Synthesis and Characterization of Novel Biodegradable Polymers Composed of Hydroxycinnamic Acid and D,L-Lactic Acid

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ABSTRACT: D,L-Lactic acid (DLLA) was polycondensed with 4-hydroxycinnamic acid (4HCA), a derivative of cinnamic acid, to prepare a novel functional biodegradable polymer. The polymer was prepared using two different methods, the solvent method, which used acetic anhydride as the solvent, and the direct method. White and brown-colored copolymers were obtained by these two methods, respectively. ^{1}H-NMR spectroscopy and UV-visible spectroscopy revealed that the double bond of 4HCA was almost completely destroyed when the copolymer was prepared by the direct method. On the other hand, copolymers in which the double bond was preserved in the 4HCA–DLLA copolymer were successfully obtained using the solvent method. The solubility of the copolymers obtained by the solvent method in organic solvent was poor. When the copolymer was prepared under a 4HCA:DLLA ratio of 20:80 using the solvent method, the resulting copolymer had high solubility in organic solvents and the double bond was preserved. Moreover, it was confirmed that the 4HCA–DLLA copolymer synthesized by the solvent method was both photoreactive and biodegradable. The 4HCA–DLLA copolymer is expected to be used as basic material for tissue engineering and drug delivery systems, in addition to applications as an orthopedic matrix and a degradable plastic. © 2001 John Wiley & Sons, Inc. J Appl Polym Sci 82: 2357–2364, 2001

Key words: polycondensation; 4-hydroxycinnamic acid; D,L-lactic acid; biodegradable; photoreactivity

INTRODUCTION

Biodegradable polymers are used in a wide variety of areas such as suture materials, bone fixation materials, drug delivery systems, and environmental materials.[1–8] Among these polymers, poly(α-hydroxy acid)s, poly(lactic acid) (PLA), poly(glycolic acid) (PGA), and their copolymers are the most common biodegradable polymers. PLA is particularly well adapted for orthopedic applications, because the mechanical properties, biodegradability, and biocompatibility of this polymer are fairly good. The good mechanical properties are attributed to high crystallinity. On the other hand, because of a simple chemical structure, PLA and PGA are lacking reactive side chains.

Novel applications of biodegradable polymers are a growing area of interest. For example, the

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formation of biodegradable scaffolds for tissue engineering is one of the most desirable applications, and PLA and PGA have been successfully utilized for this purpose. Further application of these novel biodegradable polymers requires development of special characteristics such as chemical reactivity, photoreactivity, and radical reactivity. Many studies have been reported in answer to these demands. For example, Ohya et al. synthesized polydepsipeptides that are copolymers of α-amino acids and α-hydroxy acids.[9–13] This polymer is known to be biodegradable and has a reactive side chain. Mikos et al. has prepared poly(propylene fumarate) (PPF), which is an unsaturated functional biodegradable polymer.[14–20] Hubbell et al. has prepared poly(ethylene glycol)–PLA hydrogels for the prevention of postoperative adhesions.[21,22]

Biodegradable polymers used in the medical field are ideally composed of metabolites found in the living body. Amino acids, lipids, and α-hydroxy acids that have organic functional groups or double bonds are expected to have applications as novel biodegradable functional polymers. Among the known metabolites, in the living body, we utilized adopted hydroxycinnamic acid, an α-hydroxy acid, to synthesize a novel polymer.

Cinnamic acid has been identified as a principal constituent in the botanical exudates from Benzoin (Styrax benzoin),[23] and it exists as a metabolite in other living organisms. Cinnamic acid is well known as a photosensitive compound and is widely used as a component of functional polymers, such as liquid crystal polymers and photoreactive resins made of poly(vinyl alcohol) immobilized with cinnamoyl groups.[24–36]

Hydroxycinnamic acid (HCA) is one of the derivatives of cinnamic acid. HCA similarly exists as a metabolite in the body and like cinnamic acid is also photosensitive.[37] There have been some previous reports regarding the application of HCA for the preparation of polymers.[38–40] Jin et al. used HCA in the synthesis of a degradable liquid crystal polymer.[41] They synthesized a copolymer of 4-hydroxycinnamic acid (4HCA), aromatic hydroxy acid and glycolic acid by polycondensation, and evaluated its properties. However, the application of HCA as the novel functional biodegradable polymer has never been studied detail.

