

On the design of biodegradable hydrogels both thermosensitive and pH sensitive

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A Pluronic oligo(ϵ -caprolactone) block copolymer has been synthesized by ring opening polymerization of ϵ -caprolactone monomers in the presence of poly(ethylene oxide)–poly(propylene oxide)–poly(ethylene oxide) triblock copolymers, using stannous octoate as a catalyst, and then the block copolymer was terminated with an acryloyl group. A novel biodegradable pH- and temperature sensitive hydrogel has been fabricated by free radical copolymerization of diacylated macromer–methacrylic acid aqueous solution initiated by a redox initiator. The structures of products were characterized by the Fourier transform infrared spectroscopy. Variations of the equilibrium swelling ratio in various environmental solutions confirmed the pH- and temperature sensitivity of hydrogel, which were affected by the MAA content.

Keywords: *biodegradable hydrogel; pH sensitivity; temperature sensitivity*

1. Introduction

During the last decade, a great attention has been focused on the controlled drug release technique, due to the appearance of protein drugs and their special structure. Among the current materials for controlled drug carriers, hydrogels are rather unique and especially suitable for the sustained release of hydrophilic macromolecular drugs [1]. Hydrogels are three-dimensional hydrophilic polymer networks that can be swollen to many times their mass and volume in aqueous environments [2]. As the term “network” implies, cross-linking has to be formed to avoid dissolving or losing their structural integrity in the aqueous phase [3]. Due to their diverse functionalities, intelligent hydrogels have been the subject of extensive investigations in recent years [4]. Most of the intelligent hydrogels reported respond to only one type of stimuli. Among these intelligent hydrogels, pH sensitive or temperature sensitive hy-

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drogels have been commonly investigated, because both parameters are important environmental factors in biomedical and other systems [5]. Body temperature often deviates from the normal one (near 37 °C) by the physiological presence of pathogens or pyrogens. This change of temperature may be a useful stimulus that can modulate the delivery of therapeutic drugs for diseases with accompanying fever [6]. pH sensitivity is another parameter that can be exploited in applications, and arguably has greater potential for use in biomedical devices, or biomaterials than thermosensitivity (see [7]).

From the application point of view, hydrogels, especially biodegradable hydrogels, would be highly useful if they simultaneously responded to two stimuli. Keeping this consideration in mind, our objective is to design and synthesize a novel biodegradable hydrogel that sensitive both to pH as well as to temperature. We selected Pluronic (Ploxamer), an ABA triblock copolymer of poly(ethylene oxide)–poly(propylene oxide)–poly(ethylene oxide) (PEO–PPO–PEO), as the central part of the hydrogel for its superior biocompatibility and temperature sensitivity [8–11]. Then extending it with of ϵ -caprolactone oligomer can endow the final product with biodegradability. Finally, end-capping with reactive acryloyl units allows the macromer to be polymerized. The PMAA is selected as a pH sensitive copolymer both because of its sharp pH induced volume transition in the physiological pH range and its broad range of applications in the biomaterial field [12, 13].

In the present work, the hydrogel was obtained by radical copolymerization of the diacrylated macromer–methacrylic acid aqueous solution initiated by a redox initiator. We also investigated the effect of MAA content on the temperature sensitivity and pH sensitivity of the biodegradable hydrogel.

2. Experimental

Materials. Pluronic F127 (PEO–PPO–PEO) triblock copolymer was obtained from BASF (Germany). ϵ -caprolactone monomer and tin(II)2-ethylhexanoate (stannous octoate) were purchased from Aldrich (Milwaukee, WI, USA) and Sigma (Dallas, Texas, US), respectively. All other chemicals were of analytical grades.

Synthesis of Pluronic–oligo(ϵ -caprolactone) block copolymers (PFCL). Pluronic–oligo (ϵ -caprolactone) amphiphilic block copolymers were synthesized by ring opening polymerization of ϵ -caprolactone monomers in the presence of PEO–PPO–PEO triblock copolymers, Pluronic F127, using stannous octoate as a catalyst. The Pluronic, ϵ -caprolactone monomers and stannous octoate with various weight ratios were placed into a flask connected with a vacuum outlet tube, and the mixture was preheated for 6 h at 60 °C under vacuum in order to obtain a well mixed melting phase. The mixture was purged several times with argon to displace the oxygen. Finally, the flask was sealed off under vacuum and the reactant was copolymerized at 150 °C for 24 h. The copolymerization product was cooled to the room temperature, dissolved

with dichloromethane, and then precipitated with an excess of anhydrous ether to remove unreacted Pluronic and ϵ -caprolactone monomers. The precipitate was collected by filtration and washed several times with absolute ether. The resulting product was dried under vacuum. The Pluronic–oligo(ϵ -caprolactone) block copolymer products are denoted as PFCL_X, where X is the degree of polymerization of ϵ -caprolactone at each end of the Pluronic molecule according to the feed ratio.

