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CHEMO-ENZYMATIC SYNTHESIS AND CHARACTERIZATION OF NOVEL FUNCTIONALIZED AMPHIPHILIC POLYMERS

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ABSTRACT

The condensation copolymerization of Dimethyl 5-hydroxyisophthalate (**1**) with Polyethylene glycols (PEGs) (**2a**–**2d**) of varying molecular weights, catalyzed by Novozyme-435 (immobilized *Candida antarctica* lipase B) in bulk is reported. The structures of the resulting polymers, Poly[(poly(oxyethylene)-oxy-5-hydroxyisophthaloyl] (**3a**–**3c**) were characterized by ^{1}H (1D and 2D) and ^{13}C-NMR spectroscopic experiments. Further, these polymers have been derivatized by attaching decanyl and 12-hydroxydodecanyl chains to the phenolic hydroxyl group. The resulting amphiphilic polymeric systems were characterized by detailed

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spectroscopic analysis. Light Scattering Photometry as well as Gel Permeation Chromatography were used to evaluate the particle size and molecular weights of the polymers. In principle, the method developed is flexible so that it can be used to generate a wide array of functionalized amphiphilic polymers. In the absence of biocatalytic transformation, such structural control would be extremely difficult or currently impossible to obtain.

Key Words: Chemoenzymatic; Amphiphilic polymer; Novozyme-435; Functionalized polymer; Polyethylene glycols; Dimethyl 5-hydroxyisophthalate; Poly[poly(oxyethylene)-oxy-5-hydroxyisopthaloyl]; Bromodecane; 12-Bromododecanol

INTRODUCTION

The importance of polymers in medical applications has been well recognized. The most widely used area is their use as pharmaceutical carriers in drug delivery, considerable amount of research has been directed towards the use of natural and synthetic polymers as polymeric drugs and drug delivery systems. The low molecular weight pharmaceutical surfactants, which are currently used, have low toxicity and high solubilization power. But these suffer from the drawback that they have relatively high critical micelle concentration (CMC) and are unstable upon large dilution. However, by using amphiphilic copolymers, these drawbacks can be eliminated as they have very high solubilization power and rather low CMC values, thus making them more stable in vivo.[1] Taking this into account, studies the world over have largely been confined to two different areas of research. One utilizes the insoluble polymers for the development of controlled release systems in which the drug is physically adsorbed or entrapped within an insoluble polymeric matrix, while the other being the development of soluble prodrugs or drug carriers where the drug is either chemically bound to the polymer backbone or is the part of the backbone itself.[2]

In order to minimize drug degradation and loss, to prevent harmful side effects and to increase drug bio-availability and the fraction of the drug accumulated in the required zone, various drug delivery systems have currently been developed or are under development. Under these circumstances, the drug is released from an insoluble polymeric matrix, and a therapeutic dose of drug is delivered in a constant fashion over extended periods of time. These systems have several advantages, such as the ability to deliver the drug locally, lesser overall systemic toxicity and the patients do not require to take repeated doses. Also, protecting them from the physiological environment can prolong the half-life of sensitive drugs.

Taking the above advantages of drug delivery systems into consideration, it is obvious that there is a need to develop biocompatible compounds/polymers which can be utilized for such purposes. The polymers which are currently being used or investigated for controlled drug delivery

are polyanhydrides, poly(orthoesters), polyesters (especially those derived from lactic and glycolic acids and caprolactone), polyphosphazenes and poly(amino acids). Our group has been involved in the synthesis of polymers which can be used for drug delivery and we have recently reported the chemical synthesis and characterization of a novel amphiphilic polymer based on poly(ethylene glycol) using an organometallic catalyst.[3] We used poly (ethylene glycol)s, PEGs, because they are known to be biocompatible, nontoxic and water soluble. One of the unique properties of this polymer is its ability to aggregate in specific solvents forming micelles, thus enabling it to encapsulate small molecules.