In this study, we attempted to synthesize the polyester of D,L-lactic acid (DLLA) and 4HCA for the purpose of introducing reactive groups to the main PLA chain. The copolymers of 4HCA and DLLA have a double bond, suggesting potential applications as a novel biodegradable photoreactive and radical reactive substance. 4HCA–DLLA is not an alternating copolymer. As such, the bulk properties of 4HCA–DLLA copolymers could potentially change by reaction condition. In this preliminary study, the synthesis and characterization of this copolymer are described.

EXPERIMENTAL

Materials

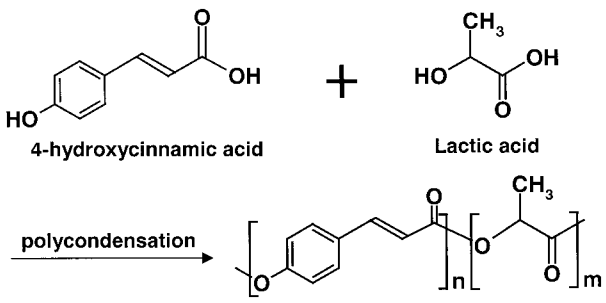
Trans-4-hydroxycinnamic acid was purchased from Tokyo Kasei (Tokyo, Japan). D,L-Lactic acid, diethyl ether, and tetrahydrofuran (THF) were purchased from Wako Pure Chemical Industries (Osaka, Japan). Other chemicals were purchased from Nacalai Tesque (Kyoto, Japan).

Instruments

^{1}H-NMR spectra were recorded on JEOL FX-400 using tetramethylsilane (TMS) as an internal standard. Fourier transform infrared (FTIR) spectra were recorded with a JASCO FT/IR-610 Fourier transformation infrared spectrometer. UV-visible measurements were performed with a JASCO V-550 recording spectrophotometer. The average molecular weight of the 4HCA–DLLA copolymer was determined by gel permeation chromatography (GPC) (Shimadzu LC-6A system with a TSK-GEL Super H2000 column), calibrated with polystyrene standards.

Synthesis of 4HCA–DLLA Copolymer Using Acetic Anhydride (Solvent Method)

The method used is that of Jin with minor modifications. Typically, the polymer was synthesized in a 500-mL, three-necked, round-bottomed flask equipped with a mechanical stirrer with a nitrogen inlet valve and a vacuum distillation outlet, which was connected to a vacuum. A total of 4.9 g (30 mmol) of 4HCA, 12.0 g (120 mmol: 90% lactic acid content) of DLLA solution ,and 14.2 mL of acetic anhydride (as a condensation reagent) were combined in the flask. The flask was then immersed in an electrostatically preheated silicone oil bath at 170°C after previous evacuation and purging with nitrogen five times at room temperature to remove moisture and residual air. The reaction mixture became a clear colorless liquid at 190°C and was maintained at this temperature



Scheme 1 Synthesis of poly(4hydroxycinnamic acid-co-D,L-lactic acid).

until almost all of the solvent had evaporated. The temperature was then raised to 200°C and this temperature was maintained during the 6 h polycondensation process. The melted polymer was removed from the flask, powdered, and then washed with acetone and diethyl ether several times to remove the residual monomers and solvent. The amount of 6.3 g of polymer was obtained with a yield of 35% mol/mol. ^{1}H-NMR (ppm, DMSO): 1.56–2.02 (d, CH_3); 5.42–5.69 (q, C*H*); 6.51–7.52 (m, C*H*CH*Ph*); 7.59–7.84 (d, CHC*HPh*). FTIR (cm^{-1}, KBr pellet): 1750 (C═O); 1610 (C═C). (See Scheme 1.)

