

Synthesis, characterization and hydrolytic degradation study of polyetheresteramide copolymers based on ϵ -caprolactone, 6-aminocaproic acid, and poly(ethylene glycol)

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Abstract In this paper, a new kind of biodegradable aliphatic polyetheresteramide copolymers (PEEA) based on ϵ -caprolactone, 6-aminocaproic acid, and poly(ethylene glycol) (PEG) were synthesized by melt polymerization method. The obtained copolymers were characterized by $^1\text{H-NMR}$. The thermal properties of PEEA copolymers were studied by DSC and TGA/DTA under nitrogen atmosphere. The water absorption and hydrolytic degradation behavior was also studied in detail. With the increase in PEG content or the decrease in caprolactone content, the water absorption of the copolymers increased accordingly. For the hydrolytic degradation behavior, with the increase in PEG content or caprolactone content, the degradation rate increased then.

Introduction

For the aliphatic polyesteramide copolymers, due to its combined properties of good degradability of polyesters and great mechanical properties of polyamides together, they were studied more extensively in the recent years [1–9].

Several kinds of polyesteramide copolymers have been studied in our laboratory [7–9]. Because of the poor solubility and lower degradation rate of polyesteramide copolymers, its application in drug delivery system was strongly restricted. So, the hydrophilic poly(ethylene glycol) was introduced into the macromolecular main chain, as a result, the solubility and the degradability increased to some extent. In this work, the polyetheresteramide copolymer was prepared from ϵ -caprolactone, 6-aminocaproic acid, and poly(ethylene glycol) successfully, and properties of the obtained copolymers were studied in detail.

Materials and methods

Materials

All the materials used in this work were analytical reagent grade, and used as received without further purification.

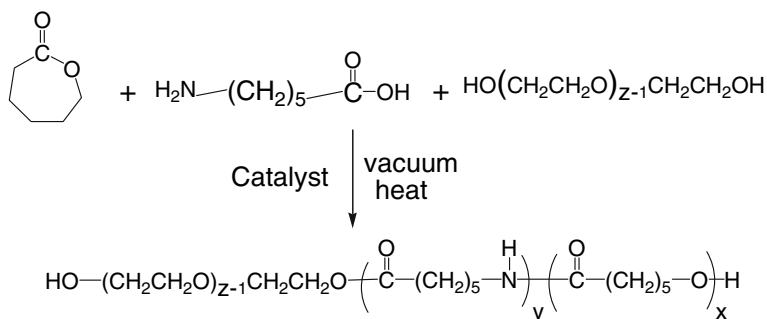
Synthesis of PEEA copolymers

PEEA copolymers were synthesized from ϵ -caprolactone (CL), 6-aminocaproic acid (AC), and PEG1540 ($M_n = 1540$) by melt polycondensation method according to Scheme 1. The typical PEEA5 copolymer was prepared as follows: 14.4 g (0.126 mol) of ϵ -caprolactone (CL), 22.8 g (0.174 mol) of 6-aminocaproic acid (AC), 1.9 g of PEG1540 (0.001 mol), 0.2 g of Irganox1010, and 0.36 g of tetrabutyl titanate were added into reaction vessel under nitrogen atmosphere. The mixture was kept at 110 °C for 1 h. Later, the temperature was gradually elevated to 160 °C over 30 min. Then, the mixture was rapidly heated to 240 °C under vacuum for another 1 h. At the end, the resultant melt was poured out into a steel plate, thus

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Scheme 1 The synthesis scheme of polyetheresteramide (PEEA) copolymers by melt polycondensation method



PEEA5 copolymer was obtained. The copolymer chips were prepared by pouring the hot melt into a steel mold (100 × 100 × 1 mm). The samples for water absorption, and hydrolytic degradation were cut from the chips and kept in desiccator before use. The other copolymers were synthesized by the same method as for PEEA5 except the mass of PEG1540 different. All the PEEA copolymers synthesized in this paper were listed in Table 1.

Purification of PEEA copolymers

The PEEA copolymers were first dissolved in AR grade trichloromethane, and reprecipitated from the filtrate using AR grade *n*-hexane. Then this mixture was filtered and vacuum dried to constant weight. The purified materials were kept in desiccators before use.

