Biodegradable Poly(vinyl alcohol)-*graft*-poly(ε-caprolactone) Comb-like Polyester: Microwave Synthesis and Its Characterization

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ABSTRACT: Poly(vinyl alcohol)-initiated microwave-assisted ring opening polymerization of ε-caprolactone in bulk was investigated, and a series of poly(vinyl alcohol)-*graft*-poly(ε-caprolactone) (PVA-*g*-PCL) copolymers were prepared, with the degree of polymerization (DP) of PCL side chains and the degree of substitution (DS) of PVA by PCL being in the range of 3–24 and 0.35–0.89, respectively. The resultant comb-like PVA-*g*-PCL copolymers were confirmed by means of FTIR, ^{1}H NMR, and viscometry measurement. The introduction of hydrophilic backbone resulted in the decrease in both melting point and crystallization property of the PVA-*g*-PCL copolymers comparing with linear PCL. With higher microwave power, the DP of PCL side chains and DS of PVA backbone were higher, and the polymerization reaction proceeded more rapidly. Both the DP and monomer conversion increased with irradiation time, while the DS increased first and then remained constant. With initiator in low concentration, the DP and DS were higher, while the monomer was converted more slowly. Microwaves dramatically improved the polymerization reaction in comparison of conventional heating method. J Appl Polym Sci 104, 3973–3979, 2007

Key words: ring opening polymerization; ε-caprolactone; poly(vinyl alcohol); poly(vinyl alcohol)-*graft*-poly(ε-caprolactone); microwave synthesis

INTRODUCTION

Aliphatic polyesters are one of the most widely utilized classes of biodegradable polymers in medicine. Recently, parenteral depot system (PDS) on the basis of biodegradable polyesters is the subject of intensive research efforts, especially for the prolonged delivery of peptides and proteins.[1] However, in many cases drug release of peptides and proteins from linear polyesters is not satisfactorily controlled, leading the undesired discontinuous or polyphasic release patterns.[2,3]

To overcome these discontinuous drug release profiles, two major modifications of the polyesters have been investigated: (1) increasing the hydrophilicity of the polyesters will result in a faster water uptake and swelling of the polymer matrix, causing a faster and more prolonged drug release[4–6]; (2) accelerating the degradation rate of linear polyesters by branching will generate many short polyester chains, reaching more rapidly the threshold of water solubility, thus promoting the polymer erosion.[7–11] An example for the first concept is linear ABA or AB block copolymers consisting of polyester A blocks and hydrophilic poly(ethylene oxide) (PEO) B block. Although the *in vitro* release profiles of proteins were found to approach constant release rates, some proteins are sensitive to PEO-induced aggregation[12]; therefore, hydrophilic backbone compatible with sensitive proteins are of particular interest for PDS. Poly (ε-caprolactone) (PCL) is a commercially attractive, degradable polyester currently used in biomedical fields.[13] Poly(vinyl alcohol) (PVA) is a well-known water-soluble polymer and biodegradable.[14] In contrast to PVA, PCL is hydrophobic and degrades very slowly. In general, graft copolymer architecture is a versatile method for providing functionality to the polymers and regulating polymer properties. A combination of PVA and PCL is therefore attractive in terms of the control of biodegradability and properties.

As an alternative method to classical thermal heating, microwave irradiation can provide an effective, selective, and fast synthetic method by heating the molecules directly through the interaction between the microwave energy and molecular dipole moments of the starting materials. It was reported that ε-caprolactone (ε-CL) could be polymerized

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by means of microwave activation.[15–19] Although the above-mentioned work satisfactorily provides PCL under microwave irradiation, metal catalysts were still necessary. The one used most is stannous octoate, which, however, as many other metal catalysts, is more or less toxic and cytotoxic. In our previous work,[20–24] we developed a metal-free method for preparing PCL by microwave-assisted ring opening polymerization (MROP) of ε-CL. A series of PCL with different molecular structure involving linear PCL and PCL-PEO-PCL triblock copolymers were synthesized under microwave irradiation, without any solvent and metal catalysts, using nontoxic acids and alcohols as initiators. The polymerization reaction was significantly enhanced by microwave energy in comparison with that activated by conventional heating.

