

Synthesis and Characterization of a Block Copolymer Consisting of Poly(propylene fumarate) and Poly(ethylene glycol)

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ABSTRACT: Poly(propylene fumarate-*co*-ethylene glycol) has been synthesized in an effort to develop a cross-linkable biomaterial for use as a vascular implant. This copolymer has been fabricated in a block configuration with two to three homopolymer units in series through a transesterification reaction between the linear polyester and the terminal hydroxyl functionalities of the poly(ethylene glycol) (PEG). A number of design parameters including the molecular weights of the two homopolymers, the copolymer reaction time, and the weight percent of PEG were varied in order to assess their effects on the properties of the resulting copolymer. This material has been characterized in terms of structure and composition as well as thermal properties and solubility behavior. All formulations of the copolymer exhibited a single glass transition temperature and a single melting temperature, with a degree of crystallinity which was dependent upon the relative amount of PEG. The copolymers were water soluble and demonstrated enhanced solubilities in organic solvents compared to the parent homopolymers.

Introduction

Restenosis is a series of events which can lead to reocclusion of the arterial space after interventional cardiovascular therapies. Several different techniques have been proposed in order to alleviate this problem, one of which is the use of a polymeric implant. Two important problems with synthetic biodegradable vascular implants have been damage to the surrounding tissue because of the implantation procedure and the thrombogenic nature of the materials in question. In an effort to address these difficulties, a block copolymer of poly(propylene fumarate-*co*-ethylene glycol) [P(PF-*co*-EG)] was developed. PPF is a linear unsaturated molecule that has previously been described as a component of an injectable biomaterial for bone replacement.^{1–6} Many methods have been proposed for the fabrication of PPF in orthopaedic applications, and our copolymer synthesis is based on the formation of PPF, which has been described by Peter et al.⁷ Once this linear polyester is made, it can be cross-linked through the fumarate double bond with an appropriate vinyl monomer.

PEG has previously been described for many biomedical applications in part because, for molecular weights up to 20 000, it is passively excreted by the body with no known toxic side effects.⁸ This particular molecule is distinctive in that it exhibits solubility in both aqueous and organic solvents. In addition, it can be derivatized readily through its terminal hydroxyl groups. It is known to be nonthrombogenic and has been covalently bound to a number of different compounds in order to decrease their thrombogenicity.⁹ Block copolymers of PEG with polyesters have previously been described for use as biomaterials. Nondegradable co-

polyesters include those with segmented polyurethanes^{10,11} and poly(urethane ureas),¹² as well as poly(ethylene terephthalate).¹³ Degradable copolyesters have also been synthesized using poly(α -hydroxy esters),^{14,15} including those with cross-linkable groups,¹⁶ as well as poly(ϵ -caprolactone),¹⁷ and poly(butylene terephthalate).¹⁸ Therefore, in a effort to optimize PPF for use in blood-contacting spaces, we have copolymerized it with PEG. This copolymer is unique in that it is a PEG copolyester which has cross-linkable carbon–carbon double bonds along the polymer backbone. In addition, we believe that by varying both the block lengths of the homopolymers and the relative compositions of the resulting copolymer, we can tailor this polymer to be nonthrombogenic, while retaining its cross-linking ability. This material may be fabricated in a prepolymeric state, mixed with the appropriate initiators, and injected into the vascular space. It will harden, causing minimal damage to the surrounding tissue, while providing a barrier between the vascular tissue and the blood space. The concept of this type of blood-vessel barrier has been previously described for use with other polymer systems.^{19,20}

In this report we describe the synthesis and characterization of P(PF-*co*-EG) in terms of molecular, thermal, and solubility properties, all of which are important considerations in the development of an *in situ* polymerizable system. In order to assess the effects of different design parameters upon physicochemical properties, a fractional factorial design has been employed.²¹ This statistical design allows the evaluation of the degree to which a design parameter affects resulting properties while performing a minimal number of experiments. This approach not only allows the characterization of the copolymer but also provides information about how changing reaction parameters can affect the material properties.

