

Synthesis and Characterization of Biodegradable Block Copolymers of Poly(propylene fumarate-*co*-sebacate)-*co*-poly(ethylene glycol) and Poly(ethylene fumarate-*co*-sebacate)-*co*-poly(ethylene glycol)

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ABSTRACT: The synthesis of two low molecular weight linear unsaturated oligoester precursors, poly(propylene fumarate-*co*-sebacate) (PPFS) and poly(ethylene fumarate-*co*-sebacate) (PEFS), are described. PPFS, PEFS, and poly(ethylene glycol) are then used to prepare poly(propylene fumarate-*co*-sebacate)-*co*-poly(ethylene glycol) (PPFS-*co*-PEG) and poly(ethylene fumarate-*co*-sebacate)-*co*-poly(ethylene glycol) (PEFS-*co*-PEG) block copolymers. The products thus obtained are investigated in terms of the molecular weight, composition, structure, thermal properties, and solubility behavior. A number of design parameters including the molecular weights of PPFS, PEFS, and PEG, the reaction

time in the polymer synthesis, and the weight ratio of PEG to PPFS or to PEFS are varied to assess their effects on the product yield and properties. The hydrolytic degradation of PPFS-*co*-PEG and PEFS-*co*-PEG in an isotonic buffer (pH 7.4, 37°C) is investigated, and it is found that the fumarate ester bond cleaves faster than does the sebacate ester bond. © 2004 Wiley Periodicals, Inc. *J Appl Polym Sci* 92: 295–300, 2004

Key words: biodegradable; block copolymers; gel permeation chromatography (GPC); differential scanning calorimetry (DSC)

INTRODUCTION

Poly(propylene fumarate) (PPF) is a linear unsaturated polyester that has been synthesized and described as an injectable biomaterial for bone replacement.^{1–4} Poly(ethylene glycol) (PEG) is nonthrombogenic, has no known toxic side effects, and is widely used in many biomedical applications.⁵ It exhibits solubility both in aqueous and organic solvents and it can be readily derivative through its terminal hydroxyl groups to produce a variety of compounds with lower thrombogenicity.^{6,7} For example, block copolymers of PEG with degradable polyesters like poly(propylene fumarate-*co*-ethylene glycol) [P(PF-*co*-EG)] have been synthesized via condensation of PPF with PEG and studied for biomedical applications.⁸

PPF and its copolymer with PEG, P(PF-*co*-EG), can be crosslinked through the fumarate double bond via an appropriate vinyl monomer. Therefore, [P(PF-*co*-EG)] can be prepared as a precursor and then mixed with appropriate initiators and vinyl monomers and injected into designated physiological sites where it

then hardens, causing minimal damage to the surrounding tissues while providing a barrier between the vascular tissues and the blood stream.^{9,10} Biodegradable unsaturated copolyesters capable of crosslinking have also been synthesized.^{11–16}

We hereby report the synthesis and characterization of poly(propylene fumarate sebacate) (PPFS) and poly(ethylene fumarate sebacate) (PEFS) precursors and their copolymerization with PEG to produce [P(PFS-*co*-EG)] and [P(EFS-*co*-EG)] and the characterization of all four products. PPFS and PEFS and their copolymers with PEG are then crosslinked in the presence of a vinyl monomer like methyl methacrylate (MMA) or styrene. The effects of some design parameters including the molecular weight of PEG, molecular weights of PPFS and PEFS, polymerization time, and ratio of PEG to PPFS or PEFS on the product properties are described.

