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A functionalizable polyester with free hydroxyl groups and tunable physiochemical and biological properties

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Abstract

Polyesters with free functional groups allow facile modifications with biomolecules, which can lead to versatile biomaterials that afford controlled interactions with cells and tissues. Efficient synthesis of functionalizable polyesters is still a challenge that greatly limits the availability and widespread applications of biofunctionalized synthetic polymers. Here we report a simple route to prepare a functionalizable polyester, poly(sebacoyl diglyceride) (PSeD) bearing free hydroxyl groups. The key synthetic step is an epoxide ring-opening polymerization, instead of the traditional polycondensation, that produces poly(glycerol sebacate) (PGS) [1]. PSeD has a more defined structure with mostly linear backbone, more free hydroxyl groups, higher molecular weight, and lower polydispersity than PGS. Crosslinking PSeD with sebacic acid yields a polymer five times tougher and more elastic than cured PGS. PSeD exhibits good cytocompatibility *in vitro*. Furthermore, functionalization by glycine proceeds with high efficiency. This versatile synthetic platform can offer a large family of biodegradable, functionalized polymers with tunable physiochemical and biological properties useful for a wide range of biomedical applications.

1. Introduction

Aliphatic polyesters such as polylactide form an important class of biomaterial with controllable degradation and excellent biocompatibility [2]. There have been extensive investigations on these biomaterials [3] and many polyesters such as polyglycolide, polylactide, and other polyhydroxyalkanoates have been widely used as resorbable sutures, drug delivery matrices, and tissue-engineering scaffolds [4-7]. Most of these polyesters are, however, semi-crystalline, hydrophobic, and lack free functional group(s) for further modification by biomolecules [5,8-10]. One way to address these drawbacks is the introduction of functional groups. The presence of functionalizable groups such as hydroxyl and carboxylate in polyesters can efficiently increase their hydrophilicity and degradability, plus modulate their mechanical, thermal, chemical, and biologic properties [8,9,11]. Furthermore, these functional groups

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Supplementary Data: The ¹H NMR spectrum of PGS, the ¹H NMR and FTIR spectra of PSeD maleic monoester, the ¹H NMR, ¹³C NMR, and FTIR spectra of PSeD glycinate are available as supplementary data in the online version.

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provide access to versatile routes to conjugate a variety of bioactive molecules such as peptides [12], saccharides [13], and biotin [14]. This can lead to novel biomaterials with diverse bioactivities. The reaction of pendant groups can further convert functionalizable linear polyesters to branched and network polymers, providing even more means to modulate their properties. Therefore, the properties of functionalized polyesters can be effectively tailored to meet a variety of demands in biomedical applications.

The state of the art in the synthesis of functionalizable polyesters has been well presented in several recent reviews [8-10,15,16]. As mentioned in these reviews, chemical preparation of functionalizable polyesters is difficult because it usually involves a complex multistep synthetic route with a low overall yield. Two general strategies are used: one is pre-functionalization via polymerization of functionalized monomer [17,18]; the other is post-polymerization functionalization via modification of non-functionalized polyester [19,20]. The former usually requires complicated monomer preparation, and tedious protection and deprotection of functional groups. The latter often has to be performed under strict conditions and sometimes it is hard to control the final chemical structure. Moreover, both approaches are often associated with degradation in the transformation after polymerization [19,21].

In light of this, efficient synthesis of linear polyesters bearing suitable functionalities is highly valuable. We designed the title polymer according to three criteria. (1) Functionality: we chose the versatile hydroxyl group as the pendant functional group in the polymer. Hydroxyl group is one of the best understood organic functional groups, and many mild reactions are available for further modifications with biomolecules such as peptides [12,22]. To minimize side reactions in subsequent biofunctionalization, hydroxyl group was designed to be the only functional group susceptible to further chemical modification. (2) Biocompatibility: this is required for the eventual application of any biomaterial. Thus, the resultant polymer and degradation products must be well tolerated by the cells and tissues. (3) Availability: this is important for widespread usage of the materials. Therefore, the principal polymer should be prepared from low-cost reagents by simple synthetic transformations in relatively fewer steps.

