Synthesis of Biodegradable Amphiphilic Thermo-Responsive Multiblock Polycarbonate and Its Self-Aggregation Behavior in Aqueous Solution

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ABSTRACT: Amphiphilic thermo-responsive multiblock polycarbonates consisting of poly(ethylene oxide) (PEO) and poly(propylene oxide) (PPO) were facilely synthesized using triphosgene as coupling agent. The structures and molecular characteristics of the polycarbonates were confirmed by ^{1}H-NMR, FT-IR and Gel permeation chromatography (GPC). The crystallization behavior and thermal properties of the polycarbonates were studied using X-ray diffraction (XRD), Differential scanning calorimetry (DSC) and thermogravimetric analysis (TGA). Surface tension measurements confirmed that the critical micelles concentration of polymeric micelles were concentration ranges, which varied from about 2–70 mg/L to 5–40 mg/L with increasing PEO/PPO composition ratio from 0.8 to 1. Dynamic light scattering (DLS) experiments showed bimodal size distributions, the aggregates size increased with increasing the concentration of the polycarbonates aqueous solutions. The size of the aggregates acquired from TEM was smaller than that from DLS owing to the fact that TEM gave size of the aggregates in dry state rather than the hydrodynamic diameter. The degradation process revealed that the degradation rate of the aggregates could be accelerated with an increase in temperature. Moreover, the more the polycarbonate was hydrophilic, the faster was its degradation. Rheological measurements suggested that these multiblock polycarbonates were thermo-responsive and by regulating the PEO/PPO composition ratio they could form a gel at 37°C. © 2009 Wiley Periodicals, Inc. J Appl Polym Sci 112: 1425–1435, 2009

Key words: block copolymers; polycarbonates; water-soluble polymers; biodegradable; viscoelastic properties

INTRODUCTION

Amphiphilic block copolymers have attracted special attention in both implantable drug delivery systems and tissue engineering applications in the last decades.[1,2] They can form aggregated structures such as spherical micelles, cylindrical micelles and vesicles. The fascinating aspect of these amphiphilic copolymers is their thermodynamic stability in physiological solution because of their low critical aggregation concentrations.[3,4] Therefore, interest in the design and characterization of novel amphiphilic copolymers, and the use of them to form micelles or micelle-like aggregates in an aqueous phase have been growing.[5–9]

Poly(ethylene oxide) (PEO)/poly(propylene oxide) (PPO)/PEO (PEO-PPO-PEO) triblocks, commercially available as Poloxamers or Pluronics, are one of the most important and extensively investigated families of amphiphilic block copolymers. They have been studied in terms of their self-assembly behavior and applications in various industries.[10–22] The appropriate selection of the various PPO/PEO composition ratio and molecular weight during the synthesis allows the production with optimum properties that meet the specific requirements of different applications. Recently, these systems have been investigated as promising candidates in gene therapies and vaccination strategies.[23–32]

However, these triblocks are nonbiodegradable, especially high molecular weight polymers cannot be eliminated by renal excretion after intramuscular injection in the form of gel. To circumvent the biodegradability issue, new polymers were synthesized by linking together PEO and PPO through degradable carbonate linkage since the carbonate bindings were hydrolyzed under physiological conditions.[33] Cohn and Sosnik[34–36] have reported various thermo-responsive polycarbonates synthesized by covalently binding PEO and PPO chains using carbonyl chloride and diacyl chlorides as the coupling molecules. They have concluded that the selection of carbonate moieties along the backbone rendered the polymers biodegradable, and moreover, microstructures formed by these novel polymers were markedly larger than those generated by PEO-PPO-PEO

triblocks. However, the connecting molecules they used are extremely poisonous. As far as we are aware, apart from these few research, not much systematical investigation has been carried out on the synthesis and the aggregation behavior as well as the potential applications of this kind of biodegradable amphiphilic thermo-responsive polycarbonates.

In this article, we describe the facile synthesis of a series of amphiphilic thermo-responsive multiblock polycarbonates comprising PEO and PPO chains [coded as EO-CO-PO-*n*, *n* shows the molar ratio between poly(ethylene glycol) (PEG) and poly(propylene glycol) (PPG)] using triphosgene as the novel coupling agent. Some of the reasons for selecting triphosgene are (a) it is a stable crystalline material (m.p. 79–80°C; b.p. 206°C) which is easy to transport, store and handle and (b) it is safe and can be exactly weighed out in milligram amounts to perform desired chemical transformations. In a word, it has recently proved to be a versatile substitute for phosgene and diphosgene. The final polycarbonates possess low polydispersity and excellent biodegradability. Rheological experiments reveal that they can form a gel at 37°C, due to their thermo-responsive behavior. The molecular characteristics of the multiblock polycarbonates were analyzed by different physicochemical techniques [^{1}H-NMR, FT-IR, Gel permeation chromatography (GPC), X-ray diffraction (XRD), Differential scanning calorimetry (DSC) and thermogravimetric analysis (TGA)] and their self-aggregation behavior in aqueous solution were studied through three methods [surface tension test, Dynamic light scattering (DLS) and Transmission electron microscope (TEM)].

EXPERIMENTAL

Materials

PEG6000 was supplied by Sinopharm Chemical Reagent and purified by dissolving in dried chloroform followed by filtration and precipitation in anhydrous ethyl ether before use. PPG2000, purchased from Sinopharm Chemical Reagent was dried at 120°C under vacuum for 2 h. Methylene chloride (CH$_2$Cl$_2$) was acquired from Tianjin Basifu Plastic Product and thoroughly purified by distillation over calcium hydride. Pyridine, received from Tianjin Basifu Plastic Product was dried with molecular sieves 4A. Triphosgene was purchased from Yao and shun import and export and used without further purification.