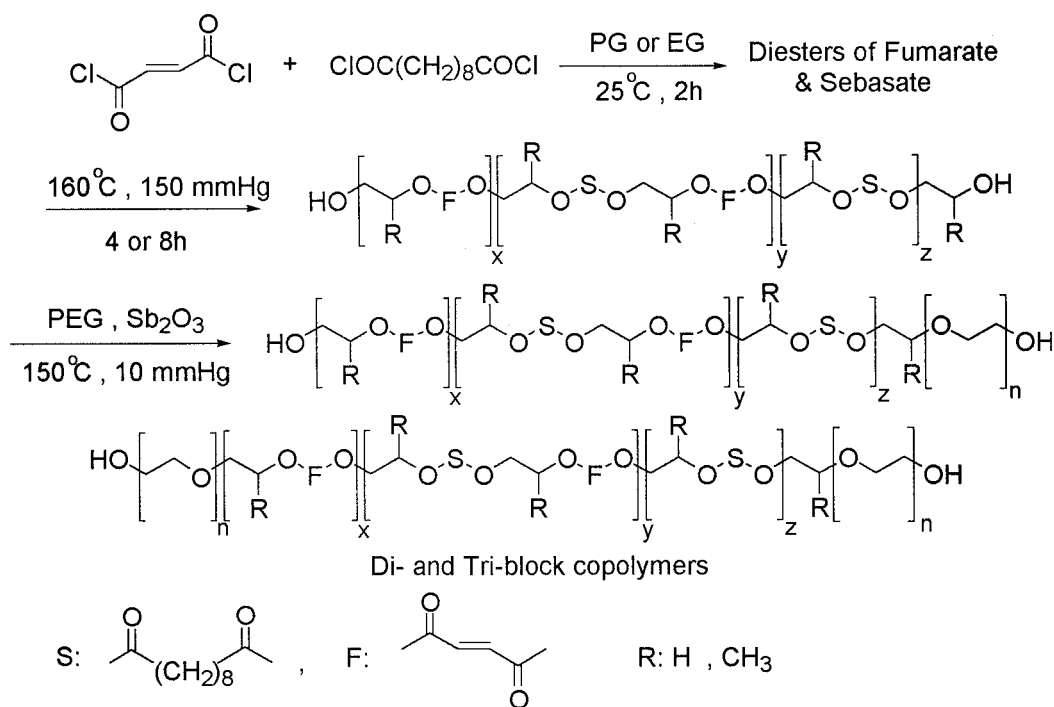
EXPERIMENTAL

Materials

All compounds and solvents used were reagent grade obtained from Merck (Darmstadt, Germany). These include sebacoyl chloride (SC), fumaryl chloride (FC), propylene glycol (PG), ethylene glycol (EG), PEG, MMA, styrene, benzoyl peroxide, antimony trioxide,

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Scheme 1

tetrahydrofuran (THF), chloroform, petroleum ether, tetramethylsilane, and diethyl ether. PG and EG were distilled, and fractions in the boiling ranges of 186–188°C and 195–197°C, respectively, were collected and dried on 0.4-nm molecular sieves.

Instrumentation

Infrared spectra were recorded on a Shimadzu-4300 FTIR (Kyoto, Japan) spectrophotometer. Polymeric samples were either in the form of a solid film or a liquid spread onto NaCl plates. Polymeric powder samples were pressed into KBr pellets. ¹H-NMR and ¹³C-NMR spectra were obtained on a Bruker AC80 (Germany) spectrophotometer using deuterated solvents and tetramethylsilane (TMS) as an internal reference. The molecular weight and molecular weight distribution of the polymers were determined by gel permeation chromatography (GPC) of polymer solutions in THF, using a Waters 150C Model equipped with Styragel columns, with a flow rate 1 mL/min at 30°C and polystyrenes of low polydispersity as standards. Differential scanning calorimetry (DSC) thermograms were obtained on a DSC 4 Perkin-Elmer at a constant heating rate of 10°C/min. Thermogravimetric analysis (TGA) was obtained on a V5.1A DuPont 2000 at a constant heating rate of 10°C/min.

Precursor synthesis

Mixed diesters of fumaric/sebacic acid with PG (or EG) were prepared by slowly adding an equimolar

mixture of FC and SC to an excess of PG (or EG) while stirring at 25°C for 2 h in the absence of any catalyst. The HCl evolved was captured in aqueous NaOH. In the next step, the transesterification of the intermediate was carried out at 160°C, 150 mmHg, for 4 or 8 h, to obtain PPFs or PEFS as the desired precursors, that is, linear unsaturated oligoesters (Scheme 1), while PG (or EG) that is cleaved off is continually removed by condensation.

Copolymer synthesis

Block copolymers of poly(propylene fumarate-*co*-sebacate)-*co*-polyethylene glycol (PPFS-*co*-PEG) and poly(ethylene fumarate-*co*-sebacate)-*co*-poly(ethylene glycol) (PEFS-*co*-PEG) were prepared by adding PEG to the precursors PPFs or PEFS, respectively, at 150°C under a vacuum (10 mmHg), using an antimony trioxide catalyst (the released PG or EG was removed). Formation of the unsaturated copolymers is shown in Scheme 1. The resulting copolymers were purified by pouring their chloroform solutions into petroleum ether (nonsolvent). Precipitates were washed with dry ether and dried under a vacuum at 40°C for 4 h.