Poly(sebacoyl diglyceride) (PSeD) (Fig. 1) satisfies these design criteria. PSeD can be viewed as a linear analog of poly(glycerol sebacate) (PGS) [1]. PGS is synthesized directly by polycondensation of glycerol and sebacic acid and has a mixed structure: some of its secondary hydroxyl groups remain free and some are converted to ester groups that link two polymer chains. The distinct synthesis method of PSeD by an epoxide ring opening polymerization leads to a well defined polymer structure with free hydroxyl groups, which is important for control of subsequent functionalization with bioactive molecules [12]. This versatile synthetic platform is applicable to other diglycidyl esters and diacids, which will lead to biodegradable and biofunctionalizable polymers with a variety of physiochemical properties.

The *in vitro* and *in vivo* biocompatibilities of PGS have been reported by multiple research groups and it is widely used in soft tissue engineering [1,23-29]. PSeD will likely have the same biocompatibility of PGS due to its structural relationship with PGS. To the best of our knowledge, common routes to synthesize polyesters by either polycondensation or ring-opening polymerization of lactones are not effective in the synthesis of linear polyesters with free functional groups without protection and deprotection steps. Glycerol-based polyesters prepared using direct chemical (Scheme 1) or lipase-catalyzed polycondensation are usually compromised by premature crosslinking, large polydispersity index (PDI), or low molecular weight [1,30,31]. We recently reported the application of epoxide ring-opening polymerization between biomolecules with primary amines and diglycidyl esters that led to polymers with free -OH groups [32,33]. We reasoned that a similar polymerization between a diacid and a diglycidyl ester would produce a useful PSeD polyester (Fig. 1). In this synthetic strategy, glycidyl group serves as both the active polymerization functionality and the precursor of the

glyceryl moiety. Thus, the ring-opening polymerization would form the polyester backbone and the pendant hydroxyl groups in one step; as an added advantage, the reaction would not produce small molecule byproducts.

2. Materials and Methods

2.1. Materials and Equipments

Sebacoyl chloride (TCI America, 90%) and glycidol (Acros, 96%), were distilled under reduced pressure. Triethylamine (Alfa Aesar, 99%) was dried by anhydrous NaOH and distilled. Anhydrous solvents toluene, dioxane, and *N,N*-dimethylformamide (DMF), were purchased from EMD. Ethyl ether, ethyl acetate, and acetone were purchased from PHARMCO-AAPER. All solvents were used without further purification. Sebacic acid (Alfa Aesar, 98%) was recrystallized three times from 95% ethanol and dried under vacuum. Tetrabutylammonium bromide (Acros, 99+%), maleic anhydride (Alfa Aesar, 99%), Boc-Gly-OH (Peptides International), *N,N'*-Dicyclohexylcarbodiimide (DCC) (Alfa Aesar, 99%), and dimethylaminopyridine (DMAP) (99%, Avocado Research Chemicals Ltd) were used without further purification.

All compound characterization was carried out at ambient temperature. The molecular weight was determined via gel permeation chromatography (GPC) on a Viscotek GPCmax VE2001 system. For PSeD, the measurement was performed on a Viscotek organic I-MBMMW-3078 column and a VE3580 differential refractive index using DMF as the eluent. Polystyrene (Varian EasiVial PS-M, Part No. 2010-0301) was used for calibration. For PSeD glycinate and maleic monoester, the measurement was performed on a PSS SDV 1000Å column and a Viscotek 270 dual detector (differential refractive index and right angle light scattering) using THF as the eluent. Polystyrene (American polymer standards PS170K) was used for calibration. ¹H NMR spectra were recorded on a Varian Mercury-400 NMR in deuterated chloroform solution with tetramethylsilane as the internal chemical reference unless otherwise specially noted. ¹³C and 2D NMR spectra were recorded on a Bruker Avance 600 NMR. Fourier transformed infrared (FTIR) spectra were recorded on a Thermo Nicolet IR-100 spectrometer via sample films coated on NaCl crystal windows unless noted otherwise. Differential scanning calorimetry (DSC) and thermal gravimetric analysis (TGA) were performed on Seiko DSC 220C and TG/DTA 320 instruments, respectively, at a heating rate of 10 °C/min under a nitrogen atmosphere.