Synthesis of PEG/PPG multiblock polycarbonates

Preparation of the polycarbonates was carried out through a one-step solution polycondensation as shown in Scheme 1. Briefly, PEG6000 (12.033 g, 2
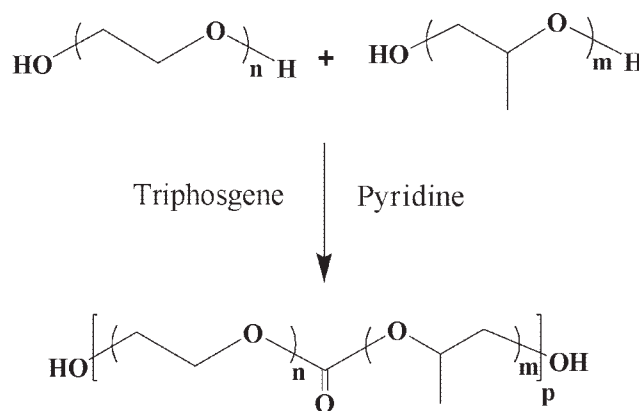
Scheme 1 Synthesis of PEG6000-PPG2000 multiblock polycarbonates.

mmol) and PPG2000 (4.008 g, 2 mmol) were dissolved in 30 mL of CH$_2$Cl$_2$ placed into a three-neck flask. Anhydrous pyridine (2.6 mL) was poured as a catalyst and the mixture was cooled in an ice bath (0–5°C). A solution of triphosgene (1.826 g; 6 mmol) in 10 mL of CH$_2$Cl$_2$ was added to this mixture dropwise during 90 min under magnetic stirring. After the dropping, the mixture was stirred for 45 min at room temperature. Then the reaction temperature was risen to 40°C and stirred for further 6 h. The polycarbonates were precipitated by slowly adding the polymer solutions into the mixture (4 : 1 in volume fraction) of anhydrous diethyl ether and dried methanol, followed by drying in vacuum oven for 3 days.

Preparation of EO-CO-PO-*n* aggregates

To investigate the degradation behavior of these multiblock polycarbonates, which is useful in drug delivery system, we prepared EO-CO-PO-*n* aggregates by a precipitation and dialysis method. First, a sample of EO-CO-PO-*n* copolymer (10 mg) was dissolved in 1 mL of *N*, *N*-dimethylformamide (DMF). Subsequently, the solution was added dropwise to 10 mL of distilled water with gentle stirring. And then this aggregative solution was dialyzed for 24 h against 2 L of distilled water using cellulose dialysis membrane (M_w cut off: 14,000 g/mol). At last, the dialyzed solution obtained was free-dried.

Degradation of EO-CO-PO-*n* aggregates

Phosphate buffer solution (20 mL) (PBS, 0.1 mol/L and pH 7.4) containing EO-CO-PO-*n* aggregates with concentration about 100 mg/L and 0.01% (w/v) sodium azide (used to prohibit the growth of bacteria) were placed into 40 mL bottles. These bottles were then incubated at 25 and 37°C, respectively. At predetermined intervals, degradation solutions were withdrawn from the bottles for DLS analysis. Then

the degradation solutions were removed by lyophilized and the samples were dried *in vacuo* at 25°C for 1 week for molecular weight measurement.

Characterization

^{1}H-NMR spectrum was recorded in CDCl$_3$ solvent on a Bruker AV-400 NMR spectrometer at 400 MHz with tetramethylasilane as an inert standard at room temperature.

FT-IR spectra were carried out using Vector-22 spectroscopy. Samples were prepared by dispersing the polycarbonates in KBr and compressing the mixture to form disks.

GPC measurements were carried out in DMF (1 mL/min) at 40°C using a Waters 515 liquid chromatography equipped with three styragel columns and a refractive index detector.

Powder XRD patterns were recorded using an X-ray diffractometer (Bruker Advance D8) with a graphite monochromator CuKα (λ = 0.15406 nm) radiation (40 kV, 40 mA). Measurements were generally taken from 8 to 40°.

DSC experiments were run using a DSC-SP Rheometric Scientific Differential Scanning Calorimeters (Rheometric Scientific). Samples were analyzed in open aluminum pans under a dry nitrogen atmosphere (25 mL/min) and heated at 10°C/min from −150 to 150°C. The degree of crystallinity of PEG block was determined from eqs. (1) and (2):

$$\Delta H_m = \Delta H / w \qquad (1)$$

$$\text{Degree of crystallinity } (X_c) = \Delta H_m / \Delta H_o \qquad (2)$$

where, ΔH is the area of endothermic peak for PEG reading from DSC patterns; w is the weight fraction of PEO blocks in the multiblock polycarbonates; ΔH_o is the enthalpy of fusion for completely crystallized PEO in J/g. ΔH_o of PEO is 205.0 J/g.[37]

TGA and corresponding DSC measurements were obtained using an SDT Q600 (TA) thermogravimetric instrument. The heating rate was 10°C/min in a nitrogen environment in the range 25–600°C.

Surface tension was measured at 25°C using the Wilhelmy plate method with a K12 processor tensiometer (Switzerland, Krüss; the precise degree of measurement is 0.01 mN/m) controlled by a circulation-water thermostatic bath (Ophterm, ECV model).

DLS was performed on Dawn Heleos, Wyatt QELS, and Optilab DSP instrument (Wyatt Technology Co., Santa Barbara, CA). The incident laser beam (λ = 658.0 nm) was polarized. Polymer solutions at concentrations of 5, 50, and 100 mg/L were measured at 25°C. The degradation aggregates in PBS were measured at 25 and 37°C, respectively. All the solutions were filtered through 0.45 μm Millipore

Durapore filter and all the measurements were made at a fixed angle of 90°. Analysis of the DLS data was performed by the software program QELS-Batch (Wyatt Technology Co., Santa Barbara, CA).

TEM was carried out on a JEM-100CX Π electron microscope. In a typical experiment, a drop of the copolymer solution was placed on copper grid, and then a drop of phosphotungstic acid (2 wt % aqueous solution) was immediately added to the grid and after 30 s for staining, excess liquid was removed.

The rheological properties of the polycarbonates aqueous solutions were measured using a HAAKE RheoStress RS75 rheometer at a frequency of 1 Hz. The shear stress was kept constant at 20 Pa, which was in the linear viscoelastic region. The temperature range was 25–75°C and equilibrium maximum waiting time was 180 s. Mineral oil was applied to the edge of the cone to prevent the dehydration during the experiments.

