Colloid Polym Sci (2006) 284: 834–842
DOI 10.1007/s00396-005-1432-0

ORIGINAL CONTRIBUTION

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Synthesis and characterization of poly-α,β-[*N*-(2-hydroxyethyl)-L-aspartamide]-*g*-poly (glycolide) amphiphilic graft copolymers as potential drug carriers

Received: 19 July 2005
Accepted: 18 November 2005
Published online: 16 March 2006

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Abstract A series of biodegradable amphiphilic graft polymers were successfully synthesized by grafting poly (glycolide) (PGA) sequences onto a water-soluble poly-α,β-[*N*-(2-hydroxyethyl)-$_L$-aspartamide] (PHEA) backbone. These novel graft polymers were synthesized by the ring-opening polymerization initiated by the macroinitiator PHEA bearing hydroxyl groups without adding any catalyst. The graft polymers were characterized by Fourier transform infrared spectroscopy (FTIR), ^{1}H nuclear magnetic resonance spectroscopy (^{1}H NMR), combined size-exclusion chromatography (SEC) and multiangle laser light scattering (MALLS) analysis, and differential scanning calorimetry (DSC). By controlling the feed ratio of the macroinitiator to the monomer, graft polymers with different branch lengths can be obtained. The degradation behaviors of the copolymers were studied. Based on the amphiphilicity of the graft copolymers, nanoparticle drug delivery systems were prepared by the direct dissolution method and the dialysis method, and the in vitro drug release behavior was investigated. Transmission electron microscopy (TEM) images demonstrated that these nanoparticles were regularly spherical in shape. The particle size and distribution of the nanoparticles were measured.

Keywords Biodegradable · Amphiphilic graft copolymers · Ring-opening polymerization · Nanoparticles · Drug controlled release

Introduction

Biodegradable polymers form a class of the most attractive biomaterials because of their wide applications in biomedical fields. Among them, amphiphilic biodegradable polymers are of special interest as biomaterials because of their unique physicochemical properties. These polymers can be used for a wide variety of applications, such as drug carriers, matrices in tissue engineering, stabilizers for stabilization [1, 2], etc. Graft polymers with hydrophilic/hydrophobic backbones and hydrophobic/hydrophilic branches represent an important type of amphiphilic polymer. Compared with amphiphilic block copolymers, the amphiphilic graft copolymers most commonly can easily form micelles and form smaller micelles because of the possibility of forming micelles within one or several polymer chains. Moreover, because graft copolymers have multigrafted hydrophobic/hydrophilic branches along a hydrophilic/hydrophobic polymer backbone, the micelle properties, such as the critical micelle concentration (CMC) and size, can be easily varied by simply adjusting the graft frequency and length of the branches. Another

advantage of graft copolymers is that the delicate hydrophilic/hydrophobic balance in graft copolymers can be readily controlled by changing the relative grafting density [2].

Most reported backbones for these graft amphiphilic polymers are natural biodegradable polymers such as polysaccharides including dextran [3, 4], starch [4], pullulan [5], chitin [6], chitosan [7] and cellulose derivatives [8, 9], and nondegradable synthetic polymers like poly(vinyl alcohol) [10, 11]. Synthetic biodegradable polymers with a well-defined structure were relatively less reported [2, 12]. In this study, we successfully synthesized a series of biodegradable amphiphilic graft polymers by grafting poly (glycolide) (PGA) sequences onto poly-α,β-[*N*-(2-hydroxyethyl)-L-aspartamide] (PHEA) backbone. Aliphatic polyesters based on homo- or copolymers of glycolide and lactide are the most extensively investigated and clinically used biodegradable polymers because of their good biocompatibility, low immunogenicity, and satisfactory mechanical property [2, 3, 5–7, 9–14]. For the amphiphilic copolymers we synthesized, the hydrophobic grafts are PGA sequences, and the hydrophilic backbone is PHEA, which is a water-soluble, nontoxic, nonantigenic biodegradable polymer [15–20]. In our investigation, by initiating the ring-opening polymerization of glycolide by the hydroxyl groups in PHEA, amphiphilic graft copolymers were obtained by one-step reaction conveniently. By varying the feed ratio of the macroinitiator PHEA to the monomer glycolide, graft copolymers with different hydrophobic branch lengths can be obtained. The resultant copolymer with a very short branch length can be regarded as the hydrophobically modified water-soluble polymer, which can also self-aggregate in aqueous solutions [17]. Through controlling the branch length, the adjustment of the physicochemical properties such as amphiphilicity, degradation rate, and drug controlled release property can be realized. Because of the amphiphilicity of these copolymers, they have promising applications in many biomedical fields.

Moreover, because the graft polymers were obtained by the ring-opening polymerization without adding any catalyst, this synthesis route is very useful in biomedical polymer fields since it permits the synthesis of biodegradable polymers with good biocompatibility without toxic impurities.

For amphiphilic polymers, generally, when their amphiphilicity is in a certain range, they can form colloidal drug delivery systems by self-assembly and are able to encapsulate drugs with different properties such as different hydrophilicities and polarities. As the drug carriers, amphiphilic polymers enjoy several advantages [21], such as significantly enhancing the water solubility of hydrophobic drugs to improve bioavailability [22–27] and having lower tendency to aggregate due to the hydrophilic parts which improve the stability in aqueous environments thermodynamically. Moreover, because of the high stability of the drug-loaded micelles in the blood stream, it is possible to realize long-circulating delivery of the encapsulated drugs to specific regions via an active and/or a passive mechanism.