2.2. Synthesis of PSeD

Preparation of monomer diglycidyl sebacate—Sebacoyl chloride (11.37 g, 47.6 mmol) was added dropwise to a solution of glycidol (7.8 ml, 116.9 mmol) and triethylamine (31.5 ml, 224.1 mmol) in 180 ml of anhydrous toluene cooled in an ice/ethanol bath (−15 °C) under a nitrogen atmosphere over 30 min. The reaction mixture was stirred for another 6 h before it was filtered and concentrated. The residue was purified by flash chromatography on silica gel (3:1 hexane:ethyl acetate) to afford diglycidyl sebacate (10.4 g, 70% yield) as a white solid. ¹H NMR (400 MHz, CDCl₃, Me₄Si) δ 4.42 (dd, *J* = 12.6, 3.0 Hz, 2H), 3.91 (dd, *J* = 11.8, 6.2 Hz, 2H), 3.19–3.23 (m, 2H), 2.85 (t, *J* = 4.4 Hz, 2H), 2.65 (dd, *J* = 5.2, 2.4 Hz, 2H), 2.35 (t, *J* = 7.8 Hz, 4H), 1.60–1.65 (m, 4H), 1.25–1.31 (m, 8H).

Synthesis of PSeD—Diglycidyl sebacate, an equimolar amount of sebacic acid, and a catalytic amount of tetrabutylammonium bromide were mixed and dissolved in anhydrous DMF or dioxane in a Schlenk flask in a glove box filled with nitrogen. The flask was sealed, transferred out of the glove box, and connected to a Schlenk line. The flask was heated and its contents were stirred under a nitrogen atmosphere. The reaction mixture was purified via

dilution in ethyl acetate, precipitation in ethyl ether, and dried under a vacuum at ambient temperature overnight. (See Table 1 for variations of the reaction parameters)

2.3. Functionalization of PSeD using the -OH groups

PSeD glycinate—PSeD (118.9 mg, 0.460 mmol), Boc-Gly-OH (88.7 mg, 0.506 mmol), DCC (189.9 mg, 0.921 mmol), and DMAP (2.81 mg, 0.023 mmol) were dissolved in anhydrous dichloromethane (8 ml). The mixture was stirred at room temperature under a nitrogen atmosphere for 18 h, before it was filtered and the filtrate was concentrated. The raw product was redissolved in acetone, precipitated using ethyl ether and washed with deionized water. The precipitate was dried to furnish PSeD glycinate (155 mg) as a colorless solid.

PSeD maleic monoester—PSeD (262.3 mg, 1.015 mmol) and maleic anhydride (199.1 mg, 2.031 mmol) were dissolved in 0.46 ml of anhydrous DMF in a Biotage 0.5-2 ml microwave vial and sealed in a glove box filled with nitrogen. The vial was transferred out of the glove box and reacted at 110 °C for 30 min using a Biotage Initiator 2.5 microwave reactor. The reaction mixture was precipitated in H₂O (18 Mohm-cm) and dried under vacuum at ambient temperature overnight to obtain the maleic monoester of PSeD (292.9 mg) as a transparent solid.

2.4. Crosslinking of PSeD and the mechanical properties of the resultant elastomer

A mixture of PSeD and sebacic acid (1.13 wt.%) was melted and poured into an aluminum mold coated with hyaluronic acid (mold release). The mixture was heated at 120 °C for 20 h to remove all the bubbles, then subjected to vacuum (1.1 Torr) at 120 °C for another 21 h to yield crosslinked PSeD elastomer.