RESULTS AND DISCUSSION

Molecular structure characterization

Preparation of PEG/PPG multiblock polycarbonates was carried out according to Scheme 1. PEG and PPG were covalently bound using triphosgene as the coupling molecule. The molecular weight and composition of the multiblock polycarbonates were controlled by the molar ratio of PEG to PPG. The structures of the polycarbonates were confirmed by ^{1}H-NMR and IR spectra. To identify the composition of the PEG/PPG multiblock copolymer, we showed the spectrum [Fig. 1(A)] of the polycarbonate synthesized using the same mole amount of PEG instead of PPG (denoted as EO-CO-EO). As it was shown, methylene protons (—OCH$_2$—CH$_2$—) along the PEO chain contributed to the signals at around 3.35–3.85 ppm while those adjacent to the polycarbonate linkages (—CH$_2$CH$_2$OCO—) appeared at 4.28 ppm. The ^{1}H-NMR spectrum of EO-CO-PO-1 was shown in Figure 1(B). The peaks at 3.35–3.85 ppm consisted of chemical shifts of the methylene protons (—OCH$_2$—CH$_2$—) in PEO blocks and methine proton together with methylene protons [—OCH(CH$_3$)—CH$_2$—] in the PPO units since they overlapped. The peak at 1.15 ppm belonged to the protons of PPO's methyl groups [—OCH (CH$_3$)—CH$_2$—]. The methylene protons (—CH$_2$CH$_2$OCO—) of PEO at the linkage between PEO and C=O in EO-CO-PO-1 appeared at almost the same position as that of EO-CO-EO. At the same time, the α-methine proton [—COOCH(CH$_3$)—CH$_2$—] of carbonyl-connecting PO units appeared at 4.88 ppm. Hence we can conclude that both PEG and PPG are attached to carbonyl chloride. As a result, the chemical shifts of the methyl protons in PPO blocks linked to α-methine
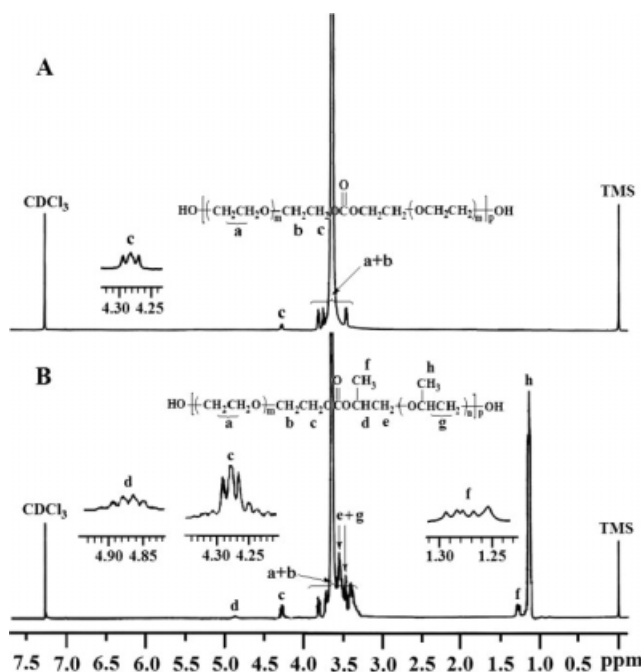
Figure 1 The 400 MHz ^{1}H-NMR spectra for (A) copolymer EO-CO-EO and (B) multiblock polycarbonate EO-CO-PO-1 in CDCl$_3$ at room temperature.

proton transferred to 1.28 ppm. The purified multiblock polycarbonates were further identified by IR. Figure 2 showed the IR spectra of PEG6000, PPG2000 and PEG6000/PPG2000 multiblock polycarbonates. For PEG, the representative C—O—C stretching vibrations of the repeated —OCH$_2$ CH$_2$ units appeared at 1150 cm^{-1} and the bands at 963 and 843 cm^{-1} were the characteristics of the crystalline phase of PEG,[38] and for PPG the C—O—C stretching vibrations of the —OCH(CH$_3$)CH$_2$ at 1099 cm^{-1}. It is of interest to note that the end OH group stretching vibrations in the range 3200–3600 cm^{-1} appear in both PEG and PPG but disappear in multiblock copolymer, indicating hydrogen bonding between the carbonyl chloride and PEG or PPG. The absorption at 1749 cm^{-1} attributed to the carbonate group further suggested the formation of polycarbonate. It is also clearly seen in Figure 2 that the band at 1264 cm^{-1} is assigned to stretching vibrations of C—O—C in multiblock polycarbonate. These results confirm the complete conjugation of PEG and PPG to triphosgene. The molecular weights and molecular weight distributions of the polycarbonates were determined by GPC and listed in Table I. All the multiblock copolymers exhibited low polydispersity between 1.22 and 1.41 as it was shown in Figure 3.

Crystallization behavior and thermal properties

The X-ray diffraction measurement is a useful tool to determine the structure and crystallinity of the

polymer matrices. Figure 4 compares the XRD patterns of PEG/PPG multiblock polycarbonates with different molar ratio between PEG and PPG. The diffraction patterns of all the samples consist of two major crystalline peaks at $2\theta = 19.3°$ and $23.5°$, which are characteristics of crystalline PEG.[39] The two peaks are sharp, corresponding to the ordered arrangement of PEG polyether segments. These observations match well with findings from FT-IR. Comparing the peak intensity of the three polycarbonates that contain PEG segments of same molecular weight, one can find that PEG crystallinity apparently decreases with increase of the component of PPG segments. This is probably because soft segment forms crystalline structure in the segmented PEG, owing to their longer chain length and ordered structure. However, the chain length of PPG segments (M_w2000) in this study is relatively short; it forms amorphous state at room temperature, which restricts the formation of PEG crystalline phase. The PEG blocks are subject to the suppression of the PPG blocks and this effect becomes more pronounced with more composition of PPG.[37,39]

Further information on the crystallization behavior of these PEG/PPG multiblock polycarbonates was obtained from DSC analysis. The DSC diagrams are shown in Figure 5 and data are presented in Table I. To remove the influence of thermal history, all the DSC curves shown here were obtained at the second heating run. PEG6000 exhibits a melting peak at 63.14°C. Expectedly, the DSC curves of PEG/PPG multiblock polycarbonates were similar to that of pristine PEG due to their structures containing PEG units whose theoretical content reached a relatively high level. However, the obtained melting enthalpy as well as melting transition temperature (T_m) of the multiblock polycarbonates was all lower than their
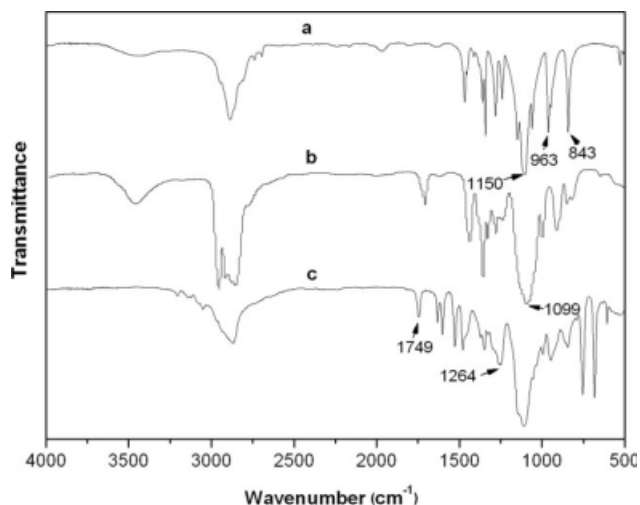

Figure 2 FT-IR spectra of pure (a) PEG, (b) PPG, and (c) EO-CO-PO-1 polycarbonate.