Due to the exponential increase in interest in the area of enzyme-catalyzed organic reactions, we tried to carry out the synthesis of functionalized polymers using enzymes. More so, because many families of enzymes can be utilized for transformation of not only their natural substrates but a wide range of unnatural substrates to yield a variety of useful compounds.[4–8] The use of enzymes in organic synthesis has several advantages also, such as superior catalytic power and high selectivity under mild conditions with regard to temperature, pressure and pH, promising substrate conversion efficiency, high diastereo-, enantio-, regio-, and chemoselectivities as well as regulating stereochemistry to provide development of new reactions.[9,10] The naturally occurring polymers are produced in vivo by enzymatic catalysis. The use of enzymes for the synthesis of useful polymers has been well exploited,[11–16] most of which are otherwise very difficult to produce by conventional chemical catalysts as they require undesirable protection-deprotection steps. These features allow the generation of functional compounds for pharmaceutical and agrochemical sectors employing non-toxic natural catalysts with "green appeal," additional advantages include catalyst recyclability and use in bulk reaction media avoiding organic solvents.[17–20]

In this study, we demonstrate the enzyme-catalyzed copolymerization of dimethyl 5-hydroxyisophthalate with poly(ethylene glycol) by using novozyme-435 in bulk. We also report the polymerization with PEGs of different molecular weights and derivatization of the resulting polymers with different alkylating agents. All the above polymers are reported for the first time and have been characterized by different physical techniques.

EXPERIMENTAL

Materials

Novozyme-435, an immobilized enzyme, was a gift from Novozymes, Denmark. All other chemicals and solvents were of analytical grade and were used as received unless otherwise noted.

Instrumentation

Gel Permeation Chromatography (GPC) was used to determine the molecular weights and molecular weight distributions, Mw/Mn of polymer samples. Light scattering data were collected by a laser light scattering photometer (Wyatt Technology DAWN Model F) equipped with a 632 nm He-Ne laser as a light source. The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Instrument Inc. 250 MHz ARX spectrometer equipped with a Silicone Graphics station.

General Method of Polymerization

Dimethyl 5-hydroxyisophthalate (**1**, 1.0 mmol, 0.21 g) and PEG [**2a**−**2d**,1.0 mmol, MWt 600 (0.6 g), 900 (0.9 g), 1500 (1.5 g) and 300 (0.3 g)] were placed in a round-bottom flask (25 mL capacity). To this mixture was added the enzyme (10% by weight w.r.t. monomers, 0.80 g−1.7 g) and the reaction flask was then placed in a constant temperature oil bath maintained at 90°C under vacuum. The reaction was allowed to proceed for 48 h, after this time it was quenched by adding chloroform and filtering off the enzyme under vacuum. The organic solvent was then evaporated under vacuum and the residue was dialyzed using membrane (MWCO 6000). After the completion of dialysis, the product polymers **3a**−**3d** were freeze-dried. The structures of the polymers were characterized using NMR spectroscopy (Bruker 250 MHz); and the molecular weights of the polymer products were determined by GPC/light scattering.

Poly[Poly(Oxyethylene-600)-Oxy-5-Hydroxyisophthaloyl] 3a

This polymer was obtained by heating dimethyl 5-hydroxyisophthalate (1 mmol, 0.21 g) with PEG 600 (1 mmol, 0.6 g) in presence of novozyme −435 (0.8 g) at 90°C in solvent free condition for 48 h under vacuum. It was obtained as a viscous oil after freeze-drying in 90% yield.

^{1}H NMR Data ($CDCl_3$): δ 3.64−3.68 (*brs*, methylene PEG protons on C-9 and C-10 carbons of the repeating units and on C-α and C-β), 3.82 (*t*, 2H, C-8H), 3.93 (*s*, 3H, -$COOCH_3$), 4.48 (*t*, 2H, C-7H), 7.71 (*m*, 2H, C-4H and C-6H) and 8.21 (*s*,1H, C-2H).

^{13}C NMR Data ($CDCl_3$): δ 52.74 (-OCH_3 end group), 62.07 (C-α), 64.74 (C-β), 69.44 (C-8), 70.93 (repeating PEG units' carbons), 72.90 (C-7), 121.43 (C-4 and C-6), 122.53 (C-2), 131.18 (C-1 and C-3), 157.57 (C-5) and 166.11 (-COOMe).

