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Synthesis and properties of ABA-type triblock copolymers of poly(glycolide-*co*-caprolactone) (A) and poly(ethylene glycol) (B)

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Abstract

Poly(glycolide-*co*-caprolactone) (A)–poly(ethylene glycol) (B) ABA-type triblock copolymers (PGCE) were synthesized by bulk ring opening polymerization, using the hydroxyl endgroups of poly(ethylene glycol) (PEG) as initiator and stannous octoate as catalyst. The resulting copolymers were characterized by various analytical techniques. Gel permeation chromatographic analysis indicated that the polymerization product was free of residual monomers, PEG and oligomers. ^{1}H NMR and differential scanning calorimeter results demonstrated that the copolymers had a structure of poly(glycolide-*co*-caprolactone) (PGC) chains chemically attached to PEG segments. All the PGCE copolymers showed improved hydrophilicity in comparison with the corresponding PGC copolymers with the same molar ratio of glycolidyl and caproyl units. The microspheres of PGCE copolymer exhibited rough surfaces quite different from the smooth surface of PGC microspheres. This phenomenon was attentively ascribed to the highly swollen ability of PGCE copolymers and the freeze-drying process in the microspheres fabrication.

Keywords: Poly(glycolide-*co*-caprolactone); Poly(ethylene glycol); Block copolymer

1. Introduction

Biodegradable polymers prepared from glycolide, lactide or ε-caprolactone have been widely used as sutures, drug carriers and implants to ensure a temporary mechanical or therapeutic function, as well as cell scaffolds in tissue engineering. Various materials with a broad range of properties can be obtained by copolymerization of different comonomers and modulation of their ratio in the copolymer, such as the reported poly(lactide-*co*-glycolide) (PLGA), poly(lactide-*co*-caprolactone) (PLC) and poly(glycolide-*co*-caprolactone) (PGC) copolymers [1–3]. Terpolymers of glycolide, lactide and caprolactone can also be synthesized by a similar route of using stannous octoate as catalyst at 160–220 °C [4,5]. Many works have been done on the degradation mechanism and toxicology of PLGA and PLC [6]. However, the copolymers of glycolide with caprolactone began to attract considerable interest only in recent years. Surgical suture made from PGC can be commercially available under the trade name Monocryl, which contains 75 mol% of glycolide [7,8]. The PGC material has low stiffness and provides excellent handling characteristics. They had been applied as implants and surgical suture with satisfactory results. But there is few literature available on the application of PGC copolymers for the controlled drug release [9]. One major reason is the poor solubility of the copolymer in common organic solvent. To prepare microspheres, the copolymers should first of all be soluble in common solvents. However, polyglycolide (PGA) is a rigid, highly crystalline material insoluble in most organic solvents, including trifluoroacetic acid [10]. Since the glycolide is much more reactive than caprolactone, the copolymerization rates of glycolide and caprolactone are quite different. As a result, PGC copolymers with PGA block sequences along the polymer chain are finally obtained. The insolubility of the PGA segments in common solvents makes the copolymers sparsely soluble if its glycolidyl units content is more than 10 mol% [9]. Thus, the materials used for microspheres fabrication should have high caproyl unit content to improve solubility. However, in that case, the copolymer would unfortunately exhibit low hydrophilicity and slow degradation rate due to the formation of crystalline polycaprolactone (PCL) domain.

The polyether–polyester block copolymers constitute a new class of biomaterials, which attracts growing interest for biomedical applications, especially for controlled drug delivery systems. Poly(ethylene glycol) (PEG) is the most widely used polyether block because of its outstanding properties including hydrophilicity, water-solubility,

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biocompatibility and nontoxicity [11]. Various A–B or ABA-type block copolymers of PEG block attaching to polylactide (PLA), PCL or PLGA blocks have been synthesized and reported [12–14]. However, few people have considered the PEG/PGC block copolymers.

The present work was aimed at the synthesis and properties of ABA-type triblock copolymers (PGCE) composed of PGC (A) and PEG (B) segments. The resulting copolymers were characterized by various analytical techniques.