Molecular Characteristics of PEG6000-PPG2000 Multiblock Polycarbonates

Polycarbonates	PEG/PPG (Mole ratio)	$M_n{}^a$	$M_w{}^a$	$M_w/M_n{}^a$	$\Delta H_m{}^b$ (J g^{-1})	$T_m{}^b$ (°C)	$X_c{}^b$ (%)
EO-CO-PO-0.8	0.8	98,000	138,000	1.41	117.3	54.21	57.22
EO-CO-PO-0.9	0.9	101,000	123,000	1.22	127.4	55.18	62.15
EO-CO-PO-1	1	99,000	127,000	1.28	154.8	56.90	75.51

[a] Obtained from GPC measurement.
[b] Determined by DSC.

PEG precursors and the reductions became greater when PPG content increased, as shown in Table I. It should be a result of hindrance from PPG to the crystallization of PEG segments, as revealed by the crystallinity of the polycarbonates (shown in Table I), from 75.51% for EO-CO-PO-1, down to 57.22% for EO-CO-PO-0.8. This conclusion is very coincident with the above XRD characterization.

In addition, the thermal stability and degradation profiles of PEG/PPG multiblock polycarbonates were evaluated using TGA. Figure 6 shows the TGA and corresponding DSC plots of a multiblock co-polymer compared with its PEG precursor. It was obviously observed from Figure 6(a) that PEG6000 showed only one decomposition step. PEG6000 was stable up to above 250°C and then decomposed rapidly at around 330°C. The degradation process was confirmed by DTG curve. Simultaneously, in the DSC curves two endothermic events were observed, one at about 60°C, indicating crystalline melting of PEG and the other, around 410°C, owing to thermal chain scission by endothermic degradation, this later was also observed in the correspondent TGA curve.

Compared to PEG monomer, the multiblock co-polymer showed decreased thermal stability [Fig. 6(b)]. It could be observed that the initial decomposi-

tion temperature is ~ 80°C, and the degradation profiles are similar to that of PEG6000. The observed profile was confirmed by the DTG curve with a maximum decomposition rate at 400°C, the same event was observed as an endothermic transition (400°C) in the corresponding DSC curve.[40]

Surface activity

Amphiphilic block polycarbonates can form micelles through self-assembly in aqueous media. Polymeric micelles can be formed only when the block copolymer concentration is higher than the critical micelles concentration (CMC) which characterizes the micelle stability. Compared with low molar mass surfactant micelles, polymeric micelles are generally more stable, exhibiting a remarkably lowered CMC.[41–43] A large difference is often noted between the CMC values determined by difference methods because their sensitivity to the quantity of monomers present in solution may vary. Furthermore, composition polydispersity, batch variations, differences in the concentration ranges covered in CMC experiments or the lack of sufficient temperature control may be responsible for the observed variations.[44–46]

Investigation of surface tension γ as a function of the concentration c of the polycarbonates aqueous
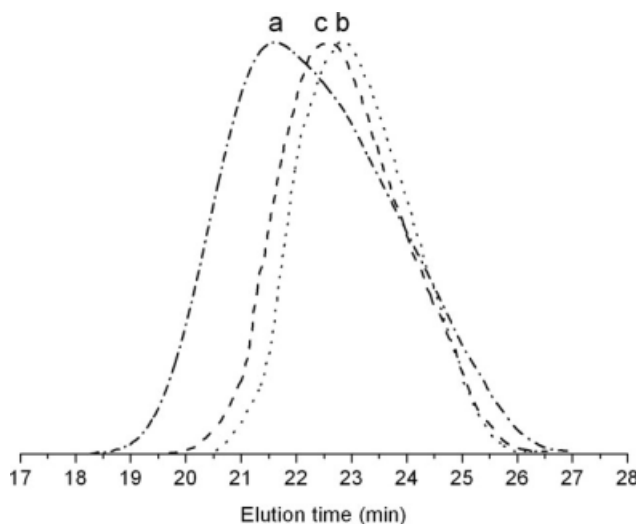

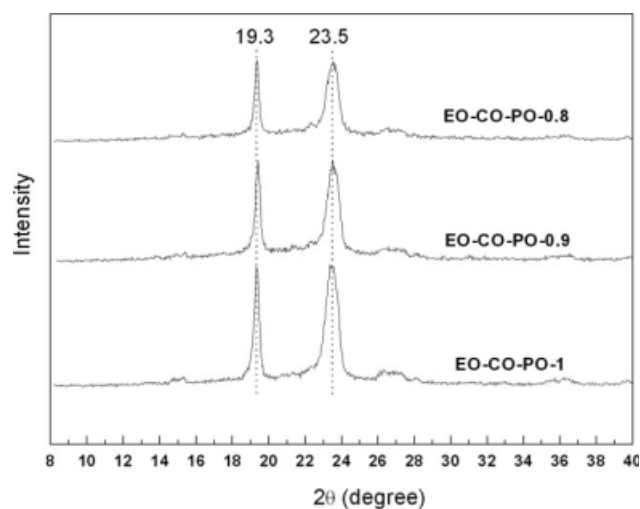**Figure 3** GPC traces of (a) EO-CO-PO-0.8, (b) EO-CO-PO-0.9, and (c) EO-CO-PO-1.