RESULTS AND DISCUSSION

Molecular characterization

Table I shows the monomer composition, reaction conditions, and average molecular weights of linear unsaturated precursors PPFs and PEFS. The molecu-

TABLE I
Monomer Composition, Reaction Conditions, and
Average Molecular Weights of Linear Unsaturated
Precursors PPFS and PEFS

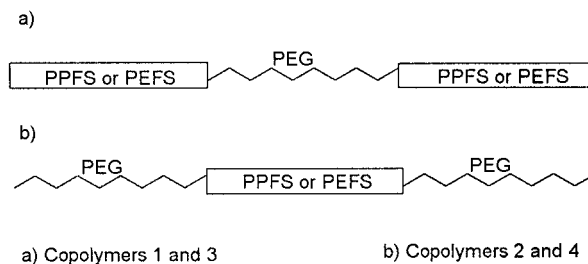
Precursor	Moles of		Reaction time 160°C, 150 mmHg	\bar{M}_n	\bar{M}_w
	FC, SC	PG or EG			
PPFS-1	1, 1	6 PG	4 h	2123	2539
PPFS-2	1, 1	6 PG	8 h	4360	6092
PEFS-1	1, 1	6 EG	4 h	3091	3716
PEFS-2	1, 1	6 EG	8 h	7391	10,768

lar weights of PPFS and PEFS increase with an increase in the reaction time. Under identical polymerization conditions, the average molecular weight of PEFS is about 1.5 that of PPFS. The block copolymers PPFS-*co*-PEG and PEFS-*co*-PEG were prepared by adding either PEG 2000 or 4000 to either of the precursors PPFS-1 or PEFS-1. Table II shows the characteristics of PPFS-1, PEFS-1, and PEG, the reaction conditions, and the properties of the copolymers obtained.

As expected, the chains of copolymers **1** or **3** generally consist of a PEG center block connected to PPFS or PEFS blocks on either of its ends, whereas in the case of copolymer **2** or **4**, PPFS or PEFS form the center block, and the PEG, the end blocks (Scheme 2). As expected, the solubility of the copolymers in water increase with an increase in the weight percent of the PEG. The PPFS precursor (linear unsaturated polyester) is a transparent viscous liquid, while the precursor PEFS is a turbid viscous cream.

¹H-NMR and ¹³C-NMR spectra of PPFS-1 were obtained in deuterated chloroform. ¹H-NMR of the PPFS-1 (Fig. 1) shows peaks belonging to CH₂ protons of PG units in the PPFS-1 chain, which appear in three regions: (a) $\delta = 3.5$ ppm belonging to CH₂ protons of the PG units connecting to terminal OH groups, (b) $\delta = 4.1$ ppm belonging to CH₂ protons of the PG units connecting to sebacate, and (c) $\delta = 4.3$ ppm belonging to CH₂ protons of the PG units connecting to fumarate. The CH protons of the PG units appear as two wide peaks at $\delta = 4.5$ and 5.1 ppm.

Figure 2 shows the ¹³C-NMR spectra of PPFS-1. The FTIR spectra of the PPFS-1 precursor and copolymer **1** are seen in Figure 3, where a broad stretching band for



Scheme 2

the C—O group in the PEG block of copolymer **1** is seen at 1095 cm⁻¹.¹⁷

Thermal analysis

The DSC thermogram of the PPFS-1 precursor [Fig. 4(a)] shows a small wide exothermic peak at 215°C, indicating the detachment and evaporation of the PG units, leading to an increase in molecular weight (due to joining of the neighboring polyester). The sharp endothermic peak at 258°C corresponds to the melting point of the newly formed polyester. Upon further increase in the temperature, more PG units are detached, leading to another exothermic peak at 287°C, indicating the formation of a higher molecular weight polyester, with a melting point that appears as a sharp endothermic peak at 292°C. Degradation of the polyester starts slowly from 295°C and appears as a broad exothermic. The GPC analyses showed that, in the case of PPFS-1 ($M_n = 2123$, $M_w = 2539$), the values increase to $M_n = 4304$ and $M_w = 6511$ at 215°C and to $M_n = 8415$ and $M_w = 12,130$ at 287°C.

