Diblock Copolymers Based on Dihydroxyacetone and Ethylene Glycol: Synthesis, Characterization, and Nanoparticle Formulation

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Polymeric biomaterials have played an integral role in tissue engineering, biomedical devices, and targeted drug delivery. Block copolymers are especially important because their physical and chemical properties can be controlled by adjusting the ratio, size, and type of constituting blocks. Herein, the synthesis and characterization of diblock copolymers composed of poly(ethylene glycol) and a polycarbonate based on the metabolic intermediate, dihydroxyacetone, are reported. The length of the dihydroxyacetone-based block was controlled by adjusting the reactant feed ratios and initiator injection conditions. Intermediates and final products were characterized via ^{1}H NMR, GPC, DSC, TGA, and diffusion-ordered NMR spectroscopy. The dihydroxyacetone-based hompolymer is insoluble in water and most organic solvents, but is hydrophilic in nature. This, coupled with poly(ethylene glycol)'s solubility characteristics, allows the block copolymer to form nanoparticles in aqueous and organic anti-solvents. Dynamic light scattering and TEM results indicated the formation of spherical nanoparticles.

Introduction

Polymeric biomaterials have played an integral role in the fields of tissue engineering, targeted drug and gene delivery, and biomedical devices.[1−4] Block copolymers, consisting of hydrophilic and hydrophobic segments, are especially important in this field because their physical and chemical properties can be controlled by adjusting the ratio, size, and type of the constituting blocks.[5−7]

The synthesis of biomaterials that possess desirable physical and chemical properties, and that also exhibit biocompatibility and low immunogenicity, can be a significant challenge. One successful strategy to developing such materials is to build block copolymers composed of well-characterized inert polymers and from naturally occurring biomolecules that, in the right ratios, can impart desirable properties for intricate biological applications.[8,9]

Poly(ethylene glycol) (PEG)-based block copolymers have received much attention in this field because of PEG's favorable chemical and biological properties, especially its hydrophilicity, solubility in water and organic solvents, termination with well-defined reactive groups, biocompatibility, and low immunogenicity.[10−12] Certain polycarbonates, both aliphatic and aromatic, have also become increasingly investigated for use in this field. Their biocompatibility and low toxicity make them attractive as biomaterials.[13−20] PEG−polycarbonate block copolymers have received some attention recently.[21−25] Their amphiphilic nature leads to the formation of micelles in aqueous environments, with the hydrophobic polymer forming the core of the micelle and the hydrophilic blocks forming the corona. The hydrophobic core allows the incorporation of certain lipophilic drugs, while the corona shell serves as a stabilizing interface between the hydrophobic core and the surrounding environment. This design has been important for the development of targeted drug delivery vehicles.[7,22,23,26−28]

Dihydroxyacetone (DHA) is a glucolytic metabolite. Specifically, it is an intermediate in the conversion of glucose to pyruvate.[29] It is accepted by the FDA for human use as the active ingredient in sunless tanning lotions and is readily manufactured as a fermentative product from corn syrup and methanol.[30,31] Previously, DHA was used as a building block for polycarbonates as well as poly(carbonate-acetals).[32,33]

In this paper, we adopted the aforementioned diblock copolymer strategy and described the synthesis and characterization of new diblock copolymers comprised of PEG and a polycarbonate based on DHA. The diblock copolymer was synthesized by ring-opening polymerization of a protected DHA-based monomer in the presence of monomethoxy-poly(ethylene glycol) (MPEG) and stannous octoate ($Sn(Oct)_2$). Subsequent deprotection in the presence of trifluoroacetic acid (TFA) and water yielded the desired polymer. This polymer incorporates some of the physical, chemical, and biological properties of both constituting polymers. In particular, the polymer spontaneously forms monodisperse nanoparticles in both aqueous and organic anti-solvents spanning a range of polarities, giving it the potential for use in systemic drug delivery applications.

Materials and Methods

Monomethoxy-poly(ethylene glycol) (MPEG) (M_w 5000) was purchased from Polysciences (Warrington, PA). Prior to use, MPEG was dried by azeotropic distillation in toluene. Dihydroxyacetone dimer (DHA), *p*-toluenesulfonic acid, trimethyl orthoformate, $Sn(Oct)_2$, ethyl chloroformate, and 5% phosphotungstic acid were purchased from Sigma-Aldrich (St. Louis, MO) and used as received. Triethylamine, tetrahydrofuran (THF), dichloromethane (CH_2Cl_2), diethyl ether, methanol, toluene, and TFA were purchased from VWR (West Chester, PA) and used as received. Carbon-coated EM grids were purchased from

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Table 1. Weight-Averaged Molecular Weight (M_w), Number-Averaged Molecular Weight (M_n), and Polydispersity Indices (PI = M_w/M_n) of Each of the VI Copolymers after Synthesis as from GPC Using Polystyrene Standards[a]

sample	GPC M_w	GPC M_n	PI	DP MPEG	M_n MPEG	DP VI	M_n VI	total M_n
VI 5000−3000	9500	8000	1.19	101	4400	13	2100	6500
VI 5000−5000	11 600	10 300	1.13	93	4300	26	4200	8500
VI 5000−10 000	18 300	15 200	1.20	99	4400	78	12 600	17 000

[a] The degree of polymerization (DP) and the M_n of each polymer were calculated from ^{1}H NMR data using end group analysis. All M_n data were rounded to the nearest 100. MPEG GPC M_w = 5900 and M_n = 5400. MPEG ^{1}H NMR DP = 127 and M_n = 5600. The discrepancy between the MPEG ^{1}H NMR DP and M_n as compared to the MPEG in the block copolymer values is possibly due to the high molecular weight impurities in commercial MPEG as was also observed in the MPEG GPC trace.