In this paper, a new method for preparing comb-like biodegradable poly(vinyl alcohol)-*graft*- poly(ε-caprolactone) (PVA-*g*-PCL) copolymers is first reported. This method involves MROP of ε-CL in bulk, using PVA as an initiator. Aoi[25] reported the synthesis of PVA-*g*-PCL by solution polymerization of ε-CL in the presence of tin(II) 2-ethylhexanoate in dimethyl sulfoxide. However, metal catalyst and organic solvent were involved. With the present metal-free method, biocompatibility *in vivo* of the resultant PVA-*g*-PCL copolymers should be improved, which makes them promising candidates for encapsulation of drugs such as proteins and peptides.

EXPERIMENTAL PROCEDURES

Materials

Commercial ε-CL (99%, Aldrich, USA) was purified by vacuum distillation over CaH_2. PVA (analytical-reagent-grade) with the degree of polymerization (DP) 124 and 1750 are designated as PVA 124 and PVA 1750, respectively. The degree of hydrolysis of PVA 124 and PVA 1750 are both 98%. PVA was dried *in vacuo* to constant weight before use. All other reagents are analytical grade and used as received.

Microwave equipment

A 2.45 GHz multimode microwave oven (Whirlpool-VIP275) with a maximum output power of 850 W was applied in this study. And the output power could be performed at 10 levels by a power on–off cycles. The temperature of materials was measured by a tin-grounded thermocouple.

Polymerization

PVA-initiated MROP of ε-CL in bulk was carried out as follows: a mixture of ε-CL with certain amount of PVA in a vacuum-sealed ampoule was irradiated at pointed microwave power for predetermined period of time and its temperature was traced and recorded. After the ampoule was quenched in an ice-water bath, the crude product was dissolved in tetrahydrofuran and precipitated by cold methanol. The precipitate was filtered off or centrifuged, and then washed with water to remove unreacted PVA before drying under vacuum at ambient temperature.

The procedure of the thermal polymerization was the same as that of microwave method, except that the polymerization was respectively, carried out with an oil bath at 210°C.

Measurements

^{1}H nuclear magnetic resonance (^{1}H NMR) spectra were recorded using a Mercury VX-300 (300 MHz) apparatus and tetramethylsilane as an internal standard and $CDCl_3$ as solvent. Fourier transform infrared (FTIR) spectra were recorded on a Perkin-Elmer Spectrum One for KBr discs. Gel permeation chromatography (GPC) measurements were performed at 35°C with chloroform as the eluant (1.0 mL/min) using a Waters HPLC system equipped with a Model 2690D separation module, a Model 2410 refractive index detector and Shodex K803 columns in series. Polystyrene standards (PS) in a narrow molar mass distribution were used for calibration. Intrinsic viscosities were determined by using an Ubbelohde capillary viscosimeter from solutions in tetrahydrofuran (THF) at 30°C with five different concentrations. The kinetic energy correction was always negligible. Huggins and Kraemer equations were used to estimate the [η] value by extrapolation to concentration (c) to be zero as follows:

$$\eta_{sp}/c = [\eta] + k'[\eta]^2 c \quad (1)$$

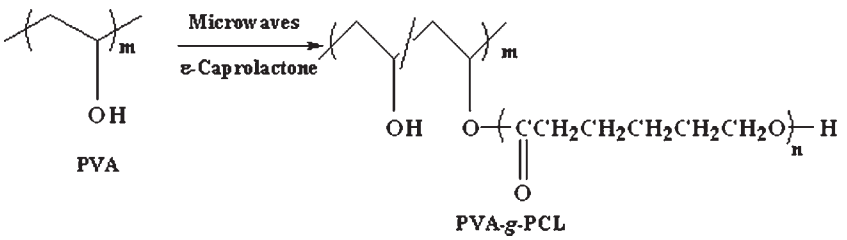
$$(\ln \eta_r)/c = [\eta] - \beta[\eta]^2 c \quad (2)$$

where k' and β are constants for a given polymer at a given temperature in a given solvent, η_{sp}/c, is the reduced specific viscosity, and $(\ln \eta_r)/c$, is the inherent viscosity. Differential scanning calorimetry (DSC) was conducted on a Perkin–Elmer instrument DSC 6. The sample was heated at 10°C/min from 25 to 100°C. Wide-angle X-ray diffraction (WAXD) analysis was conducted with a Shimadzu XRD-6000 X-ray diffractometer (40 kV, 30 mA) using Cu Kα radiation, and the scanning rate was 4°/min.