Synthesis of 4HCA–DLLA Copolymer (Direct Method)

The direct copolymerization of 4HCA and DLLA acid without solvent was performed as follows. The polymer was synthesized in a 500-mL, three-necked, round-bottomed flask equipped with a mechanical stirrer with a nitrogen inlet valve and a vacuum distillation outlet, which was connected to a vacuum. A total of 20.5 g (125 mmol) of 4HCA and 12.5 g (125 mmol: 90% lactic acid content) of DLLA solution were combined in the flask. The solution was immersed in an electrostatically preheated silicone oil bath at 200°C after the flask was previously evacuated, and purged with nitrogen five times at room temperature to remove moisture and residual air. The temperature was maintained at 200°C during the entire polycondensation process of 6 h. The melted polymer was removed from the flask, and then dissolved in acetone, and washed or precipitated with diethylether. This procedure was repeated at least two times to remove the residual monomers. The amount of 10.6 g of polymer was obtained with a yield of 41% mol/mol. ^{1}H-NMR (ppm, DMSO): 1.29–1.55 (d, CH_3); 5.20 (q, C*H*); 6.62–6.95 (m, C*H*CH*Ph*); 7.58–7.69 (d, CHC*HPh*). FTIR (cm^{-1}, KBr pellet): 1730 (C═O); 1640 (C═C).

Measurement of the 4HCA Content by UV-visible Spectrophotometer

The amount if 8.2 mg (0.05 mol) of 4HCA was dissolved in 1 mL of 1 N NaOH. This sample was diluted to 50 μM with aqueous solution (pH7.4). Similarly, the sample of 25, 12.5, 6.25, and 3.125 μM were prepared. Absorbance of 286 nm of these solutions was measured by UV-visible spectroscopy, and calibration curve was prepared. On the assumption that all of hydroxycinnamic acid is introduced in copolymers, these measurement solutions were controlled the concentration of 4HCA in copolymer solutions adjusted to 50 μM with aqueous solution (pH 7.4). Absorbance of 286 nm was measured by UV-visible spectroscopy, and 4HCA content was evaluated by calibration curve.

Photoreactivity Testing of 4HCA–DLLA Copolymer

4HCA:DLLA = 20:80 copolymer, which was synthesized by the solvent method, was dissolved in chloroform at a concentration of 5.3×10^{-3} wt/vol %. This sample was spread uniformly over the surface of crystal plate and dried at room temperature over night. This plate was coated by copolymer was irradiated with UV 400W UVL-400HA ($\lambda > 290$ nm). A fixed time later, absorbance of 286 nm was measured.

Hydrolysis Testing of 4HCA–DLLA Copolymer

The 4HCA–DLLA copolymer, which was synthesized by the solvent method, was dissolved in chloroform (50.0 mg/mL), and the resulting copolymer solution was deposited onto flat dishes. The solvent was allowed to evaporate at room temperature. Afterward, cast films were immersed in phosphate-buffered saline (; pH 7.4) at 37°C. Samples were withdrawn from the at several degradation times, and washed with distilled water. After wiping, cast films were vacuum dried at room temperature over night, and various analyses were carried out.

RESULTS AND DISCUSSION

Synthesis of 4HCA–DLLA Copolymer

The 4HCA and DLLA copolymers were obtained by both direct and solvent methods, respectively.

Table I Preparation of Poly(4HCA–DLLA)

Synthetic Method	4HCA–DLLA (mol)	Polymerization Time (h)	Yield (%)	4HCA Content[a] (mol %)	4HCA Content[b] (mol %)	Molecular Weight[c] ($M_w \times 10^3$)	Color
Direct method	0 : 100	6	31	0	0	3.20	Transparent
	25 : 75	6	30	22	8	3.87	Brown
		12	51	24	7	4.43	Brown
		17	60	20	6	4.67	Brown
	50 : 50	6	41	43	12	4.27	Brown
		12	47	53	12	6.10	Brown
		14[d]	61	—	—	—	Brown
	75 : 25	6	60	58	18	2.53	Brown
		12	69	60	16	5.33	Brown
		20[d]	70	—	—	—	Brown
	100 : 0	6[d]	83	—	—	—	Brown
Solvent method	0 : 100	6	30	0	0	3.53	Transparent
	10 : 90	6	31	12	8	3.63	Yellow-white
	20 : 80	6	35	18	14	3.60	Yellow-white
		12	48	22	11	4.68	Yellow-white
		20	54	19	9	5.43	Yellow-white
	25 : 75	6	43	ND[e]	10	ND	White
		12	58	ND	15	ND	White
	50 : 50	6	45	ND	49	ND	White
		12	60	ND	50	ND	White
		20	66	ND	46	ND	White
	75 : 25	6	85	ND	53	ND	White
		12	87	ND	60	ND	White
	100 : 0	6	90	ND	61	ND	White

[a] Estimated by ^{1}H-NMR spectrum.
[b] Estimated by UV-Visible at λ_{max} = 286 nm.
[c] Estimated by GPC (PSt standard).
[d] These samples formed gel during the reaction.
[e] ND: not dissolved.