The DSC thermogram of the PEFS-1 precursor [Fig. 4(b)] shows a small broad exothermic peak followed by a small broad endothermic one, in the range 35–53°C, which may arise from a crystalline transition. No other noticeable processes seem to occur in the range 52–210°C, while, thereafter, the thermal degradation of the PEFS precursor slowly begins.

The DSC thermograms of the block copolymers **1** and **2** have an almost identical pattern. Copolymer **1** [Fig. 5(a)] shows an endothermic peak at about 50°C for the melting point of the PEG block in the copoly-

TABLE II
Reaction Conditions and Composition of Block Copolymers Prepared from Reacting
Precursors PPFS-1 and PEFS-1 with PEG

Copolymer	Amount of PPFS-1 or PEFS-1	Amount of PEG 2000 or 4000	Reaction time (min) 150°C, 10 mmHg		
				\bar{M}_n	\bar{M}_w
1	PPFS-1 (1 g)	PEG 2000 (0.5 g)	30	5100	7828
2	PPFS-1 (1 g)	PEG 2000 (2 g)	30	7021	11,369
3	PEFS-1 (1 g)	PEG 4000 (0.5 g)	30	8742	10,440
4	PEFS-1 (1 g)	PEG 4000 (2 g)	30	7645	32,479

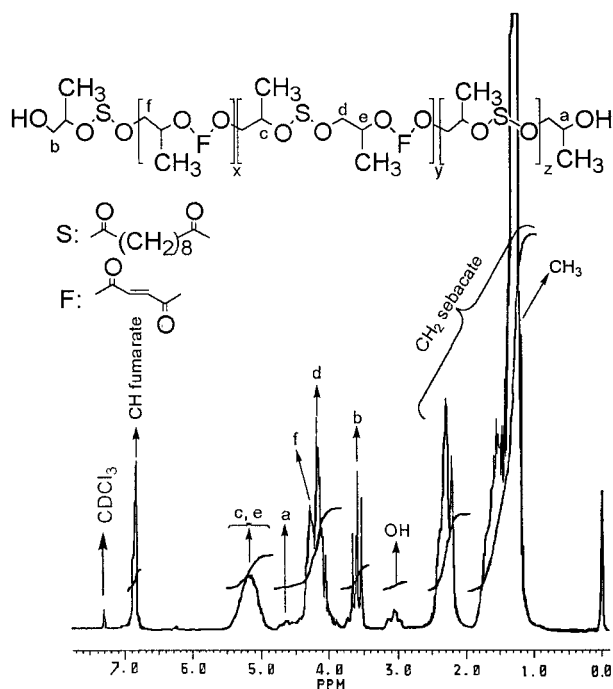


Figure 1 $^1\text{H-NMR}$ spectra of PPFS-1 with monomer composition FC, SC, and PG (1:1:6), prepared at 160°C and 150 mmHg for 4 h in CDCl_3 .

mer and a small wide exothermic peak for partial degradation of PEG at about 190°C . Thereafter begins a gradual degradation of the copolymers which peaks at about 380°C , as verified by the corresponding TGA diagrams.

The DSC thermograms of copolymers 3 and 4 have an almost identical pattern. The DSC copolymer 3 [Fig. 5(b)] has a sharp peak related to the melting point of the PEG block at 50°C . Partial degradation of the PEG block appears as a small wide peak at about 190°C ,