Electron Microscopy Science (Hatfield, PA). ^{1}H NMR spectra were recorded on an Inova 600 MHz spectrometer. Gel permeation chromatography (GPC) was carried out using PSS SDV columns 500A, 50A, and linear M (in series) with a THF mobile phase (1 mL/min) and polystyrene standards with UV (Waters 486) and RI (Waters 2410) detection. Thermal analysis was performed with either a TA instrument Q1000 calorimeter with a heating/cooling rate of 5 °C/min and nitrogen flow rate of 50 mL/min or a TA instruments Q500 thermogravimetric analyzer with a heating rate of 10 °C/min and nitrogen flow rate of 50 mL/min.

2,2-Dimethoxy-propane-1,3-diol (III). This was synthesized by modification of a previously published method.[34] DHA dimer (62.5 g, 0.3475139 mol), trimethylorthoformate (76.1 mL, 0.695 mol), and *p*-toluenesulfonic acid (250 mg) were combined in 700 mL of methanol and stirred for 12 h at room temperature. Next, 750 mg of Na_2CO_3 was added and the reaction mixture was stirred for an additional 12 h, after which the mixture was filtered and solvent was removed in vacuo. The resulting solid was recrystallized from ethyl ether to give 27.0 g of III (43%). ^{1}H NMR (D_2O) δ: 3.58 (s; 4H), 3.24 (s; 6H).

2,2-Dimethoxypropylene Carbonate (IV). This was synthesized by dropwise addition of a solution of triethylamine (27.8 mL, 0.2 mol) in 50 mL of THF to a stirring solution of III (14.3 g, 105 mmol) and ethylchloroformate (19 mL, 0.2 mol) in 200 mL of THF over 15 min in an ice bath. After the addition was complete, the reaction mixture was stirred at room temperature for 3 h, after which time the mixture was filtered and THF was removed in vacuo. The product was recrystallized from ethyl ether three times to yield IV (5.5 g, 38.5%). ^{1}H NMR ($CDCl_3$) δ: 4.28 (s; 4H), 3.30 (s; 6H). Anal. Calcd: C, 44.44; H, 6.17. Found: C, 44.60; H, 6.19.

Poly(MPEG-*b*-2,2-dimethoxy-1,3-propylene carbonate) (VI). Prior to each reaction, a 5 mL pear-shaped flask was flame-dried and evacuated for 10 min. In the 5000−3000 case, 550 mg of MPEG and 470 mg of IV were added to the reaction vessel immediately following evacuation. This was evacuated for another 5 min, immediately after which 10 μL of $Sn(Oct)_2$ was added. This was evacuated again for 5 s, and the reaction was run at 100 °C in a paraffin oil bath. In the 5000−5000 case, 250 mg of MPEG and 420 mg of IV were added, and 100 mg of MPEG and 520 mg of IV were added for the 5000−10 000 polymers. In both cases, the reaction vessel was evacuated for 5 min and placed in a 100 °C paraffin oil bath. After both components melted (1 min), the mixture was allowed to stir for 30 s, and 8.0 μL of $Sn(Oct)_2$ was quickly injected into the melt and the reaction vessel was evacuated again. All three reactions were carried out for as long as efficient magnetic stirring was possible (2−3 h), after which time the mixture was dissolved in 1 mL of dichloromethane and the polymer was obtained by dropwise addition into 25 mL of diethyl ether and dried under vacuum (5000−3000, 600 mg, 59%; 5000−5000, 400 mg, 60%; 50 000−10 000, 350 mg, 56%). Injecting the initiator into the melt in the 5000−5000 and 5000−10 000 cases was important to reproducibly obtain these higher molecular weights. Degrees of polymerization (DP) and molecular weights as obtained by GPC and ^{1}H NMR are summarized in Table 1. ^{1}H NMR ($CDCl_3$) δ: 4.28 (s; 4H), 3.30 (s; 6H), 3.65 (s; 4H), 3.40 (s; 3H).

Poly(MPEG-*b*-2-oxypropylene carbonate) (VII) (MPEG−pDHA). This was synthesized by acid deprotection of VI using a TFA−water mixture (4:1) for 12 h at room temperature. Deacetalization of 300 mg of the 5000−3000 polymer was carried out in 2.75 mL of TFA−water. The deprotected polymer was then obtained by dropwise addition into 25 mL of diethyl ether and dried under vacuum (245 mg, 82%). Deacetalization of 250 mg of the 5000−5000 polymer was carried out in 3.25 mL of TFA−water, while 200 mg of the 5000−10 000 was carried out in 3.0 mL of TFA−water. The 5000−5000 and 5000−10 000 polymers precipitated from solution and were washed with diethyl ether and dried under vacuum (220 mg, 88%, were obtained for the 5000−5000 polymer, while 150 mg, 75%, were obtained for the 5000−10 000 case). DP and molecular weights as obtained by ^{1}H NMR are summarized in Table 2. ^{1}H NMR (DMSO-d_6) δ: 5.00 (s; 4H), 3.50 (s; 4H), 3.24 (s; 3H).

