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Effect of soft segment on degradation kinetics in polyethylene glycol/poly(L-lactide) block copolymers

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SUMMARY

The hydrolytic degradation of polyethylene glycol(PEG)/poly (L-lactide)(PLLA) copolymers with various PEG wt% contents at 37℃ and pH=7 was studied by differential scanning calorimetry(DSC) and gel permeation chromatography(GPC). The effect of PEG contents in PEG/PLLA copolymers on the crystalline morphology and hydrolytic degradation rate was investigated. Due to the hydrophilic PEG segments in PEG/PLLA copolymers, the exothermic recrystallization and the shoulder portion of melting endotherm appear immediately following the hydrolysis of copolymers. Moreover, after a period of hydrolysis of 100 h. the molecular weight distribution turn to a bimodal shape from a unimodal in the original, and the polydispersity becomes greater with a value from 1.5 up to 5, which are not observed for PLLA homopolymer. The rate constants of hydrolysis for the first-order auto-catalytic kinetics, increase with the PEG content over 0 to 18.3 wt%, ranging from 1 to $6\times10^{-4}hr^{-1}$.

INTRODUCTION

Aliphatic polyesters derived from glycolic acid, L-lactic acid, DL-lactic acid and ξ-caprolactone are being used in an increasingly large number of applications such as biomedical implants(1) and prosthetics(2). It is realized that the water permeation through and dissolution of polyesters is affected by the hydrophilic compositions of polymers. As a result, means of copolymerization and blending have already been used to tailor the degradation rate and time of duration of erodible polymers. To be more specific, the alpha PEG/PLA(3-7) copolymers are a class of well known bioresorbable copolyesters. Blending of polylactic acid with poly(ξ-caprolactone) or cellulose has been reported(8,9). Notably, polypropylene glycol(PPG) and polyethylene glycol(PEG) have been incorporated into poly(L-lactide)$^{(10-12)}$ and polyethylene terephthalate(PET)$^{(4)}$, in order to increase the hydrophilicity and modulate the degradation rate of materials.

However, there is relatively little work on the morphology and degradation behavior of biodegradable polyetheresters. The morphological study$^{(13)}$ on the PEG/PLA copolymers with high PEG contents (24 to 80 mole%) revealed the size of crystallites by the x-ray diffration technique. Yet, the effect of degradation on molecular struture and morphology of the polyetheresters was not reported. In this study, the PEG segments were copolymerized in adjustable amount with PLLA and the data of molecular weight in combination with the first order kinetics were used to determine the rate constants of hydrolysis. Furthermore, the effects of the contents of PEG segments and the crystalline morphology on the hydrolytic degradation are reported as well.

EXPERIMENTAL

1.Synthesis

PEG with number-average molecular weight($\overline{M}n$)=2000 was supplied by Hanaka(Japan). The samples were thoroughly dried at 100℃ and a pressure below 10 mmHg for 10 h. and was used without further purification. Ethyl acetate and n-hexane were commercially available and purified by distillation prior to use. Stannous octoate was provided by Sigma.

The L-lactide was prepared by dehydration of L-lactic acid at 140℃ for 8 h. in the presence of 2% zinc oxide, at a pressure of 100 mmHg. The L-lactide, as it was formed, was refluxed at about 200℃ at a pressure below 10 mmHg. The crude product was recrystallized several times from ethyl acetate.

A prescribed amount of L-lactide and PEG were placed in a 100 ml round- bottomed flask equipped with a stirrer. The flask was evacuated by a vacuum pump for several hours in order to dry up the mixture thoroughly and was then filled with nitrogen gas. The reaction mixture was heated to 180℃ with stirring under a nitrogen atomsphere, and 0.05 wt% stannous octoate was then added. The mixture was stirred for 10 hours at 180℃. The final product obtained was dissolved into ethyl acetate, and cooled to 10℃. Subsequently, n-hexane was added and the resulting solution was poured into an excess amount of distilled water. The precipitated product was filtered, washed with diethyl ether, and dried finally in a vacuum oven for 24 h.

2.Characterization

^{1}H-NMR spectrum was measured at 200 MHz with a Bruker AC200 spectrometer using tetramethylsilane (TMS) as the internal standard. Differential scanning calorimetry(DSC) was perfomed under a nitrogen atomsphere on a Du Pont 912-2000 thermal analyser. The heating rate was set at 10℃/min with the sample amount of 10.0 mg. Gel permeation chromatography(GPC) was measured on a Shimadzu C-R4A analyzer fitted with a RI detector and a data processor. Two Zorbax PSM Bimodal (6.2 mm ID×25 cm) columns were used. The sample was injected at 40℃ with chloroform as the eluent at a flow rate of 1.0ml/min. The molecular weight was calibrated with monodisperse polystyrene($\overline{Mn}$=2,500, 20,400, 47,500, 122,000, and 200,000).