Poly[Poly(Oxyethylene-900)-Oxy-5-Hydroxyisophthaloyl] 3b

This polymer was obtained by condensing dimethyl 5-hydroxyisophthalate (1 mmol, 0.21 g) with PEG 900 (1 mmol, 0.9 g) in presence of novozyme −435 (1.1 g) at 90°C in solvent free condition for 48 h under vacuum. It was obtained as a waxy solid after freeze-drying in 93% yield.

^{1}H NMR Data ($CDCl_3$): δ 3.63−3.81 (*brs*, methylene PEG protons on C-9 and C-10 carbons of the repeating units and on C-α and C-β), 3.82 (*t*, 2H, C-8H), 3.92 (*s*, 3H, -$COOCH_3$), 4.46 (*t*, 2H, C-7H), 7.69 (*d*, 2H, C-4H and C-6H) and 8.73 (*s*, 1H, C-2H).

^{13}C NMR Data ($CDCl_3$): δ 52.73 (-OCH_3 end group), 62.07 (C-α), 64.72 (C-β), 69.43 (C-8), 70.90 (repeating PEG units' carbons), 72.89 (C-7), 121.43 (C-4 and C-6), 122.51 (C-2), 131.99 (C-1 and C-3), 157.56 (C-5) and 166.38 (-COOMe).

Poly[Poly(Oxyethylene-1500)-Oxy-5-Hydroxyisophthaloyl] 3c

This polymer was obtained by heating dimethyl 5-hydroxyisophthalate (1 mmol, 0.21 g) with PEG 1500 (1 mmol, 1.5 g) in the presence of novozyme −435 (1.7 g) at 90°C in solvent free condition for 48 h under vacuum. It was obtained as a white solid after freeze-drying in 90% yield.

^{1}H NMR Data ($CDCl_3$): δ 3.6−3.79 (*brs*, methylene PEG protons on C-9 and C-10 carbons of the repeating units and on C-α and C-β), 3.86 (*t*, 2H, C-8H), 3.96 (*s*, 3H, -$COOCH_3$ end group), 4.51 (*t*, 2H, C-7H), 7.75 (*s*, 2H, C-4H and C-6H) and 8.24 (*s*, 1H, C-2H).

^{13}C NMR Data ($CDCl_3$): δ 52.69 (-OCH_3 end group), 62.02 (C-α), 64.70 (C-β), 69.43 (C-8), 70.90 (repeating PEG units' carbons), 72.91 (C-7), 121.48 (C-4 and C-6), 122.38 (C-2), 131.95 (C-1 and C-3), 157.62 (C-5) and 166.07 (-COOMe).

General Method of Coupling of Bromodecane (4) and 12-Bromododecanol (5) with Poly[Poly(Oxyethylene)-Oxy-5-Hydroxyisophthaloyl] (3a, 3b, and 3c)

Equimolar quantities of **3a**–**3c** (0.8, 1.1 and 1.7 g) and **4** or **5** (0.22 or 0.26 g) were dissolved in dry acetone (10 mL) and to the resultant solution was added equimolar amount of anhydrous potassium carbonate (0.13 g). The reaction mixture was refluxed at 60°C and progress of the reaction was monitored by TLC using ethyl acetate in petroleum ether (30%). After completion, the potassium carbonate was removed by filtration and the solvent was removed under vacuum to give the products **6a**−**6c** and **7a**−**7c** from **4** and **5**, respectively (Table 1).