Experimental Section

Polymer Synthesis. Prior to synthesis, the starting reagents, fumaryl chloride (Aldrich, Milwaukee, WI) and

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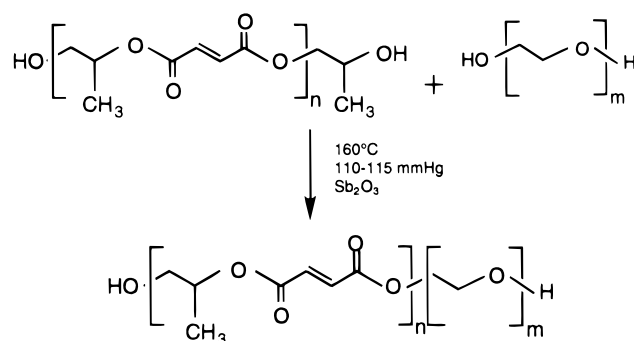
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Scheme 1



propylene glycol (Acros, Pittsburgh, PA), were distilled with boiling ranges of 161–164 and 186–188 °C, respectively. All other chemicals and reagents were used as received from the manufacturer.

PPF was produced as previously described.⁷ Briefly, fumaryl chloride was added dropwise to a 3-fold molar excess of propylene glycol at room temperature in the absence of any catalyst. HCl was given off as a gas and trapped in aqueous NaOH. The resulting intermediate fumaric diester was then purified by solution–precipitation in chloroform and petroleum ether, respectively. The second step was a transesterification of the intermediate to form the linear polyester. Finally, the copolymer was formed by adding poly(ethylene glycol) (Aldrich, Milwaukee, WI) to the reaction vessel at 160 °C under a vacuum of approximately 115 mmHg. Antimony trioxide was added as a basic catalyst, and propylene glycol was removed by condensation. The entire reaction was performed under nitrogen by the use of a sparging apparatus within the reaction vessel. The extent of the copolymerization reaction was monitored using thin layer chromatography as described below. The resulting copolymer was again purified by solution–precipitation as described above. Excess chloroform and petroleum ether were removed by rotoevaporation. Formation of the unsaturated copolymer is shown in Scheme 1.

Thin Layer Chromatography. Thin layer chromatography was used to monitor the disappearance of the PEG homopolymer. Samples of the copolymer were taken every 2 h during the reaction. These samples were then dissolved at a concentration of about 2% (w/v) in chloroform and filtered. Silica gel plates were spotted with 1 mL of this solution and were eluted in 25% (v/v) pyridine in tetrahydrofuran. The plates were then visualized with a 1% solution of iodine in methanol.

Gel Permeation Chromatography. The homopolymer and copolymer molecular weight distributions as well as the copolymer compositions were determined by GPC using a differential refractometer (Waters, Model 410, Milford, MA) and a tunable absorbance detector or ultraviolet detector (Waters, Model 486) connected in series. A Phenogel guard column (50 × 7.8 mm, 5 mm, mixed bed, Phenomenex, Torrance, CA) and a Phenogel column (300 × 7.8 mm, 5 mm, mixed bed, Phenomenex) were used to elute the samples at a 1 mL/min chloroform flow rate. Polystyrene standards were used to obtain a universal calibration curve, and this was then used to calculate the polymer molecular weights.

In addition, the concentrations and compositions of the copolymers were determined by evaluating the total area output of both detectors.²² The area output from each of the starting homopolymer standards was assumed to be directly proportional to the concentration in order to create a number of calibration curves. The concentration of each type of homopolymer in the block copolymer was then determined from the peak area of the copolymer signal. The composition of each copolymer could be calculated as well as the amount of PPF which had been incorporated. The average number of PEG blocks in each copolymer formulation, \bar{b} , was also determined based on the copolymer number average molecular weight, $\bar{M}_{n,\text{copolymer}}$, the starting PEG number average molecular weight, $\bar{M}_{n,\text{PEG}}$, and the weight fraction of PEG, w .

Table 1. Resolution IV Fractional Factorial Design Showing the Eight Combinations of High and Low Values for Four Different Design Parameters

run no.	nominal molecular weight of PEG	reaction time (h)		% PEG by wt
		PPF	copolymer	
1	2000	5	5	0.66
2	2000	5	10	0.33
3	2000	10	5	0.33
4	2000	10	10	0.66
5	4600	5	5	0.33
6	4600	5	10	0.66
7	4600	10	5	0.66
8	4600	10	10	0.33

Number average molecular weight was used as described by Yan and Yuan.²³

$$\bar{b} = \frac{\bar{M}_{n,\text{copolymer}}}{\bar{M}_{n,\text{PEG}}} w \quad (1)$$

Fourier Transform Infrared Spectroscopy. Infrared spectra were taken on a Nicolet 550 spectrometer (Madison, WI). All copolymers were analyzed using a zinc selenide ATR crystal. The resolution of the instrument was specified as 4 cm⁻¹ at a wavenumber of 1000 cm⁻¹.