Synthesis of diacrylated macromer (PFCL-D). Dried Pluronic–oligo(ϵ -caprolactone) block copolymer product and triethylamine were dissolved in dichloromethane in a 250 cm³ round bottom flask. Acryloyl chloride in dichloromethane was drop-wise added. The reaction mixture was stirred with an agitator at 0 °C for 12 h and then for next 12 h at room temperature. The reaction product was filtrated and extracted with an excess of anhydrous ether. The precipitate was collected by filtration and dried under vacuum. The diacrylated macromer of Pluronic–oligo(ϵ -caprolactone) block copolymer is denoted as PFCL_X-D.

Synthesis of pH- and temperature sensitive hydrogels (PFCL-MAA). Hydrogels were obtained by free radical copolymerization in distilled water. Ammonium persulfate (APS) was selected as a redox initiator and *N,N,N',N'*-tetramethylene diamine (TEMED) was used as an accelerator. PFCL_X-D and MAA monomers were dissolved in distilled water. Then a appropriate amounts of APS and TEMED were added to the mixtures. The mixture solution was poured onto a glass dish and crosslinked to form a hydrogel film at 60 °C. The wet hydrogel films were dried under vacuum for several days. The hydrogels PFCL_X-MAA-*Y*, were obtained where *Y* is the wt. % of MAA in diacrylated macromer of Pluronic–oligo(ϵ -caprolactone).

FTIR characterization. The dried products were analyzed in KBr discs with a FTIR spectrophotometer (FTIR-8400S, Japan) in the range of 500–4000 cm⁻¹.

Temperature sensitivity. The temperature dependence of the swelling ratio in the range of 4–37 °C was investigated by the classical gravimetric method. Dried hydrogel samples were immersed in distilled water at a given temperature for at least 24 h. Then any excess water on the swollen hydrogel surface was removed by wet filter paper. The equilibrium swelling ratio (ESR) is defined as follows:

$$\text{ESR} = \frac{m_s - m_d}{m_d} \quad (1)$$

where m_s is the weight of the equilibrium swollen hydrogel and m_d is its initial weight.

pH sensitivity. The hydrogels were immersed in buffer solutions of various pH (from 2 to 8) at 4 °C and 37 °C for at least 24 h, in order to achieve swelling equilibrium. Then the hydrogels were weighed, and the swelling ratio at each pH was calculated according to Eq. (1).

3. Results and discussion

3.1. Characterization of chemical structures of macromers

FTIR spectroscopy has been employed to characterize the chemical structure of Pluronic, a series of PFCL block copolymers and PFCL-D macromers (Fig. 1).

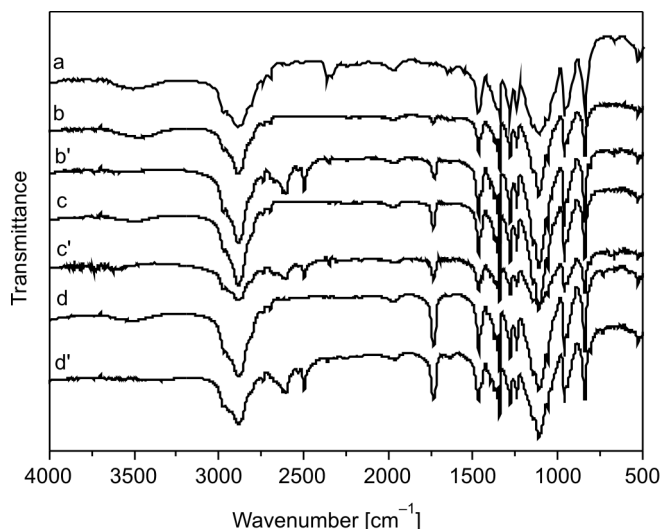


Fig. 1. FTIR spectra of: a) Pluronic F127, a series of PFCL block copolymers – b) PFCL₄, c) PFCL₈, d) PFCL₁₂ and PFCL-D macromers – b') PFCL₄-D, c') PFCL₈-D, d') PFCL₁₂-D