Table 2. Number-Averaged Molecular Weight (M_n) of the MPEG and pDHA Segments of Each Polymer Calculated from ^{1}H NMR Data Using End Group Analysis[a]

sample	DP MPEG	M_n MPEG	DP pDHA	M_n pDHA	total M_n
MPEG−pDHA 5000−3000	102	4500	16	1800	6300
MPEG−pDHA 5000−5000	92	4000	25	2900	6900

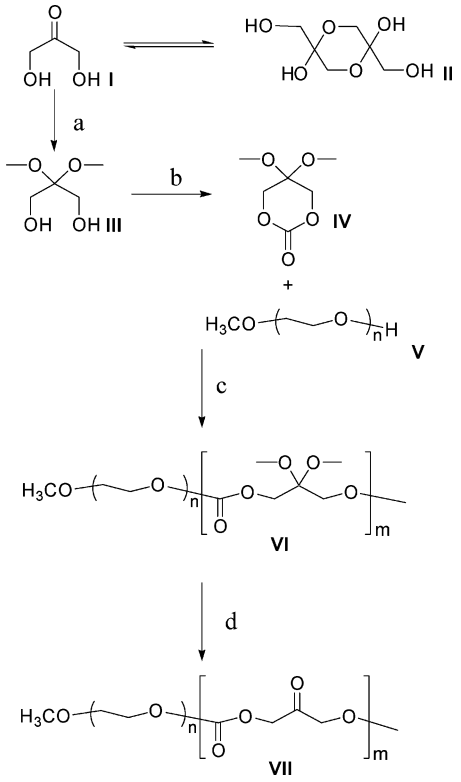
[a] All M_n data were rounded to the nearest 100.

Diffusion-Ordered NMR Spectroscopy (DOSY). Typically 5−6 mg of sample was dissolved in 1 mL of DMSO-d_6. ^{1}H and ^{1}H detected DOSY experiments were performed at 22 °C on an Inova 600 MHz spectrometer equipped with a triple resonance probehead capable of producing gradients in the *z* direction with strength of up to 70 G cm^{-1}. DOSY experiments were performed using a bipolar pulse pair stimulated echo experiment (Dbppste). The gradient strength was logarithmically incremented in 16 steps from 1.15 to 60 G cm^{-1}. Diffusion times and gradient pulse durations were optimized for each experiment to achieve a 90% decrease in the resonance intensity at the largest gradient amplitude. Diffusion times varied between 600 and 900 ms, and bipolar rectangular gradient pulses of 2 ms were employed. Data were analyzed using the VnmrJ 1.1B, Varian Inc. software package.

Poly(2-oxypropylene carbonate) (pDHA). A 5 mL pear-shaped flask was flame-dried and evacuated for 10 min prior to the reaction. Immediately following the evacuation, 200 mg of IV was added to the reaction vessel. This was evacuated for 5 min, after which 100 μL of $Sn(Oct)_2$ was added. This was evacuated for 15 s, and the reaction was run at 100 °C in a paraffin oil bath. The reaction was carried out for as long as efficient magnetic stirring was possible (2−3 h), after which time the mixture was dissolved in 1 mL of dichloromethane and the polymer, poly(2,2-dimethoxy-1,3-propylene carbonate), was obtained by precipitation into methanol and dried under vacuum (110 mg, 55%). ^{1}H NMR ($CDCl_3$) δ: 4.28 (s; 4H), 3.30 (s; 6H); M_n = 5700, M_w = 7700. Partial deprotection was carried out using 90 mg of polymer in 0.80 mL of TFA−water (4:1 v/v). This ratio was lower than the previously published ratio of 1 mL of TFA−water (4:1 v/v) per 100 mg of polymer to ensure partial deprotection and polymer solubility.[33] ^{1}H NMR (DMSO-d_6) δ: 5.00 (s; 4H), 4.18 (s; 4H), 3.20 (s; 6H). This resulted in 85% deprotection based on the ratio of the deprotected polymer protons (δ 5.00) to the total polymer protons in the backbone (δ 4.90 + δ 4.18) as obtained using ^{1}H NMR in DMSO-d_6.

Nanoparticle Preparation and Characterization. Three types of nanoparticles were prepared using three different anti-solvents. In the

Scheme 1. Synthetic Route to Poly(MPEG-*b*-2-oxypropylene carbonate), MPEG−pDHA (VII): (a) Trimethyl Orthoformate/*p*-Toluene Sulfonic Acid; (b) Ethylchloroformate/Triethylamine; (c) Stannous Octoate/100 °C; (d) Trifluoroacetic Acid/H_2O[a]



[a] Nomenclature: (I) DHA; (II) DHA dimer; (III) 2,2-dimethoxy-1,3-propane diol; (IV) 2,2-dimethoxy-1,3-propylene carbonate; (V) monomethoxy-PEG (MPEG); (VI) poly(MPEG-*b*-2,2-dimethoxy-1,3-propylene carbonate); (VII) poly(MPEG-*b*-2-oxypropylene carbonate) (pDHA).

