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Solute diffusion through degradable semicrystalline polyethylene glycol/poly(L-lactide) copolymers

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SUMMARY

The diffusion of C.I. direct orange 34(MW = 299) and benzoic acid(MW = 122) through degraded semicrystalline polyethylene glycol(PEG)/poly(L-lactide)(PLLA) block copolymers with various PEG contents and PEG segment lengths at 37℃ was studied by UV-visible spectroscopy, differential scanning calorimetry(DSC), wide angle X-ray diffractometer(WAXS) and scanning electron microscopy(SEM). The influences of the PEG contents, PEG segment lengths and hydrolytic degradation of PEG/PLLA copolymers on the solute diffusion coefficient and mode for transport were investigated. It is concluded that the diffusion rate increases with the increase of PEG contents and PEG segment lengths in PEG/PLLA copolymers. This is understandable that the increase of PEG content and PEG segment length both make the degree of crystallinity decrease. The steady state of mass flux could not be reached at the diffusion times up to 1000 h, because the copolymers underwent hydrolysis reaction during this period. Furthermore, it is understood that the characteristic time of diffusion as defined by the square of film thickness at an instant of time over the diffusion coefficient of solute through polymer decreases with the increasing diffusion time.

INTRODUCTION

Aliphatic polyesters of the poly(α-hydroxy acid) which are derived from metabolites such as lactic acid enantiomers(LA) and glycolic acid(GA), have been investigated extensively, especially with respect to their potential for medical[1,2] and pharmaceutical[3] applications. However, the high crystallinity[2,4,5] and low hydrophilicity of[6] these polymers interfere with their controlled degradation. As a result, means of copolymerization have already been used to tailor the degradation rate and duration of erodible polymers[7-9].

Polymer composition and morphology play important roles in governing polymer degradation. In general, the degradation of semi-crystalline polyesters proceeds in two stages, first in amorphous regions and then in crystalline ones[10]. The transport of solutes through semicrystalline membranes is affected by the presence of crystallites in the polymer structure. The crystallites reduces the available space for solute diffusion and increase the characteristic diffusion length[11].

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The physical and biological properties in vitro of polyethylene glycol/poly(DL-lactide) copolymers have been investigated[12,13]. The results indicate that this amorphous material might be used as a drug carrier in medical applications. A series of semicrystalline PEG/PLLA block copolymers, covering a wide range of compositions and segmental lengths, was synthesized. In this study, the influences of copolymer composition and hydrolysis on the solute diffusion coefficient and mode for release were investigated. The diffusion experiment with PEG/PLLA copolymers was carried out in aqueous solutions with diffusing solutes such as C.I. direct orange 34(MW=299) and benzoic acid(MW=122). The change in the surface morphology of the hydrolyzed polymer films was observed by scanning electron microscopy(SEM). The diffusant concentration in the diffusion experiment was measured by UV-visible spectroscopy and the degree of crystallinity was measured by WAXS and DSC.

EXPERIMENTAL

1.Synthesis

PEG with number-average molecular weights($\overline{M}n$) from 1000 to 6000 was supplied by Hanawa(Japan). The samples were thoroughly dried at 100℃ and a pressure below 10 mmHg for 10 h. and were 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

The gel permeation chromatography(GPC) was measured on a Shimadzu C-R4A analyzer fitted with a RID-6A 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 1.0 ml/min. The molecular weight was calibrated with monodisperse polystyrene ($\overline{M}n$=2,500, 20,400, 47,500, 122,000, and 200,000).

3.Film Preparation

The 15 wt% PEG/PLLA copolymer solution in chloroform was used to cast the films with thicknesses from 30 to 50 μm, and the films were dried in a vacuum oven at 60 ℃ for 12 h.