Table 1. Amounts of the Reactants, Solvent, Potassium Carbonate Used and Isolated Yield in Coupling Reactions

Polymer	Weight of the Polymer (g)	Bromodecane (4) (g)	12-Hydroxy Bromododecanol (5) (g)	Potassium Carbonate (g)	Acetone (mL)	Products (g, %)
PEG600-co-dimethyl 5-hydroxyisophtha late (**3a**)	0.81	0.22	–	0.13	10	**6a** (viscous oil) (0.96, 80%)
PEG900-co-dimethyl 5-hydroxyisophtha late (**3b**)	1.10	0.22	–	0.13	10	**6b** (viscous oil) (1.26, 85%)
PEG1500-co-dimethyl 5-hydroxyisophtha late (**3c**)	1.71	0.22	–	0.13	10	**6c** (white solid) (1.67, 80%)
PEG600-co-dimethyl 5-hydroxyisophtha late (**3a**)	0.81	–	0.26	0.13	10	**7a** (viscous oil), (0.98, 75%)
PEG900-co-dimethyl 5-hydroxyisophtha late (**3b**)	1.10	–	0.26	0.13	10	**7b** (waxy solid) (1.26, 80%)
PEG1500-co-dimethyl 5-hydroxyisophtha late (**3c**)	1.71	–	0.26	0.13	10	**7c** (white solid) (1.85, 85%)

Poly[(Polyoxyethylene-600)-Oxy-5-Decanyloxyisophthaloyl] 6a

^{1}H NMR Data ($CDCl_3$): δ 0.86–0.92 (*bs*, 3H C-20H), 1.27–1.38 (*m*, C-13H to C-19H), 1.75–1.85 (*m*, 2H, C-12H), 3.65–3.67 (*brs*, methylene PEG protons on C-9 and C-10 carbons of the repeating units and on C-α and C-β), 3.76 (*t*, 2H, C-8H), 3.95 (*s*, 3H, -$COOCH_3$ end group), 4.06 (*t*, 2H, C-11H), 4.51 (*t*, 2H, C-7H), 7.75 (*m*, 2H, C-4H and C-6H) and 8.36 (*s*, 1H, C-2H).

^{13}C-NMR Data ($CDCl_3$): δ 14.52 (C-20), 23.05–32.26 (C-12 to C-19), 52.79 (-OCH_3 end group), 61.76 (C-α), 64.81 (C-β), 69.46 (C-8 and C-11), 70.38–70.95 (repeating PEG units' carbons), 72.87 (C-7), 120.04 (C-4 and C-6), 123.32 (C-2), 131.99 (C-1 and C-3), 159.53 (C-5) and 166.07 (-COOMe).

Poly[(Polyoxyethylene-900)-Oxy-5-Decanyloxyisophthaloyl] 6b

^{1}H NMR Data ($CDCl_3$): δ 0.75–0.87 (*bs*, 3H, C-20H), 1.25–1.36 (*m*, C-13H to C-19H), 1.77–1.83 (*m*, 2H, C-12H), 3.66–3.69 (*brs*, methylene PEG protons on C-9 and C-10 carbons of the repeating units and on C-α and C-β), 3.82 (bs, 2H, C-8H), 3.96 (*s*, 3H, -COOMe end group), 4.03–4.06 (*t*, 2H, C-11H), 4.51 (*t*, 2H, C-7H), 7.77 (*m*, 2H, C-4H and C-6H) and 8.30 (*s*, 1H, C-2H).

^{13}C-NMR Data ($CDCl_3$): δ 14.50 (C-20), 23.03–32.24 (C-12 to C-19), 52.77 (-OCH_3 end group), 61.86 (C-α), 64.80 (C-β), 69.45 (C-8 and C-11), 70.46–70.87 (repeating PEG units' carbons), 72.86 (C-7), 120.26 (C-4 and C-6), 123.16 (C-2), 131.98 (C-1 and C-3), 159.53 (C-5) and 166.06 (-COOMe).

Poly[(Polyoxyethylene-1500)-Oxy-5-Decanyloxyisophthaloyl] 6c

^{1}H NMR Data ($CDCl_3$): δ 0.90 (*t*, 3H C-20H), 1.31 (*m*, C-13H to C-19H), 1.81 (*m*, 2H, C-12H), 3.66–3.69 (*brs*, methylene PEG protons on C-9 and C-10 carbons of the repeating units and on C-α and C-β carbons), 3.87 (*t*, 2H, C-8H), 3.96 (*s*, 3H, -$COOCH_3$ end group), 4.10 (*t*, 2H, C-11H), 4.51 (*t*, 2H, C-7H), 7.77 (*m*, 2H, C-4H and C-6H) and 8.30 (*s*, 1H, C-2H).