Tensile strength testing was conducted on an MTS insight mechanical analyzer equipped with a 50 Newton load cell according to ASTM standard D142-06a. Three dog bone-shaped samples (D142-06a die A design scaled by 1/4, 14.75 mm × 3 mm × 1.3 mm, length × width × thickness) were tested and averaged. Deflection speed was kept at 125 mm/min. In the simple tensile strength test, the sample was elongated to failure. In the cyclic tensile strength test, the sample was pulled to 50%, then allowed to recover to 1% before immediately stretched to 50% five times.

2.5. Evaluation of in vitro biocompatibility of PSeD

The wells of a tissue culture-treated polystyrene (TCPS) 24-well plate were coated with 80 µl of 1 g/l PSeD solution in MeOH (0.2 µm filtered). The plate was dried under vacuum overnight after evaporation of the solvent in air. Both the TCPS plate and the polymer-coated plate were sterilized by UV light for 30 min, then washed with 1 ml phosphate buffered saline three times and with 1 ml culture medium once with gentle shaking (20 rpm). Each well was seeded with 50,000 nonimmortalized smooth muscle cells (passage 12) isolated from the carotid arteries of 4-year-old male baboons (*Papio cyncephalus*) in 1 ml of MCDB 131 medium supplemented with 10% FBS, 1% L-glutamine, and 20 µg/ml gentamycin. The cells were incubated at 37 °C with 5% CO₂. Medium was exchanged every 2 days. The number of metabolically active cells was determined colorimetrically by the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay according to a previously published protocol [34] via absorption at 570 nm measured with a Molecular Devices SpectraMax M2/M2e Microplate Reader. Statistical analysis was performed using a two-tailed Student's *t* test. A *p* value of ± 0.05 was considered statistically significant. All values are reported as mean $\pm$ standard deviation. Both polymer wells and the control were imaged on day 3 using an inverted phase contrast microscope [Nikon TE-2000U (Melville, NY) equipped with a 4 MP Diagnostics Spot Flex digital camera (Sterling Heights, MI)].

3. Results

3.1. Synthesis of PSeD

The first step of the synthesis was the preparation of the monomer - diglycidyl sebacate. Due to the high reactivity of the epoxide groups, our preliminary attempts, including $\text{Ti}(\text{OAc})_3$ -catalyzed transesterification, DCC/DMAP-mediated condensation, and the reaction between sodium sebacate and epichlorohydrin [35], led to complex reaction mixture and very low yields, and were therefore considered to be failures. Later, we prepared diglycidyl sebacate by epoxidation of diallyl sebacate, which was prepared via esterification of allyl alcohol and sebacic acid [33]. The yield was only approximately 60%, however, despite attempts to vary conditions such as reaction temperature, reaction time, and reactant ratio. Furthermore, excessive amounts of the oxidant *m*-chloroperoxybenzoic acid had to be used to accomplish the epoxidation. *m*-Chloroperoxybenzoic acid and its byproduct *m*-chlorobenzoic acid were difficult to remove completely and often led to lower purified yield (50%) in relatively large scale (2.6 g) reactions. Therefore, we explored the esterification of sebacoyl chloride by glycidol in toluene as a way to synthesize diglycidyl sebacate (Fig. 2) [36]. We found that the side reaction, ring-opening of the epoxide moiety by HCl, could be efficiently prevented using excessive triethylamine (5 $\times$) as an acceptor of HCl and lowering the reaction temperature to $-15\text{ }^\circ\text{C}$. No ring-opened byproducts were observed in the ^1H NMR spectra of the reaction mixture. The purification was convenient because the byproduct, triethylamine hydrochloride, was only sparingly soluble in toluene and could be removed by a simple filtration. Under optimized conditions, diglycidyl sebacate was produced at 70% purified yield on a 10-g scale.