2. Experimental

2.1. Materials

Glycolide was synthesized from glycolic acid according to Ref. [15], and purified by recrystallization from ethylacetate, then was dried and kept over P_2O_5 in vacuo. ε-Caprolactone was purchased from Acros Chemica, N.V., and purified by distillation over CaH_2. PEG with M_n of 10 000 ($PEG_{10\,000}$) (purchased from Yili Chemical Reagent Ltd, China) was dried by freeze-drying and then stored over P_2O_5 in vacuo prior to use. Stannous octoate (from Sigma) was used as received. Ethylacetate was dried over P_2O_5 overnight and distilled before use. All other reagents were of analytical grade and used without further purification.

2.2. Polymerization and characterization

2.2.1. Synthesis of PGCE ABA-type triblock copolymers

Glycolide, ε-caprolactone, $PEG_{10\,000}$ and 0.05 wt% of stannous octoate were weighed into a rigorously dried polymerization tube. After the system was purged by argon for three times, the tube was sealed under vacuum. Then the tube was immersed and kept in an oil bath thermostated at 160 °C for 28–30 h. The raw product was dissolved in chloroform, and precipitated into cold ethanol [1:3–1:5 (v/v)]. The obtained polymer was dried under vacuum at room temperature until constant weight.

2.2.2. Synthesis of PGC copolymers

The reaction was carried out as described earlier, except that the $PEG_{10\,000}$ was absent and the polymerization time was about 20 h.

2.2.3. Characterization

Gel permeation chromatographic (GPC) analysis was performed at 35 °C on Waters apparatus equipped with Shodex KF-800 columns at a flow rate of 1 ml min^{-1}. Chloroform was served as solvent and a differential refractometer as detector. Polystyrene-standards were used for calibration. ^1H NMR spectra were recorded with a Bruker DMX 300 spectrometer and $CDCl_3$ was used as solvent. Differential scanning calorimeter (DSC) measurements were carried out at a heating rate of 10 °C min^{-1} on a DuPont Instrument Series 2100 thermal analyzer with N_2 gas protection. Tensile strength was measured on a Shinkch Testing Machine at a speed of 100 mm min^{-1} at room temperature. Contact angle of polymer films were measured statically on a FACE CA-D contact angle meter (Kyowa Kaimenkagaku Co, Japan). And water sorption was evaluated by immersing polymer films in distilled water for 72 h at room temperature and calculated as follows

$$\text{Water sorption}(\%) = \{[W_{wet} - W_{dry}]/W_{dry}\} \times 100$$

where W_{wet} was the weight of the polymer film just being taken out of the water and removed the surface water by filter paper, and W_{dry} was the weight of the wet film after rigorously drying under vacuum at room temperature.

2.3. Degradation of PGCE copolymers in vitro

PGCE or PGC films with a thickness of 0.5 mm were cast from a 8–10 wt% polymeric dichloromethane solution of the polymers onto polytetrafluoroethylene molds. After most of the solvent had evaporated in air, the films were further dried in vacuo to remove the residual solvent at room temperature until constant weight. Subsequently, films were cut into specimens of 0.25–0.35 g. Degradation experiments in vitro were carried out by immersing the specimens of PGCE or PGC samples in phosphate buffer solution (pH 7.4) at 37 °C. The buffer solution was renewed every week. At preset time intervals, the samples were taken out and dried under vacuum at room temperature to constant weight. The changes of inherent viscosity ($[\eta]$), weight loss and water sorption, as well as composition of the degraded samples, were determined as described in a previous paper [16].

2.4. Preparation of PGCE and PGC microspheres

The PGCE and PGC microspheres were prepared by oil-in-water emulsion technique at room temperature. Firstly, the PGCE or PGC copolymer (500 mg) was dissolved in dichloromethane (5–10 ml). Then, the solution was intensively mixed with the external phase (200 ml of 1% poly(vinyl alcohol) aqueous solution containing 0.05% Tween 60 as emulsifier). After stirring for an hour and the solvent evaporated, the microspheres were collected by centrifugation and washed with distilled water, then freeze-dried. The morphology of the microspheres was observed by a Hitachi S-530 Scanning Electronic Microscope (SEM).