The results are summarized in Table I. The copolymer synthesized by the direct method was brown in color and had high solubility in organic solvents. On the other hand, the copolymer synthesized by the solvent method was milky-white in color and demonstrated poor solubility in organic solvents (the solvents tested were acetone, tetrahydrofuran, dichloromethane, ethyl acetate, carbon tetrachloride, chloroform, isopropanol, ethanol, dimethylsulfoxide, methanol, *N,N*-dimethylformamide, acetonitrile, benzene, and toluene). When the 4HCA content was less than 20 mol %, the copolymers were soluble in some organic solvents (acetone, tetrahydrofuran, dichloromethane, chloroform, dimethylsulfoxide, *N,N*-dimethylformamide, and acetonitrile). The 4HCA content estimated by UV-visible spectra of copolymers prepared by the direct method was lower than that estimated by ^{1}H-NMR spectra. The brown color of the copolymer prepared by the direct method was apparently due to destruction of the 4HCA structure. The color of the copolymer synthesized by the solvent method was milky-white, and there was no difference in 4HCA content based on UV-visible spectra and ^{1}H-NMR spectra. The chemical structure of 4HCA was apparently not destroyed by this method of synthesis. The 4HCA segments maintained their functionality, including photocrosslinkability and radical reactivity, throughout the polycondensation process.

The 4HCA content of copolymers was prepared by both direct and solvent methods were independent of polymerization time, and have good agreement in feed. This indicated that the reaction rate of 4HCA and D,L-lactic acid was continually constant. Yield and molecular weight tended to increase with an increase of polymerization time.