In the present work, based on the different properties of our amphiphilic copolymers with different compositions, nanoparticle drug delivery systems were prepared by the direct dissolution method and the dialysis method. A poorly water-soluble drug, prednisone acetate, was encapsulated into polymeric nanoparticles. The in vitro release behavior of prednisone acetate from polymeric nanoparticles was studied.

Experimental

Materials

Glycolide was purchased from Beijing Conan Polymer R&D Center and purified by recrystallization from ethyl acetate. L-Aspartic acid and phosphoric acid (Shanghai Chemical Co., China) were of analytical grade and used as supplied. Ethanolamine (Shanghai Chemical Co.) was distilled before use. *N*,*N*-Dimethylformamide (DMF) was purified by distillation over P_2O_5 and CaH_2. Prednisone acetate was purified from prednisone acetate tablets (Zhejiang Xianju Pharmaceutical Co. Ltd., China). The prednisone acetate tablets were ground and dissolved in chloroform. After the removal of the starch in drug tablets by filtration, prednisone acetate was obtained after vacuum drying.

Synthesis of graft polymers

PHEA was synthesized according to a literature procedure [16]. Poly-α,β-[*N*-(2-hydroxyethyl)-L-aspartamide]-*graft*-poly(glycolide) (PHEA-*g*-PGA) copolymers were synthesized by the ring-opening polymerization of glycolide using PHEA with pendant hydroxyl groups as a macroinitiator without adding any catalyst. Graft polymers coded as PHEA-*g*-PGA-1, PHEA-*g*-PGA-2, PHEA-*g*-PGA-3, and PHEA-*g*-PGA-4 with different compositions were prepared. The feed ratios of the hydroxyl groups in PHEA to the glycolide monomer were 50:50, 20:80, 10:90, and 5:95 for PHEA-*g*-PGA-1, PHEA-*g*-PGA-2, PHEA-*g*-PGA-3, and PHEA-*g*-PGA-4, respectively. Using PHEA-*g*-PGA-1 as an example, the details of graft polymerization are as follows. Glycolide (0.423 g) and PHEA (0.577 g) were well mixed and placed in a dried silanized glass flask with a magnetic stirring bar. The flask was evacuated, purged with argon three times and sealed, then immersed in an oil bath at 200°C for 5 min. Then the reaction was allowed to proceed for 10 h at 120°C. After the graft polymerization, the product was dissolved in water and dialyzed for 48 h. Then the solution was dried in a freeze dry system (LANCONCO). To obtain PHEA-*g*-PGA-2, the product of graft polymerization was dissolved in DMF and

poured into methanol to precipitate the polymer, which was further washed with H_2O and dried in a vacuum oven. To obtain PHEA-*g*-PGA-3 and PHEA-*g*-PGA-4, the products were washed with H_2O and methanol and dried in a vacuum oven.

Sample PHEA-2 was obtained after processing the PHEA under the same reaction conditions without adding glycolide to examine the molecular weight change of PHEA backbone during the heating.

Characterizations

^{1}H NMR spectra were recorded on a Mercury VX-300 spectrometer at 300 MHz. FTIR spectra were obtained on a PerkinElmer-2 spectrometer. The samples were in KBr pellets. Combined size-exclusion chromatography (SEC) and multiangle laser light scattering (MALLS) analysis was carried out at 25°C to determine the molecular weights of graft copolymers. A dual detector system, consisting of a MALLS device and a differential refractometer, was used. The SEC system (Waters) was equipped with Ultrahydrogel 120, 250, and 2000 columns when using 6‰ NaCl water solution as an eluent for samples PHEA, PHEA-2, and PHEA-*g*-PGA-1 and Waters Styragel HR1 and HR4 columns when using DMF as an eluent for sample PHEA-*g*-PGA-2. The dn/dc values for PHEA, PHEA-2, and PHEA-*g*-PGA-1 in 6‰ NaCl water solution were 0.169, 0.169, and 0.145 mL/g, respectively. The dn/dc value PHEA-*g*-PGA-2 in DMF was 0.196 mL/g. The polymer concentration was about 3 mg/mL, and flow rate was 1 mL/min. The MALLS (DAWN DSP, Wyatt Technology Co.) detector was operated at a laser wavelength of 632.8 nm.

Differential scanning calorimetry (DSC) was performed in a PerkinElmer DSC Pyris 1 thermal analyzer. Samples were heated from 50 to 200°C at a heating rate of 20°C/min and then cooled down to 50°C, followed by the second scan immediately. Peak melting temperature (T_m) and melting enthalpy (ΔH_m) were measured based on the second scan.

The water uptake was measured after incubating the polymer pellet samples with a thickness of 0.5 mm in distilled water at 37°C for 24 h. The weights of wet samples were measured gravimetrically after blotting the excess surface water with filter paper, and the weights of the dried samples were measured after the samples were dried in a vacuum oven for 24 h.