2.5. Release of 5-fluorouracil from tablet in vitro

2.5.1. Preparation of 5-fluorouracil tablets

5-Fluorouracil (5-Fu) powder was ground and sieved (mesh 400) before use and then dispersed in the dichloromethane solutions of PGCE or PGC copolymers. After the solvent evaporating and further drying under vacuum, the 5-Fu containing polymeric films were thermo-pressed with a polytetrafluoroethylene mold. The obtained tablets weighed 0.09 g with a diameter of 10 mm and a thickness of 0.5 mm. The drug loading was 12.5% (w/w).

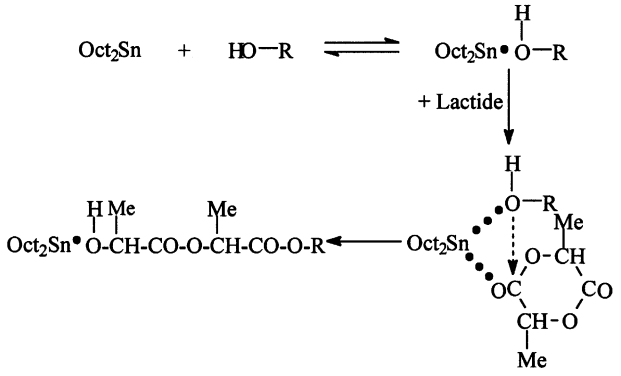

Fig. 1. The Sn(II)octoate-initiated polymerization mechanism of lactone in the presence of hydroxyl-containing compound.

2.5.2. 5-Fu release experiment in vitro

Test tubes that contained 5-Fu tablet and 20 ml of 0.1 M phosphate buffer solution (pH 7.4) were incubated at 37 °C under continuous orbital rotation at 50 cycles min^{-1}. At predetermined time intervals, 0.2 ml of the sample medium was taken out and 0.2 ml of new buffer solution was added. Then the 0.2 ml of sample medium was diluted to 10 ml. The concentration of 5-Fu in the medium was determined photometrically at 266 nm.

3. Results and discussion

3.1. Synthesis of the PGCE triblock copolymer and PGC copolymer

Stannous octoate is a well-known catalyst with medium activity and often used in promoting the polymerization of lactones. Its initiating mechanism of ring-opening polymerization of lactone in the presence of hydroxyl-containing compound can be described as Fig. 1 that was put forward by Kricheldorf [17]. Thus, ABA-type PGCE copolymers could be obtained by copolymerization of a mixture of glycolide, caprolactone, PEG and stannous octoate, as many authors did the synthesis of block copolymer of PEG and other lactones [14,18].

Fig. 2 represents the results of GPC analysis. The polydispersity of $PEG_{10\,000}$ was found to be about 1.05, which was shown as a very sharp peak (curve B) in the figure.

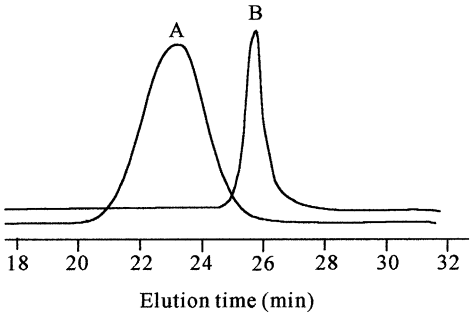

Fig. 2. GPC chromatographs of PGCE-1 copolymer (A) and $PEG_{10\,000}$ (B).