Nuclear Magnetic Resonance Spectroscopy. Proton and carbon NMR spectra were acquired on a Bruker AC250 NMR spectrometer (¹H = 250 MHz, ¹³C = 62.9 MHz) using CDCl₃ solutions containing TMS. To obtain ¹H spectra with accurate relative signal intensities, conservative conditions were used: 9.3-μs 90° pulse, 2994 Hz (12.0 ppm) spectral width, 10.945 s FID acquisition time, and 5 s relaxation delay before repeating the sequence to improve signal-to-noise. No line broadening was used to process the FID. DEPT-135 ¹³C parameters for the PPF and copolymer samples were as follows: 10 638 Hz (169 ppm) spectral width, 3.08 s FID acquisition time with low power proton decoupling (WALTZ-16 sequence with 109 μs 90° ¹H pulse), and 4 s relaxation delay before repeating the sequence. Line broadening of 0.3 Hz was used to process the FID and improve signal-to-noise. The DEPT-135 ¹³C parameters for the PEG samples were a 5495 Hz (87 ppm) spectral width and a 2.98 s FID acquisition time.

Differential Scanning Calorimetry. A TA Instruments Model 2920 modulated DSC with a mechanical cooling accessory (Newcastle, DE) was used to measure melting points, glass transition temperatures, and heats of fusion for all of the polymer compositions. The sample cell was calibrated with indium (T_m = 429.8 K) and filled with dry helium in order to optimize heat transfer.

The glass transition temperatures were determined from thermal scanning after quenching to -70 °C from a 70 °C melt and then ramping up to 70 °C again at 15 °C/min. Melting temperatures were found after annealing from 70 to -50 °C at 1 °C/min. This was done in order to bring the sample below the crystallization temperature, and then scanning was performed at 10 °C/min to 100 °C. All samples weighed between 4 and 6 mg. Both the onset and midpoint of the T_g and the onset and maximum of the T_m were recorded.

The heat of fusion, ΔH_m , in cal/g was also recorded, and the degree of PEG crystallization, X , was determined from the following equation:

$$X = [\Delta H_m / (\Delta H_m^f w)] 100 \quad (2)$$

Here, w is the weight fraction of PEG in the sample (as determined by GPC) and ΔH_m^f is the theoretical heat of fusion of 100% crystalline PEG (49 cal/g).²⁴

Solubility Determination. Polymers were placed in nine different solvents including water, chloroform, tetrahydrofuran, acetone, dimethylformamide, methanol, toluene, cyclohexane, and ethyl ether. Approximately 0.03 g of sample was dissolved in 3 mL of solvent to create a 1% solution and allowed to sit for 24 h at room temperature.

Table 2. Molecular Weights and Compositions of P(PF-co-EG) Copolymers

polymer	copolymer/PEG ^a		PPF ^b		% PEG in copolymer	% PPF converted	PEG block no., \bar{b}
	\bar{M}_w	\bar{M}_n	\bar{M}_w	\bar{M}_n			
PEG 2K	4570 ± 40	4050 ± 30					
PEG 4.6K	10700 ± 90	9170 ± 370					
PPF 5 h			1200 ± 20	700 ± 20			
PPF 10 h			4120 ± 20	1780 ± 10			
copolymer 1	11170 ± 120	8200 ± 150	900 ± 70	530 ± 20	71	70	1.4
copolymer 2	9400 ± 30	7370 ± 10	1460 ± 120	860 ± 40	58	51	1.1
copolymer 3	10660 ± 20	8050 ± 20	1540 ± 40	1010 ± 90	47	55	0.9
copolymer 4	14060 ± 40	10060 ± 90	1070 ± 130	690 ± 150	65	83	1.6
copolymer 5	14500 ± 30	13090 ± 20	1770 ± 30	930 ± 50	74	21	1.1
copolymer 6	16340 ± 40	13950 ± 40	1340 ± 40	750 ± 30	81	49	1.2
copolymer 7	16740 ± 40	14200 ± 70	1810 ± 20	1050 ± 40	77	59	1.2
copolymer 8	15890 ± 100	14081 ± 160	2310 ± 40	1330 ± 30	59	30	0.9

^a Determined from either the copolymer peak or the starting PEG homopolymer. ^b Determined from either the unconverted PPF peak or the starting PPF homopolymer.