4. Diffusion Experiment

The diffusion apparatus consists of two identical horizontal cylindrical cells and other accessories. In a typical transport experiment, the film thickness was measured and the film was then mounted in the diffusion cell. The 120 ml of initial solution was added to the donor cell and the 120 ml of distilling water added to the receptor cell. The initial concentration of solutes, C.I. direct orange 34 (MW=299, ICI) and benzoic acid (MW=122, Hanawa), is 0.05 g/l. The adsorbance of the receptor side was recorded (UV-240, Shimadzu) at set time increments. The solute diffusion coefficient is obtained from the mass flux data in the initial diffusion period by the following equation[14]:

$$\ln [t^{1/2} \times F(t)] = \ln [2C_1 (D/\pi)^{1/2} - l^2/4Dt] \cdots\cdots\cdots\cdots (1)$$

where F(t) : the rate of mass flow per unit area of polymer film
D : solute diffussion coefficient
C_1 : initial concentration of solute
l : thickness of film

5.Crystallinity of the Copolymers

The crystallinity of the copolymer was measured by WAXS(Philips PW1700 Automated Powder Diffractometer System 1) and DSC(du Pont 912-2000 thermal analyser). The method of WAXS[15] is based on the assumption that it is possible to separate the intensity contributions arising from crystalline and amorphous regions. The degree of crystallinity is calculated as the ratio of the area of resolved crystalline region to the total area under unresolved normalized X -ray scattering curve. The area under the background line is assigned to the amorphous component of polymers quenched at 0 ℃ from the molten state at 200 ℃. The crystallinty from DSC is calculated with the aid of the enthalpy of fusion of 93.7 J/g for the perfectly crystalline PLLA.

6.Surface Morphology

Surface morphology was observed by a scanning electron microscope (JEOL JSM-5200, Tokyo) at 15kV.

RESULTS AND DISCUSSION

The PEG/PLLA copolymers were prepared by copolymerization of L-lactide and polyethylene glycol with $\bar{M}n$ from 1000 to 6000. The composition and $\bar{M}n$ of the synthysized PEG/PLLA copolymers are shown in Tab.1. It is seen that the PEG content in the copolymers varies from 2 to 10 wt%, and $\bar{M}n$ ranges from 9.8×10^3 to 2.4×10^4.

Tab.1 $\bar{M}n$, PEG contents and PEG segment lengths for PEG/PLLA copolymers

Sample No.	PEG content in feed(wt%)	$\bar{M}n$ of PEG segment	$\bar{M}n$ of PEG/PLLA copolymer
S-1	2	2000	24100
S-2	3	2000	19812
S-3	5	2000	15783
S-4	10	2000	9801
S-5	10	4000	21035
S-6	10	6000	30780

1.Hydrolysis

The GPC data in Figure 1 show that molecular weights of PEG/PLLA copolymers are decreased with the increasing hydrolysis time. The molecular weight distribution is unimodal prior to hydrolysis. After 200 h of hydrolysis the molecular weight distribution is changed to the bimodal. The rate constants of hydrolysis calculated by the molecular weights of samples with the aid of the first-order kinetic model increase with the PEG content over 0 to 18.3 wt%, ranging from 1 to 6×10^4 hr^{-1}. The estimation of rate constants using the bimodal curves on gel permeation chromatograms is described in the reference 16.

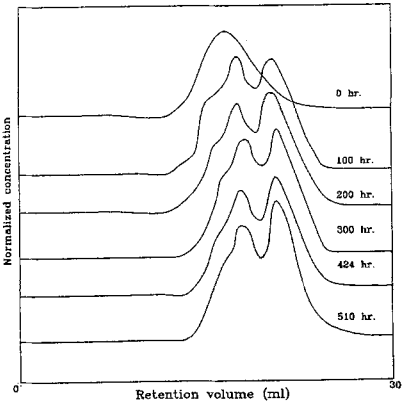

Fig.1 GPC chromatograms of PEG/PLLA copolymer(S-4) in degradation at various times.