The peaks between 3000 and 4000 cm^{-1} are assigned to symmetric and asymmetric stretching vibration modes of the hydroxyl group. As compared with the FTIR spectra of F127, PFCL block copolymers (Fig. 1, b–e) display a new and strong carbonyl band at 1734 cm^{-1} , which is attributed to the C=O stretching mode of the ϵ -caprolactone units in the copolymers. The ϵ -caprolactone units are extended into the ends of Pluronic molecules. The intensity of the peaks at 1734 cm^{-1} increases as the number of ϵ -caprolactone units increases. Ding et al. reported similar results [14, 15]. Furthermore, the peaks at 3500 cm^{-1} disappear for PFCL-D macromers as shown in Fig. 1b'–d'. It may be concluded that the hydroxyl group at both ends of F127-oligoCL was substituted by the acryloyl group in the macromers.

3.2. Temperature sensitivity

The temperature dependence of the equilibrium swelling ratio (ESR) over a temperature range from 4 to 37 $^{\circ}\text{C}$ is shown in Fig. 2. All obtained hydrogels display

a good temperature response. For example, at 4 °C, the ESR value of the samples PFCL4-MMA-10, PFCL4-MMA-20, and PFCL4-MMA-30 is 7.22, 4.76 and 3.93, respectively, whereas the corresponding values at 37 °C are 3.99, 3.28 and 2.63, respectively.

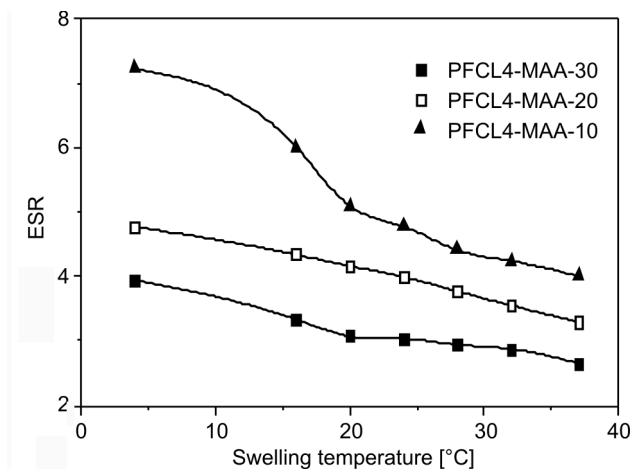


Fig. 2. Temperature dependence of the swelling ratio in hydrogels

The negative temperature sensitivity of the hydrogels originates from the lower critical solution temperature (LCST) behaviour of PEO–PPO–PEO block copolymers in water. Clearly, the swelling ratio of hydrogels decreases as the MAA content increases, which may be attributed to the formation of a more compact network after the incorporation of MAA segments.

3.3. pH sensitivity

The investigations of the swelling properties of the hydrogels were carried out in various buffer solutions (pH from 2 to 8) at 4 °C and 37 °C, respectively. An evident swelling transition is observed with pH change (Figs. 3 and 4). Additionally, with the increase in the MAA content, the ESR value decreases before the swelling transition: this is in contrast to the increase of ESR at high pH. For example, at pH = 5 and 4 °C (or 37 °C), the ESR values of PFCL8-MMA-10, PFCL8-MMA-20, and PFCL8-MMA-30 samples are 6.87 (3.91), 4.50 (3.20), and 3.01 (2.21), respectively. Their corresponding ESR values at pH = 8, however, are increased to 25.42 (18.61), 33.17 (27.07), and 38.66 (30.63), respectively. Such behaviours demonstrate that the PFCL–MMA hydrogels show both pH and temperature sensitivity. The pH sensitivity is related to the pH dependent ionization of side carboxylic acid (–COOH) groups of PMAA.