To study the in vitro hydrolytic degradation of copolymers, polymer pellet samples with a thickness of 0.5 mm were prepared by compression molding at 180°C, followed by rapid cooling at room temperature. Then the hydrolytic degradation study was carried out in 10 mL of phosphate-buffered solution (PBS) with pH 7.4 at 37°C in a shaking water bath. The medium was refreshed every week. At preset time intervals, the samples were taken out, rinsed with distilled water, and subsequently vacuum-dried at 40°C for 24 h before being subjected to measurements. The weight loss of samples was measured gravimetrically. The surfaces of the polymer pellet samples were observed using a Hitachi 650 scanning electron microscope (SEM) after coating with gold.

Preparation of drug delivery systems and in vitro drug release study

Nanoparticles of PHEA-*g*-PGA-1 containing prednisone acetate were prepared by the direct dissolution method. To a suspension of PHEA-*g*-PGA-1 (40 mg) micelle in distilled water (10 mL), a solution of prednisone acetate (4 mg) in dichloromethane (2 mL) was added dropwise with vigorous stirring at room temperature and stirred overnight to remove the organic solvent completely. To remove the free drug, the solution was dialyzed against distilled water for 24 h using the dialysis membrane [molecular weight cut off (MWCO) 8,000–12,000]. The dialyzed solution was freeze-dried in a freeze dry system (LANCONCO).

Nanoparticles of PHEA-*g*-PGA-2 containing prednisone acetate were prepared by the dialysis method. PHEA-*g*-PGA-2 (15 mg) was dissolved in 10 mL of DMF and stirred, whereupon prednisone acetate (2 mg) was added. The solution was stirred overnight at room temperature. To

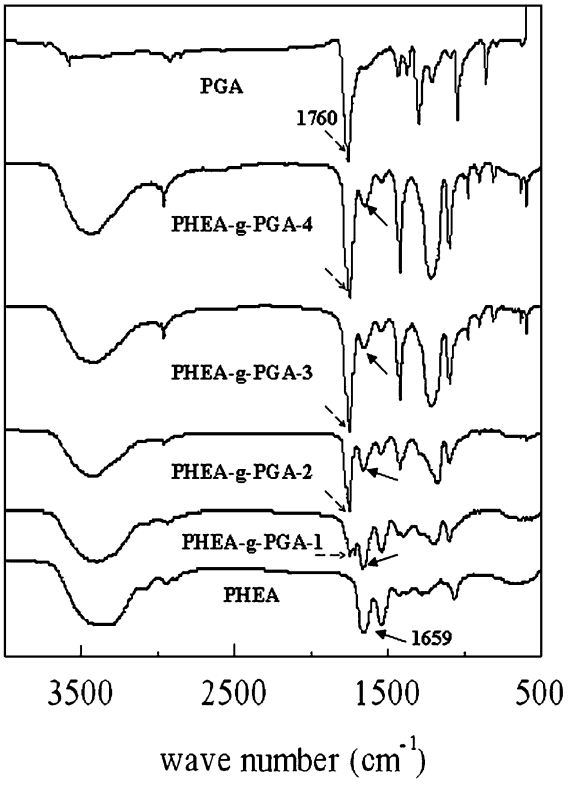

Fig. 1 FTIR spectra of PGA, PHEA, and PHEA-*g*-PGA copolymers

form drug-loaded nanoparticles and remove the free drug, the solution was dialyzed against distilled water using the dialysis membrane (MWCO 8,000–12,000) for 24 h. The dialyzed solution was freeze-dried in a freeze dry system (LANCONCO).

The morphology of nanoparticles was visualized by JEOL JEM-100CXII transmission electron microscope (TEM). Before visualization, a drop of nanoparticle suspension was placed on copper grid with Formvar film and dried. The particle size and distribution of the nanoparticles were measured using a Zetasizer 3000 (Malvern Instruments).

Drug-loaded nanoparticles were suspended in 5 mL of PBS (0.1 M, pH 7.4) in a dialysis bag. The dialysis bag was sealed and then shaken in 25 mL of PBS at 37°C in a shaking water bath. At predetermined intervals, the drug concentrations were determined by UV spectroscopy (PerkinElmer Lambda Bio 40 UV/VIS spectrometer) at 242 nm.