RESULTS AND DISCUSSION

Characterization

PVA was hardly soluble in ε-CL at ambient temperature due to its well-known strong intermolecular



Scheme 1 Synthesis of PVA-*g*-PCL copolymer under microwave irradiation.

and intramolecular hydrogen bonding. Under microwave irradiation, the mixtures of PVA and ε-CL gradually became homogeneous and transparent solutions. After purification, the removed solid or semisolid products hardly dissolved in water. This result suggested that the recovered products were not PVA and that copolymerization did occur. Moreover, no polymeric product was obtained when the sole ε-CL was irradiated under microwave, by which the initiation effect of PVA on the MROP of ε-CL was supported. The microwave synthesis of PVA-*g*-PCL copolymers is depicted in Scheme 1.

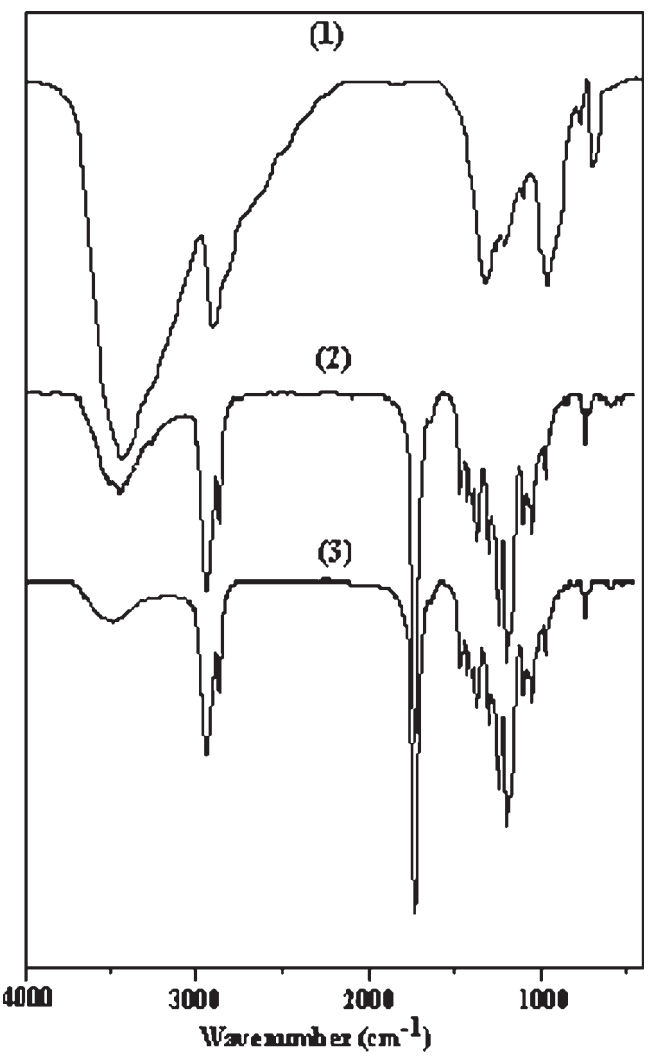


Figure 1 Comparison of FTIR spectra of (1) PVA124, (2) PCL, and (3) PVA124-*g*-PCL.

The product is confirmed as PVA-*g*-PCL copolymer by means of FTIR and ^{1}H NMR. Typical FTIR spectra are shown in Figure 1. The FTIR spectrum of product showed characteristic absorption of PCL; however, no signals of PVA backbone could be observed.