^{13}C NMR Data ($CDCl_3$): δ 14.54 (C-20), 23.06–32.26 (C-12 to C-19), 52.80 (-OCH_3 end group), 61.89 (C-α), 64.76 (C-β), 69.22 (C-8 and C-11), 70.52–70.91 (repeating PEG units' carbons), 72.87 (C-7), 120.26 (C-4 and C-6), 123.34 (C-2), 131.99 (C-1 and C-3), 159.53 (C-5) and 166.08 (-COOMe).

Poly[(Polyoxyethylene-600)-Oxy-5-(12-Hydroxydodecanyloxy)-Isophthaloyl] 7a

^{1}H NMR Data ($CDCl_3$): δ 1.31 (*bs*, C-13H to C-20H), 1.54–1.57 (*m*, 2H, C-21H), 1.82 (*m*, 2H, C-12H), 3.31–3.43 (*t*, 2H, C-22H), 3.60–3.67 (*brs*, methylene PEG protons on C-9 and C-10 carbons of the repeating units and

on C-α and C-β carbons), 3.86 (*t*, 2H, C-8H), 3.95 (*s*, 3H, -$COOCH_3$ end group), 4.05 (*t*, 2H, C-11H), 4.51 (*t*, 2H, C-7H), 7.76 (*bs*, 2H, C-4H and C-6H) and 8.28 (*s*, 1H, C-2H).

^{13}C NMR Data ($CDCl_3$): δ 26.16−33.15 (C-12 to C-21), 52.80 (-OCH_3 end group), 61.82 (C-α), 63.23 (C-22), 64.83 (C-β), 69.49 (C-8 and C-11), 70.45−70.96 (repeating PEG units' carbons), 72.94 (C-7), 120.26 (C-4 and C-6), 123.34 (C-2), 132.02 (C-1 and C-3), 159.57 (C-5) and 166.07 (-COOMe).

Poly[(Polyoxyethylene-900)-Oxy-5-(12-Hydroxydodecanyloxy)-Isophthaloyl] 7b

^{1}H-NMR Data ($CDCl_3$): δ 1.29 (*bs*, C-13H to C-20H), 1.43−1.49 (*m*, 2H, C-21H), 1.78−1.85 (*m*, 2H, C-12H), 3.37−3.47 (*t*, 2H, C-22H), 3.60−3.68 (*brs*, methylene PEG protons on C-9 and C-10 carbons of the repeating units and on C-α and C-β carbons), 3.86 (*t*, 2H, C-8H), 3.94 (*s*, 3H, -$COOCH_3$ end group), 4.05 (*t*, 2H, C-11H), 4.51 (*t*, 2H, C-7H), 7.76 (*m*, 2H, C-4H and C-6H) and 8.21 (*s*, 1H, C-2H).

^{13}C-NMR Data ($CDCl_3$): δ 26.16−33.20 (C-12 to C-21), 52.83 (-OCH_3 end group), 61.82 (C-α), 63.38 (C-22), 64.84 (C-β), 69.00 (C-8 and C-11), 70.93 (repeating PEG units' carbons), 72.90 (C-7), 120.34 (C-4 and C-6), 123.38 (C-2), 132.02 (C-1 and C-3), 159.54 (C-5) and 166.12 (-COOMe).