PGCE-1 copolymer showed a symmetric peak at a higher molecular weight than $PEG_{10\,000}$ (curve A) and it also had a relative narrow molecular weight distribution. Its free from PEG signal could confirm that the PEG had completely reacted with the lactone monomers. Besides, the symmetric peak showed no hint of bimodal or shoulder peaks, which could further prove that the PGCE copolymer was not contaminated by PGC copolymer. All the quantitative data on weight average molecular weight (M_w) and polydispersity (d) of the copolymers are listed in Table 1. The polydispersity was a little higher than that of $PEG_{10\,000}$ due to the transesterification.

On the other hand, it needs to be noted that the obtained PGC copolymers in this study could dissolve well in $CHCl_3$, though they contained more than 10 mol% of glycolidyl unfits. It seemed contradictory with the common rule that the copolymer should be sparsely soluble in common organic solvent when it contained more than 10 mol% glycolidyl units, as given in Section 1. This could be ascribed to the elevated copolymerization temperature in synthesizing PGC copolymers in this work. Although the reactivity difference between glycolide and caprolactone tended to form PGA block sequences along the polymer chain, but this difference would be reduced if the reaction temperature was increased. Thus, the possibility of forming long PGA sequences was lowered. So that even the produced PGC copolymers contained about 20–30 mol% of glycolidyl units, they could still dissolve easily in $CHCl_3$.

3.2. Characterization of PGCE triblock copolymers

In order to gain insight into their chemical structure, the various PEG–PGC copolymerization products were subjected to ^1H NMR measurements. A typical spectrum of PGCE-3 copolymer (trace A) is shown in Fig. 3, together with that of PGC-2 polymer (trace B). Trace B had two triplets groups of equal intensity at 4.1 and 2.4 ppm, which were attributed to the α,ω-methylene protons of caproyl units, and the four sharp singlets exhibiting at about 4.7 ppm were attributed to the methylene protons of glycolidyl units. This spectrum was very similar to the reported spectra [19] and all the signals were assigned on the spectrum. The complicated split in these peaks was due to the random copolymerization of glycolide and caprolactone. According to Ref. [19], it could further assigned the strongest singlet among band a (at the most right position) to the formation of CapGCap sequence, and the weakest sharp singlet (at the most left position) to the GGG sequence. So that, nearly no long PGA sequences were formed in the PGC copolymers synthesized, though the glycolidyl unit contents were a little higher than literature data. On the other hand, the two group signals around 4.1 and 2.4 ppm attributing to the α,ω-methylene protons of caproyl units, also could be subdivided into two triplets each. The triplets at a higher chemical shift in the two groups were attributed to the GCap sequence, and the other triplets at the lower chemical shift

Table 1
Main properties of PGCE and PGC copolymers with different compositions

Sample	[Glycotyl]/[caproxyl]/[CH_2CH_2O]		$[\eta]$[a] (dl/g)	M_w ($\times 10^{-4}$)	d	σ (MPa)	Contact angle (°)	Water sorption (%)
	Feeding dose	Product[b]						
PGCE-1	16/64/20	16.6/64.0/19.4	1.24	6.56	1.50	13.7	61.6	18.2
PGCE-2	27/63/10	28.0/62.4/9.6	1.28	7.20	1.68	11.2	64.0	7.7
PGCE-3	24/56/20	27.2/54.6/18.2	1.14	6.35	1.57	8.3	61.0	25.1
PGCE-4	21/49/30	20.8/50.0/29.2	0.90	5.00	1.44	4.0	57.6	72.3
PGCE-5	48/32/20	46.2/35.2/18.6	0.87	4.75	1.83	–[c]	59.0	71.2
PGC-1	20/80/0	19.2/80.8/0	2.77	13.1	1.92	32.9	70.7	1.17
PGC-2	30/70/0	28.2/71.8/0	2.56	14.0	2.03	–[c]	63.5	5.44

[a] Determined using chloroform as solvent at 30 °C with a solution concentration of 0.5 g/dl.
[b] Determined by ^{1}H NMR.
[c] These samples are tacky and hard to be processed for the measurement.

belonged to the formation of CapCap sequences, which was obviously stronger than the signals of GCap sequences. Therefore, it could be inferred that the long PCL segments should exist in the polymer chain of PGC-2, which might lead to the crystallization of PCL segments in the copolymer.