The second step of the synthesis was the epoxide ring-opening polymerization between diglycidyl sebacate and sebacic acid to yield PSeD. To minimize side reactions, we performed this reaction at relatively low temperature and, therefore, we chose solution polymerization instead of bulk polymerization because the melting point of sebacic acid is $132\text{ }^\circ\text{C}$. Diglycidyl sebacate and sebacic acid were first polymerized in DMF without catalyst at $90\text{ }^\circ\text{C}$ to produce PSeD (Table 1, entry 1). The resultant polymer had a moderate molecular weight ($M_n = 11.5\text{ kDa}$) and a high PDI (6.5). Quaternary ammonium salts have been reported to be efficient catalysts for addition reactions of epoxy compounds,[37] so we expected that they would be useful in our polymerization. When equimolar amount of diglycidyl sebacate and sebacic acid reacted in the presence of 3.4% $n\text{Bu}_4\text{NBr}$ at $100\text{ }^\circ\text{C}$ in dioxane (Table 1, entry 2), however, the catalyst induced gelation and the resultant polymer did not dissolve in common solvents such as CH_2Cl_2 , THF, acetone, ethanol, and DMF. This indicated that the polymer was crosslinked. Reducing the $n\text{Bu}_4\text{NBr}$ concentration and lowering the reaction temperature successfully prevented crosslinking of the polymer (Table 1, entry 3); however, the resultant polymer had a high PDI (5.9). A more significant reduction in catalyst concentration and a slight elevation of reaction temperature [0.1% molar ratio $n\text{Bu}_4\text{NBr}$ at $95\text{ }^\circ\text{C}$ (Table 1, entry 4)] yielded PSeD with an increased molecular weight ($M_n = 16.6\text{ kDa}$), a narrower polydispersity (PDI = 2.5), and an excellent isolated yield (90%).

3.2. Structural Characterization of PSeD

The polymer was characterized by standard analytical methods. Its structure was analyzed by FT-NMR and FTIR spectroscopy. In the ^1H NMR spectrum (Fig. 3A), the three signals marked 'a' at δ 1.31, 1.62 and 2.35 ppm were ascribed to the sebacoyl moiety in the polymer backbone. The broad peak marked 'b' at δ 2.89 ppm indicated the presence of a hydroxyl group (-OH). The signal at chemical shift 3.55-4.54 ppm marked 'c, d' corresponded to the CH protons of the glyceryl moiety. Comparison of the integrations of the various protons suggested that each polymer repeating unit consisted of one -OH group. Moreover, it revealed that essentially all the epoxide functionalities had been consumed because no proton signals associated with epoxy groups (δ around 3.0 ppm, please see the ^1H NMR data of diglycidyl sebacate in the

experimental section) were observed. The ^{13}C NMR spectrum of PSeD (Fig. 3B) further confirmed its structure. The three signals marked 'a' at δ 24.78, 28.95 and 34.05 ppm were attributed to the sebacoyl moiety in the backbone of the polymer. The signals at chemical shifts 61.31 and 72.08 ppm marked 'c, d' were attributed to the carbons of glyceryl moiety. The signal marked 'b' at δ 173.94 ppm corresponded to carbon of the ester group.

To examine the linearity of PSeD and the relative amount of free -OH groups, ^{13}C DEPT 135 (distortionless enhancement by polarization transfer) (Fig. 4A) and ^1H - ^{13}C HETCOR (heteronuclear correlation) NMR experiments (Fig. 4B) were performed. In the ^{13}C DEPT 135 NMR spectrum (Fig. 4A), the glyceryl CH_2 groups (c) appeared as negative peaks and the CH (d) appeared as positive peaks. When glyceryl OH groups were converted to esters, their signals shifted downfield (d') because of the electron withdrawing effect of the carbonyl group. The intensity of d is much higher than that of d', indicating most of the -OH groups remain free. The ^1H - ^{13}C HETCOR NMR spectrum (Fig. 4B) revealed that most of the proton signals of the glyceryl moiety appeared around δ 4.00 ppm (strong peaks marked with an *). The weak proton signal at 5.09 ppm (#) was associated with the carbon at 72.06 ppm (d'), a negative peak in the DEPT 135 NMR spectrum indicating a glyceryl CH group. Furthermore, the downfield chemical shift of the # peak suggested that it was an ester CH group (d'). The higher intensity of the d signal vs. d' again indicated the linear diglyceride structure of PSeD and the fact that most of the hydroxyl groups are free. A ratio of the free glyceryl OH groups vs. glyceryl ester group was estimated using ^1H NMR. We set the proton integration of sebacoyl moiety (δ 1.31, 1.62 and 2.35 ppm) as 16 protons and the integration of the CH group (d+d') in glyceryl moiety as 1 proton (Fig. 4C), which corresponded to one PSeD repeating unit. The resulting integration of 0.1 for the glyceryl ester moieties (δ 5.09 to 5.28 ppm, d', Fig. 3C), representing the branched PSeD, corresponded to approximately 10%. In summary, about 90% of the glyceryl hydroxyl groups in PSeD are free, that is, PSeD is approximately 90% linear, 10% branched. A similar analysis of PGS revealed that only 45% of the hydroxyl groups are free (see supplementary data Fig. S1).