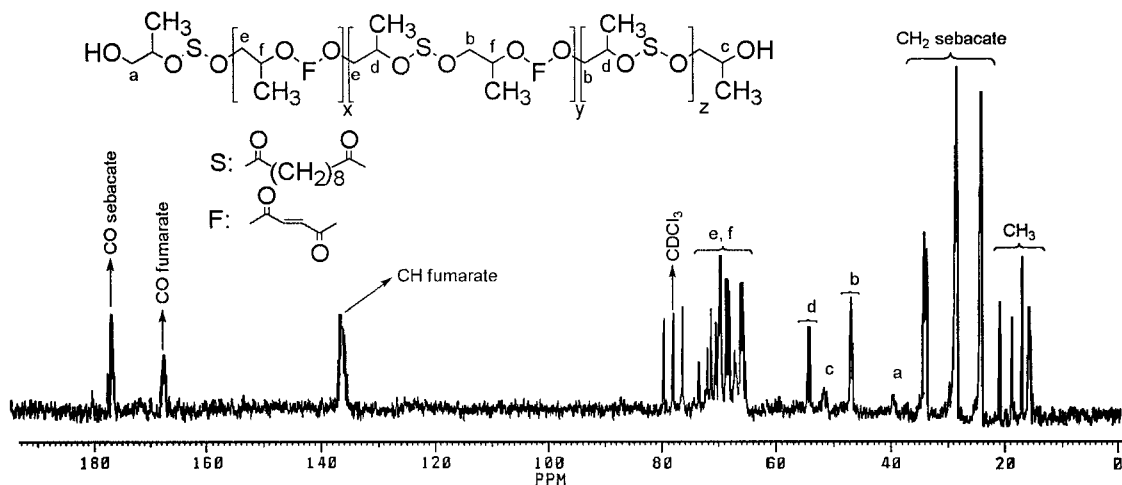


Figure 2 $^{13}\text{C-NMR}$ spectra of PPFS-1 with monomer composition FC, SC, and PG (1:1:6), prepared at 160°C and 150 mmHg for 4 h in CDCl_3 .

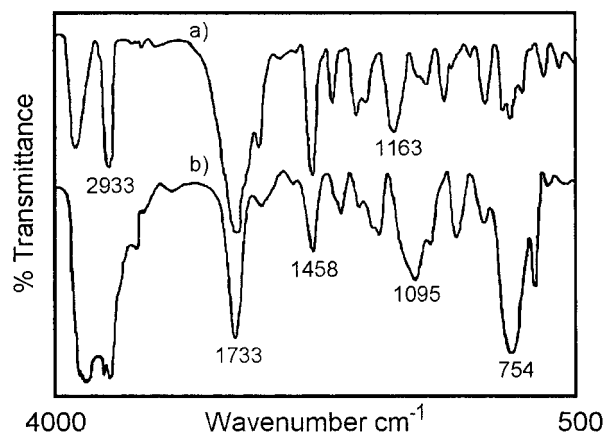


Figure 3 FTIR spectra of (a) PPFS-1 precursor and (b) copolymer 1 showing the frequencies of several important peaks.

and, afterward, the overall degradation of the copolymer slowly initiates, with the main process occurring in the range $380\text{--}400^\circ\text{C}$, as verified by their corresponding TGA diagrams.

The TGA of the PPFS-1 precursor (Fig. 6) was recorded at a temperature scan rate of $10^\circ\text{C}/\text{min}$. About 19% of the weight loss occurs in the range of $175\text{--}280^\circ\text{C}$, due to detachment of the PG units. Most of the weight loss (64.8%) occurs in the range $280\text{--}400^\circ\text{C}$. It is expected that the PG units are first to detach and, after that, fumarate and sebacate monomers are released from the polyester chain. In the range $400\text{--}550^\circ\text{C}$, another weight loss of about 10% is observed.

The TGA diagram of the PEFS-1 precursor (Fig. 6) shows that its thermal degradation occurs in four steps in the range $200\text{--}550^\circ\text{C}$. As expected, at first, the EG units from the chain terminals are released, leading to an increase in the molecular weight of the

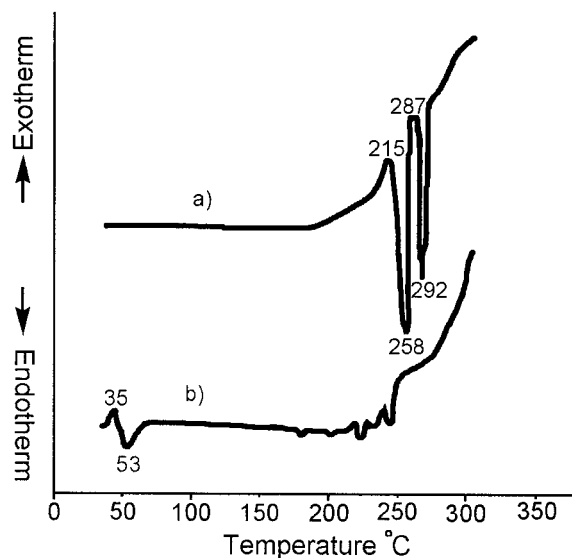


Figure 4 DSC thermograms of (a) PPFS-1 and (b) PEFS-1 precursors between 30 and 300°C at a temperature scan rate of 10°C/min.

polyester. Subsequently, as the temperature increases, the polyester chains begin to degrade, making possible the release of the interior EG units, followed by fumarate and sebacate monomers.