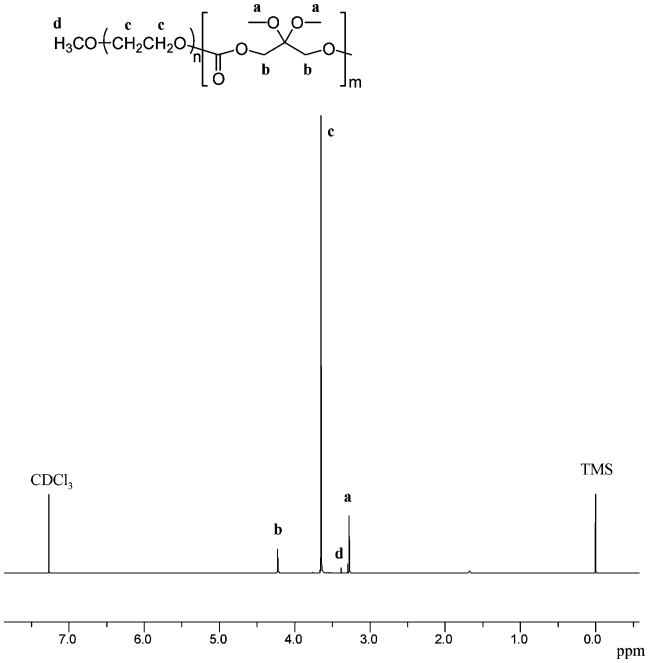


Figure 1. ^{1}H NMR spectrum of poly(MPEG-*b*-2,2-dimethoxy-1,3-propylene carbonate) (VI) in $CDCl_3$.

first case, 100 mg of MPEG−pDHA 5000−3000 was dissolved in 1.0 mL of DMSO. This was added to a 100 mL Erlenmeyer flask containing 50 mL of water gently stirring at room temperature. After addition was complete, the solution was allowed to stir gently at room temperature for 5 min. In the second case, 90 mg of MPEG−pDHA

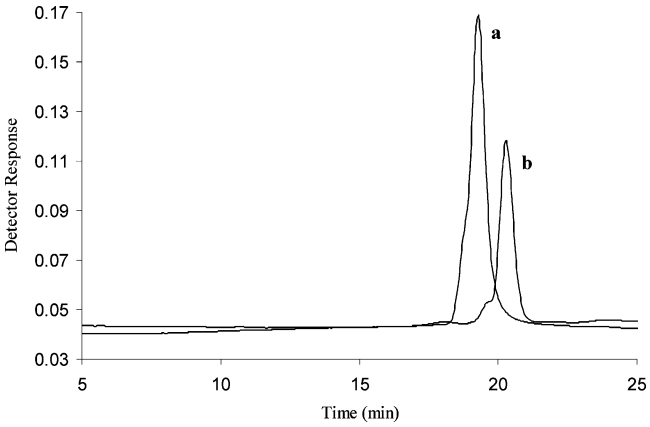


Figure 2. An example of (a) poly(MPEG-*b*-2,2-dimethoxy-1,3-propylene carbonate) (VI) and (b) MPEG GPC. This illustrates the formation of a block copolymer with a narrow molecular weight distribution and the absence of homopolymerization.

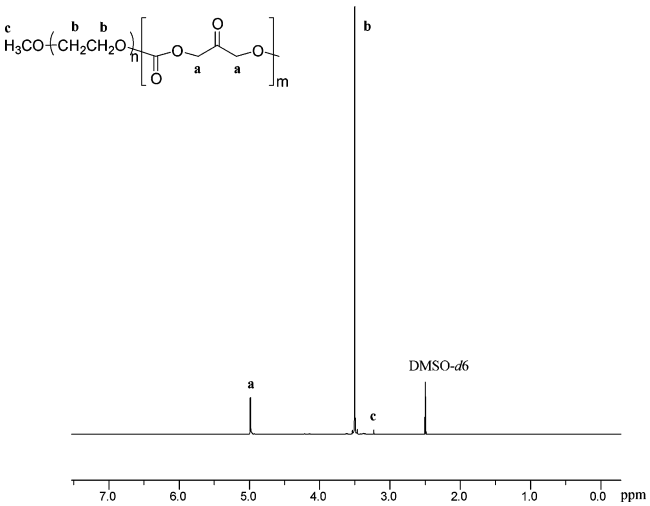


Figure 3. ^{1}H NMR spectrum of poly(MPEG-*b*-2-oxypropylene carbonate) (VII) in DMSO-d_6.

5000−3000 was dissolved in 10 mL of DMSO. This was added to a 250 mL Erlenmeyer flask containing 90 mL of ethanol gently stirring at room temperature. In the third case, 70 mg of MPEG-pDHA 5000−3000 was dissolved in 1.0 mL of DMSO. This was added to a 100 mL Erlenmeyer flask containing 50 mL of dichloromethane gently stirring at room temperature. After addition was complete, the solution was allowed to stir gently at room temperature for 5 min. The size distribution, determined by dynamic light scattering (DLS), and zeta potential measurements of the nanoparticles were determined with a 4 mW He−Ne laser at 25 °C (Zetasizer nano ZS, Malvern Instruments).

The size and morphology of the nanoparticles were also investigated using transmission electron microscopy (TEM, 80 kV Phillips Morgagni 268). Specimens were prepared by first diluting the water-suspended nanoparticles 2-fold, and then dropping 10 μL of solution onto carbon-coated EM grids. The solution was allowed to settle on the grid for 10 min, and then dried off the surface by gentle adsorption with a tissue. The nanoparticles on the grid were then stained with 5 wt % phosphotungstic acid.