The characteristic functional groups of PSeD were corroborated by FTIR investigation (Fig. 5). The ester bond in the backbone and the presence of hydroxyl groups on the side chain showed a sharp, intense C=O stretch at 1740 cm^{-1} and a broad, intense O-H stretch at 3461 cm^{-1} , respectively.

3.3. Physical properties of PSeD and PGS prepolymer

In order to compare PSeD with PGS prepolymer synthesized by direct polycondensation of glycerol and sebacic acid, we prepared PGS prepolymer as previously reported [38] and characterized it under identical conditions as PSeD. The results are summarized in Table 2. The polymers' thermal properties were determined by DSC and TGA. Similar to PGS, the glass transition temperature (T_g) of PSeD was very low ($< -100\text{ }^\circ\text{C}$), which suggested that, after curing, it would be an elastomer at ambient temperature. PSeD, however, showed higher melting (T_m) and crystallization (T_c) temperatures than PGS prepolymer. This was consistent with a linear structure for PSeD, different from the branched structure of PGS. Furthermore, the TGA experiment revealed that PSeD had a high decomposition temperature (T_d) at $382.9\text{ }^\circ\text{C}$ and therefore, it could be used in a wide temperature range.

PSeD was designed to be a versatile intermediate for further functionalization, so we tested its solubility in various solvents at ambient conditions. PSeD was soluble in most common organic solvents except those with low polarities (Table 3), which made it easy to be cast into various

*Functionalizable polymer is defined as a polymer with functional groups that readily react with biomolecules and functionalized biomaterial as one already modified with biomolecules.

shapes and ready for further functionalization. It also indicated that the polymer had few crosslinks [31,39]. The polymer was insoluble in water, making it a candidate for a tissue engineering scaffold and various implantation applications. Moreover, PSeD can be stored for more than one year without significant change in solubility. In contrast, PGS became insoluble after storage under the same conditions for 3 months, likely due to crosslinking of the polymer. This improved property makes PSeD more amenable to practical use.

3.4. Functionalization of PSeD

To demonstrate the potential ability to use the -OH groups of PSeD for biofunctionalization, we investigated the coupling reaction between PSeD and glycine, a representative for biomolecules. PSeD readily reacted with *N*-*tert*-butoxycarbonyl (Boc)-protected glycine in the presence of excess DCC and a catalytic amount of DMAP at room temperature to yield PSeD-glycinate (Fig. 6, $M_n = 25.1$ kDa, PDI = 1.4) with around 90% glycation (according to the relative integrations in ^1H NMR spectrum; see supplementary data Fig. S2A).

To further explore the potential of PSeD for derivatization and to illustrate the versatility of PSeD, we reacted PSeD with excess maleic anhydride at 110 °C in DMF by microwave-assisted esterification (Fig. 7). The reaction was performed for 30 min and produced PSeD-maleic monoester ($M_n = 20.3$ kDa, PDI = 2.0) with around 80% esterification (according to the relative integrations in ^1H NMR spectrum; see supplementary data Fig. S3A).