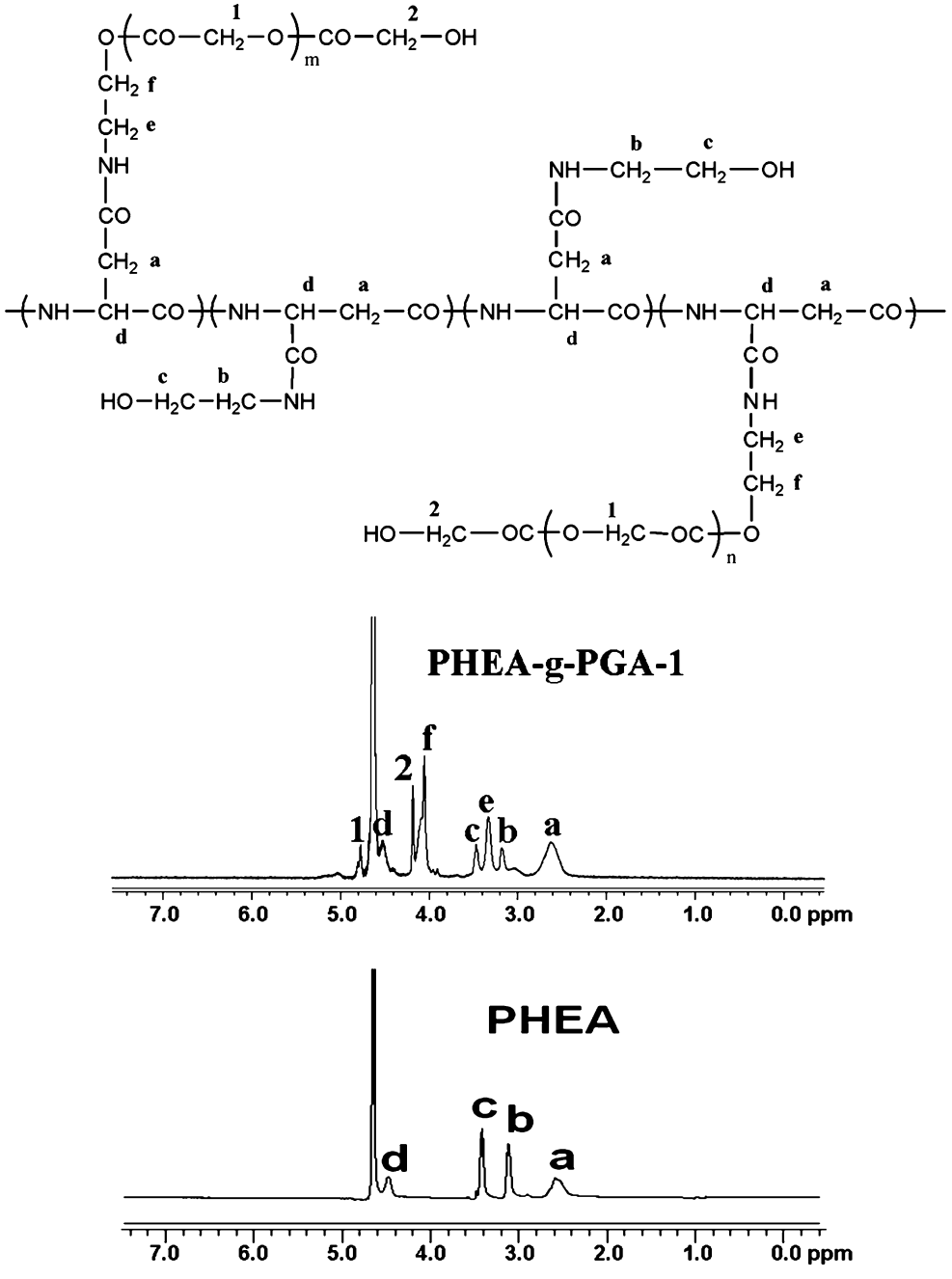

Fig. 2 ^{1}H NMR spectra of PHEA and PHEA-*g*-PGA-1. The solvent for PHEA and PHEA-*g*-PGA-1 was D_2O

Results and discussion

Synthesis and characterization of amphiphilic graft copolymers

In our study, all graft polymers were synthesized under rigorously anhydrous conditions. PHEA was carefully dried to avoid the initiation by water, which would lead to a mixture of linear and graft products. The optimized ring-opening polymerization conditions were identified to be 5 min at 200°C followed by 10 h at 120°C. A further prolonged reaction time and a higher temperature accelerated the thermal degradation of PHEA backbone, leading to a decreased molecular weight and an increased polydispersity of the resultant graft polymer.

Under the optimized reaction conditions, the monomer glycolide could be efficiently initiated by the –OH groups in PHEA and thus grafted onto the PHEA backbone. The successful grafting of PGA sequences onto PHEA was verified by FTIR and ^{1}H NMR. As shown in FTIR spectra (Fig. 1), compared with PHEA, all graft polymers show a new peak in 1,760 cm^{-1} corresponding to the C=O groups in PGA branches. In addition, compared with PGA, all graft polymers show a new peak in 1,659 cm^{-1}, which is attributed to the C=O groups in PHEA backbones. In our study, the sample PHEA-*g*-PGA-1 can be dissolved in water, and during the purification of PHEA-*g*-PGA-2, PHEA-*g*-PGA-3, and PHEA-*g*-PGA-4, the polymerization products were obtained by washing carefully with H_2O. Thus, the appearance of the new peaks indicates the PGA sequences were grafted onto the PHEA backbones.

Figure 2 shows the ^{1}H NMR spectra of PHEA and the graft polymer PHEA-*g*-PGA-1 as a typical example. In the spectrum of PHEA-*g*-PGA-1, the typical signals from PGA branches and PHEA backbone can be observed at 4.76–4.81 ppm (PGA: C**H$_2$**), 2.63 ppm (PHEA: CH**CH$_2$**CONH), 3.18 ppm (PHEA: NH**CH$_2$**CH$_2$OH), 3.47 ppm (PHEA: CH$_2$**CH$_2$**OH), and 4.52 ppm [PHEA: NH**CH**(CO)CH$_2$]. Several new signals appear in the spectra because of the graft structure at 3.34 ppm (PHEA: **CH$_2$**CH$_2$OCO), 4.05 ppm (PHEA: CH$_2$**CH$_2$**OCO), and 4.19 ppm (terminal glycolide unit: **CH$_2$**OH). From these ^{1}H NMR spectra, we can further confirm that the grafting is successful.