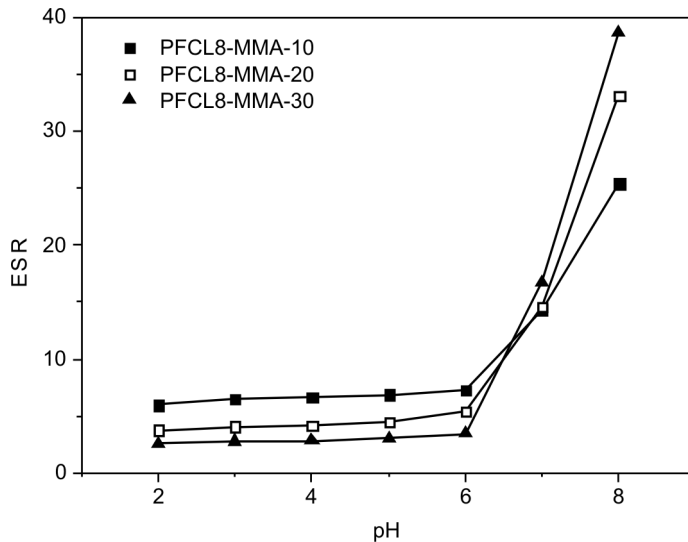


Fig. 3. Dependence of the swelling ratio on pH plot in hydrogels at 4 °C

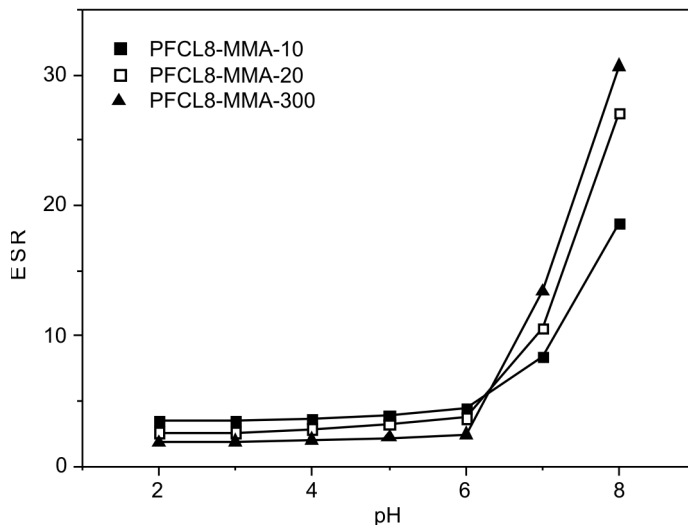


Fig. 4. Dependence of the swelling ratio on pH plot in hydrogels at 37 °C

3.4. The temperature and pH dependent swelling mechanism

Obviously, the temperature and pH-sensitivity of PFCL-MAA hydrogels are related with the network structure and the associated interactions (such as hydrophobic and hydrophilic interaction). We hypothesize that there are three different structures in the network of the PFCL-MAA hydrogel (Fig. 5).

The temperature sensitivity of PFCL-MAA hydrogel contributes to the moiety of Pluronic in the network. Hydrogen bonding between hydrophilic segments of the macromer chain and water molecules dominates at low temperatures, leading to enhanced dissolution in water of the copolymer hydrogel. Hydrophobic interactions among hydrophobic segments, especially PPO segments, however, are strengthened at high temperatures, resulting in association and shrinking of the network.