Intrinsic viscosity measurement

Intrinsic viscosity $[\eta]$ was measured by using an Ubbelohde viscometer at 30 ± 0.1 °C. All the copolymers were dissolved in *m*-cresol to prepare solutions at a concentration of ca. 0.5 g/dL. $[\eta]$ was calculated using Eq. 1:

$$[\eta] = \frac{\sqrt{2\left(\frac{t}{t_0} - 1 - \ln \frac{t}{t_0}\right)}}{C} \quad (1)$$

where C is concentration of solution, t is flow time of solution; t_0 is flow time of pure solvent.

Fourier transform infrared spectroscopy (FTIR)

FTIR (KBr) spectra of copolymers were taken in NICOLET-560 (Nicolet co. USA) Infrared Spectrophotometer.

¹H-nuclear magnetic resonance (¹H-NMR)

¹H-NMR spectra (in CDCl₃) were recorded on Varian 400 spectrometer (Varian, USA) at 400 MHz using tetramethylsilane (TMS) as internal reference standard.

Differential scanning calorimetry (DSC)

Nonisothermal crystallization behavior of these copolymers was characterized on differential scanning calorimeter (NETSCZ 200, Germany). The purified samples were used for DSC test. The specimen were first heated from 25 °C to 240 °C under nitrogen atmosphere at a heating rate of 10 °C/min, and reheated to 240 °C at the same rate after quenched to 25 °C, at last the specimen was cooled to 25 °C again at the rate of 10 °C /min.

Table 1 Chemical composition and inherent viscosity of the samples used in this paper

PEEA	PEG (%W _t)		ε-CL (%W _t)		ε-CL/AC/PEG1540 (%mol)		$[\eta]^b$ (dl/g)
	Feed	Exp ^a	Feed	Exp ^a	Feed	Exp ^a	
PEA1	0	– ^c	27.2	–	30/70/0	–	0.56
PEA2	0	0	38.7	45.0	42/58/0	44.8/55.2/0	0.74
PEA3	0	–	50.6	–	54/46/0	–	0.58
PEEA4	2.6	–	37.7	–	41.9/57.9/0.2	–	0.51
PEEA5	4.9	23.4	36.8	33.8	41.8/57.8/0.4	43.0/54.8/2.2	0.47

^a Determined by ¹H-NMR

^b Measured at 30 °C in *m*-cresol at a concentration of ca.0.5 g/dl

^c Not determined

Thermal gravimetric analysis of PEEA copolymers

Thermogravimetric measurements (TGA/DTA) were characterized on thermogravimetric analyzer (TA 2910, DuPont, USA) under a steady flow of nitrogen atmosphere at a heating rate of 10 °C/min in the range of room temperature to 600 °C.

Water absorption behavior of PEEA copolymers

Water absorption experiment was carried out as following: the copolymer chips were immersed in distilled water at 37 °C for different period, and then were taken out and the surplus surface water were removed by filter paper. The value was calculated according to Eq. 2:

$$\text{Water absorption}\% = \frac{W_{\text{ht}} - W_{\text{d}}}{W_{\text{d}}} \times 100 \quad (2)$$

where W_{d} is the initial weight of dry sample, and W_{ht} is the weight of humid sample at time t .

Hydrolytic degradation behavior

In vitro degradation tests were carried out as following: the chips (with a thickness of ca. 1 mm, 100–300 mg) were placed in 10 mL of PBS saline with pH = 4.02, 6.84, and 9.10, respectively at 37 °C. The PBS saline was refreshed every 2 weeks. The samples were removed from the bottles at predetermined time, rinsed thoroughly with distilled water and dried in vacuum at 40 °C for 12 h. Degree of degradation was calculated by the weight loss:

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

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

Results and discussion

Synthesis of PEEA copolymers

FTIR and $^1\text{H-NMR}$ were used to characterize the chemical structure of PEEA copolymers. Because the weight fraction of PEG is lower than 10 wt%, the peak due to PEG couldn't be observed in FTIR spectra (data not shown). $^1\text{H-NMR}$ spectra of PEA2 and PEEA5 copolymers were shown in Fig. 1. The characteristic absorption peaks were also indicated in this figure. With the increase in PEG content, the integral area of the peak at ca. 3.7 ppm ($-\text{CH}_2\text{CH}_2\text{O}-$ of PEG main chain) increased accordingly.