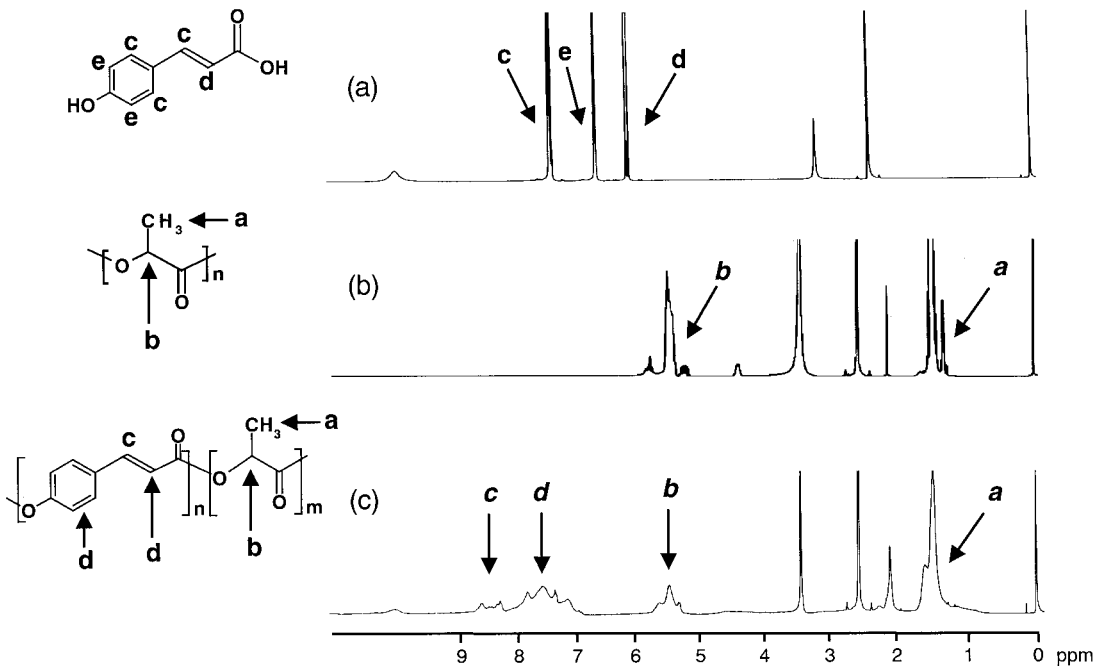


Figure 1 ^{1}H-NMR spectra of 4HCA, DLLA homopolymer, and 4HCA–DLLA copolymer in DMSO-d_6. This copolymer was prepared by the solvent method using a molar ratio of 4HCA:DLLA = 20:80 over a 6 h time course: (a) 4HCA, (b) DLLA homopolymer, and (c) 4HCA–DLLA copolymer.

The result in Table I indicated that the possibility of control of 4HCA and molecular weight to change the polymerization time and synthesis condition.

Figure 1 shows the ^{1}H-NMR spectra of the 4HCA–DLLA copolymer. In the 4HCA–DLLA copolymer, the characteristic peaks representing 4HCA and PDLLA were observed. The double bond peak of 4HCA was shifted from 7.6 ppm in 4HCA to 8.2 ppm in the copolymer. These results indicate that 4HCA was introduced into the copolymer. As shown in Table I, the 4HCA content estimated by ^{1}H-NMR showed good agreement with the molar ratios of 4HCA in feed. These results suggest that the reactivity of 4HCA and DLLA for polycondensation was almost the same.

To confirm that the copolymer obtained was a 4HCA–DLLA copolymer, FTIR spectra analysis was performed. Figure 2 clearly shows that the spectrum of the carbonyl group (C═O; 1750 cm^{-1}) of the 4HCA–DLLA copolymer was different from that of the DLLA homopolymer, 4HCA homopolymer, and their mixtures. These results confirmed that the polymer obtained was the 4HCA–DLLA copolymer. The unsaturated group of 4HCA in the copolymer is shown in Figure 2(2). It is known that a saturated fatty acid polyester is represented by the 1735–1750 cm^{-1} peak of its carbonyl group, and an unsaturated fatty acid polyester is represented by a 1750 cm^{-1} peak. The 4HCA–DLLA copolymer had relatively peak (1750–1770 cm^{-1}), suggesting that the unsaturated group of the 4HCA–DLLA copolymer was preserved through the polycondensation.

Figure 3 shows the GPC profile of the 4HCA–DLLA copolymer. The GPC profile of the copolymer had a single one peak, indicating that the polymer obtained was not a mixture of the respective homopolymers. Overall, the ^{1}H-NMR, FTIR, and GPC results confirmed that the polymer prepared here was the 4HCA–DLLA copolymer.

The molecular weights of the 4HCA–DLLA copolymer obtained were from 2000 to 5000 g/mol. In this study, the target molecular weight was established at less than 10,000, because the 4HCA–DLLA copolymers seemed to have low solubility due to high hydrophobicity and limited flexibility. Moreover, one of the practical uses of the 4HCA–DLLA copolymer is as an additive to poly(α-hydroxy acid)s for improving their functionality, especially surface modifiability when they were molded into the desirable form (films, threads, and sponges).