3.Hydrolytic Degradation

The 15wt% PEG/PLLA and PLLA solutions in chloroform was used to cast the films with a thickness of 30 to 50 μm, and the films were dried in a vacuum oven at 60℃ for 12 h. The dried films were immersed in the buffer solutions with pH=4, 7 and 10 at a temperature of 37℃. The hydrolyzed sampled were subsequently characterized at several time intervals to uncover the structural change of polymers.

RESULTS AND DISCUSSION

After several times of recrystallization from ethyl acetate, was obtained L-lactide with melting temperature at approximately 98℃. The yield of the polymerization reaction lies from 84 to 90%. The solid product appears transparent, pale yellow in color. The incorporation of PEG segments to PLLA in the PEG/PLLA copolymers was supported by the following spectroscopic data : the chemical shift(δ) at 1.57 ppm for $-CH_3$ in PLLA, 3.64 ppm for $-CH_2-$ in PEG and 5.16 ppm for CH in PLLA was determined by ^{1}H-NMR(Fig.1). The determination of PEG and PLLA segment contents were based on a method detailed in Zhu et al(14). The number average molecular weights($\overline{Mn}$) and PEG contents of PEG/PLLA copolymers are shown in Table 1. The PEG contents of PEG/PLLA copolymers determined by ^{1}H-NMR is higher than those in feed. Because PEG doesn't decompose in this reaction(14) and the PEG mole ratio is quite low, it was reacted completely. However, L-lactide could not be reacted completely, because of its high mole ratio and sublimation.

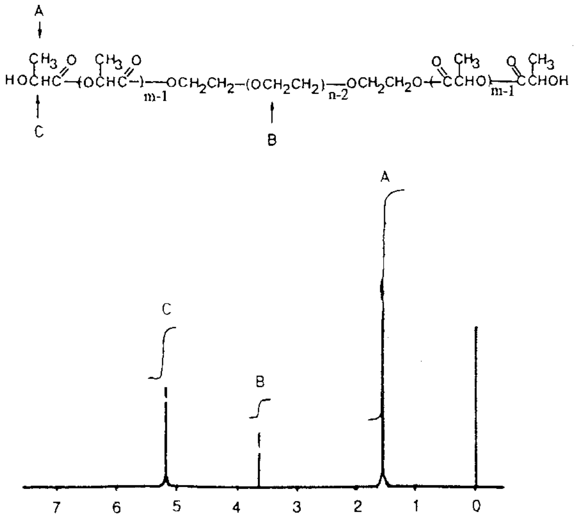

Fig.1. 200 MHz ^{1}H -NMR sepctrum of PEG/PLLA copolymer, PEG wt% =6 ($\overline{Mn}$ of PEG segment = 2000)

Table 1 Structural characteristic of block copolymers of L-lactide with PEG 2000

PEG wt% in Feed	PEG wt% in Copoymer (NMR)	Yield %	Melting Point °C	Tg °C	Molecular Weight(Mn) (GPC)
2	4.4	84	161.2	51.1	24100
3	5.4	86	157.8	44.8	19812
5	9.6	90	149.8	43.1	15783
10	18.3	84	134.2	42.6	9801
0	-	-	174.7	58.9	78964

The effect of PEG content on the molecular weight of PEG/PLLA copolymers is shown in Table 1. It is clear that the $\overline{Mn}$ of the PEG/PLLA copolymers decreases with the increase of PEG content. This is due to the fact that the increase of PEG content leads to the increase of ratio of total number of hydroxyl groups to that of carboxy group in the reaction. Therefore, that reduces the molecular weight of PEG/PLLA copolymers.

In the DSC study, the exothermic recrystallization and the shoulder portion in the melting endotherm appear at lower temperatures than the melting point , by incorporation of hydrophilic PEG segments in PEG/PLLA copolymers. As shown in Fig. 2, the endothermic peak becomes broader gradually, as the hydrolysis goes on. Besides, there is a slight decrease of glass transition and melting temperature while the shoulder portion becomes more distinct. In Fig. 3, the melting temperatures of PLLA homopolymers decrease with the increase of hydrolysis time up to 315 h. The exothermic recrystallization and the shoulder portion for melting was not observed for PLLA homopolymers.