Results and Discussion

The utilization of DHA in organic chemistry is hindered because it exists as both a monomer and a dihemiacetal dimer (II) in solution and is also reactive with primary amines.[31] To synthesize DHA-based polycarbonates, a synthetic strategy was employed to lock DHA in its monomeric form through conversion of its C2 carbonyl into a dimethoxy acetal (III),

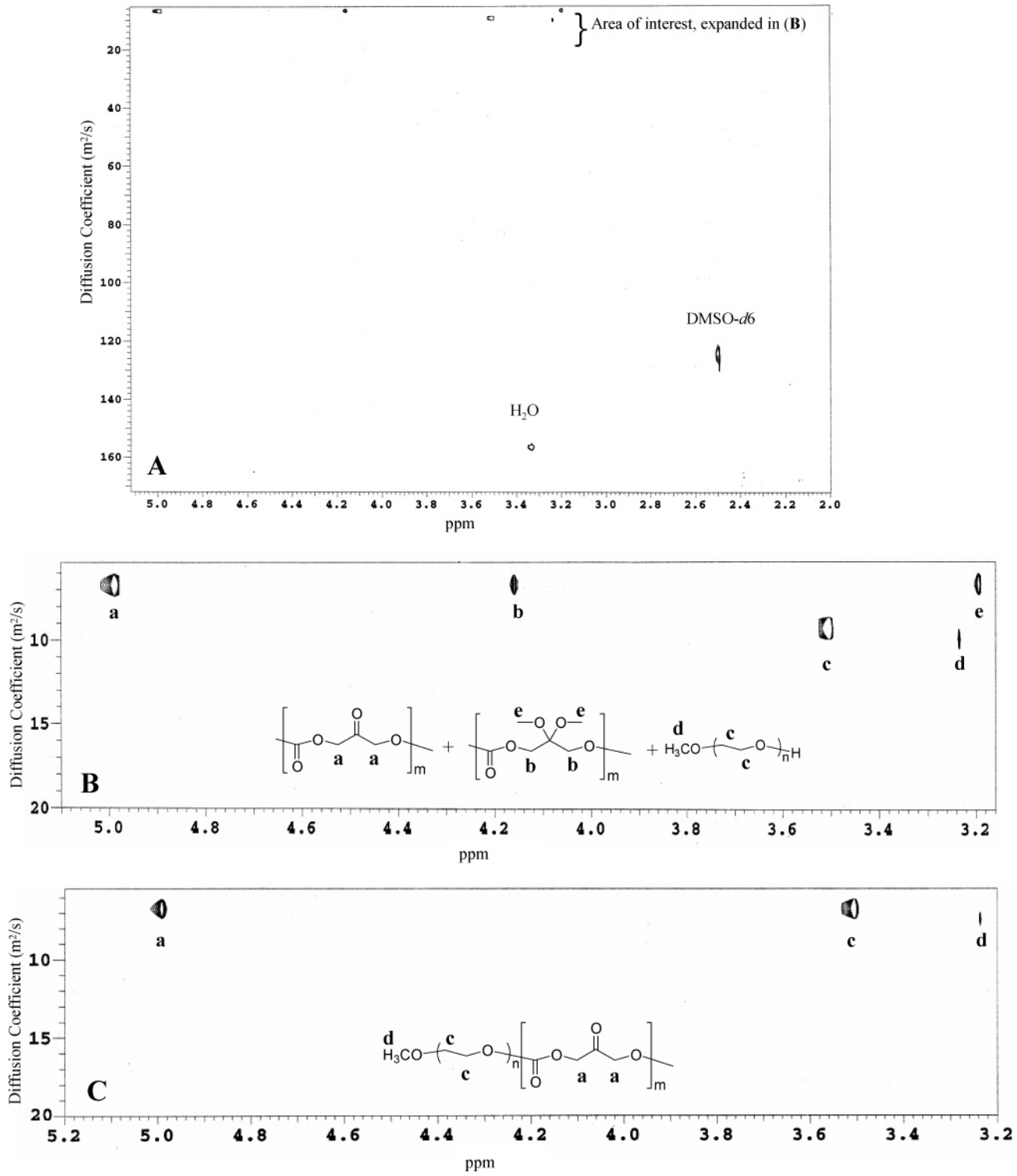


Figure 4. ^{1}H NMR DOSY analysis on the MPEG/pDHA mixture and MPEG−pDHA diblock copolymers. (A) The MPEG and partially deprotected pDHA (M_n = 5700) mixture in DMSO-d_6. This is an overall view of the DOSY and shows the difference between the diffusion coefficients of the polymers and those of the DMSO solvent and trace H_2O. (B) An enlarged view of the region of interest of (A) showing the different diffusion coefficients of the individual hompolymers. (C) DOSY of the MPEG−pDHA 5000−5000 showing the similar diffusion coefficient for the diblock copolymer. Similar results were obtained for MPEG−pDHA 5000−3000, VI 5000−3000, and VI 5000−5000.

which was then converted into a six-membered cyclic carbonate (IV)[33] (Scheme 1). VI was synthesized by adopting the well-established strategy of growing a polymer chain to the active end of a preexisting one.[35]

2,2-Dimethoxypropylene carbonate (IV) can undergo ring-opening polymerization in the presence of a nucleophile and coordination catalyst.[33] In this reaction, the terminal hydroxyl group of MPEG acts as the nucleophile and chain growth propagates by ring-opening polymerization of IV.[36,37] Control over the DHA block length was maintained by adjusting the feed ratio of MPEG/IV and the $Sn(Oct)_2$ injection conditions. Injecting the initiator into the melt in the 5000−5000 and 5000−10 000 cases was important to reproducibly obtain these higher molecular weights. Injecting the initiator at room temperature, regardless of the ratio of MPEG/IV, did not yield an M_n value higher than 4000 for the VI block.