Figure 4 XRD patterns of PEG/PPG multiblock polycarbonates with different molar ratio between PEG and PPG.
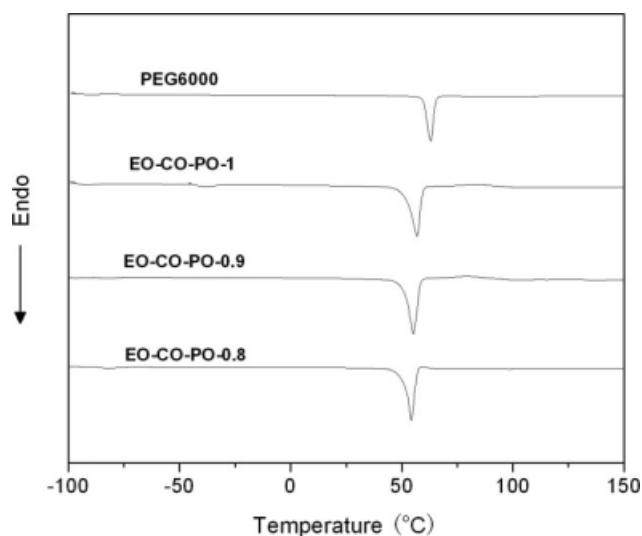
Figure 5 DSC curves of PEG and PEG/PPG multiblock polycarbonates with different molar ratio between PEG and PPG.

solutions shows that the multiblock polycarbonates are surface-active (Fig. 7). The copolymer in water can reduce its surface tension from 72 to less than 40 mN m^{-1} at the concentration studied. We can see γ versus log c plots were different from those of conventional nonionic surfactant where a sharp inflection can be seen at CMC. Two breaks appeared in the three plots when the concentration increased, after the first break the surface tension values continued to decrease until a plateau was reached. For EO-CO-PO-0.8, as shown in Figure 7(a), the CMC range was about from 2 to 70 mg/L, while for EO-CO-PO-0.9 and EO-CO-PO-1, the CMC ranges were
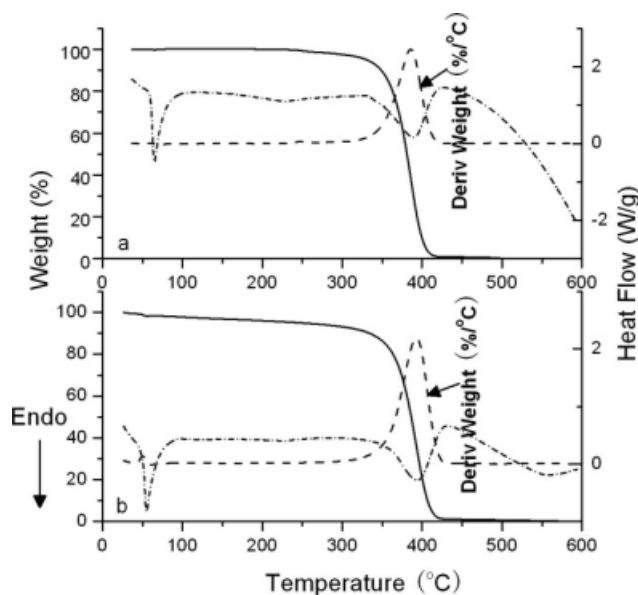
4–50 mg/L and 5–40 mg/L [Fig. 7(b,c)]. The range of CMC became narrower with increasing PEO content. The shape of the plots is to some extent similar to that of Pluronics.

It has been suggested that the low-concentration break in the surface tension versus copolymer concentration curves is owing to a change in configuration (structural transition) of the copolymer molecules at the air-water interface. Constant surface coverage has been attained at bulk copolymer concentrations ranging from about 0.2 to 2 mg/L, with the copolymer molecules adsorbed at the interface possibly as an inverted "U" (this is one of the proposed orientations for homopolymer PEO at the interface) and the PEO chains located at the air-

Figure 6 TGA and corresponding DSC plots for (a) PEG6000 and (b) EO-CO-PO-0.9.
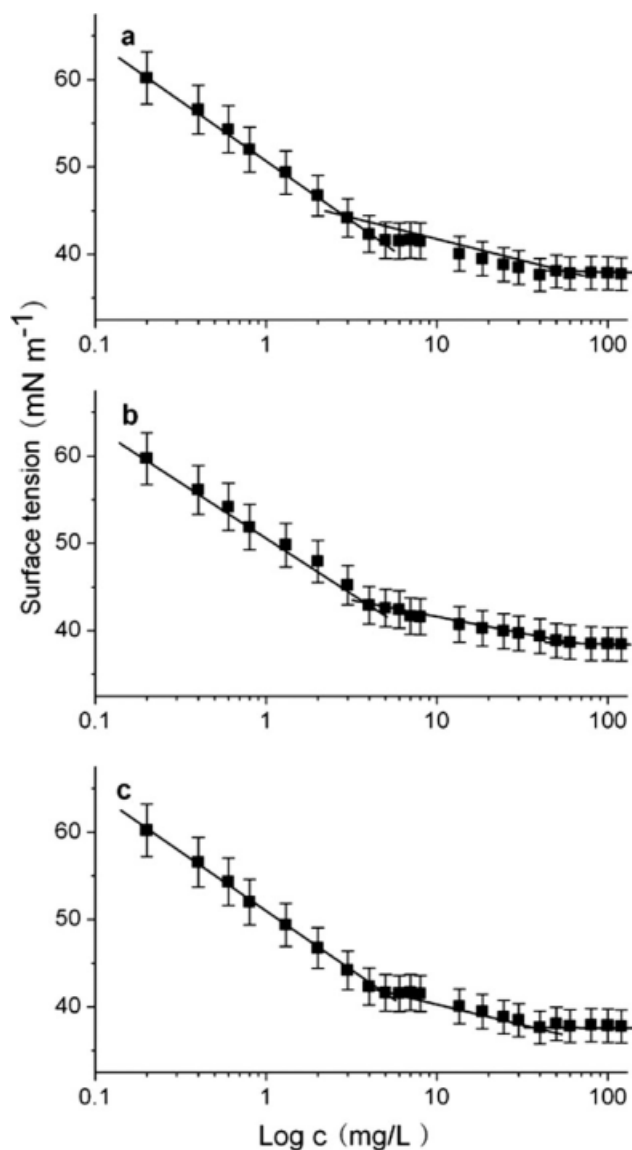