3.5. Curing PSeD and the mechanical properties of the resultant elastomer

To keep crosslinking low and elasticity high for the final network, PSeD was cured with a small amount sebacic acid (1.1% by weight) under moderate vacuum at 120 °C. Tensile tests of the cured PSeD revealed a stress-strain curve characteristic of an elastomeric and tough material (Table 4, Fig. 8A). The Young's modulus of the original linear region was found to be 1.57 ± 0.48 MPa and the ultimate tensile stress was found to be 1.83 ± 0.06 MPa. The elongation at break was up to 409 ± 29 %. Moreover, cyclic tensile testing was performed with 50% strain for 5 cycles (Fig. 8B). Only limited hysteresis was observed.

3.6. Biocompatibility of PSeD

The biocompatibility of PSeD was tested by examining the metabolic activity of nonimmortalized baboon smooth muscle cells seeded onto PSeD-coated 24-well plates. TCPS was used as a control. The cells showed similar long spindle morphology on PSeD and TCPS (Fig. 9A and B). Identical numbers of cells were seeded on all surfaces. From day 1 to day 3, MTT assays revealed a significantly higher number of metabolically active cells ($P < 0.05$) on PSeD surfaces than on TCPS surfaces (Fig. 9C). On day 4, cells approached confluence on both PSeD and TCPS surfaces and there was no difference in cell number statistically. This demonstrated that PSeD was at least as cytocompatible as TCPS *in vitro*.

4. Discussion

Functionalized polyesters are promising new biomaterials because they add tunable biodegradability, physical, chemical, and biological properties to established polyesters such as polylactide and polyglycolide. The free functional groups allow facile modifications with biomolecules that lead to versatile biomaterials with controlled interactions with cells and tissues. Efficient synthesis of functionalizable polyesters is, however, still a major challenge that greatly limits the availability and widespread applications of biofunctionalized synthetic polyesters. Here we have presented a simple strategy to prepare functionalizable polyester with free hydroxyl groups. The epoxide ring-opening polymerization between a dicarboxylic acid and the corresponding diglycidyl ester produces the target functionalizable polyester in one step without the need for protection and deprotection (Fig. 1, Table 1). The synthetic strategy

is versatile and can be used with other diacids and diepoxides to yield various linear functionalizable polyesters. Compared to other current approaches to functionalized polyester [8-10,15,16], it is simpler and more efficient.

PSeD exhibits several unique advantages over PGS prepolymer synthesized by polycondensation of glycerol and sebacic acid (Table 2): better defined structure with more free -OH groups and higher linearity (10% vs. 55% branching); higher molecular weight (16.6 kD vs. 9.0 kD); narrower polydispersity (2.5 vs. 9.3); and longer shelf time (>1 year vs. 3 months). In addition, the direct polycondensation for PGS requires higher temperature (120 °C) and vacuum (40 mTorr) to remove H₂O and accelerate the reaction [1]. PSeD synthesis proceeds at lower temperature (95 °C) with no need for vacuum to remove small molecule byproducts (Fig. 1).

The more defined structure of PSeD provides a suitable platform for further biofunctionalization. We selected glycine as the representative for biomolecules. The DCC coupling reaction ran smoothly and produced PSeD glycinate in high yield. Since many biomolecules, such as amino acids, peptides, proteins, glycans, and biotin contain free carboxylates, the reaction described here (Fig. 6) would serve as an effective bioconjugation route for PSeD. In addition, microwave-assisted esterification with maleic anhydride provides PSeD maleic monoester with good purity and yield (Fig. 7). This is a much more efficient synthetic route than a similar coupling reaction reported between hydroxylated polyester and succinic anhydride (reaction time: 30 min vs. 10 days) [12]. The free α , β -unsaturated carboxylic acid groups in PSeD-maleic monoester can easily react with a biomolecule through esterification, amidation, Michael addition, and photo-crosslinking [12,40-42]. This further enriches the variety of chemistry that can be performed to functionalize PSeD to obtained biomaterials with unique mechanical and biological properties.