The chemical compositions were determined by $^1\text{H-NMR}$ spectra according to Eqs. 4–6.

$$X_{\text{PCL}} = \frac{I_{\text{e}}}{I_{\text{e}} + I_{\text{j}} + I_{\text{m}}} \quad (4)$$

$$X_{\text{PAC}} = \frac{I_{\text{j}}}{I_{\text{e}} + I_{\text{j}} + I_{\text{m}}} \quad (5)$$

$$X_{\text{PEG}} = \frac{I_{\text{m}}}{I_{\text{e}} + I_{\text{j}} + I_{\text{m}}} \quad (6)$$

where I_{e} , I_{j} , and I_{m} is the integral intensities of methylene hydrogen of PCL blocks at ca. 4.05 ppm, methylene hydrogen of PAC blocks at ca. 3.2 ppm, and methylene hydrogen of PEG blocks at ca. 4.2 ppm respectively shown in Fig. 1.

The chemical compositions of PEEA copolymers were listed in Table 1.

Thermal property of PEEA copolymers

The information on thermal property of PEEA copolymers was obtained from DSC analysis. The results were summarized in Table 2 and Fig. 2. Figure 2 is the 2nd heating run of PEEA copolymers. With the increase in ϵ -CL content, the melting temperature and heat of fusion decreased accordingly. The insertion of ϵ -CL units into poly(6-aminocaproic acid) lattices reduces the density of amide groups, thus diminishing the number of hydrogen bonds and lowering the melting temperature. When PEG was incorporated into the polyesteramide main chain, the thermal properties of PEEA copolymers changed accordingly. And with the increase in PEG content, the melting peaks became wider, and the melting temperature decreased, which might be due to the increase in flexibility of macromolecule main chain when small amounts of PEG are incorporated. This phenomenon is similar to thermal property of poly(ethylene terephthalate)(PET)/PEG copolymers [10, 11] and the polyetheresteramide copolymers (PEEA) based on ϵ -caprolactone, 11-aminoundecanoic acid, and poly(ethylene glycol) [7, 12].

Thermogravimetric analysis

The thermal degradation behavior of PEEA was studied by TGA/DTG under nitrogen atmosphere, and the data were shown in Table 3 and Fig. 3. With the increase in ϵ -CL content, the thermal decomposition temperature $T_{\text{d},5\%}$ and $T_{\text{d},50\%}$ decreased accordingly. But the thermal decomposition temperature $T_{\text{d,onset}}$ and $T_{\text{d,max}}$ did not show a clear relationship with ϵ -Caprolactone (ϵ -CL) units content. With the decrease in PEG content, the decomposition