Figure 7 Surface tension isotherms of (a) EO-CO-PO-0.8, (b) EO-CO-PO-0.9, and (c) EO-CO-PO-1 at 25°C. Data represent the mean and standard deviation of three independent experiments.
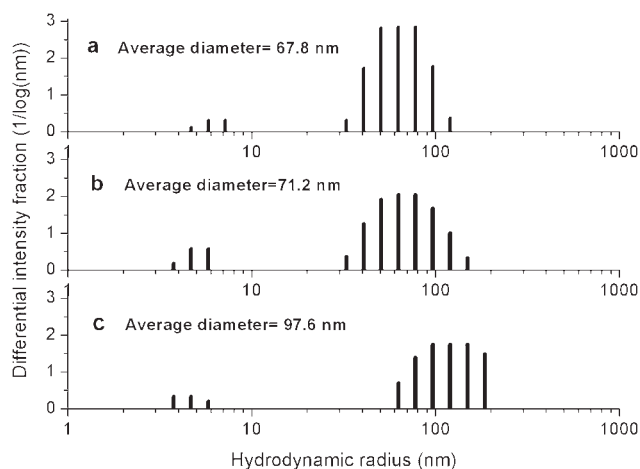
Figure 8 Size distribution of the aggregates formed by polycarbonates EO-CO-PO-0.9 in aqueous solutions at the concentrations of (a) 5 mg/L, (b) 50 mg/L, and (c) 100 mg/L, determined by DLS at 25°C.

water interface. At a bulk concentration of $\sim$ 2 mg/L, a structural transition occurs and the copolymer layer becomes more compact; water is expelled and PEO segments protrude into the aqueous solution or fold around PPO. More copolymer molecules can fit at the interface (causing it to become thicker) and the surface tension continues to decrease with increasing bulk copolymer concentration, but at a slower rate. On formation of micelles in the bulk, a

further increase in the number of copolymer molecules in the bulk is accommodated by an increase in the number of micelles, the activity of the copolymer in the bulk remains approximately constant, and the surface tension attains a steady value that does not change with further increase in the bulk copolymer concentration.[19,45,47–50]

Size and morphology of the aggregates

The particle size and size distribution of the obtained aggregates were determined by DLS. Figure 8 shows the size distribution of copolymer EO-CO-PO-0.9 aggregates in aqueous solutions at concentration of 5, 50, and 100 mg/L. We can see that all the polymer solutions revealed bimodal size distributions with a first peak around 5 nm and the other varying from 60 to 100 nm. DLS studies have showed that bimodal distributions are commonly observed for amphiphilic polymers in aqueous solutions, since depending on the polymer composition single molecules or small "oligomolecular" aggregates can coexist with the larger ones. Therefore the first peak corresponding to small particles may be due either to single multiblock polycarbonate molecules or to small aggregates having just a few polymer chains, while the second distribution indicate the presence of aggregates resulting from intermolecular association.[51–53] It can be seen that the size of
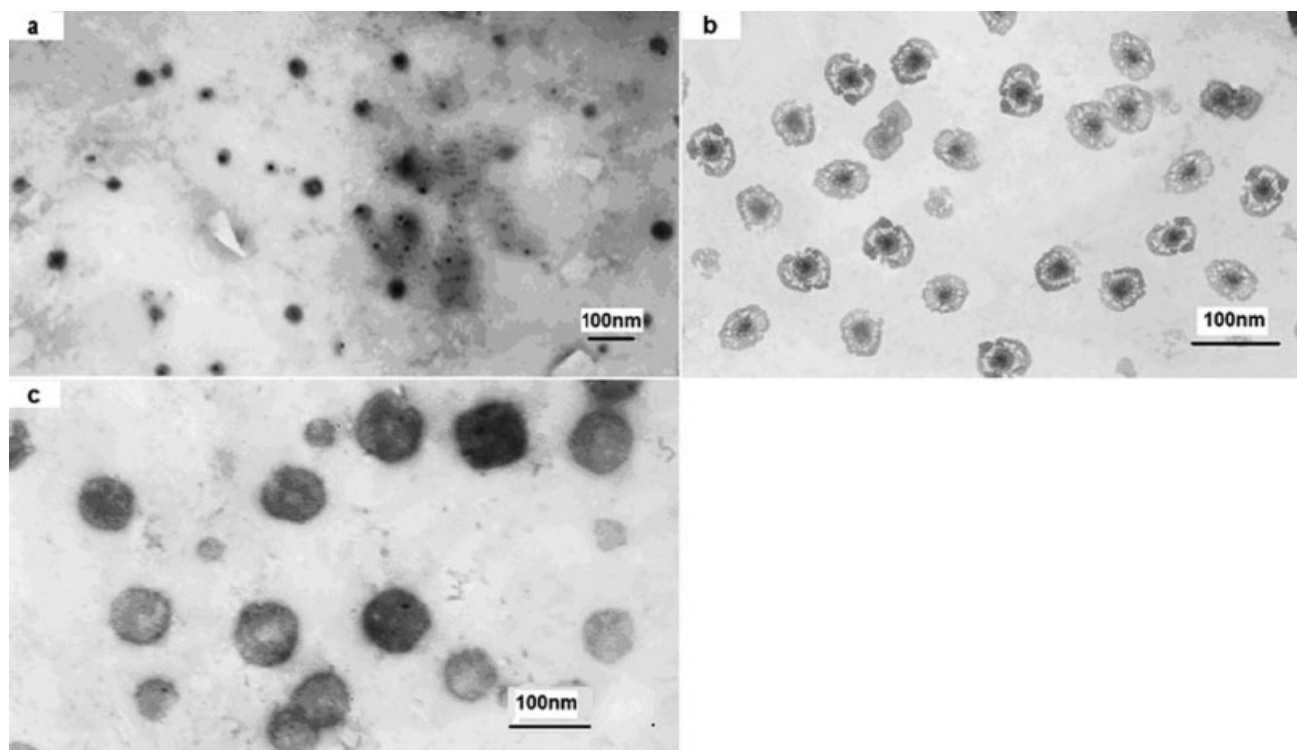

Figure 9 Transmission electron micrographs of copolymer EO-CO-PO-0.9 in aqueous solution at the concentration of (a) 5 mg/L, (b) 50 mg/L, and (c) 100 mg/L.

the larger population increased with the increasing concentration of the polycarbonate. Similar trends were observed for other polycarbonates. This suggests that the aggregates are dynamic systems and are stable upon dilutions, which are suitable for injectable drug carriers.

The size and morphology of the formed aggregates was further observed by a TEM technique. As shown in Figure 9, globular micelles with diameters ranging from 30 to 40 nm were observed at concentration of 5 mg/L. As the concentration rose to 50 mg/L, a more complex morphology could be seen and consists of a compartmented sphere; we refer to it as a large compound vesicle, these vesicles had an average diameter of 60 nm. When the concentration reached 100 mg/L, uniform spheres formed. It could be confirmed that these dark and discrete spheres are also micelles. The morphology of these aggregates changed as the variation of the concentration of the polycarbonates aqueous solution. By regulating the morphology, amphiphilic block copolymer system can be explored as potential drug carriers. The size of these aggregates is smaller than that determined by DLS in water, presumably arising from the dry state of the TEM measurement.