The gel permeation chromatograms of PEG/PLLA copolymers indicate the change of molecular weight distribution from a unimodal shape to a bimodal in the first 100 h. of hydrolysis, as shown in Fig. 4. During the hydrolysis period , the GPC peak area for the higher molecular-weight portion becomes decreasing, and the total mass of lower molecular-weight portion increases at the same moment.

In contrast with Fig. 4, the gel permeation chromatograms of PLLA homopolymers are shown in Fig. 5. It shows that molecular weights of PLLA homopolymers are decreased with the increasing the hydrolysis time, whereas the molecular weight distribution is still in a unimodal shape with the increasing hydrolysis time up to 600 h.

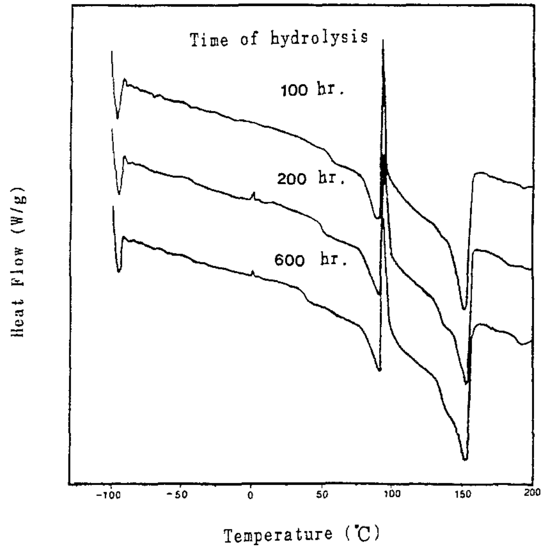

Fig.2. DSC thermograms for PEG/PLLA copolymers (PEG wt% = 18.3 , $\overline{\text{Mn}}$ of PEG segment = 2000) after hydrolysis, at pH=7 and 37℃.

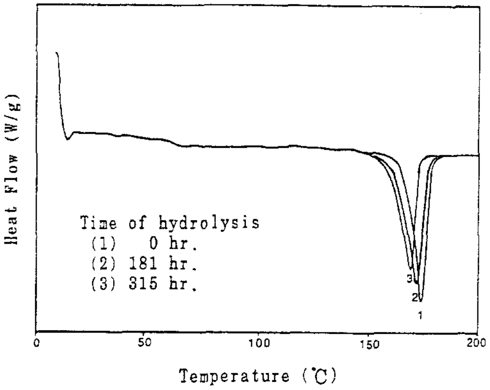

Fig.3.DSC thermograms for PLLA homopolymers after hydrolysis, at pH=7 and 37℃.

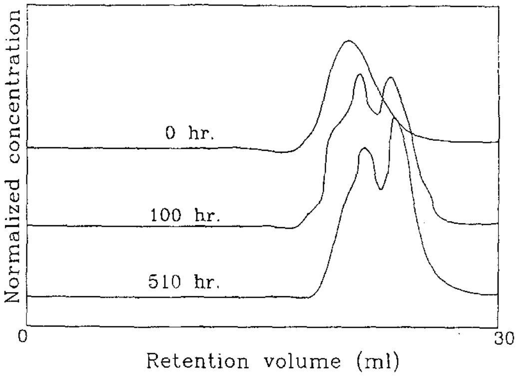

Fig.4. GPC chromatograms of PEG/PLLA copolymers (PEG wt % = 18.3 , $\overline{Mn}$ of PEG segment = 2000), at various hydrolysis times, at pH = 7 and 37℃

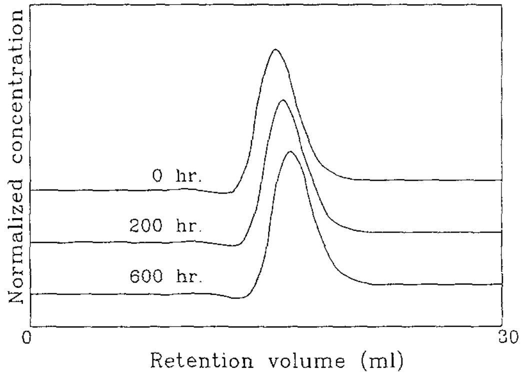

Fig.5. GPC chromatograms of PLLA homopolymers at various hydrolysis times, at pH =7 and 37℃.