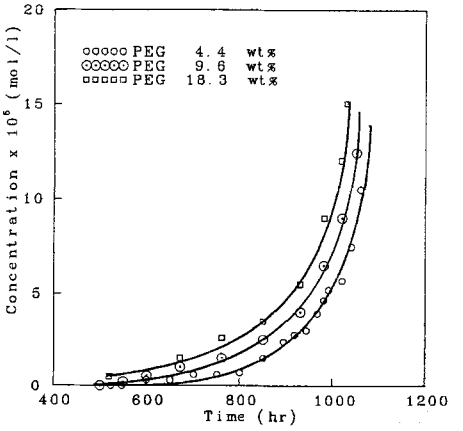

Fig.4 Plots of concentration vs. diffusion time for C.I. direct orange 34 through PEG/PLLA copolymers (PEG segment length $\overline{Mn}$= 2000), with various PEG contents at 37℃.

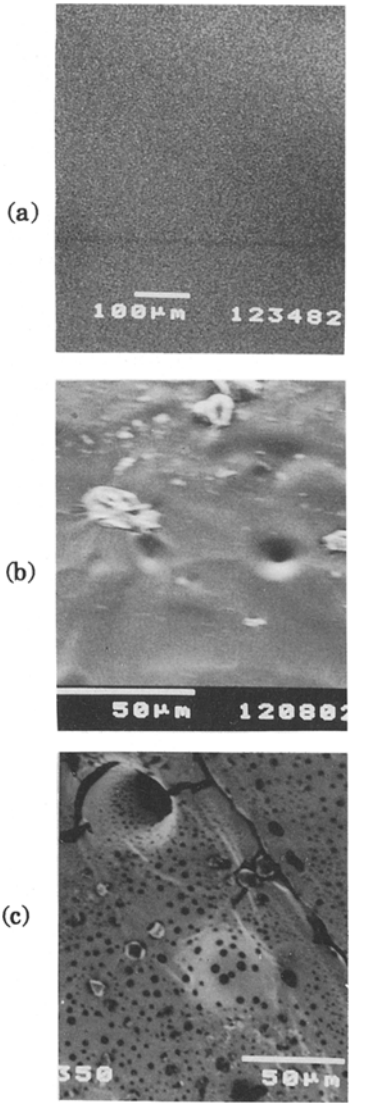

Fig.2 SEM photography of PEG /PLLA copolymers (S-1) at various times of hydrolysis at 37℃ : (a) 0 h, (b) 600 h, (c) 1000 h.

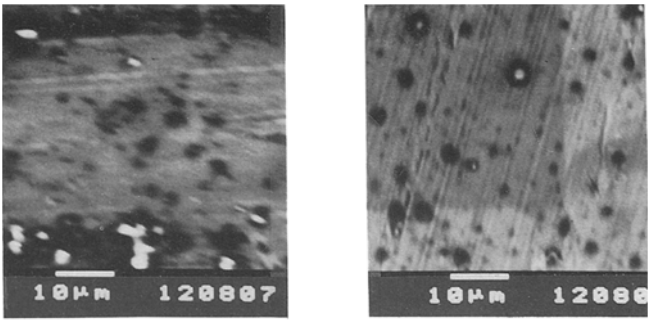

Fig.3 SEM photography of PEG/PLLA copolymers (S-4) at various times of hydrolysis at 37℃ : (a) 600 h, (b) 1000 h.

Tab.2 The relative crystallinity of PEG/PLLA copolymers(with PEG content = 10 wt % in feed) with various chain lengths of PEG

Sample no.	Mn of PEG segment	Xc(%) (DSC)	Xc(%) (X-ray)
S-4	2000	33.5(34.8[1])	33.9(35.7[1])
S-5	4000	31.7(33.6[1])	32.0(35.5[1])
S-6	6000	30.5(32.3[1])	29.4(32.2[1])

1. After 200 h. hydrolysis.

2.Surface Morphology

From the SEM study, it is seen that the surface of PEG/PLLA copolymer films was found to be smooth at the beginning, as shown in Fig.2(a). The micropores appeared on the surface of PEG/PLLA copolymers(S-4) after 500 h. hydrolysis in the diffusion cell and at 37℃. The time before micropores begin to form becomes longer with the lower PEG content in the PEG/PLLA copolymers. As shown in Fig.2 and Fig.3, the density and diameter of the micropores increase with the increase of diffusion time.