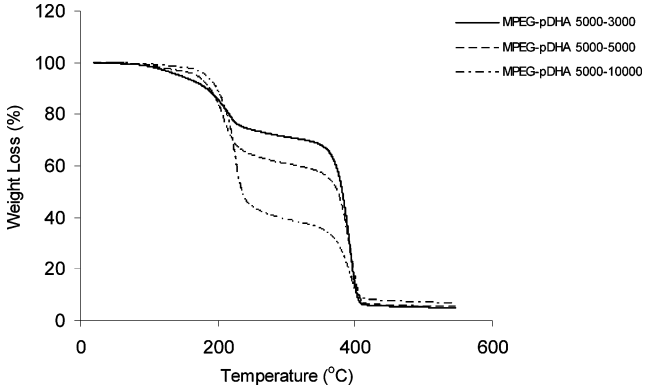


Figure 5. TGA of MPEG−pDHA. The percentage weight loss at each temperature depends on the characteristic block length.

Table 3. TGA and DSC Results for MPEG−pDHA[a]

sample	T_{d1} (°C)	T_{d2} (°C)	wt loss (%) at T_{d1}	wt % pDHA	T_m (°C)	ΔH (J/g)
MPEG−pDHA 5000−3000	196	375	25	26	54	98.0
MPEG−pDHA 5000−5000	192	376	40	43	48	48.0
MPEG−pDHA 5000−10 000	204	373	56.73		36	14.5

[a] The wt % of pDHA was calculated from the ^{1}H NMR data.

Altering block length is one way to tailor the properties of a diblock copolymer. Figure 1 is a typical ^{1}H NMR spectrum of VI in $CDCl_3$. The peaks marked with letters are assigned to the characteristic signals of protons in the repeat units. Table 1 includes the M_n and DP for VI as calculated by ^{1}H NMR in $CDCl_3$ using end group analysis. Table 1 also includes the GPC data for all of the synthesized polymers, as estimated using polystyrene standards. The GPC curve for VI presented a single peak as shown in Figure 2 and illustrates a narrow molecular weight distribution and the absence of pDHA homopolymerization. It also displays the difference in elution time between MPEG 5000 and VI 5000−10 000, further supporting the evidence for the formation of a block copolymer. The observed high molecular weight species in the MPEG GPC trace most probably results from high molecular weight impurities present in the starting commercial MPEG.

VI was deprotected to form MPEG−pDHA in the presence of trifluoroacetic acid and water (Scheme 1). The amount of the TFA−water mixture added was increased with increasing pDHA block length. In the 5000−3000 case, the MPEG dominated the solubility of the copolymer, and it had to be precipitated from the solution after completion of the reaction. In both the 5000−5000 and the 5000−10 000 cases, the pDHA dominated and it precipitated from solution. The 5000−3000 and 5000−5000 copolymers dissolve in DMSO and swell in water and most common organic solvents, while the 5000−10 000 only swells but does not dissolve in DMSO, water, or any other common organic solvents. Figure 3 is a typical ^{1}H NMR spectrum of MPEG−pDHA in DMSO-d_6. The peaks marked with letters are assigned to the characteristic signals of protons in the repeat units. Table 2 includes the M_n and DP for MPEG−pDHA as calculated by ^{1}H NMR in DMSO-d_6 using end group analysis. Molecular weight data for the 5000−10 000 pDHA were not determined due to its low solubility in DMSO. The pDHA homopolymer exhibits poor solubility,[33] and the solubility trend observed supports this because the block copolymer solubility deteriorates with increasing pDHA block length.

As shown in Tables 1 and 2, deprotection did not alter the degree of polymerization of these polymers. The ^{1}H NMR results, the consistency in the degrees of polymerization, and

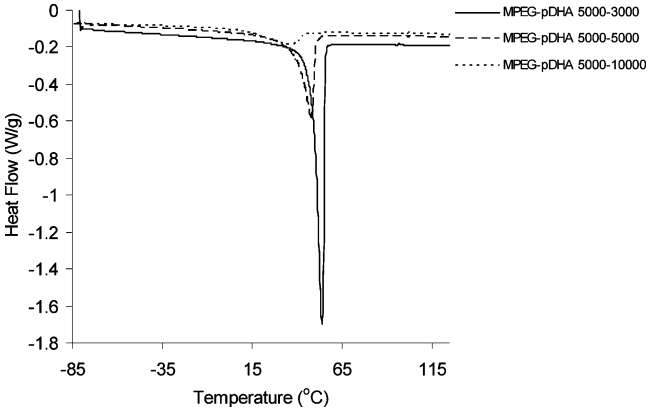


Figure 6. DSC of MPEG−pDHA. An increase in the pDHA block length results in a decrease in the melting temperature and the enthalpy of melting.