The Plots of $\ln(\overline{Mn}/\overline{Mn}^0)$ vs. hydrolysis time for two distinct populations with quite different molecular weights in hydrolyzed PEG/PLLA copolymers at pH=7 and 37℃ are shown in Fig. 6. The rate constants of the hydrolysis in terms of the first order kinetics are 4.0×10^{-4} hr^{-1} (the lower $\overline{Mn}$ portion) and 2.9×10^{-4} hr^{-1} (the higher $\overline{Mn}$ portion), respectively, at the hydrolysis time from 100 to 600 h. Moreover, Tung's method(16) was used in this study to determine molecular weights of PEG/PLLA block copolymers. First, the relations between number-average molecular weights and elution volumes of the two homopolymers, constituting the two ingredients of the copolymers, were found out individually.

The number-average molecular weights of two homopolymer ingredients for copolymers, $\overline{M}n(A)$ and $\overline{M}n(B)$, were determined with the elution volume data of the homopolymers. Then the weight average molecular weight $\overline{M}w$ of the copolymer was calculated from the following equation:

$$\log\overline{M}w = \log\overline{M}n(A) \cdot x + \log\overline{M}n(B) \cdot (1-x) \ldots\ldots\ldots\ldots (1)$$

where x is the composition fraction of ingredient A in the copolymer, obtained from the ^{1}H-NMR data in Table 1. The relations between molecular weights and elution volumes(Ve) of PLLA and PEG homopolymers, respectively, are determined experimentally in this study :

$$\log\overline{M}n(PLLA) = 8.92 - 0.24\ Ve \ldots\ldots\ldots\ldots (2)$$

$$\log\overline{M}n(PEG) = 8.84 - 0.24\ Ve \ldots\ldots\ldots\ldots (3)$$

Finally, the hydrolysis rate constant (100 to 600 h.) for MW-time data is calculated by this method and the data of Fig. 4 gives a rate constant is 3.5×10^{-4} hr^{-1}. This value is between those of two populations with significantly diffrerent molecular weights.

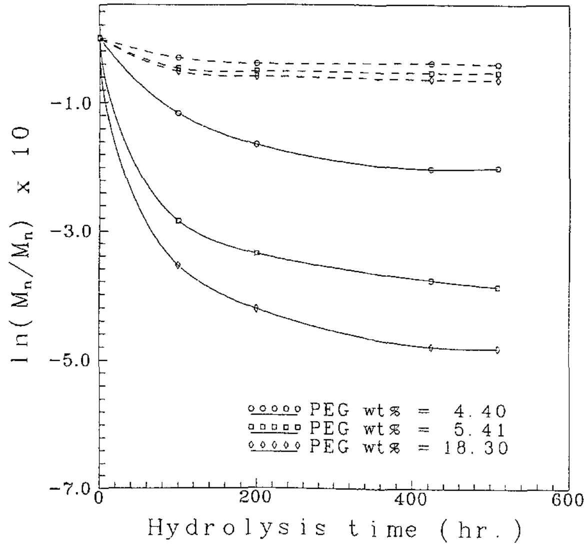

Fig.6. Ln($\overline{M}n/\overline{M}n^o$) vs. hydrolysis time for PEG/PLLA copolymers at pH=7 and 37℃ ($\overline{M}n$ of PEG segment = 2000). (-------------the lower $\overline{M}n$ portion, ———— the higher $\overline{M}n$ portion)

According to the first order kinetics, the hydrolysis rate constants are 1 to 6×10^{-4} hr^{-1} for copolymers with various PEG contents in Fig. 6. It is shown that while the PEG contents of PEG/PLLA copolymers are less than 18.3 wt%, the more PEG content is, the faster hydrolysis rate goes. It is also suggested that the exothermic recrystallization peak of PEG/PLLA copolymer in the DSC scan is related to the crystallization of the PLLA segments that are not completely crystallized at room temperature, as interfered by the PEG segments. Similar results have been reported by Cohn et al.(11) that the values of crystallinity of PEG/PLLA copolymers are lower than that of PLLA homopolymer. This study shows that PEG segments make the hydrophilicity of PEG/PLLA copolymers increase and the crystallinity of PEG/PLLA copolymers decrease. It is understandable that the water molecules enter the polymer structure containing hydrophilic PEG segments, causing amorphous region, tie chains, chain folds, and chain ends in crystalline segments of copolymers to hydrolyze more easily than PLLA homopolymer. Conclusively, the incorporation of proper PEG hydrophilic segments into degradable PLLA segments have an obvious effect on the hydrolysis rate of copolymers.

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