From the ^{1}H NMR spectra, we can calculate the molar ratio of HEA unit to glycolide unit in the graft polymers by comparing the integration values of the 2.63 ppm (PHEA: CH**CH$_2$**CONH) peak with the 4.76–4.81 ppm (PGA: C**H$_2$**) and 4.19 ppm (terminal glycolide unit: **CH$_2$**OH) peaks. In addition, the percentage of the unreacted –OH groups that remained in PHEA backbones after the grafting can also be calculated through comparing the integration values of the 3.34 ppm (**CH$_2$**CH$_2$OCO) peak with the 2.63 ppm (CH**CH$_2$**CONH) peak in the PHEA backbone. Furthermore, we can estimate the chain length of the branches in the graft polymers through comparing the integration values of the 4.76–4.81 ppm (PGA: C**H$_2$**) and 4.19 ppm (terminal glycolide unit: **CH$_2$**OH) peaks with the 3.34 ppm (**CH$_2$**CH$_2$OCO) peak of the reacted –OH groups in PHEA backbones. The results are listed in Table 1. In our study,

Table 1 Synthesis and properties of PHEA and PHEA-*g*-PGA copolymers

Polymer	–OH/glycolide feed ratio (mol/mol)	Yield (%)	^{1}H NMR			SEC–MALLS			DSC	
			HEA/glycolide unit in polymer (mol/mol)	Unreacted –OH groups (%)	Glycolide unit number in each branch	M_w (g/mol)	M_w/M_n	R_g (nm)	T_m (°C)	ΔH_m (J/g)
PHEA	–	–	–	100	–	41,600	1.27	18.1	–	–
PHEA-2	100:0	97	100:0	100	–	6,680	1.10	–	–	–
PHEA-*g*-PGA-1	50:50	65	52:48	31	1.3	196,500	1.61	39.2	–	–
PHEA-*g*-PGA-2	20:80	71	38:62	25	2.2	24,100	1.43	29.0	132.6	24.9
PHEA-*g*-PGA-3	10:90	87	–	–	–	–	–	–	161.0	76.0
PHEA-*g*-PGA-4	5:95	91	–	–	–	–	–	–	171.7	95.3

In ^{1}H NMR characterization, D_2O was used as a solvent for PHEA-*g*-PGA-1, and DMSO-d_6 was used as a solvent for PHEA-*g*-PGA-2. The data for PHEA-*g*-PGA-3 and PHEA-*g*-PGA-4 are not available because the samples cannot be dissolved in common solvents

In SEC–MALLS analysis, 6‰ NaCl water solution was used as an eluent for PHEA, PHEA-2, and PHEA-*g*-PGA-1, and DMF was used as an eluent for PHEA-*g*-PGA-2. The data for PHEA-*g*-PGA-3 and PHEA-*g*-PGA-4 are not available because the samples cannot be dissolved in common solvents

In DSC characterization, the T_m and ΔH_m values for PHEA, PHEA-2, and PHEA-*g*-PGA-1 are not available because the samples are amorphous

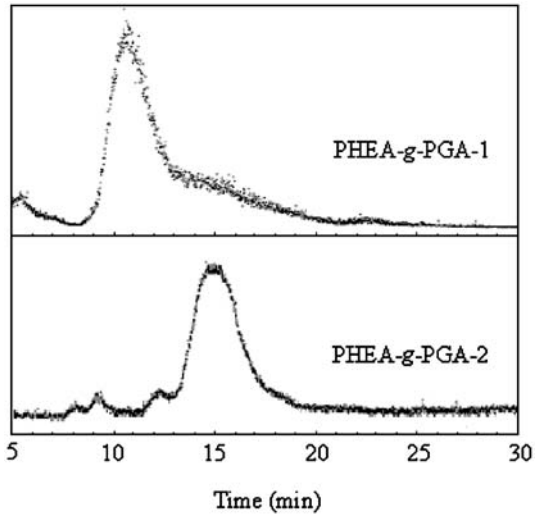

Fig. 3 SEC–MALLS chromatograms of PHEA-*g*-PGA-1 and PHEA-*g*-PGA-2. The eluent for PHEA-*g*-PGA-1 was 6‰ NaCl water solution, and the eluent for PHEA-*g*-PGA-2 was DMF

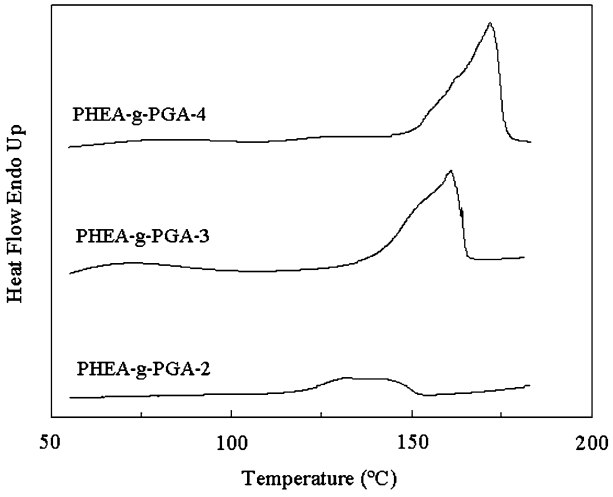

Fig. 4 DSC thermograms (second scan) of PHEA-*g*-PGA copolymers

PHEA-*g*-PGA-1 has a very short branch length, which can be regarded as a hydrophobically modified PHEA. With a decrease in the –OH/glycolide feed ratio, the length of the branches in the resultant copolymers increases and the percentage of the unreacted –OH groups in PHEA backbones decreases. This implies that the brushlike structure of PHEA-*g*-PGA can be adjusted by controlling the feed ratio of the macroinitiator PHEA to the monomer glycolide.