the solubility behavior of the block copolymer suggest that the polymer backbone remained intact following deprotection. Diffusion-ordered NMR spectroscopy analysis (DOSY) was performed to further confirm that deprotection had not degraded the pDHA polymer backbone and that both blocks remained conjugated to each other. This pulsed field gradient NMR (PFGNMR) experiment yields a 2D spectrum with NMR chemical shifts on the horizontal axis and diffusion coefficients on the vertical axis.[38] This method has been used for the separation analysis of polymer mixtures to determine the molecular weight of polymer samples.[39,40] In this paper, DOSY was utilized to confirm that the components of the block copolymer were diffusing at a similar rate, and thus no degradation was taking place during deprotection.

To first establish the diffusion coefficient of each block as a homopolymer, MPEG (M_n = 5000) and the aforementioned partially deprotected pDHA (M_n = 5700) were dissolved in DMSO-d_6, and DOSY was performed. Partial deprotection was performed to ensure polymer solubility because a fully deprotected pDHA homopolymer displays poor solubility.[33] As shown in Figure 4A and B, the diffusion coefficients for the characteristic protons on both backbones are different because both polymers were not conjugated to each other. Figure 4A is the full DOSY spectrum; it illustrates what a typical DOSY spectrum looks like and shows the difference between the diffusion coefficients of the polymers and those of the DMSO solvent and trace H_2O. Figure 4B is an expansion of the region of interest from Figure 4A. The 5000−3000 and 5000−5000 VI and MPEG−pDHA DOSY experiments resulted in similar diffusion coefficients for the characteristic protons on both backbones, signifying that the diblock copolymers were still intact. Figure 4C of the 5000−5000 MPEG−pDHA block copolymer is a representative example. If the blocks were no longer conjugated after deprotection, a result similar to Figure 4A and B would be expected. Additionally, if deprotection had degraded the pDHA backbone, then the diffusion coefficient for its characteristic proton would be significantly higher and the diffusion coefficients for both polymer backbones would not match as closely as observed in Figure 4C. These results provide strong evidence that the MPEG−pDHA block copolymer remains intact and further confirms the GPC results for VI.

To further characterize this new material, thermal analysis was also performed. According to the TGA, the pDHA homopolymer exhibits a T_d of ~230 °C,[33] and the MPEG T_d was ~377 °C. In the case of the block copolymer, each of the components degrades at its own characteristic T_d, resulting in