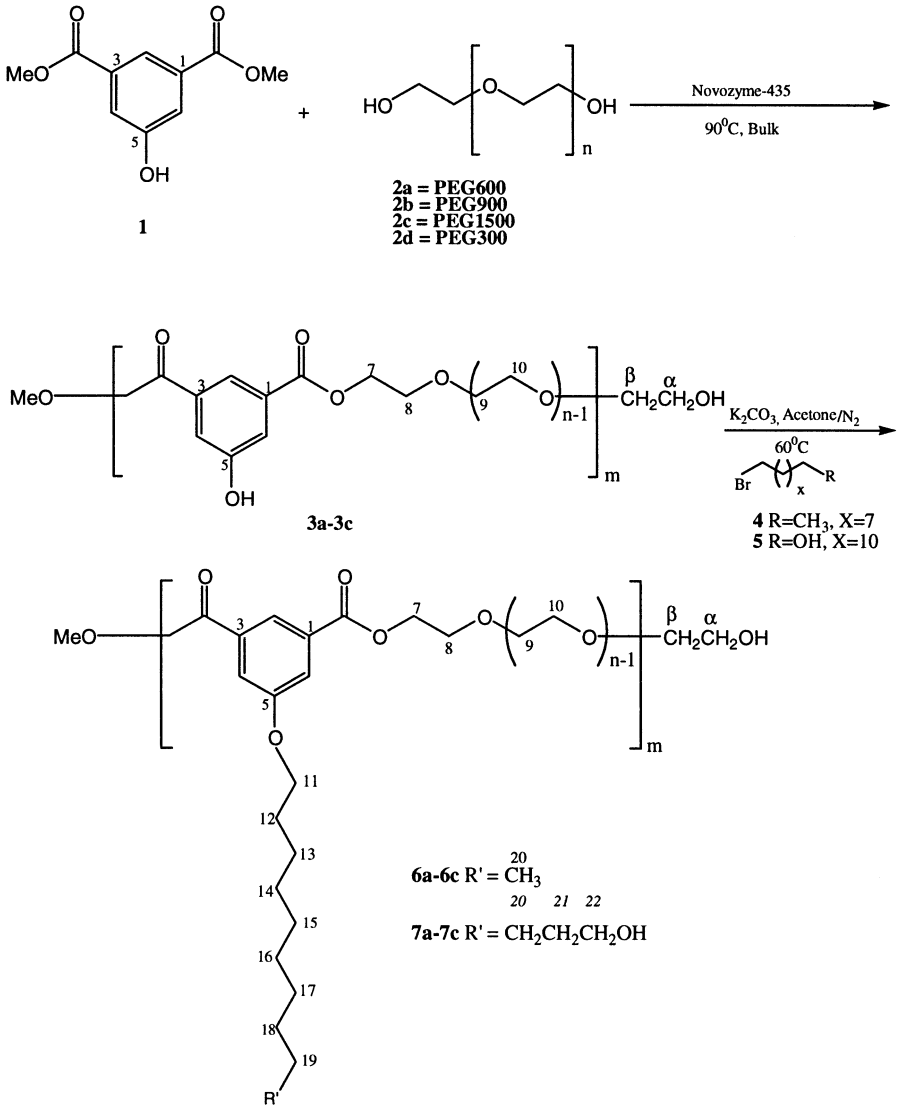
Poly[(Polyoxyethylene-1500)-Oxy-5-(12-Hydroxydodecanyloxy)-Isophthaloyl] 7c

^{1}H-NMR Data ($CDCl_3$): δ 1.31 (*bs*, C-13H to C-20H), 1.54−1.57 (*m*, 2H, C-21H), 1.82 (*bs*, 2H, C-12H), 3.43 (*t*, 2H, C-22H), 3.67−3.74 (*brs*, methylene PEG protons on C-9 and C-10 carbons of the repeating units and on C-α and C-β carbons), 3.86 (*t*, 2H, C-8H), 3.95 (*s*, 3H, -$COOCH_3$ end group), 4.05 (*t*, 2H, C-11H), 4.51 (*t*, 2H, C-7H), 7.76 (*bs*, 2H, C-4H and C-6H) and 8.28 (*s*, 1H, C-2H).

^{13}C NMR Data ($CDCl_3$): δ 26.15−33.18 (C-12 to C-21), 52.82 (-OCH_3 end group), 61.82 (C-α), 63.36 (C-22), 64.83 (C-β), 69.49 (C-8 and C-11), 70.90 (repeating PEG units' carbons), 72.89 (C-7), 120.33 (C-4 and C-6), 123.37 (C-2), 132.01 (C-1 and C-3), 159.52 (C-5) and 166.07 (-COOMe).