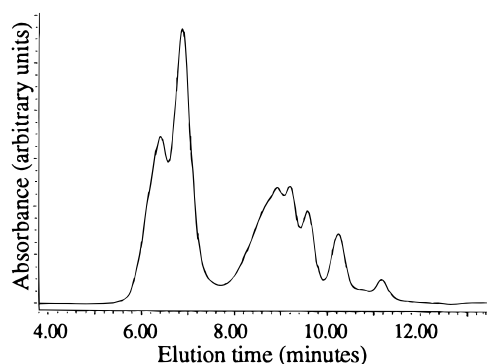


Figure 1. Sample GPC chromatogram showing the copolymer peak at an elution time of 5.8–7.6 min along with the unconverted PPF homopolymer.

Statistical Design. Several parameters were varied in order to assess their effects on the properties of the copolymer. This was accomplished through the use of a resolution IV, two-level, fractional factorial design.²¹ The parameters varied were as follows: PEG nominal molecular weight was 2000 or 4600, transesterification time for the PPF homopolymer was 5 or 10 h, copolymer transesterification time was 5 or 10 h, and the weight percent of PEG was 33% or 66%. The design is given in Table 1. In total, eight copolymers were made.

Results and Discussion

Molecular Characterization. The copolymerization reaction times were chosen such that the PEG could react completely with the PPF, which was in excess in terms of reactive groups. The extent of reaction was monitored by TLC. All of the PEG was shown to disappear within 4 h, and although this technique is primarily qualitative, we and others²⁵ have found TLC to be sensitive down to a 1% homopolymer concentration in a copolymer mixture.

The molecular weights of the starting materials as well as the molecular weights and compositions of the resulting copolymer as determined by GPC are given in Table 2. The molecular weights of the starting PEG polymers are significantly higher than those of the nominal values. This is due to the fact that polystyrene standards were used, and calibration curves were generated using Mark–Houwink constants of $\alpha = 1$ and $K = 0$, in order to remain consistent, since the constants for the copolymer were not known. A sample chromatogram is given in Figure 1. The high molecular weight polymer peak, which occurred from 5.8 to 7.6 min, is the copolymer peak from which the composition was determined. The low molecular weight peaks, from 7.6 to 11.6 min, represent the PPF which had not been

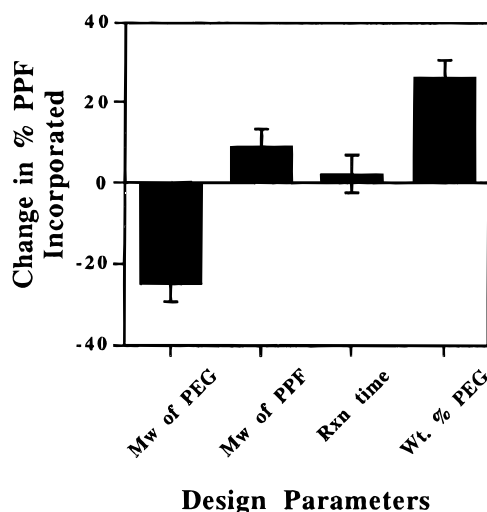


Figure 2. Magnitude of the change on the percent PPF that is incorporated into the copolymers caused by the increasing the values of the four different design parameters. ($n = 3$; standard error = 4.6%).

converted, based on chromatograms of the PPF homopolymer (not shown). The molecular weights of the resulting polymers as compared to the parent homopolymers show that, at most, they are diblock or triblock copolymers, which could explain the bimodal copolymer peak. Additionally, the average number of PEG blocks in each copolymer, \bar{b} , support this conclusion in that there are between one and two PEG blocks in each copolymer formulation.