In comparison, trace A exhibited most of its signals similar to those in trace B, except that a new signal appeared as a sharp singlet at 3.7 ppm. This new singlet was attributed to the methylene protons of the oxyethylene units of PEG. Since the PGCE copolymer had been proved to be free from residual lactone monomers, $PEG_{10\,000}$ polymer and oligomers, as shown in Fig. 2, it could be concluded that an ABA triblock copolymer was obtained, consisting of chemically joined PGC and PEG as A and B blocks, respectively. The composition of the copolymer was determined from the ratio of the integral peak area of the methylene protons,

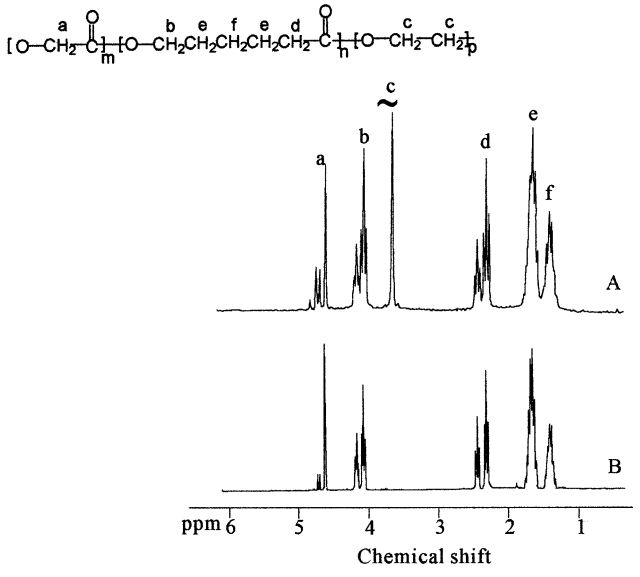

Fig. 3. Comparison of ^{1}H NMR spectra between PGCE-3 (A) and PGC-2 copolymers (B).

namely bands a, b and c. The calculated results are listed in Table 1. In comparison with the feeding doses, they clearly showed the similarity.

Analysis of the thermal behavior of PGCE block copolymers and PGC copolymers was carried out by DSC measurements. Thermograms of $PEG_{10\,000}$, PGC and PGCE copolymers with different compositions are shown in Fig. 4.

Compared to homo-PCL, whose melting point is 60 °C [10], PGC copolymers were observed the melting endotherms at 15–40 °C, which corresponded to the content of caproyl units. It was considered that the random copolymerization of caprolactone with glycolide caused a shift of the melting peak to lower temperatures, which could be proved by the two different sequences formation of CapCap and GCap illustrated by ^{1}H NMR. For PGCE copolymers, the DSC thermograms were very similar to those of the corresponding PGC copolymers with the same molar ratio of glycolidyl and caproyl units, except that a new melting endotherm appeared at 50 °C due to the incorporation of PEG. In comparison with homo-PEG, the melting temperature was reduced from 69.8 to 50 °C by approximately 20 °C. Since PGCE polymers had been identified as a copolymer and not a blend by GPC analysis, this change in melt temperature could further confirm that the PEG was synthetically attached to the PGC segments, namely that the obtained PGCE copolymers were ABA-type triblock copolymers.

