization of the carboxylic acid groups, and the polymer chains extend more in the higher pH as the ionic groups repel each other. These data implied the pH-sensitive characterization of the demonstrated hydrogel.

Compared with the P(CL–MAA–EG) hydrogel synthesized in our previous work (Chao et al., 2008), obvious pH-sensitive characterization of hydrogel could be seen in Fig. 4. For these P(CFC–MAA–MEG) hydrogel, they have better pH RI than P(CL–MAA–EG) hydrogel. Generally, this distinctive characteristic between two hydrogels can be attributed to the unique and rapid alternation of the hydrophilic and hydrophobic states. In order to overcome the poor responsibility of P(CL–MAA–EG) hydrogel, we used the MPEG–MA monomer for this new kind of hydrogel instead of PEG–DMA monomer (Chao et al., 2008). The pH-responsibility has been greatly enhanced, and the results show that the hydrogels have good re-swelling ability and maintain the high sensitivity to pH. It was due to increase of the length of hydrophilic chain and the content of free carboxylic acid groups, whereas the RI decreased slightly with increase of PCFC content according to Fig. 4(A) and Table 1. Effect of BIS content on RI value was depicted in

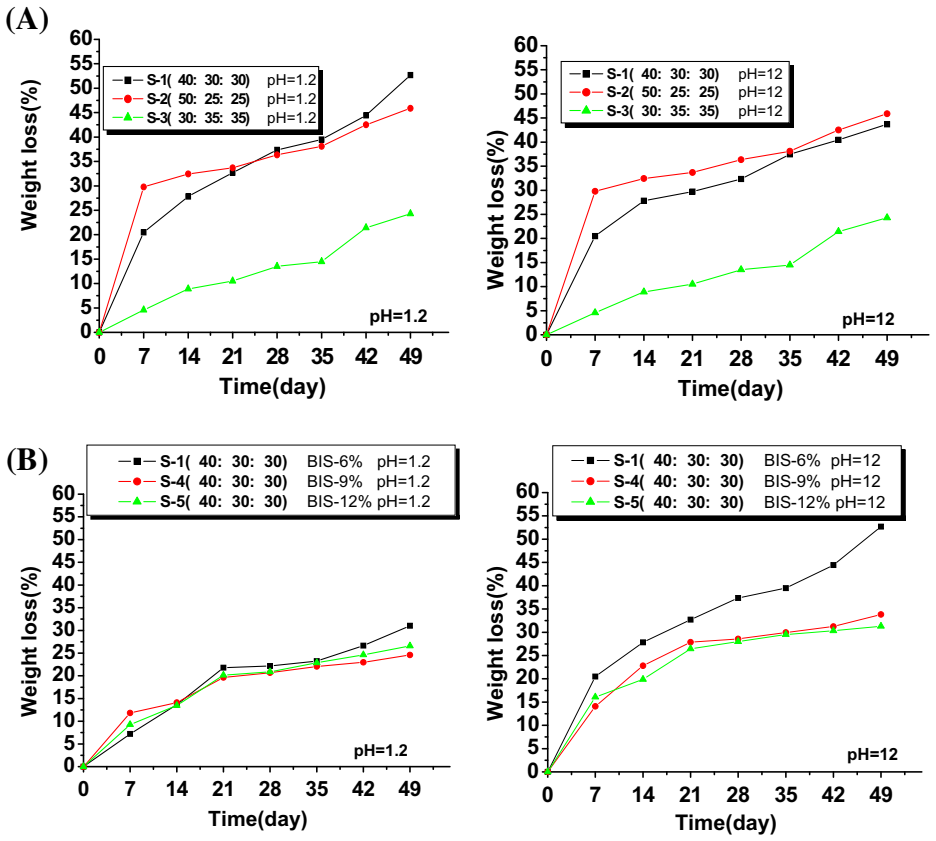
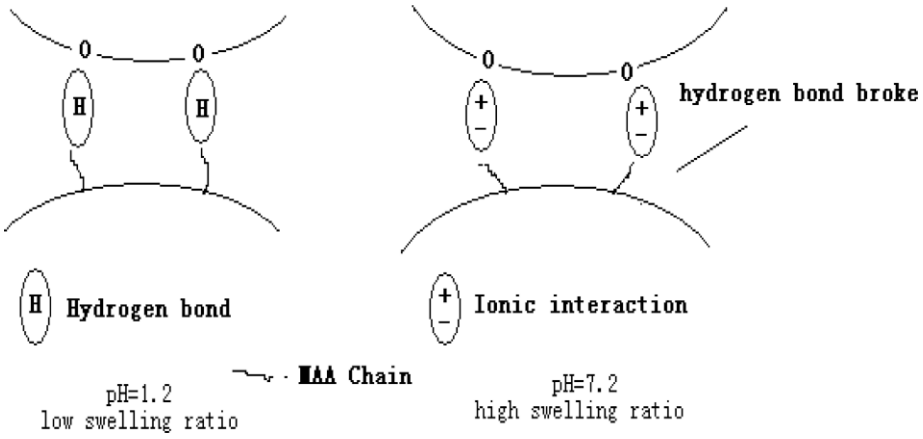