The effects of the design parameters described in Table 1 on the percentage of PPF which is incorporated into the copolymers are shown in Figure 2. Increasing the reaction time of the starting PPF homopolymer from 5 to 10 h increases the percentage of PPF incorporated by increasing its relative length in the copolymer chain. Increasing the weight percent of PEG from 33% to 66% increases the percentage of PPF incorporated due to the increase in hydroxyl groups that are available to react, while increasing the weight average molecular weight of PEG from 4570 to 10700 decreases the percentage of PPF incorporated due to the relative decrease in available hydroxyl groups. Increasing the copolymerization reaction time from 5 to 10 h has no significant effect due to the fact that all the PEG has already reacted.

The FTIR spectra of copolymers 1 and 5 as well as representative spectra of the starting homopolymers are given in Figure 3. The carbonyl stretch occurs at 1725 cm^{-1} for PPF and copolymers 1–4. For copolymers 5–8 this peak shifted slightly to 1721 cm^{-1} . This peak

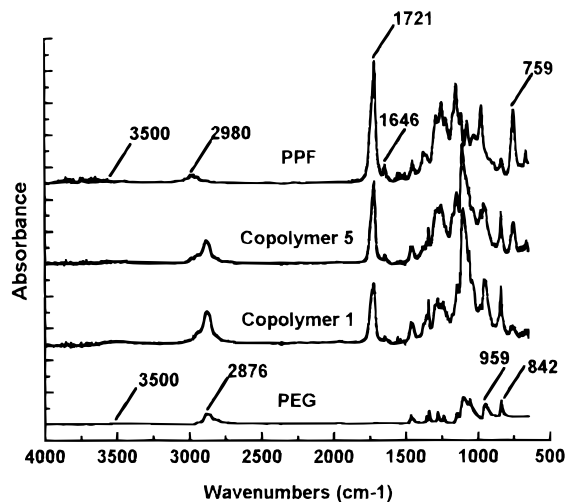


Figure 3. FTIR spectra of copolymer formulations **1** and **5** as well as representative homopolymer spectra showing the frequencies of several important peaks. The spectra were acquired neat and are plotted on a common scale and are offset by 0.5 absorbance units.

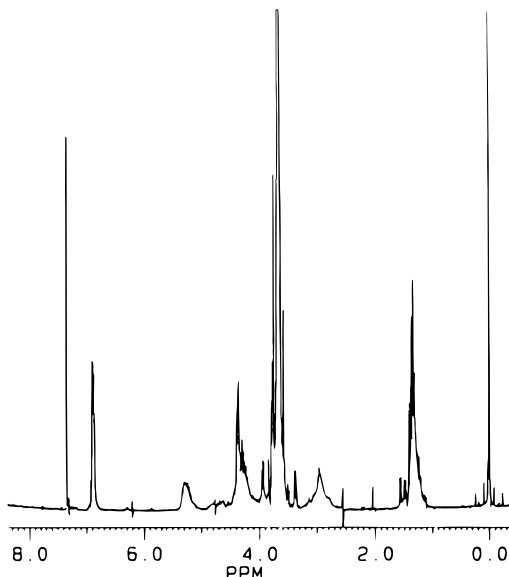


Figure 4. ^1H NMR spectrum of copolymer **4** in CDCl_3 .

moved to lower wavenumbers with increasing molecular weight of the starting PEG. This is probably due to vibrational coupling, which is known to depend upon the length of the polymer chain.^{26,27} The bands at 959 and 842 cm^{-1} are known to be characteristic of the crystalline phase of PEG.²⁸ The peak at 959 cm^{-1} is absent in copolymers **2** and **3**, and the intensity relative to the crystalline bands is lowered in copolymers **5** and **8**. Both of these findings correlate well with the DSC results. The peak at 759 cm^{-1} was assigned to the amorphous phase of the copolymer.

The ^1H NMR spectrum of copolymer **4** is given in Figure 4. The peaks of the expected functional groups can be assigned as follows based on 2-D and DEPT-135 spectra^{26,27} of the intermediate fumaric diester (not shown): olefinic protons at 6.8–7.0 ppm, methyl protons at 1.0–1.6 ppm, and two sets of terminal methine and methylene protons from the addition of the propylene glycol in two possible orientations. The secondary alcohol gives propyl methine protons and propyl methylene protons both at 4.1 ppm. The primary alcohol gives propyl methine protons at 5.2 ppm and propyl methylene protons at 3.8 ppm.⁷ The internal propyl