Degradation behavior of the aggregates

The aggregation behavior of these amphiphilic multiblock polycarbonates we studied indicates that they have potential application as drug delivery carriers. However, biodegradability is required for medical use. Therefore we investigated the biodegradability of the multiblock copolymer aggregates from the changes in their hydrodynamic radius and molecular weight following the hydrolytic degradation at 25 and 37°C, respectively. Figure 10 shows the size changes of the EO-CO-PO-n aggregates as a function of standing period in PBS. The size of the aggregates decreased gradually upon increasing the degradation time, moreover, it decreased slower when degraded at 25°C than that of 37°C. For example, for the aggregates formed by EO-CO-PO-0.8, the particle size dropped from 109.5 to 81.4 nm after 144 h incubation at 25°C, however, it decreased from 109.5 to 58.4 nm when incubated at 37°C. Similar changes were observed from the other two aggregates. These results indicate that the degradation rate could be accelerated with an increase in temperature. Goto and Kunioka[54] have also reported the effect of temperature on the degradation of nanoparticles formed by amphiphilic copolymers. Furthermore, the aggregates formed by EO-CO-PO-1 degraded faster than that of EO-CO-PO-0.9 and EO-CO-PO-0.8 when incubated at 25°C; meanwhile, they performed to some extent similar to that of 25°C when incubated at 37°C. These results suggest that
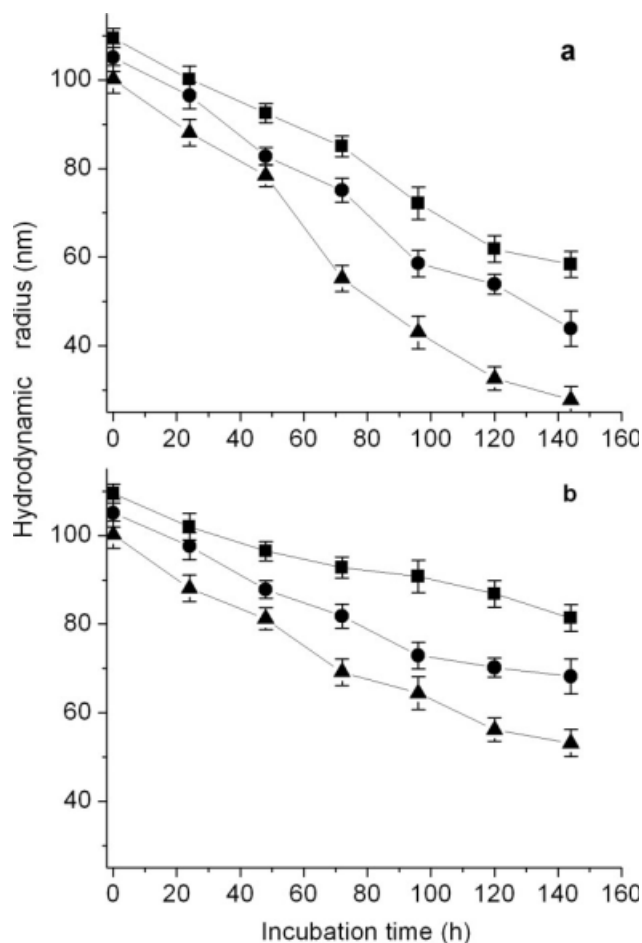

Figure 10 Changes in the particle size of the multiblock copolymer aggregates prepared from EO-CO-PO-0.8 (squares), EO-CO-PO-0.9 (circles) and EO-CO-PO-1 (triangles) as a function of the degradation time in PBS at (a) 25°C and (b) 37°C measured by DLS. Data represent the mean and standard deviation of three independent experiments.

the length of hydrophilic block is an important factor for the degradation behavior of amphiphilic copolymers. The more the copolymer is hydrophilic and the faster is its degradation. The results have also been confirmed by Akagi et al. and Dorati et al.[55,56]

Figure 11 shows the change in average molecular weight during the degradation process at 25 and 37°C, respectively. It appears that average M_w of the aggregates made of polycarbonates before degradation are 141,000, 132,000, and 137,000, which is comparable to that of the corresponding polymer. Analogous phenomena were observed from poly (ethylene glycol-co-D,L-lactide) (PEG-D,L-PLA) system.[56] Then a progressive decrease of the average molecular weight was observed for the three aggregates at both temperatures. This could be attribute to the cleavage of carbonate bond between PEO and PPO. However, the degradation rate at 37°C was
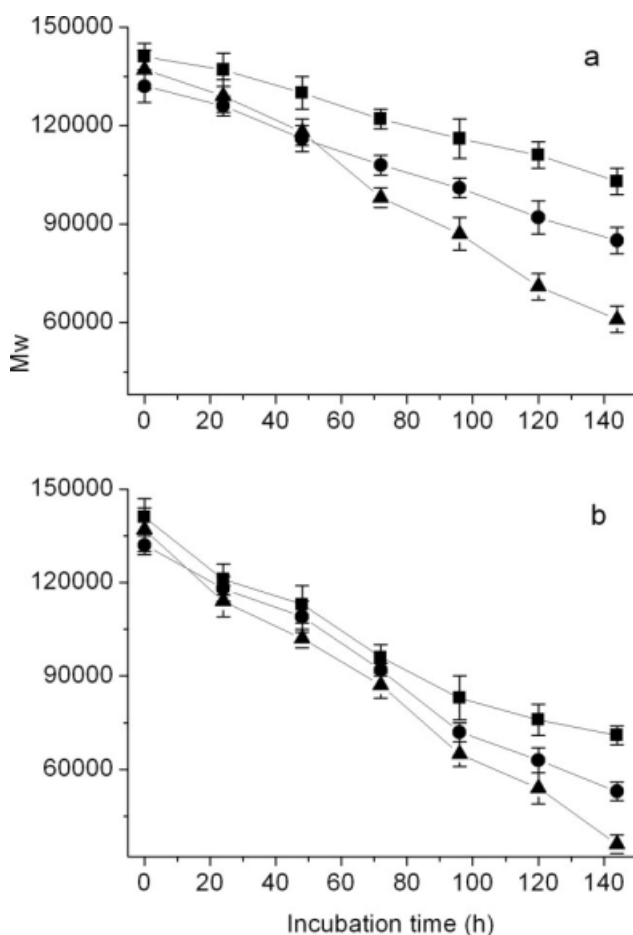
Figure 11 Changes in average M_w of the multiblock copolymer aggregates prepared from EO-CO-PO-0.8 (squares), EO-CO-PO-0.9 (circles) and EO-CO-PO-1 (triangles) as a function of the degradation time in PBS at (a) 25°C and (b) 37°C measured by GPC. Data represent the mean and standard deviation of three independent experiments.

found to be higher compared to 25°C. Obviously, the enhanced temperature accelerates the alkaline hydrolysis of the polycarbonates. Moreover, the degradation rate of the aggregates was found to be dependent on the hydrophilic block length of the corresponding polycarbonates when incubated at the same temperature. The longer hydrophilic block in the polymer leads to higher degradation rate. These results indicated that aggregates with varied degradation rate could be obtained by regulating the length of hydrophilic segment, which allows the production of aggregates with different degradable properties that meet the biodegradable requirements in biomedical application.