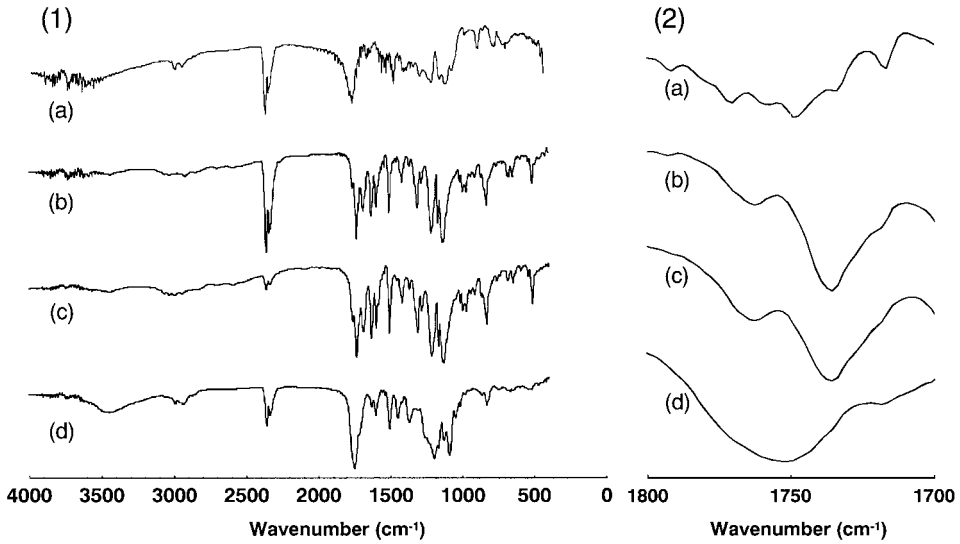


Figure 2 FTIR spectra of the respective homopolymers and the 4HCA–DLLA copolymer. This copolymer was prepared by the solvent method using a molar ratio of 4HCA:DLLA = 20:80 over a 6 h time course: (a) DLLA homopolymer, (b) 4HCA homopolymer, (c) mixture of DLLA homopolymer and 4HCA homopolymer, and (d) 4HCA–DLLA copolymer.

Ajioka et al. reported that high molecular weight PLA (over 3.0×10^5 g/mol) could be synthesized using the proper catalyst under high pressure.[42] It may be possible to obtain a higher molecular weight 4HCA–DLLA copolymer using this method. This is the next goal of our subsequent studies.

Photoreactivity of The Copolymer

Figure 4 shows the UV adsorption spectral changes of the 4HCA–DLLA copolymer film with 400 W UVL-400 HA irradiation ($\lambda > 290$ nm) for 1 h. The absorption peak at 286 nm decreased and shifted with an increase in irradiation time. Cinnamic acid was isomerized with the *cis* and *trans* form and cyclodimerized with UV ($\lambda > 290$ nm) irradiation. In this study, both *cis–trans* isomerization and cyclodimerization occurred. The resulting 4HCA–DLLA copolymer films demonstrated photoreactivity with UV exposure.

Degradation of Copolymer

Figure 5 shows the hydrolysis profiles of the 4HCA–DLLA copolymer and PDLLA films. These

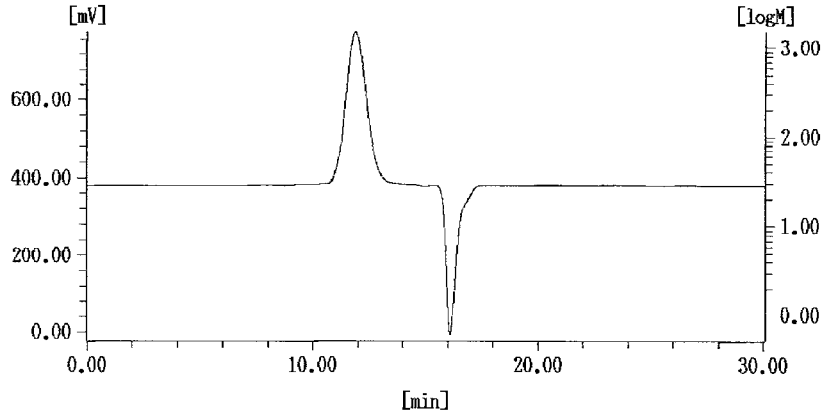


Figure 3 GPC profile of the 4HCA–DLLA copolymer. This copolymer was prepared by the solvent method using a molar ratio of 4HCA:DLLA = 20:80 over a 6 h time course.