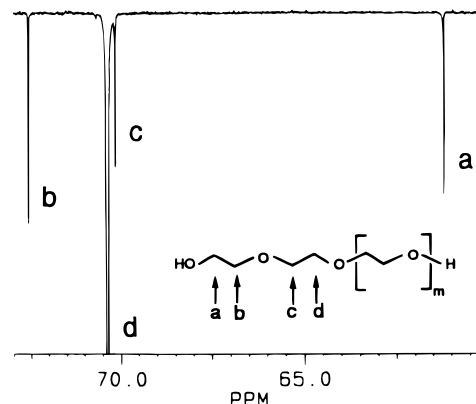


Figure 5. DEPT-135 ^{13}C NMR spectra of PEG with $\bar{M}_w = 4570$ in CDCl_3 .

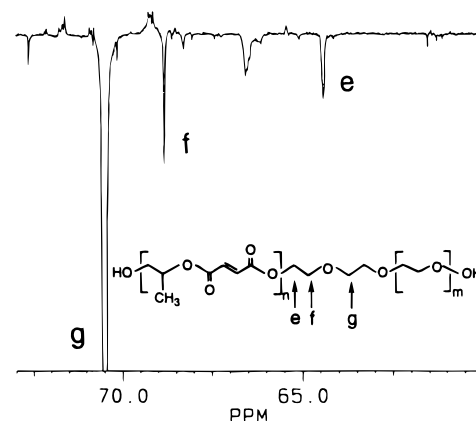


Figure 6. DEPT-135 ^{13}C NMR spectra of copolymer **4**, made from PEG with $\bar{M}_w = 4570$ in CDCl_3 .

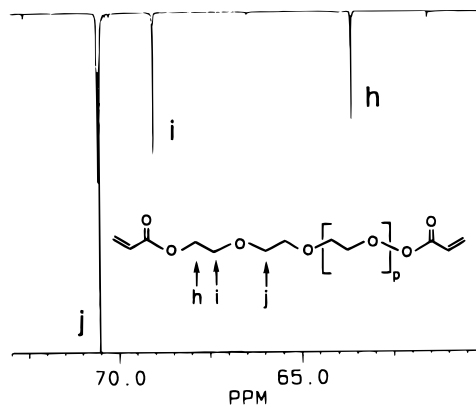


Figure 7. DEPT-135 ^{13}C NMR spectra of PEG-diacrylate with $\bar{M}_n = 500$ in CDCl_3 .

group on the polymer gives methylene protons at 4.1–4.3 ppm and methine protons at 5.2–5.4 ppm. The main ethylene peak is found at a chemical shift of 3.65 ppm with peaks of the ethylene protons near the ester linkage at 3.7 and 5.4 ppm. Products have also been determined which result in the partial saturation of this molecule and which complicate the spectra.⁷ The formation of these products prohibits quantitative analysis of the copolymer composition based on NMR.

The DEPT-135 ^{13}C spectra of the starting PEG homopolymer with a weight average molecular weight, \bar{M}_w , of 4570, copolymer **4**, and PEG-diacrylate (Aldrich, Milwaukee, WI) are given in Figures 5–7, respectively. The spectra of the parent PEG homopolymer shows the interior methylene group carbons all resonating at 70.4 ppm. The three carbon atoms adjacent to the terminal

Table 3. Thermal Properties of P(PF-co-EG) Copolymers

polymer	T_m onset (°C)	T_m max (°C)	T_g onset (°C)	T_g midpt. (°C)	ΔH_f (cal/g)	% crystalline PEG
PEG 2K	47.8 ± 0.4	52.4 ± 0.1			39.1 ± 0.9	
PEG 4.6K	54.8 ± 0.2	58.6 ± 0.4			41.2 ± 1.0	
PPF 5 h			-31.4 ± 1.9	-27.0 ± 1.8		
PPF 10 h			-20.4 ± 0.1	-14.8 ± 0.2		
copolymer 1	26.5 ± 0.3	34.6 ± 0.3	-54.1 ± 0.2	-51.4 ± 0.1	17.5 ± 0.7	13.5
copolymer 2	24.2 ± 0.6	29.7 ± 0.1	-42.2 ± 0.1	-37.7 ± 0.1	0.3 ± 0.1	0.4
copolymer 3	25.0 ± 0.8	28.4 ± 0.8	-43.5 ± 1.3	-38.2 ± 1.2	0.2 ± 0.1	0.2
copolymer 4	28.0 ± 1.7	36.0 ± 0.8	-43.8 ± 2.2	-36.1 ± 2.8	15.4 ± 0.5	12.4
copolymer 5	27.7 ± 1.4	36.7 ± 0.5	-46.1 ± 0.5	-41.9 ± 1.1	9.9 ± 0.2	12.8
copolymer 6	37.7 ± 0.5	45.2 ± 0.2	-46.1 ± 0.8	-41.3 ± 0.6	21.2 ± 0.2	15.2
copolymer 7	39.7 ± 0.6	46.4 ± 0.7	-44.6 ± 3.4	-38.7 ± 4.9	20.1 ± 0.3	15.0
copolymer 8	30.4 ± 0.9	38.8 ± 0.6	-43.7 ± 1.1	-38.1 ± 0.7	8.8 ± 0.3	14.0