To accurately determine the molecular weights of graft polymers, we combined the SEC with a MALLS to characterize the graft polymers. As shown in Table 1, the molecular weight M_w of PHEA-2 is much lower than that of PHEA, indicating that the degradation occurs during the heating. Generally, the backbone degradation does not affect the composition of the resultant copolymer. However, the degradation of backbone ultimately leads to a lower M_w of the resulting graft polymer. Nevertheless, the M_w of the graft polymers are still reasonably high, confirming that the graft polymerization is successful and –OH groups in PHEA are effective propagation centers. As shown in Fig. 3, SEC–MALLS chromatograms show that PHEA-*g*-PGA-1 and PHEA-*g*-PGA-2 have unimodal molecular weight distributions. In a dilute solution, the root-mean-square radius of gyration (R_g) of a polymer is dependent on the molecular architecture and the average molecular weight. From SEC–MALLS (Table 1), it can be found that both M_w and R_g of PHEA-*g*-PGA-1 are much higher compared with PHEA-*g*-PGA-2. This is due to the micellization of the amphiphilic PHEA-*g*-PGA-1 in the aqueous solution. However, it should be noted that a common solvent for our samples is not available because of the different hydrophilicities of different samples; as a result, the M_w and R_g values of PHEA-*g*-PGA-1 and PHEA-*g*-PGA-2 are not very comparable because the samples were measured in different solvents (aqueous solution and DMF). The molecular weights of PHEA-*g*-PGA-3 and PHEA-*g*-PGA-4 are unavailable because of the insufficient solubilities of PHEA-*g*-PGA-3 and PHEA-*g*-PGA-4 in common solvents which cause difficulties in measurements.

Figure 4 shows the DSC thermograms of graft copolymers with different compositions. The T_m and ΔH_m values obtained from DSC characterization are listed in Table 1. As the length of PGA branches decreases, the melting transition shifts to a lower temperature. Also, the enthalpy change of fusion decreases with increasing PHEA content, implying that the crystallization is retarded due to the presence of PHEA backbones.