The mechanical properties of PGCE and PGC copolymers were evaluated by measuring tensile strength (σ), and the data are shown in Table 1. The tensile strength of the PGCE block copolymer was observed to be much lower than those of PGC copolymers. This was considered mainly due to the incorporation of PEG, which would limit the molecular weight of the copolymer because of the polymerization mechanism. In other words, with the introduction or increase the content of PEG, the molar ratio of the hydroxyl increased, and the ratio of lactone monomer content to hydroxyl content decreased, namely the molecular weight

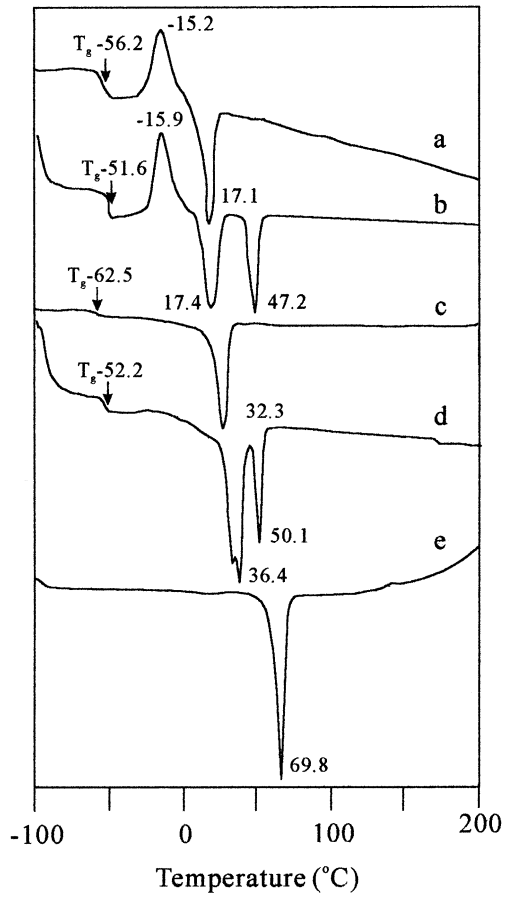

Fig. 4. Comparison of the thermal behaviors among PGCE, PGC copolymers and homo-PEG. (a) PGC-2; (b) PGCE-3; (c) PGC-1; (d) PGCE-1; (e) $PEG_{10\,000}$.

of the copolymer decreased. And this could be further proved by the fact that the tensile strength went down with the PEG content increasing, for that higher the molecular weight the materials, higher their tensile strength. However, this decrease in the mechanical strength would not influence our study significantly, since we wanted to use the PGCE copolymers as drug carriers, which had little strict demand on mechanical properties.

But the hydrophilicity of the copolymer was a very important property because it could affect the drug release behavior of the polymer significantly. To inspect the hydrophilicity of the copolymers, measurements of contact angle and water sorption were carried out. As shown in Table 1, the PGCE triblock copolymers exhibited lower contact angle and obviously higher water sorption than the PGC random copolymers. And the hydrophilicity of the PGCE increased with the PEG content increasing. It was easy to understand that these phenomena were all the results of the incorporation of hydrophilic PEG segment. These features would make the material more liable to swell in an aqueous condition and favorable for releasing hydrophilic drugs, such as protein and peptide.

3.3. The degradation of PGC–PEG–PGC tri-block copolymers in vitro

Degradation in vitro of PGCE block copolymers were evaluated by inherent viscosity and weight loss, after immersion in pH 7.4 phosphate buffer solution for predetermined time spans, and the results are listed in Fig. 5 as functions of time.

As shown in the figure, the inherent viscosity decreased continuously in all the cases, and the weight loss increased significantly with the decrease in inherent viscosity. It could be observed that the weight loss was pushed with increasing PEG content in the copolymer. In the degradation study, the PGCE specimens were seen macroscopically swelling several times of their original volumes within weeks, and the water sorption is closely related to the hydrophilic PEG content. It was proposed that the incorporation of PEG into polylactone polymers would lead to form microphase separation structure [20]. This structure could account for the rapid water uptake of PGCE copolymers. As a result, it led to a preferential scission of PGCE in the vicinity of the PGC/PEG interface and should result in a rapid weight loss for the release of PEG segments. The fact that the weight loss of PGCE copolymers took place from the beginning of