Fig. 5. Effect of PCFC and BIS content on hydrolytic degradation behavior of hydrogels in different solution with pH 1.2 and pH 7.2 at 37 °C, respectively.



Scheme 2. Schematic illustration of the swelling behavior of pH-sensitive and biodegradable P(CFC–MAA–MEG) hydrogel at different pH.

Fig. 4(B). And there was no obvious difference in RI between them. In all, pH sensitivity of these biodegradable and pH-sensitive P(CFC–MAA–MEG) hydrogels was mainly determined by content of free carboxylic acid groups.

The hydrolytic degradation behavior of P(CFC–MAA–MEG) hydrogels in PBS solution was also studied in this article. According to Seppälä's opinion (Malin, Hiljanen-Vainio, Karjalainen, & Seppälä, 1996), the hydrolytic degradation behavior of semicrystalline polymers was determined on chemical composition, degree of crystallinity, hydropoilicity, and pH value of degradation medium. The hydrolysis of P(CFC–MAA–MEG) hydrogels occurs at its PCL segment accompanying cleavage of ester bond, meanwhile, molecular weight decreased and the chemical composition changed. As a result, the degradation rate was accelerated based on the content of PCL. Fig. 5(A) indicated the relationship of the weight loss of the hydrogels and PCL content.

The degradation rate was not only determined by PCL content, but also affected by BIS content. According to the water absorption study in this paper, the more the BIS content was incorporated into the hydrogels, the faster the swelling will decrease. And the hydrolytic degradation rate decreased steadily due to ester bond along PCL chain segment might hardly hydrolyze after water molecular entered into the hydrogel network. The cross-linking density and macro-mesh decreased with decrease of BIS content accompanying the water more easily entered into the hydrogel network. According to Fig. 5(B), it could be seen that the degradation rate increased

accordingly with decrease in BIS content. The reasons mentioned above might cause the furthermore hydrolyzation of hydrogels. These results, mentioned above, indicated that the pH-sensitive of P(CFC–MAA–MEG) hydrogels could control the diffusion of protein drug in different pH value and specific to immune response, while maintaining the bioactivity of protein drug or other drugs. So this biodegradable pH-sensitive hydrogel might have great potential application in oral drug delivery system.

5. Conclusion

A series pH-sensitive P(CFC–MAA–MEG) hydrogels were successfully synthesized by UV initialed free radical polymerization method. This hydrogel is biodegradable and has apparently pH-sensitive characterization. The water absorption behavior, including effect of MAA, PCL, PEG, BIS content and Pluronic molecular weight on the swelling ratio were studied in detail. The dynamic swelling/deswelling behavior and hydrolytic degradation behavior were also investigated in detail. The described biodegradable pH-sensitive hydrogels might have great potential application in drug delivery system.

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