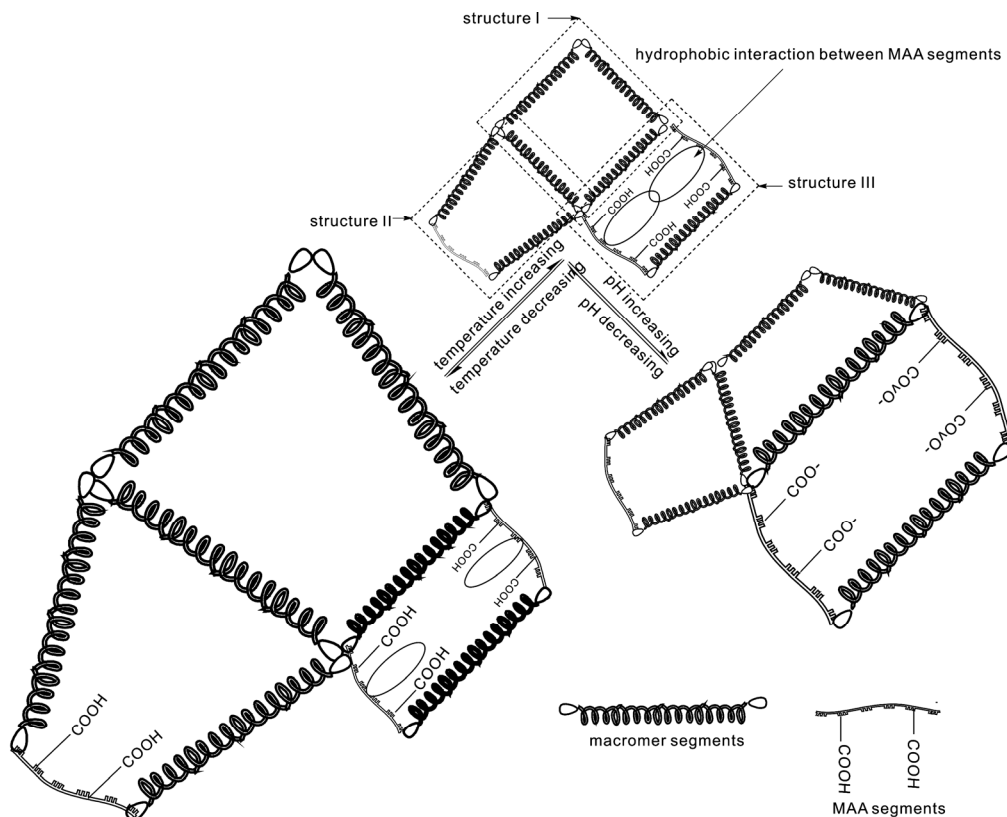


Fig. 5. Scheme of temperature and pH dependence of swelling mechanism of the PFCL-MAA hydrogel

As expected, using MAA as a pH sensitive co-monomer of PFCL-D macromer, the PFCL-MAA hydrogel is highly responsive to changes in pH, just like PMAA itself. Due to the existence of carboxylic acid groups in MAA segments, the hydrophobic units can undergo stable hydrophobic interaction in an acid medium. The hydrophobic interaction can restrict the movement or relaxation of network chains. Therefore, a more compact hydrogel network is formed, with a lower swelling capacity. But in a neutral and alkaline media, the ionization of the carboxylic acid groups of MAA occurs, disrupts the hydrophobic interaction and generates electrostatic repulsion among hydrogel chains. This repulsive force is strong enough to push the network

chain segments apart and attract more water into the hydrogel, so a higher swelling ratio is observed.

Moreover, it is easy to explain different swelling behaviour of PFCL-MAA hydrogel for different MAA contents, as is observed in Fig. 5. Clearly, all of these three structures in Fig. 5, are highly responsive to temperature changes. The swelling capacity, however, is different and is described by the sequence: structure I > structure II > structure III. Therefore, it is not surprising that the ESR values decrease as the MAA content increases, since the content of the latter two structures increases at high MAA content. We also suspect that only structure III can sensitively respond to the change of pH, since it can interact hydrophobically with MAA segments in an acidic medium which causes shrinkage of polymer chains, water molecules cannot easily diffuse and permeate into a more compact network. Since the hindrance effect increases as the MAA content in the PFCL-MAA hydrogel increases, the ESR values certainly decrease with MAA content increasing at acidic swelling solution. As the pH of the swelling solution increases, ionization of the carboxylic acid groups occurs and their electrostatic repulsions cause a great degree of swelling of the hydrogel. In this case, the resulting hydrophobic interaction between MAA segments becomes weaker and finally vanishes, leading to expansion of structure III and therefore an increase in the ESR value. The electrostatic repulsions become much stronger if the MAA content is high. As such, the degree of swelling of the hydrogel increases as the MAA content increases.

4. Conclusions

A series of Pluronic–oligo(ϵ -caprolactone) (PFCL) block copolymer was synthesized by ring opening polymerization of ϵ -caprolactone monomers in the presence of PEO–PPO–PEO triblock copolymers (Pluronic), and was then subsequently end-capped with the acryloyl groups. The FTIR spectra verified that the diacrylated macromer successfully has been synthesized.

This novel, pH-sensitive and temperature sensitive PFCL-MAA hydrogel was obtained by free radical copolymerization of the diacrylated macromer–methacrylic acid aqueous solution initiated by a redox initiator. The equilibrium swelling ratio of hydrogel in various solutions indicated that the PFCL-MAA hydrogel displayed both temperature- and pH sensitivity, which were affected by the MAA content. The MAA content caused the ESR values to decrease at specific swelling temperatures. With the increase in the MAA moiety of the PFCLMAA hydrogel, the degree of swelling at an acidic medium decreased due to the presence of hydrophobic interaction. It, however, decreased at neutral and alkaline media since lack of hydrophobic interaction offered the hydrogel much stronger electrostatic repulsions in the case of high MAA content.

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