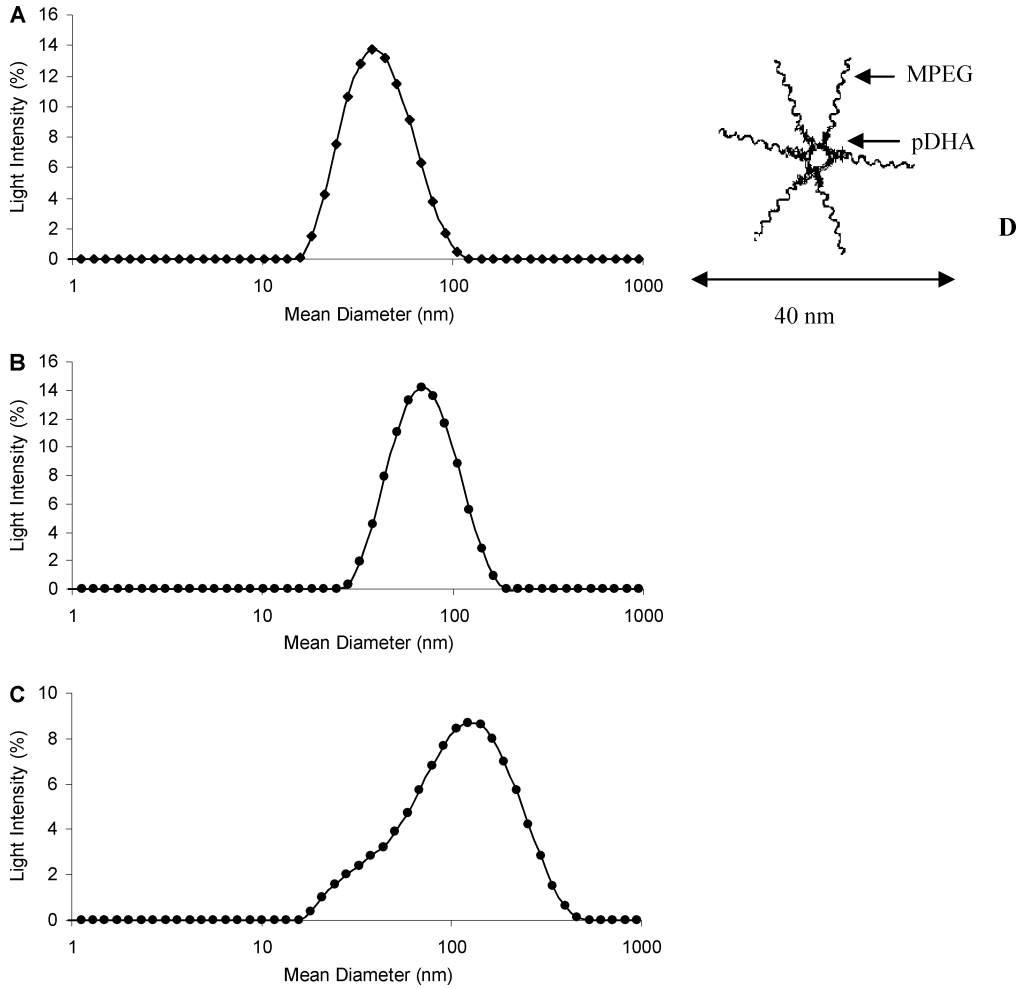


Figure 7. DLS results. (A) Particles with an average diameter of 45 ± 1 nm (PDI = 0.162) were formed in water. (B) Particles with an average diameter of 70 ± 1 nm (PDI = 0.226) were formed in ethanol. (C) Particles with an average diameter of 94 ± 1 nm (PDI = 0.372) were formed in dichloromethane. (D) Proposed nanoparticle structure, with a pDHA core and MPEG shell. Standard deviations were obtained from multiple measurements of the same formulation. The size results were repeatable for multiple formulations.

two degradation temperatures. The percentage weight loss at each temperature depends on the block length. This is proportional to the weight fraction of each component as calculated by the ^{1}H NMR ratio of the M_n of each component to the total M_n. These results are shown in Figure 5 and Table 3, and clearly illustrate the trend of increasing percentage weight loss at the pDHA T_d with increasing pDHA block length. DSC measurements were performed to measure the melting temperature and obtain a quantitative evaluation of melting enthalpy necessary for the melting of the initially crystalline fraction of the polymer. As shown in Table 3 and Figure 6, an increase in the pDHA fraction resulted in a drop in the melting temperature and melting enthalpy (area under the curve) as compared to pure MPEG (T_m = 56 °C, and ΔH = 172 J/g). This trend continues as the pDHA block length becomes larger. This can be explained by the decrease in the size of the crystalline domain with the increase in the pDHA block length.[41] A glass transition temperature (T_g) was not observed for any of the block copolymers.

The advantages of polymeric nanoparticles in systemic drug delivery have been heavily reviewed.[7,26,27] The nanoparticles described in such systems are usually composed of a hydrophobic core and hydrophilic corona and are typically used in hydrophobic drug encapsulation for systemic drug delivery.[7,22,23,26,27] The MPEG−pDHA 5000−3000 was used to form nanoparticles in water, ethanol, and dichloromethane. The uniqueness of this polymer is derived from the pDHA block, which is insoluble in water and most common organic solvents and hydrophilic based on contact angle measurement,[33] thus allowing it to form nanoparticles in aqueous and organic antisolvents spanning a range of polarities. The MPEG chains serve as the outer shell stabilizing the nanoparticle, while the pDHA constitutes the particle core. Because the pDHA is poorly soluble in both aqueous and organic solvents, we studied how the amphiphilic nature of this polymer can be used to create stable nanoparticles in both solvents. As shown in Figure 7, the DLS results illustrate that particles with an average diameter of 45 ± 1 nm (PDI = 0.162) were formed in water, particles with an average diameter of 70 ± 1 nm (PDI = 0.226) were formed in ethanol, and particles with an average diameter of 94 ± 1 nm (PDI = 0.372) were formed in dichloromethane. The particles formed in water and ethanol exhibited a unimodal size distribution as indicated by the narrow PDI and as shown in Figure 7A and B. The particles formed in dichloromethane exhibited a large PDI and slight bump on the left-hand side of the curve (Figure 7C), illustrating a shift toward a bimodal size distribution. Particles formed in water displayed a neutral surface charge based on zeta potential measurements. As shown in Figure 8, TEM on the nanoparticles in water indicated the formation of spherical particles with a size distribution comparable to that of DLS results. Further analysis of these nanoparticles is underway specifically for applications in systemic drug delivery.

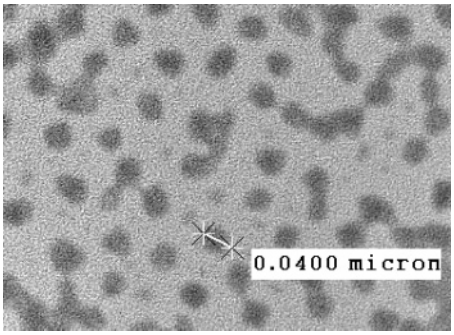


Figure 8. TEM results for the nanoparticles in water. This supports the DLS size results and shows the spherical morphology of the nanoparticles.

Conclusion

A diblock copolymer, VI, was obtained by the ring-opening polymerization of a protected DHA-based monomer in the presence of MPEG and $Sn(Oct)_2$. VI was subsequently deprotected to form MPEG−pDHA (VII) in the presence of TFA and water. The length of the pDHA block could be controlled by adjusting the reactant feed ratios and initiator injections conditions during polymerization. ^{1}H NMR, GPC, DOSY, DSC, and TGA analysis indicated that the intermediate and final products were successfully synthesized. The block copolymer formed nanoparticles in both aqueous and organic environments as confirmed by DLS. These micelles are composed of a hydrophilic MPEG surface and a hydrophilic water-insoluble pDHA core, giving it potential for use in a wide range of systemic drug delivery applications.

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