Fig. 1 $^1\text{H-NMR}$ spectrum of PEA2 and PEEA5 copolymers

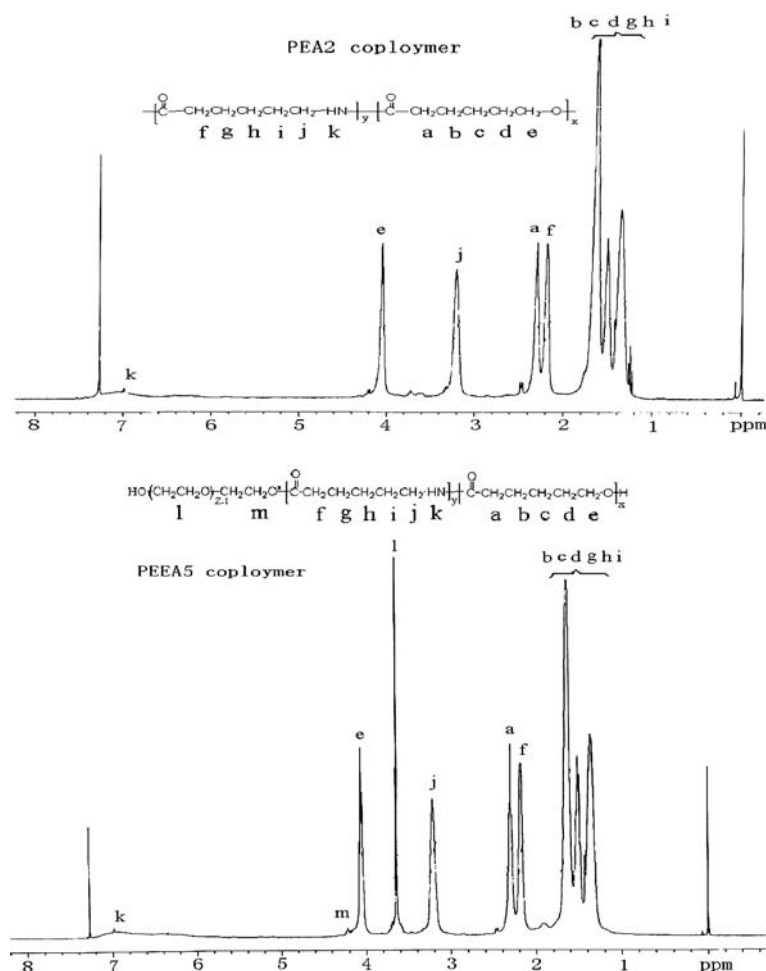


Table 2 Thermal properties of PEEA copolymers^a

Sample	T_m (°C)	ΔH_m (J/g)
PEA1	145.4	21.31
PEA2	105.9	27.31
PEA3	65.1	36.92
PEEA4	105.3	26.34
PEEA5	109.4	21.89

^a Obtained from the 2nd heating run of PEEA copolymers

temperature including $T_{d,5\%}$, $T_{d,95\%}$, increased accordingly, but $T_{d,max}$ decreased to some extent., which might be due to the increase in macromolecular weight and the increase in crystallinity.

Water absorption

For these hydrophilic PEEA copolymers, its water absorption was mainly determined by the CL/AC molar ratio and PEG content, and the results were shown in Fig. 4.

Fig. 2 DSC curves of PEEA copolymers under nitrogen atmosphere

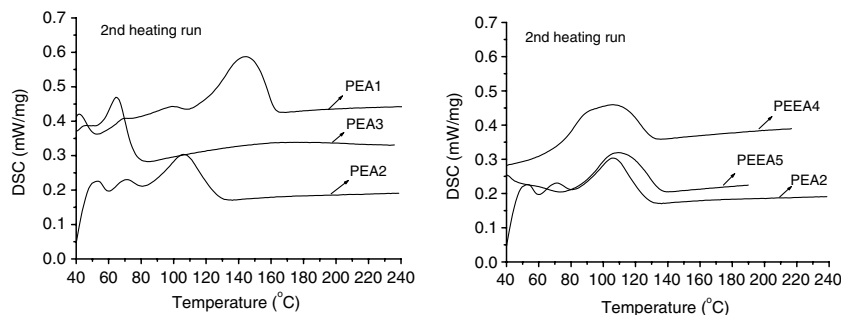


Table 3 TGA/DTA data of PEEA copolymers at a heating rate of 10 °C /min in nitrogen

Sample	$T_{d,5\%}^a$ (°C)	$T_{d,50\%}^b$ (°C)	$T_{d,95\%}^c$ (°C)	$T_{d,onset}^d$ (°C)	$T_{d,max}^e$ (°C)
PEA1	313.39	399.00	482.04	369.10	394.84
PEA2	320.09	395.00	449.91	370.36	395.77
PEA3	291.96	393.73	456.95	370.22	394.75
PEEA4	285.27	394.82	439.20	371.62	402.49
PEEA5	267.86	395.23	435.18	369.52	401.46

- ^a Temperature at which weight loss of 5%
- ^b Temperature at which weight loss of 50%
- ^c Temperature at which weight loss of 95%
- ^d Temperature at which the decomposition started
- ^e Temperature of the largest decomposition rate during the stage

Effect of the molar ratio of CL/AC

Figure 4a showed that water absorption increased with incubation time. About 25 h later, it reached the equilibrium value. For these three kinds of PEA copolymers, with

the increase in ϵ -CL content, water absorption decreased accordingly, which might be due to the increase in crystallinity and the decrease in hydrophilicity of copolymers. But for these PEA1, PEA2, and PEA3 copolymers, there is no great difference between the equilibrium water absorption in distilled water at 37 °C.