3.Effects of PEG Segment Content and Length on Diffusion

Fig.4 shows the relationships between the concentration for a variety of samples of the diffusing C.I. direct orange 34 in the receptor side and the diffusion time. It is shown that the diffusion rate increases with the increase of PEG content in PEG/PLLA copolymers at a fixed PEG segment length $\overline{Mn}$=2000. The higher PEG content make the hydrophilicity of PEG/PLLA copolymers increase, which causes the water molecules to enter the film more easily. The more take-up of water causes the films of PEG/PLLA copolymers to show a faster degrdation rate. Therefore, the higher PEG segment content tends to lead to the faster formation of micropores on the surface and bulk and makes the diffusion rate increase.

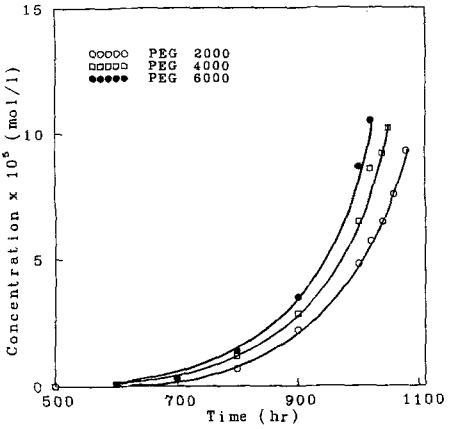

Fig.5 Plots of concentration vs. diffusion time for C.I. direct orange 34 through PEG/PLLA copolymers (PEG content =10 wt % in feed), with various PEG segment lengths at 37℃.

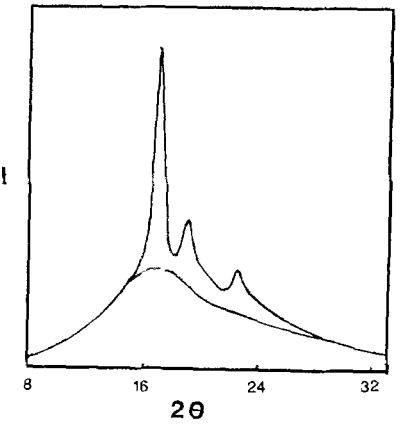

Fig.6 X-ray diffraction curves for PEG/PLLA copolymer(S-3) resolved into the crystalline peaks(c) and amorphous(a) background.

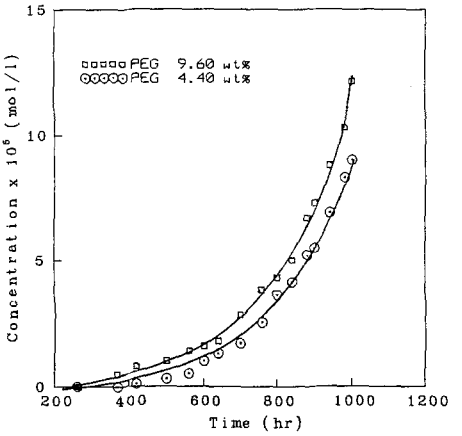

Fig.7 Plots of concentration vs. diffusion time for benzoic acid solution through PEG/PLLA copolymers (PEG segment length Mn = 2000), with various PEG contents at 37℃.