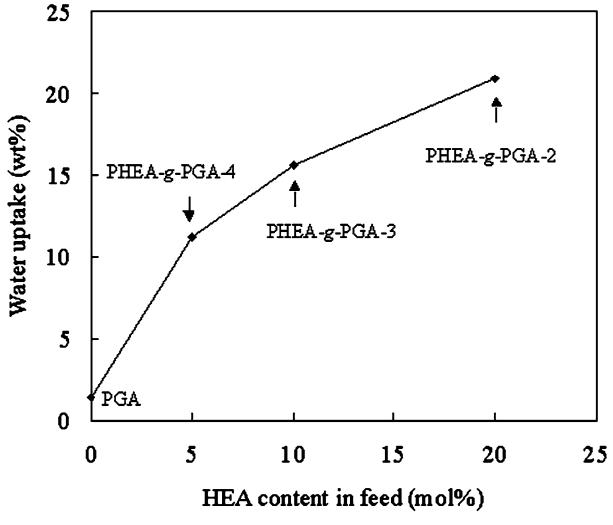

Fig. 5 Dependence of the water uptake of polymers on the HEA content in feed

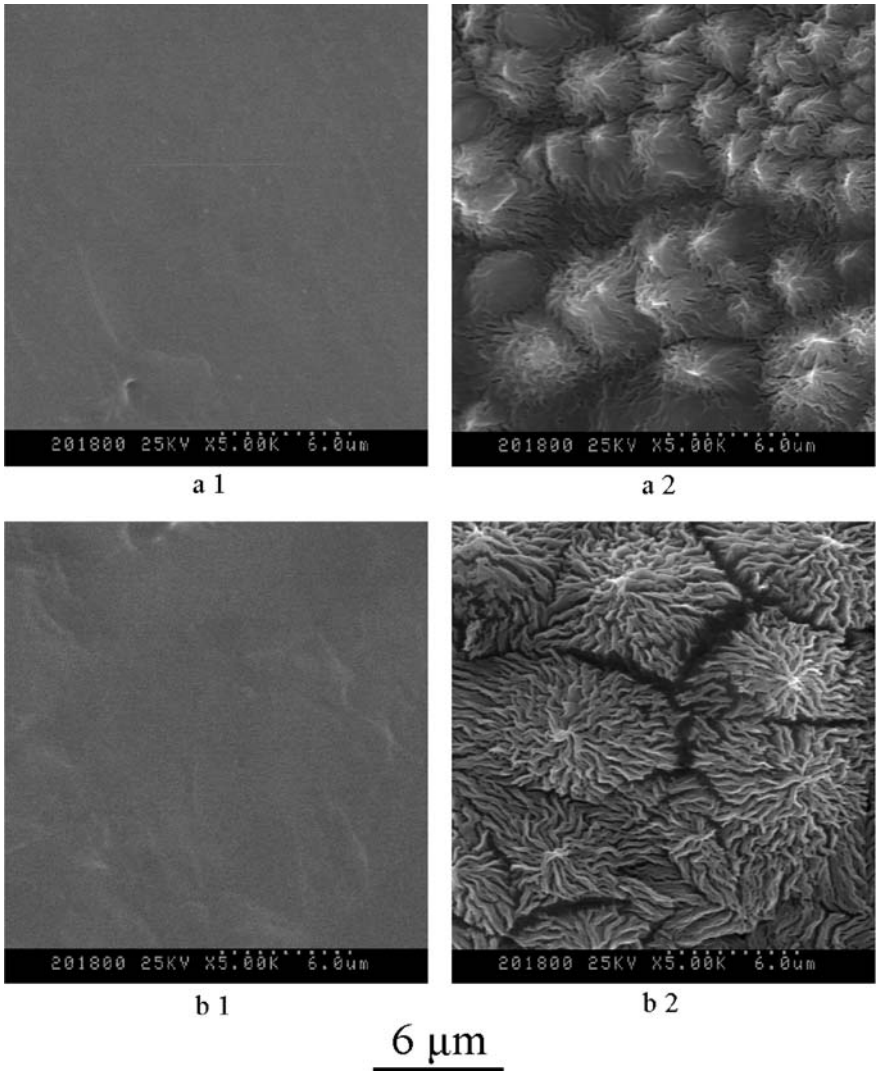

Fig. 6 SEM images of the surfaces of **a1** PHEA-*g*-PGA-3 before degradation, **a2** PHEA-*g*-PGA-3 after degradation for 14 days, **b1** PHEA-*g*-PGA-4 before degradation, and **b2** PHEA-*g*-PGA-4 after degradation for 14 days

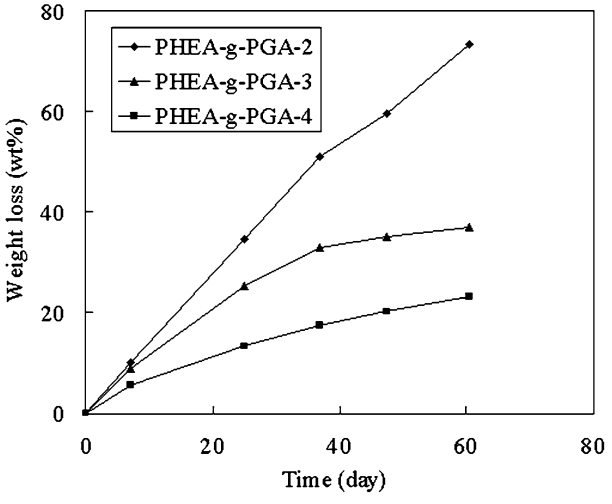

Fig. 7 Weight loss of PHEA-*g*-PGA copolymers during hydrolytic degradation

The water uptake of graft polymers is shown in Fig. 5. Clearly, the water uptake increases with increasing HEA content in feed, which indicates that the amphiphilicity of these polymers can be adjusted.

In our investigation, we studied the hydrolytic degradation for the graft copolymers that are insoluble in water. The surface morphologies of copolymers were observed by SEM. As can be seen in Fig. 6, before degradation, the samples have smooth surfaces. After the hydrolytic degradation for 14 days, the spherulitic structures are

Table 2 Drug loading content, entrapment efficiency, and particle yield of nanoparticle drug delivery systems

Nanoparticle drug delivery system	Loading content (%)	Entrapment efficiency (%)	Particle yield (%)
PHEA-*g*-PGA-1	1.3	12.9	87.6
PHEA-*g*-PGA-2	2.4	15.8	70.5

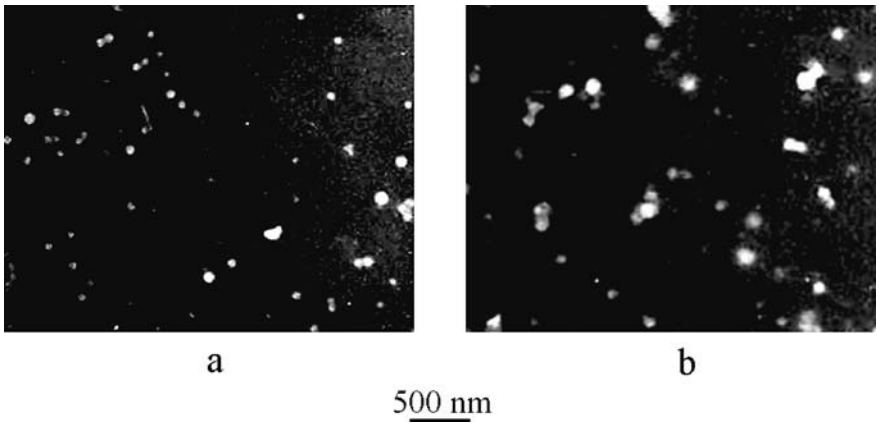

Fig. 8 TEM images of **a** PHEA-*g*-PGA-1 and **b** PHEA-*g*-PGA-2 nanoparticle drug delivery systems

noticed for both PHEA-*g*-PGA-3 and PHEA-*g*-PGA-4 due to predominant hydrolysis and removal of amorphous regions between the crystalline regions. The weight loss values in Fig. 7 are in agreement with the SEM observation. Obviously, PHEA-*g*-PGA-2 has the fastest degradation rate among these three copolymers. This is due to the high content of hydrophilic PHEA main chain in PHEA-*g*-PGA-2, which could facilitate the water absorption and diffusion and the cleavage of ester bond thereof. With an increase in the hydrophobic branch content, the degradation rate becomes slow. Thus, PHEA-*g*-PGA-4 has the slowest degradation rate.