hydroxyl groups resonate at 70.1, 72.6, and 61.2 ppm. In the ^{13}C spectrum of copolymer 4, the internal methylene carbons are present at 70.5 ppm, while those peaks representing the terminal carbons are absent or their intensity is greatly reduced relative to the internal peaks. In addition, two new peaks are formed that are not present in either of the starting materials. In order to determine whether these peaks were the result of the terminal ester linkage on the PEG, the spectra of a model compound of PEG-diacrylate was acquired. The internal methylene carbons are present at 70.5 ppm with some residual hydroxy-terminated signals at 70.2, 72.6, and 61.5 ppm. The methylene groups near the ester linkage resonate at 63.6 and 69.0 ppm which correspond well to the new peaks in the copolymer at 64.4 and 68.8 ppm. The peak at 66.5 ppm appears to be an impurity.

Thermal Analysis. The melting temperatures, glass transition temperatures, heats of fusion, and percentages of crystalline PEG as determined by DSC are given in Table 3. Each of the copolymers exhibited a melting peak, although the peaks for the copolymer formulations in which the PEG content was less than or equal to 58% were very small. Below this value the PPF concentration was too high for the copolymer to form many crystallites. As the PEG concentration increased, the melting peaks increased in temperature and narrowed, which indicates that larger and more uniform crystallites were being formed. The changes in the melting temperature due to changes in the reaction design parameters given in Table 1 indicate that the only significant increases in the melting temperature were caused by increasing either the molecular weight or the percentage of the PEG component. A similar analysis on the effects of the design parameters on the percent crystalline PEG again indicates that the most significant increases are achieved by increasing either the molecular weight or the weight percent of PEG (data not shown).

The glass transition temperatures of PPF were -31.35 and -20.44 °C for the low and high molecular weight polymers, respectively. The glass transition temperature for PEG was not evident even when the scanning run was initiated at -150 °C; however, the literature value for PEG of nominal molecular weight 2000 is -60 °C.²⁹ A single glass transition temperature was observed in all copolymer formulations between -42.24 and -54.14 °C. The presence of a single T_g between that of the starting homopolymers suggests the absence of microphase separation for all formulations of the copolymer.³⁰

Solubility Properties. The solubility data demonstrated that the copolymer formulations were highly amphiphilic. Both molecular weights of PEG examined were insoluble in ethyl ether and cyclohexane, but the

high molecular weight PEG was also insoluble in acetone, toluene, DMF, and THF. The low molecular weight formulation of PPF was insoluble in water and cyclohexane, while the high molecular weight formulation, which had been reacted for 10 h, was insoluble in water, methanol, and cyclohexane. The resulting copolymers, however, were soluble in water as well as all organic solvents with the exception of ethyl ether and cyclohexane. Thus, the copolymer retained the good solubility characteristics of both the parent homopolymers.

Conclusions

The terminal hydroxyl groups of poly(ethylene glycol) were reacted with poly(propylene fumarate) in a transesterification reaction to form an ester linkage between the two homopolymers. Several different copolymer formulations were investigated, and their molecular weights and compositions were determined. It was found that this reaction scheme produced a copolymer consisting primarily of diblock and triblock forms with the average PEG block number between 0.9 and 1.6. These copolymers all showed a melting peak and a single glass transition temperature, and there was no evidence of microphase separation. In addition, these copolymers showed enhanced solubilities compared to those of the parent homopolymers.

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