^{1}H NMR spectra of the copolymers are demonstrated in Figure 2. A weak signal at 5.10 ppm is assigned to the methine proton connected to the PCL side chain,[25] and the methine proton adjacent to the remaining unreacted hydroxyl group appeared at 4.05 ppm overlapping with the peak of protons of the PCL repeating units. The results indicated that the methine proton signals of PVA were obviously shown in the ^{1}H NMR spectra of the graft copolymers, which confirmed that the hydroxyl group of PVA initiated the MROP of ε-CL. In addition, the DP of PCL side chains was calculated from the intensities of the signal at 2.30 ppm, which are attributed to methylene protons —C(O) $CH^*_2(CH_2)_4O$— of PCL segment, and the signal at 3.65 ppm, assigned to terminal methylene protons of PCL branch. The peaks at 1.40–1.65 ppm are assigned to methylene protons of PCL segment as well as overlapped methylene protons of PVA main chain. Also, the degree of substitution (DS) of PVA by PCL side chains was calculated from the intensities of peaks assigned to PCL side chain and PVA backbone according to the literature.[25] The DP and DS are given by equations as follows:

$$\mathrm{DP} = I_{2.30}/I_{3.65} \tag{3}$$

$$\mathrm{DS} = I_{5.10}/(I_{1.40-1.65} - I_{2.30})/2 \tag{4}$$

where $I_{2.30}$, $I_{3.65}$, $I_{5.10}$, and $I_{1.40-1.65}$ are the intensities of the signals at 2.30, 3.65, 5.10, and 1.40–1.65 ppm, respectively. As exemplified in Figure 2(1) PVA124 was selected as backbone and the DP was 3.0; therefore, the corresponding graft copolymer was designated as PVA124-*g*-PCL3.0. The following designation for the copolymers is analogous. With the increase in DP of PCL chain, the intensities of the signals attributed to methine proton of PVA and terminal methylene protons of PCL branch weakened.

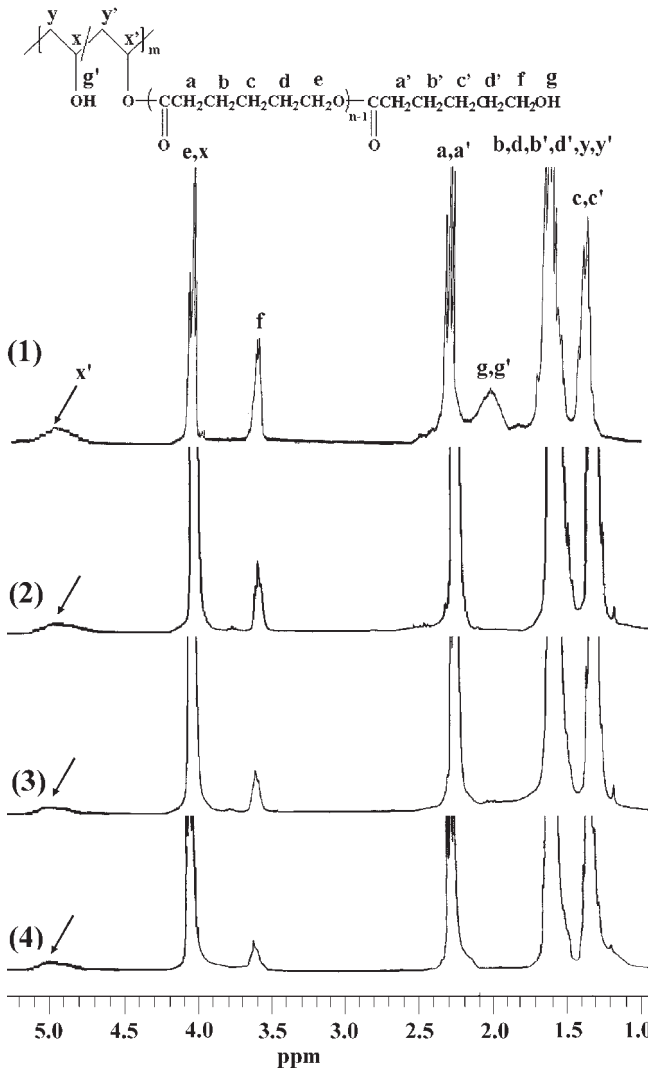


Figure 2 ^{1}H NMR spectra of PVA124-*g*-PCL in $CDCl_3$ [(1): PVA124-*g*-PCL3.0; (2): PVA124-*g*-PCL7.8; (3): PVA124-*g*-PCL8.8; (4): PVA124-*g*-PCL9.9].