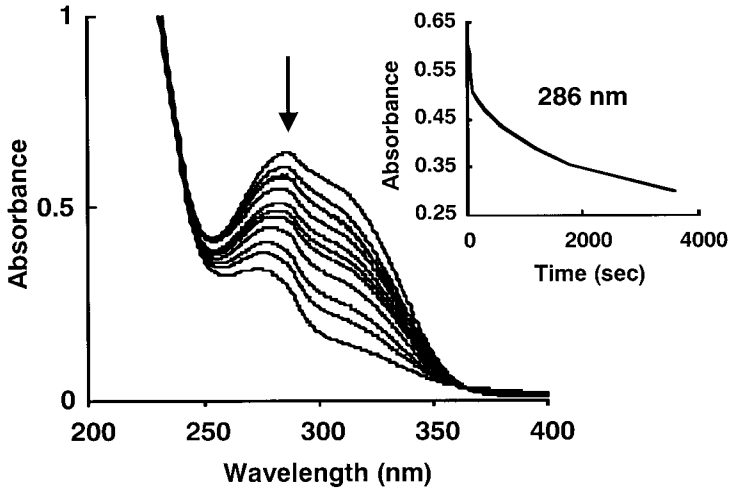


Figure 4 Change of absorbance of 4HCA–DLLA copolymer film with UV irradiation. This copolymer was prepared by the solvent method using a molar ratio of 4HCA:DLLA = 20:80 over a 6 h time course.

results show that the degradation rate of the 4HCA–DLLA copolymer was lower than that of PDLLA. The 4HCA–DLLA copolymer film remained its film shape for 4 weeks, while the PDLLA film degraded in less than 1 week. This difference is due to differences in the diffusion rate of water in polymers, i.e., differences in the hydrophobicity of the bulk polymers. These results clearly indicated that the 4HCA–DLLA copolymer was biodegradable and the degradability of the copolymer can apparently be altered by 4HCA content.

In order to clarify the hydrolytic activity of the copolymer and mimic the degradation *in vivo,* the hydrolysis test was examined in PBS. The detail study of hydrolysis of the copolymer (pH change, autocatalytic reaction and enzymatic degradation) will be a next target.

CONCLUSION

This study confirmed that polyesters of 4HCA and DLLA can be successfully prepared. Among these

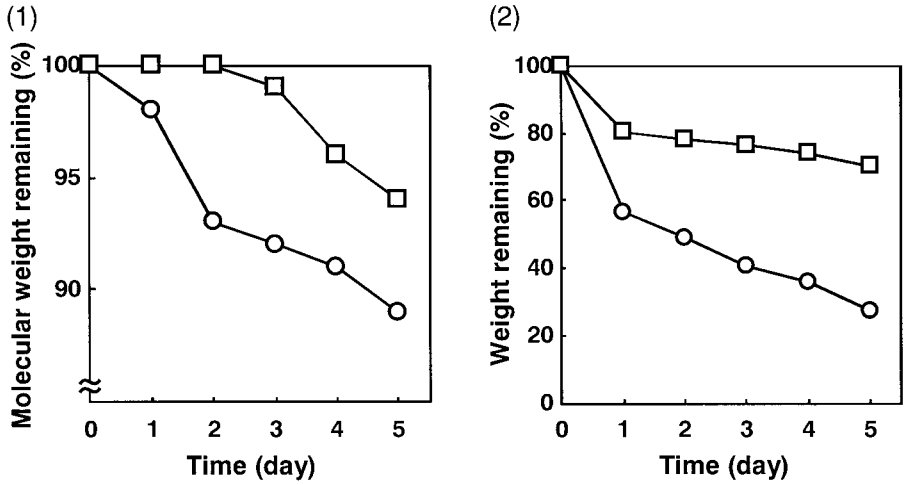


Figure 5 Degradation behavior of DLLA homopolymer (○) and 4HCA-DLLA copolymer (□) in phosphate-buffered saline (pH 7.4) at 37°C: (1) molecular weight remaining and (2) weight remaining.

polyesters, the copolymer with a molar ratio of 4HCA:DLLA = 20:80, which was prepared by the solvent method, had high solubility in organic solvents. It was also confirmed that the 4HCA–DLLA copolymer prepared by the solvent method demonstrated both photoreactivity and biodegradablility. As the resulting 4HCA–DLLA copolymer was comprised of metabolite monomers, the copolymer is anticipated to be biocompatible and to have low toxicity. The practical applications of these copolymers include scaffolding for tissue engineering, matrixes for drug delivery systems, bone graft substitutes, and orthopedic fixation materials. Moreover, it is anticipated that the surface of the 4HCA–DLLA copolymer could be modified by radical addition reactions and photoreactivity, using unsaturated groups. Further studies involving the preparation of a wide variety of copolymers of cinnamic acid derivatives (such as 3HCA and 2HCA) and other α-hydroxy acids (such as glycolic acid) are now in progress.

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