Drug release behavior of amphiphilic graft copolymers

The choice of the nanoparticle preparation method usually depends on the solubility of a polymer in an aqueous medium [21]. In our study, among the graft copolymers we prepared, PHEA-*g*-PGA-1 is the most hydrophilic one, and PHEA-*g*-PGA-2 has a lower hydrophilicity than PHEA-*g*-PGA-1. Therefore, the nanoparticle drug delivery system of PHEA-*g*-PGA-1 was prepared by the direct dissolution method, and the nanoparticle drug delivery system of PHEA-*g*-PGA-2 was prepared by the dialysis method.

The drug loading content and entrapment efficiency of the two kinds of nanoparticles we prepared are summarized in Table 2. Drug loading content and entrapment efficiency are strongly affected by the composition of the copolymers. For the two amphiphilic copolymers we studied, PHEA-*g*-PGA-2 is more hydrophobic compared with PHEA-*g*-PGA-1. In addition, the drug encapsulated, prednisone acetate, is hydrophobic. Thus, both drug loading content and entrapment efficiency of PHEA-*g*-PGA-2 are higher than that of PHEA-*g*-PGA-1.

Morphology of nanoparticle drug delivery systems was observed by TEM, and the images demonstrate that PHEA-*g*-PGA-1 and PHEA-*g*-PGA-2 nanoparticles are regularly spherical in shape (Fig. 8). The PHEA-*g*-PGA-1 nanoparticles are smaller than the PHEA-*g*-PGA-2 nanoparticles. The difference in size is caused by the property of copolymers as well as the preparation method. The particle size and distribution of the nanoparticle drug delivery systems were measured using a Zetasizer. As shown in Table 3, these results are in agreement with the TEM observation.

In our study on the in vitro drug release property of copolymers, the release profile was determined from UV absorbance of prednisone acetate at 242 nm. From Fig. 9, it can be found that the release rate of PHEA-*g*-PGA-1 system is faster than that of PHEA-*g*-PGA-2 system. The

Table 3 Particle size and distribution of nanoparticle drug delivery systems

Nanoparticle drug delivery system	Mean diameter (nm)	Polydispersity index (PI)
PHEA-*g*-PGA-1	49	0.31
PHEA-*g*-PGA-2	113	0.53

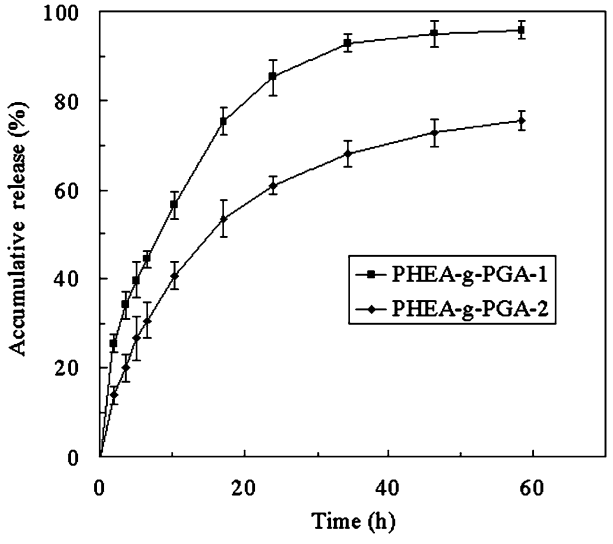

Fig. 9 In vitro release of prednisone acetate from PHEA-*g*-PGA-1 and PHEA-*g*-PGA-2 nanoparticle drug delivery systems

release rate depends on many factors, such as the property of polymer matrix, the property of the drug entrapped, and the size and structure of the delivery system. Generally, the drug release rate is relatively faster for the delivery system with a smaller size because of the higher surface area. In our study, the PHEA-*g*-PGA-1 system has a smaller size, as well as a polymer matrix with a faster degradation rate and a higher hydrophilicity. Thus, it has a faster release rate.

Conclusions

Amphiphilic graft copolymers were synthesized by grafting hydrophobic PGA branches to the hydrophilic PHEA backbone. Structure characterizations confirm the brushlike structure of the graft polymers. By controlling the feed ratio of the macroinitiator to the monomer, the graft copolymers with different branch lengths, degradation rates, and amphiphilicities can be obtained. Nanoparticle drug delivery systems were successfully prepared by the direct dissolution method and the dialysis method. The study on in vitro drug release shows that the release of the drug can be effectively sustained by entrapping into the nanoparticles.

Acknowledgements This research was supported by grants from the National Natural Science Foundation of China (20204010 and 20474046). One of the authors, Si-Xue Cheng, is grateful to the Ministry of Education of China for the financial support of "Trans-Century Training Programme Foundation for the Talents." Special thanks are due to Ms. Qing-Rong Wang for the SEC–MALLS measurement.

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