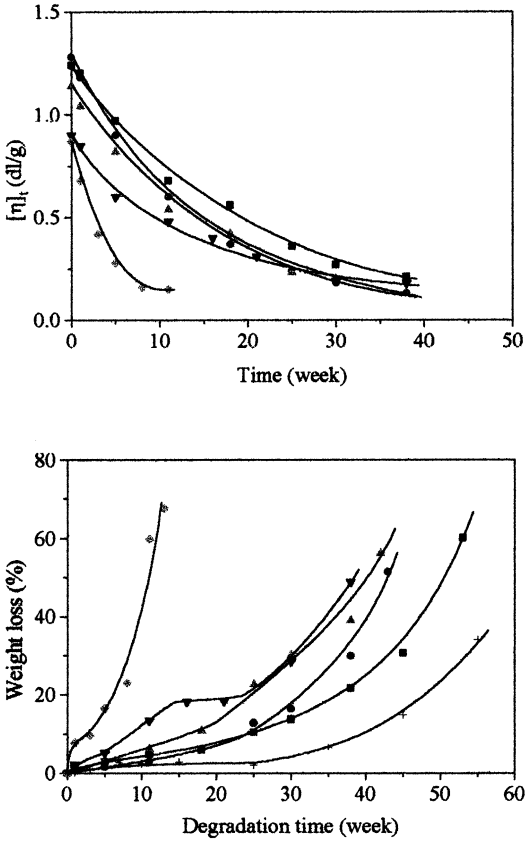

Fig. 5. The degradation behaviors of various PGCE block copolymers under pH 7.4 and 37 °C. (■) PGCE-1, (●) PGCE-2, (▲) PGCE-3, (▼) PGCE-4, (◆) PGCE-5, and (+) PGC-1.

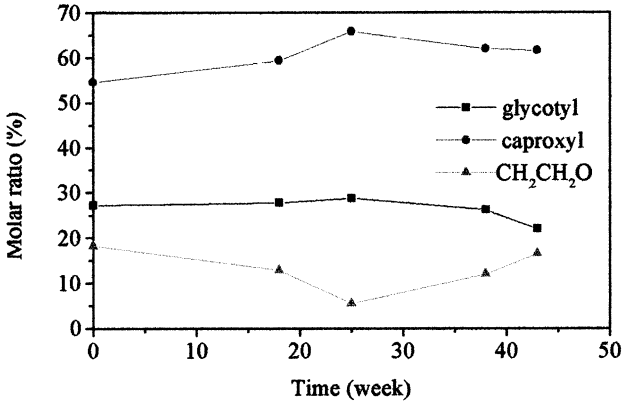

Fig. 6. Dependence of molar ratio of components on degradation time in the PGCE-3 block copolymer.

degradation, could clearly demonstrate such a viewpoint when it was compared with the degradation of PGC copolymer, which showed small weight loss in a period of 35 weeks degradation. And the decrease of PEG content (from 18 to 5%) in the PGCE copolymer with the degradation further verified such an inference, basing on the data presented in Fig. 6. However, the PEG content in the copolymer increased (from 5 to 16%) at the later stage of degradation, especially when the weight loss was large, however, the content of glycolidyl and caproyl units began to decrease. It could be inferred from these results that the short PGC segments, which were cut from the PGCE main chain with the preferential loss of PEG, were degraded rapidly at the later stage. Thus, it caused a significant increase in weight loss and made the PEG content in the degradation product increase relatively.

On the other hand, PGCE-1 had the slowest and PGCE-5 had the fastest degradation rate among the five samples. And the degradation rate of PGCE-1 was slower than that of PGCE-3. Besides the PEG content, a reason that should not be neglected was the glycolidyl units content. As it has been well known that the glycolidyl unit was relatively more hydrophilic than the caproyl unit, then it would also be preferentially lost as verified by the data listed in Fig. 6, that the ratio of caproyl/glycolidyl units increased from the original 67/33 to 74/26 with the degradation of PGCE-1. So, since PGCE-5 had glycolidyl units content as high as 46.2 mol% and the smallest original inherent viscosity among the samples, its degradation rate should be the fastest.