The determination of the intrinstic viscosities is an effective method of investigating and proving the molecular structure of polymers. With the similar molecular weight, the grafted polymers have lower intrinstic viscosities because of their smaller hydrodynamic volume in solution compared with linear polymers.[8] Therefore, intrinsic viscosities of linear PCL sample and graft copolymers were determined by using an Ubbelohde capillary viscosimeter from solutions in THF at 30°C. As shown in Table I, PVA1750-*g*-PCL11.1 with M_w = 723,000 g/mol and PVA1750-*g*-PCL13.7 with M_w = 1033,000 g/mol determined by GPC, even had lower intrinsic viscosities, although their M_w were much higher than that of linear PCL (M_w = 80,000, supplied by Solvay company), confirming their smaller hydrodynamic volume in solution as a consequence of the grafted structure.

TABLE I
Comparison of Intrinsic Viscosities of PVA-*g*-PCL and Linear PCL

Sample	M_w[a] (g/mol)	Intrinsic viscosity $[\eta]$[b] (dmL/g)
Linear PCL	80,000	135.2
PVA1750-*g*-PCL11.1	723,000	128.1
PVA1750-*g*-PCL13.7	1,033,000	131.9

[a] Determined by GPC.
[b] Derived from Huggins equation ($\eta_{sp}/c = [\eta] + k'[\eta]^2c$) and Kraemer equation $\{(\ln \eta_r)/c = [\eta] - \beta[\eta]^2c\}$.

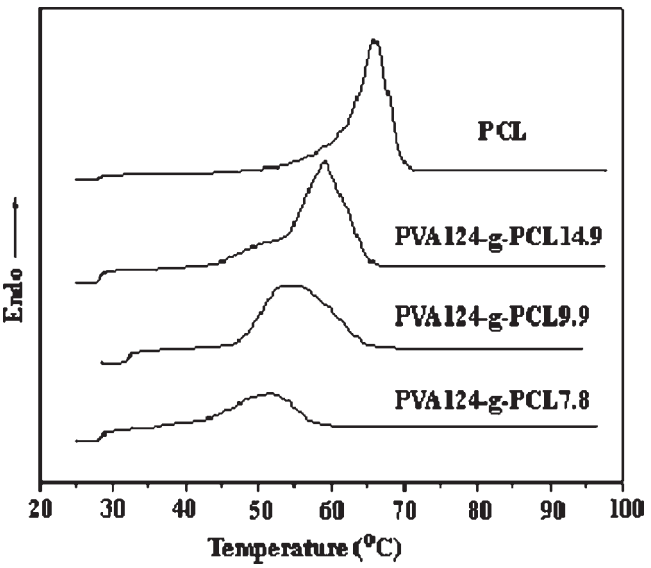


Figure 3 Thermal properties of PVA-*g*-PCL and linear PCL (M_w = 44,800 g/mol).

DSC analysis was used to investigate the influence of introduced hydrophilic PVA backbone on thermal properties of the copolymers (Fig. 3). When the samples were heated at 10°C/min from 25 to 100°C, all DSC traces of the copolymers showed only one melting point (T_m), indicating that PVA and PCL components are totally miscible and did not lead to phase separation. However, the graft copolymer PVA124-*g*-PCL3.0 (DP = 3.0, DS = 0.35) with short PCL chain and low DS was amorphous. In comparison of PCL sample, the decreases in T_m of the copolymers could be observed with increasing PVA/PCL ratio due to higher chain mobility. Taking the area of melting peak into account, the crystallization property of PVA-*g*-PCL copolymers gradually decreased as well.

The crystallization properties of the corresponding samples in Figure 3 were studied by WAXD analysis. Figure 4 illustrated that the diffraction pattern of copolymers exhibited the two intense diffraction peaks located at 2θ = 19.4 and 23.6, which are characteristic of crystallized PCL.[26] The results coincided with those DSC measurements, indicating that no phase separation in copolymer occurred. Moreover,