Rheological measurements

The rheological properties of multiblock polycarbonates were measured by temperature sweep experiments. Figure 12 showed the influence of tem-

perature on storage modulus G' and loss modulus G'' for 15 wt % aqueous solutions of EO-CO-PO-0.8 and EO-CO-PO-0.9. For copolymer EO-CO-PO-0.8 [in Fig. 12(a)], it was generally observed that when the temperature was lower, the systems showed a liquid-like behavior with $G'' > G'$. Both of them increased with the rising of the temperature. However, G' increased more sharply than G''. As it was near 32°C, a crossover of G' and G'' occurred, indicating the samples undergone a sol-gel transition, forming an elastic network.[57] Then, G' and G'' kept on increasing together until they got to the maximum values. As the temperature increased further, at about 45°C, G' dropped rapidly to very low values, a gel to sol transition was detected around 51°C, due to the breakdown of gelatin physical network.

Qualitatively similar trends have been observed for copolymer EO-CO-PO-0.9 [in Fig. 12(b)]; nevertheless, the two crossover points for copolymer
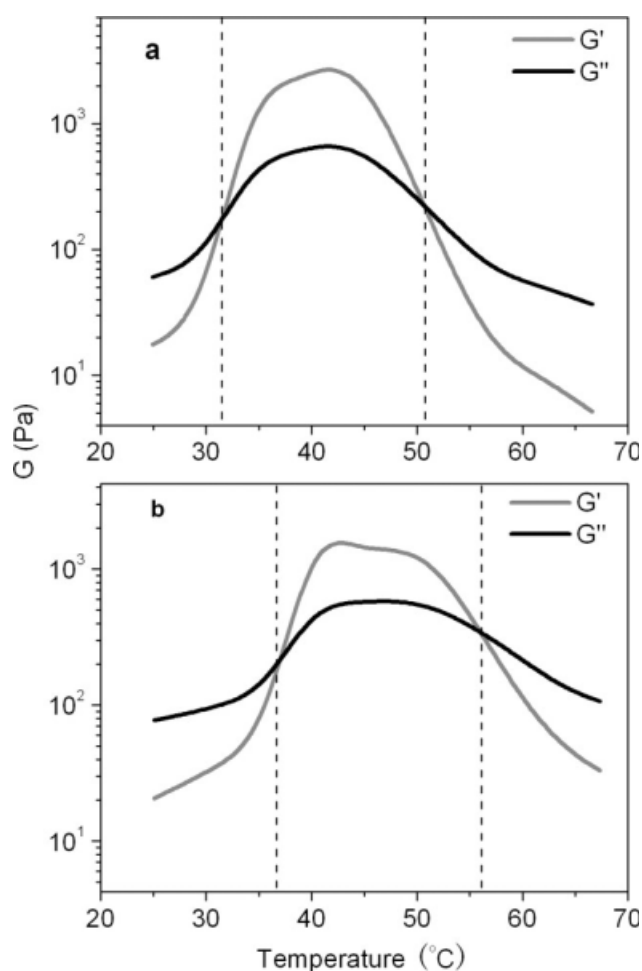

Figure 12 Storage modulus G' and loss modulus G'' versus temperature for polycarbonate (a) EO-CO-PO-0.8 and (b) EO-CO-PO-0.9 in 15 wt % water solution when the system heating up from 25 to 75°C.

EO-CO-PO-0.9 (around 37 and 56°C) appeared later than that of EO-CO-PO-0.8. Furthermore, the maximal values of G' and G'' obtained from EO-CO-PO-0.9 were smaller than that from EO-CO-PO-0.8. These may be attribute to the different PEO/PPO composition ratios of the two polycarbonates. It has been proved that G' have a strong dependence on the hydrophone length, gel strength improves as the length of the hydrophobic block increases. From the above results we can conclude that the multiblock polycarbonates are thermo-responsive. Hydrogel can be formed at 37°C from aqueous solutions of EO-CO-PO-0.9 with PEO/PPO composition ratios of 0.9/1 at the concentration of 15 wt %. One can thus imagine injecting an aqueous solution containing both copolymer and drug into the body. A hydrogel will be formed *in situ* and play as a sustained release matrix for the drugs.

CONCLUSIONS

A series of biodegradable amphiphilic thermo-responsive multiblock polycarbonates consisting of PEO and PPO were facilely synthesized by reaction of the two chains using triphosgene as the coupling molecule. The molecular weight and composition of the multiblock polycarbonates were controlled by the molar ratio of PEG to PPG. The structures and molecular characteristics of the multiblock polycarbonates were studied by ^{1}H-NMR, FT-IR and GPC. XRD and DSC analysis showed that the melting temperature and the crystallinity of the multiblock polycarbonates were affected by the composing of the polycarbonates. TGA results showed that the multiblock polycarbonates undergone thermal degradation in one step and had decreased thermal stability compared to PEG. CMC values were obtained by surface tension tests. An increase of hydrophilic components in the copolymer brought a narrower CMC range. DLS experiments showed that the average size of the aggregates increased with the increasing of the polycarbonates concentration. The morphology of the aggregates also changed with the variation of the concentration of the multiblock polycarbonates. Furthermore, the degradation rate of the aggregates formed by the polycarbonates can be accelerated with an increase in temperature. The more the copolymer is hydrophilic, the faster is its degradation. These multiblock polycarbonates were proved to be thermo-responsive through rheological experiments and by regulating the PEO/PPO composition ratio they could form a gel at 37°C. They are useful in controlled drug delivery and other biomedical applications where fast degradation is required. The drug release measurements are underway in our laboratory.

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