RESULTS AND DISCUSSION

The novozyme-435 catalyzed synthesis of amphiphilic polymers-poly[(polyoxyethylene)-oxy-5-(alkoxy)-isophthaloyl] (**6a**−**6c** and **7a**−**7c**) is described. Scheme 1 represents the general strategy that was used for the synthesis of these compounds starting with dimethyl 5-hydroxyisophthalate (**1**) and PEG-diols **2a**−**2d** (Mn 1500, 900, 600 and 300). The monomer



Scheme 1. Synthesis of amphiphilic polymers, poly[(polyoxyethylene) 5-decanyloxy-isophthaloyl] **(6a–c)**, poly[(polyoxyethylene)-oxy-5-(12-hydroxydodecanyloxy)-isophthaloyl] **(7a–c)**.

containing an aromatic moiety and a phenolic group, dimethyl 5-hydroxyisophthalate **(1)** was used for the first time in enzymatic polymerizations. Based on the literature reports, we have used the *Candida antarctica* lipase B due to its high catalytic activity for ester synthesis, high thermal stability and the immobilization on the large surface area material.

The novozyme-435 catalyzed condensation of **1** and PEG (M_n 1500, 900 and 600) under solvent-less conditions gave the polymers **3a–3c**. In the

polymerization without enzyme (control experiment), the monomers were recovered unchanged. Furthermore, no polymer formation was observed by using the deactivated *Candida antaractica* lipase B. These data imply that the present polymerizations proceeded through lipase catalysis. As regards the polymerization of **1** with PEG-300 (**2d**) under the same reaction conditions, it was observed that there was practically no conversion to the copolymer, the reaction was therefore not examined any further in this case. As these polymerization reactions have been performed in bulk (PEG acting as solvent also), the very low copolymer yield in the case of poly(ethylene glycol), PEG−300 (**2d**) may be because this PEG is of low molecular weight and its amount taken (in molar ratio to **1**) is much less than that in the cases of **2a**−**2c**. The reaction system of **2d** and **1** would then be non-homogeneous and the polymerization reaction of the mixture of **2d** and **1** would not proceed well.

The structures of the repeating units of the polymers were identified using ^{1}H 2D (COSY) NMR experiments. The number average molecular weight of the polymers formed (**3a**, **3b** and **3c**) were evaluated by GPC.

Poly[Poly(Oxyethylene)-Oxy-5-Hydroxyisophthaloyl] (3a−3c)

The structures of the synthesized polymers were identified by the ^{1}H and ^{13}C-NMR spectra. In the ^{1}H NMR spectrum, the appearance of the signal around δ 4.50 for two protons in **3a**−**3c** indicated the formation of the ester linkages in the polymer, this was further confirmed by the much decreased intensity of the signal due to the methoxy protons of dimethyl 5-hydroxy-isophthalate. In the ^{1}H-^{1}H correlation spectrum, the signal around δ 4.5 shows coupling with the signal around δ 3.9, i.e., the C-8 protons of the PEG end group. The aromatic protons appeared in the aromatic region at δ 8.28 (integrating for one proton) and at δ 7.76 (integrating for two protons), whereas a broad peak in the region δ 3.6−3.7 was due to the PEG protons. The number average molecular weight of the polymers **3a**−**3c** was found to be between 18,000−23,000 Da, evaluated by GPC.

Functionalization of 3a−3c: Synthesis of Poly[Poly(Oxyethylene)-Oxy-5-(Alkoxy)-Isophthaloyl] (6a−6c and 7a−7c)

The polymers **3a**−**3c** were functionalized by coupling them with bromodecane (**4**) and 12-bromododecanol (**5**) using anhydrous potassium carbonate and acetone as shown in Sch. 1. The structures of the functionalized polymers were established by ^{1}H, ^{13}C-NMR spectra and also by their ^{1}H-^{1}H correlation spectrum (COSY). The representative example of each class is being discussed here.