Effect of the content of PEG1540

When the PEG macromonomer was incorporated into the polyesteramide main chain, the hydrophilicity increased then. For these PEEA copolymers, water absorption increased with PEG content, which were shown in Fig. 4b. This increase in water absorption with PEG might be due to the decrease in crystallinity of the overall copolymers.

Hydrolytic degradation

The PEEA samples with the thickness of about 1 mm were incubated in PBS with pH = 4.02, 6.84, and 9.10 respectively at 37 °C. The degradation results were shown in

Fig. 3 TGA/DTG curves of PEEA copolymers in nitrogen atmosphere

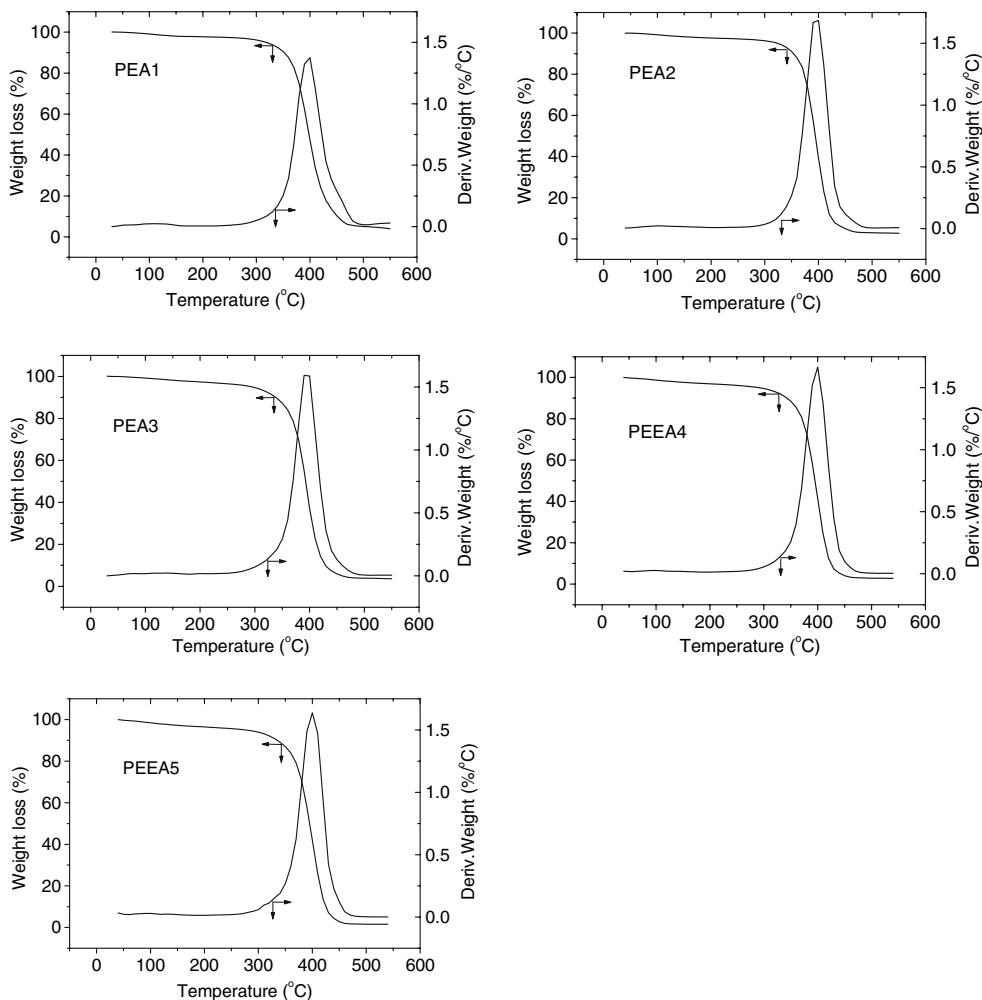


Fig. 4 Water absorption behavior of PEEA copolymers in distilled water at 37 °C

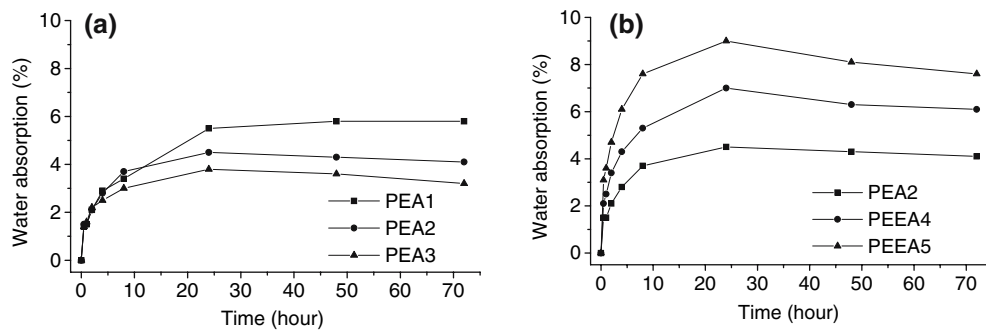


Fig. 5 Effect of CL content on degradation behavior in PBS (pH = 4.02, 6.84, and 9.10, respectively) at 37 °C

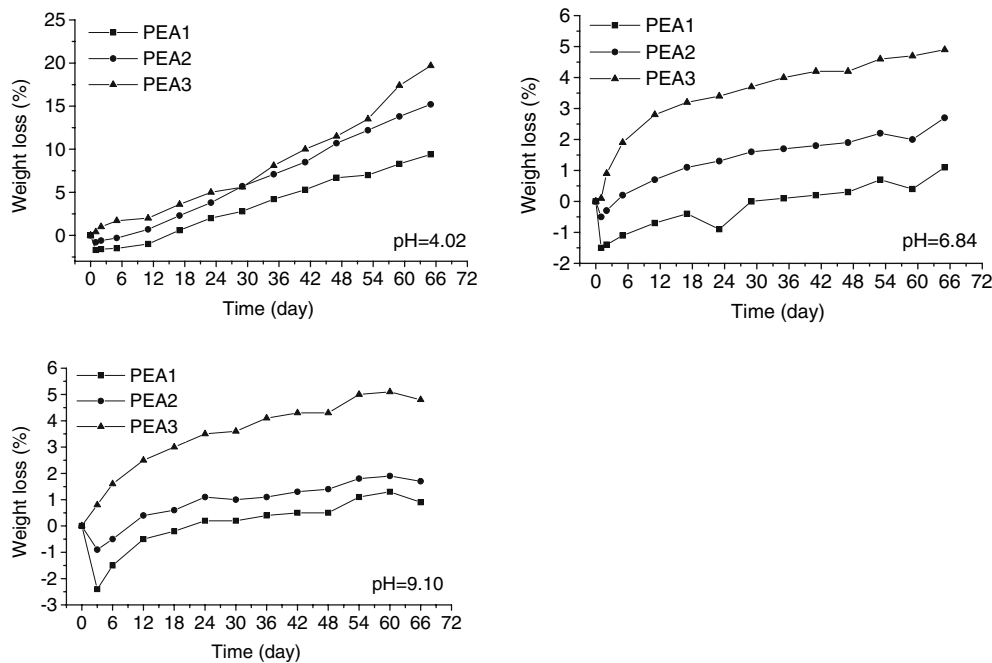


Fig. 6 Effect of PEG content on degradation behavior in PBS (pH = 4.02, 6.84, and 9.10, respectively) at 37 °C