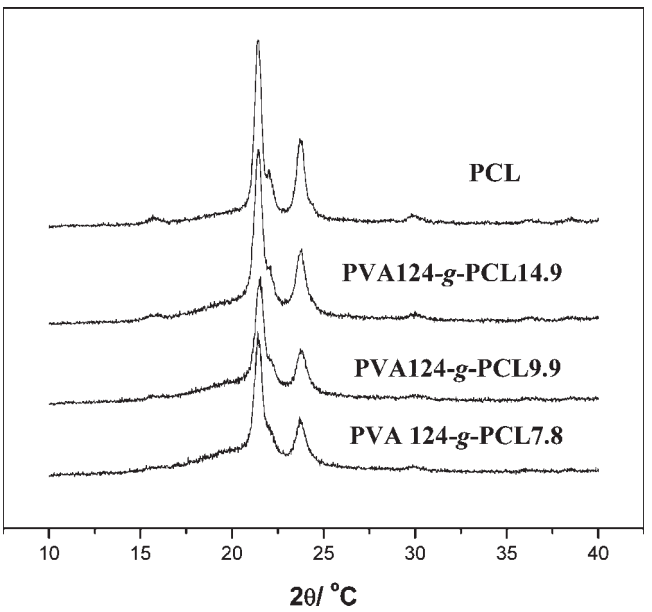


Figure 4 X-ray diffractograms of PVA-*g*-PCL and linear PCL (M_w = 44,800 g/mol).

the crystallinity of PCL was 32.4%, while those of PVA124-*g*-PCL14.9, PVA124-*g*-PCL9.9, and PVA124-*g*-PCL7.8 were 21.8, 18.8, and 17.8%, respectively. The crystallinity of the copolymer decreased with PVA/PCL ratio increasing, suggesting the introduction of PVA backbone restricted the crystallization behavior of PCL. Since aliphatic polyesters are thought to degrade by a random hydrolytic cleavage of the ester bonds, crystallinity and water uptake are the key factors determining the rate of polymer degradation, which can be manipulated specially with the present comb-like PVA-*g*-PCL copolymers.

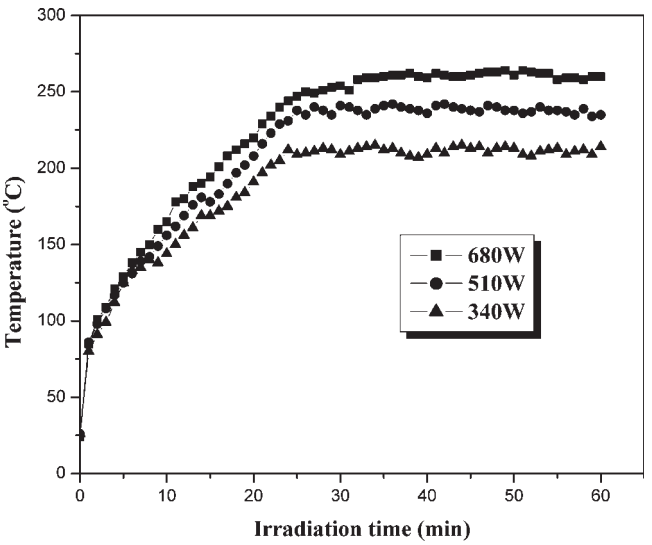


Figure 5 Heat effect of microwave energy on ε-CL/PVA mixture at different microwave power (PVA124, [CL]/[OH] = 8 in feed).

Heating characteristics of ε-CL/PVA mixtures under microwave irradiation

In our previous work,[23] the heat effect of microwave energy had great influence on the ROP of ε-CL, the temperatures of polymerization mixtures under microwave irradiation were thus measured. Figure 5 showed the temperatures of ε-CL/PVA mixtures at various microwave power levels with molar ratio of ε-CL and hydroxyl group of PVA in feed ([CL]/[OH]) equaling to 8. The temperature increased rapidly to a high value within 30 min (340 W: 210°C; 510 W: 240°C; and 680 W: 260°C), and the increase increased slowly until a constant value was achieved. The higher the microwave power was, the higher the equilibrium temperature.

The heating behavior of reaction mixtures with various [CL]/[OH] was also investigated and the results are shown in Figure 6. With microwave power 680 W and [CL]/[OH] ranging from 4 to 32, the thermal equilibrium appeared after 25–30 min for each mixture and the equilibrium temperatures were 300, 255, 230, and 210°C, respectively. The more the PVA in the mixture, the higher the temperature was.