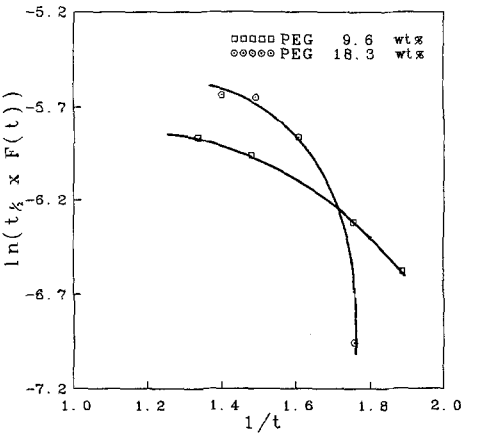

Fig.8 Plots of $\ln(t^{1/2} \times F(t))$ vs. 1/t for dye through PEG/PLLA copolymers (PEG segment lengt--Mn =2000) with various PEG contents.

Fig.5 indicates the accumulated concentration in the receptor side versus the diffusion time for the dye through PEG/PLLA copolymers films with fixed PEG content, 10 wt% in feed, and the various PEG segment lengths. It is shown that the diffusion rate is relatively slow during the initial 400 h and gets faster when the diffusion time is over 700 h. The transport of solutes through semicrystalline films is affected by the presence of crystallites in the polymer structure. The crystallites reduce the available space for solute diffusion and increase the characteristic diffusion length. The solute permeability is dependent on the amount of crystallites in the semicrystalline films. Tab.2 shows the degree of crystallinity of PEG/PLLA copolymers with fixed PEG content, 10 wt% in feed, and the various PEG segment lengths. Figur 6 presents the experimental diffraction curve for the PEG/PLLA copolymer(S-3). For the curve of semi-crystalline sample, the scattering peaks occur at 2θ=16.5, 19, and 22° . The experimental curve was resolved into crystalline peaks and the amorphous background. The degree of crystallinity is decreased with the increase of PEG segment length. Moreover, the diffusion rates are increased with the increase of PEG segment lengths in PEG/PLLA copolymers owing to the increase of content of the amorphous region. It is concluded that the diffusion rates increased with the increase of PEG segment content and length in PEG/PLLA copolymers. This is because that the increase of PEG segment content and length both make the degree of crystallinity decrease, and tend to lead to the increase of the degradation rate. After 1000 h diffusion experiment, the increase in the density and diameter of the micropores on PEG/PLLA copolymers films accelerate the solute drift, and the accumulated concentration of diffusing solute increases significantly after this period.

4.Solute Effect on Diffusion

The diffusion characteristics of dye and benzoic acid through with the fixed PEG segment length and various PEG contents of PEG/PLLA copolymers are shown in Fig.3 and Fig.7. In conjunction with Fig.5, it is apparent that the faster diffusion rate is caused by solute with the lesser molecular weight. The accumulated concentration of benzoic acid increase significantly at 600 h and that of C.I. direct orange 34 exhibit a similar phenomenon though at 650 h. This result indicates that benzoic acid has a faster diffusion rate in PEG/PLLA copolymer films than the dye.

5.Estimation of Diffusion Coefficient

By equation(1), the plots of $\ln(t^{1/2} \times F(t))$ versus 1/t for dye diffusion through PEG/PLLA copolymers with fixed the PEG segment length $\overline{Mn}$=2000, with various PEG contents, are shown in Fig.8. It should be mentioned that, in Fig.4, 5,and 7, the concentrations do not reach asymptotic lines indicating the steady-state mass transfer, and the time lag method for data at long diffusion time cannot be applied to yield the diffusion coefficient. Basically, solute transport through biodegradable matrices can be caused by, (a) molecular diffusion through the polymer continuum, (b) liberation due to of matrix degradation or by bulk degradation, and (c) diffusion via connected channels in the polymer matirx, depending on the polymer-solute combination[16]. Fig.7 does not show a linear plot, implying (l^2/4D) is not a constant over the time period. In this study, the steady state of mass flux could not be reached in the range of diffusion time from 0 to 1000 h, because the morphology of PEG/PLLA copolymers films is changing in the diffusion experiment owing to the degradation. Therefore, it is understood that characteristic time of diffusion as defined by the square of film thickness(l^2) over the diffusion coefficient of solute(D) through polymer decreased with the increase of diffusion time.

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