Poly[Poly(Oxyethylene-1500)-Oxy-5-Decanyloxyisophthaloyl] (6c)

The compound **6c** was obtained as a white solid after refluxing **3c** with bromodecane in acetone with fused potassium carbonate. After completion, the solvent was removed under vacuum and the product freeze-dried to get **6c** in 80% yield. The structure of **6c** was established by its ^{1}H, ^{13}C and ^{1}H-^{1}H COSY NMR spectra. In its ^{1}H NMR spectrum, the appearance of a signal at δ 4.10 indicated the presence of a methylene group attached to the phenoxy moiety of the polymer (i.e., C-11 H), which was earlier not there in the ^{1}H NMR spectrum of **3c**. This showed the coupling of decane chain to the polymer, which was further supported by the appearance of peaks corresponding to other protons of the alkyl chain in the ^{1}H NMR spectrum of **6c**. The huge peak in the region δ 3.66−3.69 represents the PEG main chain protons, except the protons at C-7H near the ester functionality (which appeared as a triplet at δ 4.51) and the C-8H, which appeared at δ 3.87. The ^{1}H-^{1}H correlation spectrum of 6c also confirmed the coupling of the alkyl chain to the polymer. The peak at δ 4.10 (C-11H) showed interaction with the one at δ 1.81 (C-12H) of the alkyl chain. The peak at δ 4.51 (C-7H) showed interaction with the one at δ 3.87 (C-8H). Similarly, all other chemical shift values matched well and the structure of the alkylated polymer **6c** was unambiguously determined.

Poly[Poly(Oxyethylene-1500)-Oxy-5-(12-Hydroxydodecanyloxy)-Isophthaloyl] (7c)

This polymer was obtained as a white waxy solid by refluxing **3c** with 12-bromododecanol in anhydrous acetone in the presence of fused potassium carbonate. After completion, the solvent was removed under vacuum and the product freeze dried to get 7c in 85% yield. Its structure was fully characterized by ^{1}H, ^{13}C and ^{1}H-^{1}H correlation NMR spectroscopy. In its ^{1}H-NMR spectrum, the appearance of a peak at δ 4.05 for the two methylene group protons attached to the phenoxy moiety indicated the coupling of 12-bromododecanol with the polymer. The number of three bonds connectivity of the chemical shifts were revealed in the COSY spectrum of **7c**, which include the interactions H_7-H_8, H_{11}-H_{12}, H_{12}-H_{13} and so on. In the ^{1}H NMR spectrum of **7c**, the huge peak in the region δ 3.67−3.74 was assigned to the PEG main chain methylene protons, except the methylene protons next to the ester functionality, i.e., C-7 protons (which appeared as a triplet at δ 4.51) and the C-8 protons, which appeared at δ 3.86. This was also evident from the ^{1}H-^{1}H correlation spectrum of **7c**, which showed interactions between the signal at δ 4.51 and the one at δ 3.86 for the C-8 protons. Further the triplet at δ 4.05 showed correlation with the peak at δ 1.82 and these were assigned to the C-11 and C-12 protons, respectively. In addition, weaker interactions could be seen by increasing the intensity between C-2H, and C-4H and C-6H

and between the C-9H and C-10H. Thus the structure of **7c** was unambiguously established as Poly[poly(oxyethylene)-oxy-5-(12-hydroxydodecanyloxy)-isophthaloyl].

CONCLUSION

Candida antarctica lipase efficiently catalyzed the polycondensation of dimethyl 5-hydroxyisophthalate and polyethylene glycols in a solvent-free system. The molecular weights of the polyethylene glycol units strongly affected the polymerization behavior. The polymer molecular weight increased under reduced pressure and at higher temperatures. The synthesized polymers were functionalized with alkyl groups of varying chain lengths carrying a polar functionality at the end of the chain. The present reaction system affords a variety of biodegradable amphiphilic polymers via non-toxic enzymatic catalysis under mild reaction conditions without organic solvents. Therefore, it is environmentally benign and provides an example of "Green Polymer Chemistry."

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