PVA-initiated MROP of ε-CL

The influence of microwave power on MROP of ε-CL initiated by PVA was investigated and the results are shown in Figure 7. The reaction mixture with [CL]/[OH] = 8 in feed was irradiated by microwaves at 340, 510, and 680 W, and the DP of PCL side chains, DS of PVA by PCL and monomer conversion were measured and plotted as a function of microwave power. The results indicated that the DP and DS were higher at higher microwave power. The

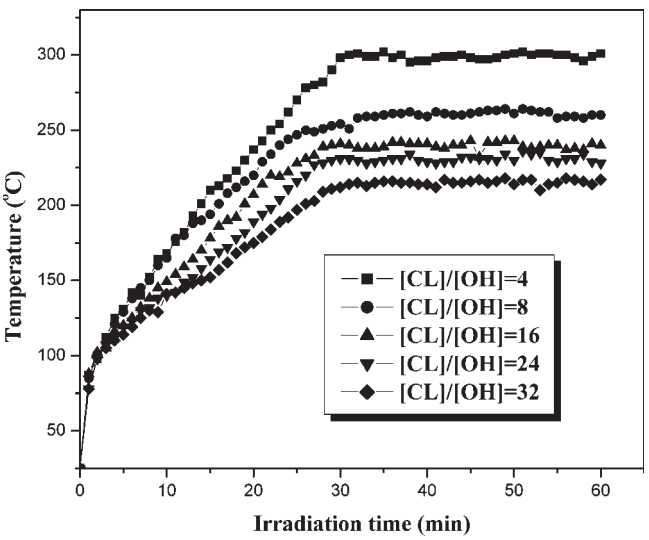


Figure 6 Heat effect of microwave energy on ε-CL/PVA mixture with different amount of PVA (PVA124, 680 W).

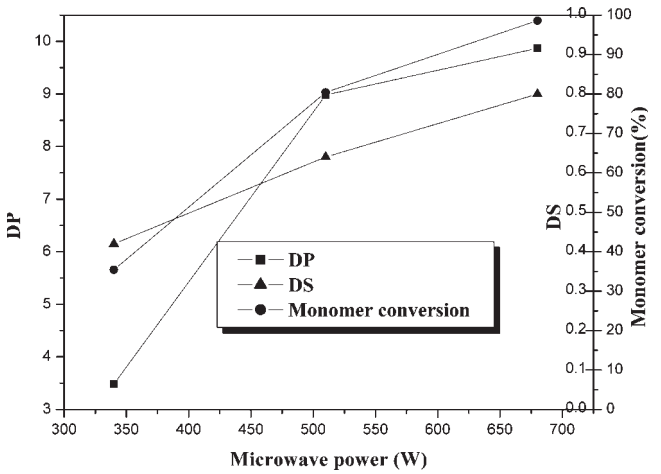


Figure 7 Dependence of DP, DS, and monomer conversion on microwave power (PVA124, [CL]/[OH] = 8 in feed, 180 min).

monomer conversion was higher as well, indicating the polymerization reaction proceeded more rapidly at higher microwave power. Combination of the results shown in Figures 5 and 7, it was concluded that heat effect of microwave energy dramatically influenced the polymerization and higher temperature accelerated the polymerization process. On the basis of this finding, 680 W was selected as suitable microwave power for the rest of our investigations.

The influence of the microwave irradiation time could not be neglected (Fig. 8). With [CL]/[OH] = 8, the DP and monomer conversion both increased with the irradiation time increasing. For the DS, it reached 0.53 at 60 min and increased to 0.83 at 90 min, and then it remained constant. As regards the polymerization mechanism, it is similar to the previously reported for the active-hydrogen-initiated polymerization of ε-CL.[27] The polymerization involved the addition of ε-CL onto the PVA hydroxyl groups to yield the corresponding ε-hydroxy ester, through selective acyl-oxygen cleavage of the lactone ring. Therefore, the copolymer formation proceeded, step by step, with the growing centers of ε-hydroxy ester and excess of ε-CL monomer according to the same ring-opening mechanism. The variation of DS indicated that the monomer was mainly consumed by the formation of growing centers at the beginning stage of the polymerization since one center initiated the growth of one PCL side chain, while the monomer was mainly consumed by prorogation of PCL branch with the polymerization proceeded.