3.4. The morphology of microspheres made of PGCE and PGC copolymer

Microspheres made of PGCE-1 and PGC-1 copolymers were prepared by oil-in-water emulsion method. Their morphology were inspected under SEM and the results are compared in Fig. 7. Interestingly, it could be seen that the microspheres made of PGC-1 were with smooth surface, however, PGCE-1 microspheres showed a rough surface.

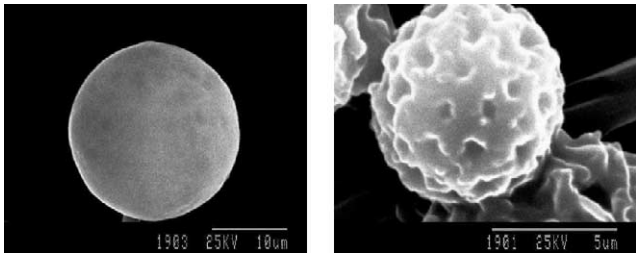

Fig. 7. Comparison of the morphology of microspheres made of PGC (left) and PGCE copolymers (right).

This phenomenon was considered to be due to the difference in water sorption of the two kinds of copolymers. As mentioned earlier, PGCE-1 showed a higher hydrophilicity than PGC-1, thus, the PGCE-1 microspheres should be in a swollen state when they were prepared by oil-in-water emulsion method. And during the following freeze-drying process, the microspheres kept their spherical shape, but the surface would shrink with the water evaporating to form the microspheres with uneven surface, as shown in Fig. 7.

3.5. 5-Fu release behavior of PGC and PGCE copolymer in vitro

5-Fu was a hydrophilic antimetabolism drug. Theoretically, it could be conceived that the release rate of 5-Fu should be faster from the more hydrophilic drug carrier. And in fact, no controversy was observed in our practical in vitro release experiment. As shown in Table 1, the water sorption of PGCE-1 could reach up to 18.2%, which was much larger than the 1.2% of PGC-1 because the hydrophilic PEG segment was added into the PGC copolymer. And as shown in Fig. 8, the 5-Fu was released significantly faster from PGCE-1 than that from PGC-1, and both cases were faster than from homo-PCL.

The ability of PGCE block copolymers to be highly swollen by water uptake, would be very valuable for the polymers used as drug carriers for the water-soluble drugs, such as protein and peptide. The PGCE copolymers

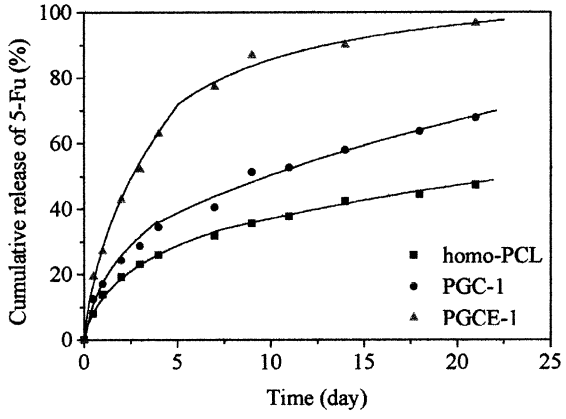

Fig. 8. Comparison of 5-Fu release behaviors among PGCE, PGC copolymers and homo-PCL.

might avoid the biphasic or polyphasic release behavior which was usually observed in the cases of PLA or PLGA [21].

4. Conclusion

PGCE ABA-type triblock copolymers could be obtained by chemically attaching PGC segments to the central PEG segment in the presence of stannous octoate as catalyst. These copolymers presented improved hydrophilicity in comparison with PGC copolymers by incorporating hydrophilic PEG segments. This endowed the PGCE block copolymers' strong tendency to take in much water and swell, and caused the microspheres of PGCE to form a rough surface. This property might be valuable for the polymers used to control release of water-soluble drugs, such as protein or peptide. It could avoid the biphasic or polyphasic release behavior. Further investigations are under way to examine the drug release behavior of proteins from these block copolymers.

Acknowledgements

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