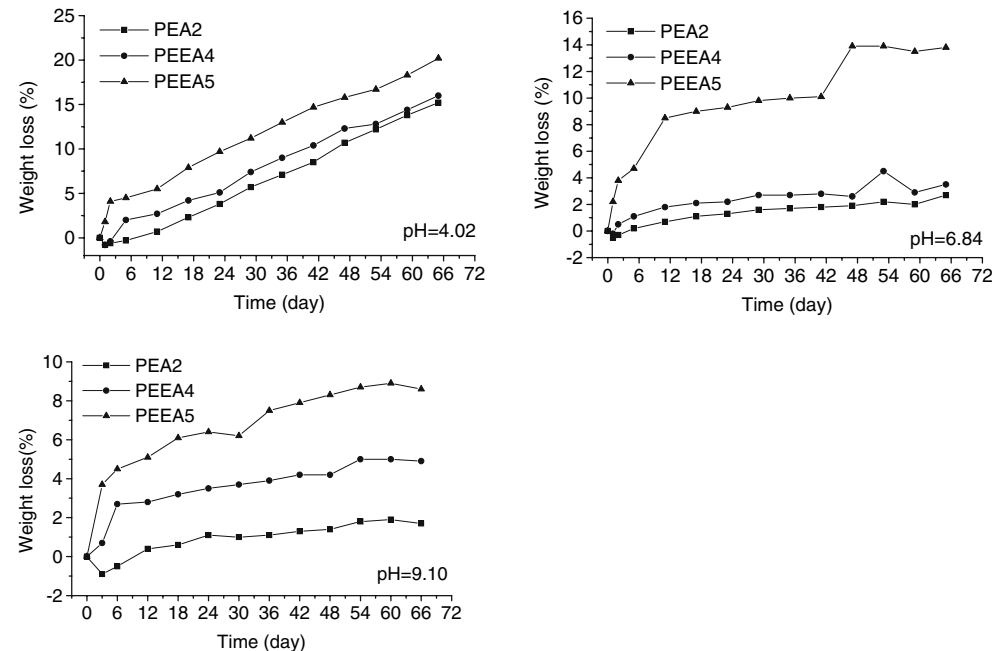
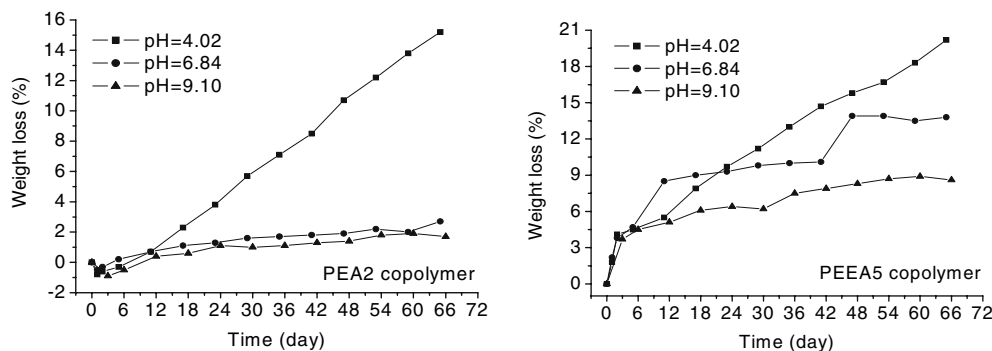


Fig. 7 Effect of pH value on degradation behavior of PEA2 and PEEA5 at 37 °C, respectively



Figs. 5–7. According to Seppälä's opinion [13], the hydrolytic degradation behavior of semicrystalline polymers was determined on chemical composition (the molar ratio of CL/AC), degree of crystallinity, hydrophilicity (the content of PEG1540), and pH value of degradation medium.

Effect of the molar ratio of CL/AC

With the increase in ϵ -CL content, there is an increase in degradation rate. The lowest degradation rate of PEA1 copolymer might be due to the highest amide content, number of hydrogen bonds, and overall crystallinity, which is very similar to the PEEA studied in our laboratory before [7, 12].

Effect of the content of PEG

According to the water absorption study in this paper, we know that when PEG was incorporated into the polyesteramide main chains, the hydrophilicity increased then. As was shown in Fig. 6, with the increase in PEG content, the hydrolytic degradation rate increased steadily. This hydrolytic degradation behavior of PEEA copolymers is similar to PET/PEG copolymers [10] and the polyetheresteramide copolymer studied before [12].

Effect of the pH value of the degradation medium

PEEA copolymer chips were incubated in degradation media at different pH at 37 °C. According to Fig. 7, the degradation rate decreased with increase in pH of the medium from 4.02 to 9.10, which is due to an acid catalysis process.

Conclusion

In this paper, amphiphilic PEEA were synthesized by the melt polycondensation method. The thermal crystallization behavior and thermal degradation behavior of the PEEA copolymers were studied in detail. The water absorption and hydrolytic degradation behavior were also studied. When the hydrophilic PEG was incorporated into the polyesteramide main chain, the hydrophilicity and the hydrolytic degradation rate enhanced then.

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