The TGA thermograms of copolymers 1 and 2 look quite similar. In general, the thermal stability of the block copolymers are higher than that of the PPFS-1 precursor, which may be attributed to the presence of heteroatoms in the PEG blocks.¹⁸ The thermal degra-

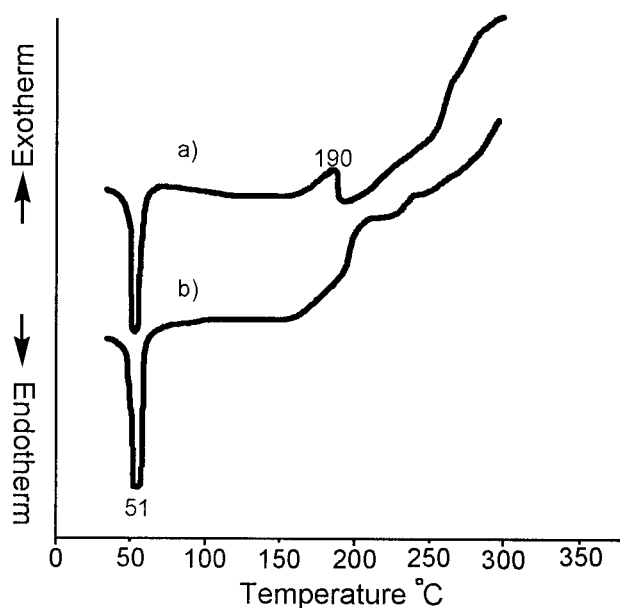


Figure 5 DSC thermograms of copolymers (a) 1 and (b) 3 between 30 and 300°C at a temperature scan rate of 10°C/min.

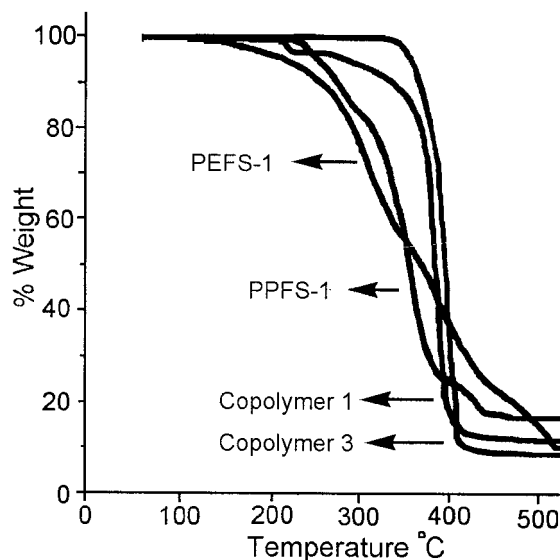


Figure 6 TGA diagrams of PPFS-1 and PEFS-1 precursors and copolymers 1 and 3 between 50 and 550°C at a temperature scan rate of 10°C/min.

dation of copolymer 1 (Fig. 6) is almost complete (98%) at about 400°C.

Copolymerization of the PEFS and PEG yields a thermally more stable product (due probably to PEG heteroatoms in the copolymer). About 5% of the weight loss in copolymer 3 (Fig. 6) occurs below 380°C; about 90%, in the range 380–400°C; and about 5%, above 400°C. A comparison of the TGA data related to copolymers 1 and 3 reveals the superior thermal stability of the latter.

Hydrolytic degradation

The hydrolytic degradations of PPFS-*co*-PEG, copolymer 1, and PEFS-*co*-PEG, copolymer 3, were investigated. For this purpose, 1 g of the desired copolymers 1 and 3 were each stirred in 10 mL of isotonic buffer (pH 7.4) at 37°C for 2 weeks. At different time intervals, 5 mL of the medium (copolymer in water) was removed and centrifuged for 15 min at 14,000 g, the precipitate then dried, and the ¹H-NMR spectra obtained. It was found that the fumarate ester bond cleaves faster than that of the sebacate. Figure 7(a) shows the percent decrease in the area under the ¹H-NMR peak corresponding to the fumarate monomers as a function of hydrolysis time. The fumarate content of the copolymer PPFS-*co*-PEG was completely cleaved off after 10 days, whereas it took 14 days in the case of the copolymer PEFS-*co*-PEG. Figure 7(b) shows the percent transmittance of the OH carboxylic acid prepared by hydrolytic degradation of the copolymer solution that was obtained by the FTIR spectra copolymer solution. Fig-