Furthermore, the amount of PVA significantly affected the MROP of ε-CL (Fig. 9). With [CL]/[OH] in the range of 4–32, it was observed that the DP and DS were higher with initiator in low concentration. It might be attributed to that less PVA dissolved well in ε-CL, namely PVA chain more extended, which enhanced the reactivity of hydroxyl group. Moreover, to obtain completely monomer depletion, longer irradiation time was necessary with less initiator used, which suggested that the monomer was converted more slowly. With [CL]/[OH] = 32, the DP and DS were respectively 24.1 and 0.89, and the monomer conversion reached above 95% within 360 min. For comparison, the same reaction mixture was heated by the conventional method at 210°C, which was chosen according to Figure 6, the polymerization could hardly occurred within 360 min as no graft copolymer was detected by FTIR and ^{1}H NMR. It seemed that ''microwave'' effect of microwave energy had more or less influence on MROP of ε-CL, however, which was still under further investigation and needed more experimental data to support.

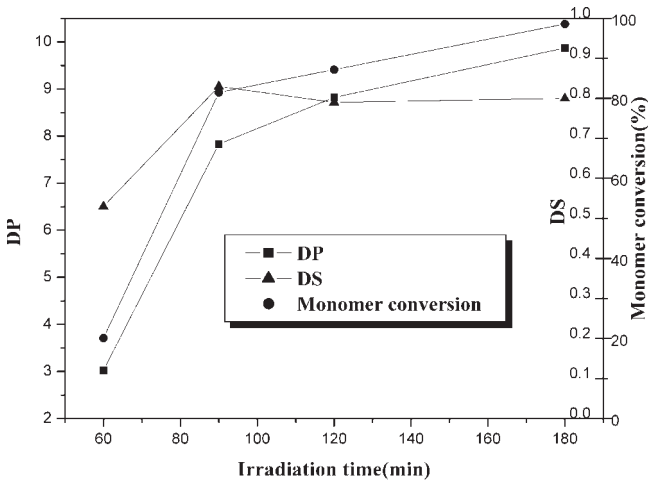


Figure 8 Dependence of DP, DS, and monomer conversion on irradiation time (PVA124, [CL]/[OH] = 8 in feed, 680 W).

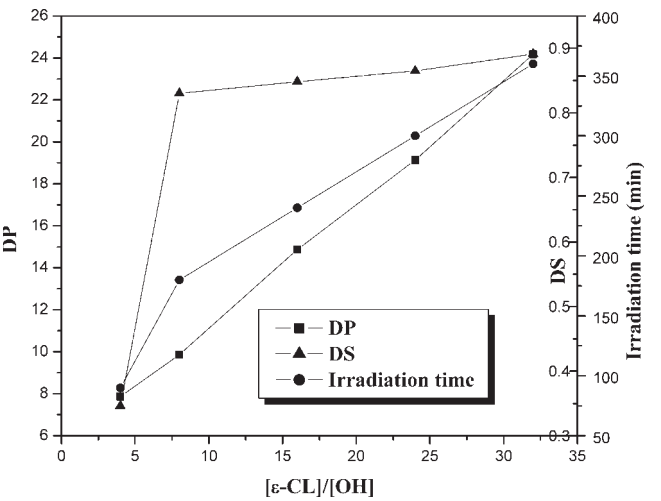


Figure 9 Dependence of DP, DS, and irradiation time on the amount of PVA (PVA124, 680 W).

CONCLUSIONS

Ring opening polymerization of ε-CL initiated by PVA in bulk is significantly improved by microwave energy, and a series of comb-like PVA-*g*-PCL copolymers with different chain length were successfully prepared. The introduction of hydrophilic backbone resulted in the decrease in both melting point and crystallization property of the PVA-*g*-PCL copolymers comparing with linear PCL. The DP of PCL side chain, DS of PVA by PCL and monomer conversion are affected by microwave power, irradiation time and initiator concentration. The introduced hydrophilic backbone and the adjustable crystallinity make the PVA-*g*-PCL copolymers promising candidates for encapsulation of drugs such as proteins and peptides.

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