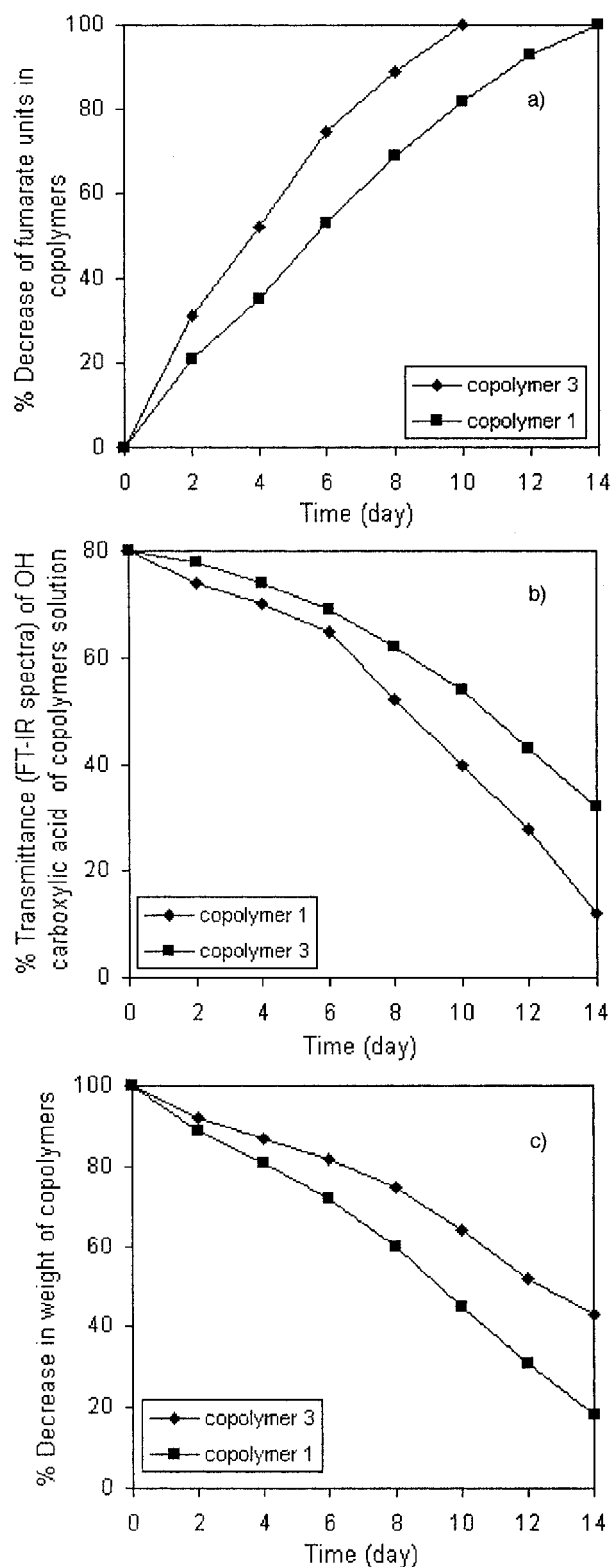


Figure 7 Hydrolytic degradation of copolymers 1 and 3 in 100 mL of isotonic buffer (pH 7.4) at 37°C for 2 weeks: (a) percent decrease of fumarate protons ($^1\text{H-NMR}$ spectra) in copolymers; (b) percent transmittance of OH carboxylic acid (FTIR spectra) in copolymer solution; (c) percent decrease in weight of copolymers.

ure 7(c) shows the percent decrease of the weight of the copolymers at 2 weeks.

CONCLUSIONS

Low molecular weight linear unsaturated polyesters PPFS and PEFS were synthesized. PPFS, PEFS, and PEG were then used to prepare PPFS-*co*-PEG and PEFS-*co*-PEG block copolymers. PPFS and PEFS and their copolymers with PEG were then crosslinked in the presence of a vinyl monomer like MMA or styrene. The products thus obtained were investigated in terms of the molecular weight, composition, structure, and thermal properties by GPC, DSC, TGA, NMR, and FTIR spectroscopies. The hydrolytic degradation of PPFS-*co*-PEG and PEFS-*co*-PEG in aqueous media (pH 7.3, 37°C) shows that the fumarate ester bond cleaves faster than that of the sebacate ester bond. During of hydrolytic degradation of PPFS-*co*-PEG, fumarate units are completely cleaved off after 10 days, whereas it takes 14 days in the case of PEFS-*co*-PEG.

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