For applications in tissue engineering, biomaterials that mimic the mechanical aspect of native extracellular matrix by transducing mechanical stimuli to cells and tissues may be advantageous [43-46]. Since many soft tissues such as blood vessels and lungs are elastic, several biodegradable elastomers have been developed [1,47-56]. Among them, crosslinked elastomers made from aliphatic polyesters have received much attention recently [24,49,51, 56]. They show good biocompatibility and biodegradability. Their mechanical properties are in the range of soft tissues and they primarily degrade by surface erosion, retaining their structural integrity and mechanical stability during degradation *in vivo* [57]. Most crosslinked polyester elastomers are typically synthesized by random polycondensation [1,49-53]. This method produces prepolymers with relatively low molecular weight, high polydispersity, undefined branched structure, and are prone to premature crosslinking. This compromises the mechanical properties of the elastomer. Various approaches from several different laboratories have been used to improve the mechanical properties of PGS; these include modulating monomer feeding ratios, curing conditions, and crosslinking reagents [24,50,58-60], and all of these relied on polycondensation as the synthetic method. Consequently, the resultant polymers have mechanical properties very similar to the original PGS [1]. We reasoned that polymeric networks produced by crosslinking linear functionalized polyester with higher molecular weight and narrower polydispersity would provide more elastic materials than their counterparts obtained by direct polycondensation. Accordingly, we investigated the crosslinking of PSeD with sebacic acid to produce a biodegradable elastomer that would be structurally related to PGS. The motivation was to maintain the good biocompatibility of PGS while improving its mechanical properties. As expected, sebacic-acid cured PSeD demonstrated a much tougher (approximately 5 times greater area under curve) and more elastic properties than cured PGS (Table 4, Fig. 8): 5 times higher Young's modulus; > 3 times higher tensile strength; and greater maximum strain at break. It therefore resembles bovine ligament elastin mechanically (tensile strength and Young's modulus of 2 MPa and 1.1 MPa, respectively

[61]). The strain at break was higher than that of most soft tissues (for examples, arteries and veins can be elongated up to 260% [62]). To the best of our knowledge, the elongation at break of the cured PSeD is one of the highest among crosslinked polyester elastomers used in biomedical applications. In addition, the cyclic tensile test revealed the elastomer's ability to recover from deformations (Fig. 8B), indicating that it is suitable for applications in a mechanically dynamic environment. Moreover, the mechanical properties of PSeD can be further modulated via controlling curing conditions and selecting different types and amount of crosslinking reagents (data will be reported elsewhere).

The *in vitro* cytocompatibility of PSeD was evaluated by monitoring metabolic activities of nonimmortalized baboon smooth muscle cells seeded on PSeD surfaces. Examination of the morphology of cells and the number of metabolically active cells on PSeD film suggested that cells on PSeD surfaces proliferate at least as well as those on TCPS surfaces (Fig. 9). This suggests that PSeD may be suitable for many biomedical applications including tissue engineering, wound healing, and drug delivery. We are currently investigating the *in vivo* biocompatibility of PSeD.

PSeD and PGS exhibit several T_m values and one distinct T_c in their thermograms. This could be caused by melt-recrystallization during the DSC heating cycle. The polymer was first heated from room temperature to 100 °C, then cooled to -100 °C before being heated again. Cooling of the polymer might yield a less thermodynamically stable form. Upon heating the crystalline domains melted and the molten polymers recrystallized into a more stable form that subsequently melted. Because the two melting transitions were adjacent to each other, a distinct T_c was not observed. We are investigating possible deconvolution of the transitions using advanced software to further characterize the thermal behavior of the polymer.

5. Conclusions

A functionalizable polyester bearing free hydroxyl groups was designed and successfully synthesized in two simple steps from commercially available starting materials. The synthetic route is practical, featuring easily synthesized monomers, mild polymerization conditions, and no protection and deprotection steps. The usefulness of this approach has been demonstrated by the tougher and more elastic nature of the cured polymer as compared to the first generation PGS, and the ready functionalization with glycine. The enhanced mechanical properties and easy derivatizations of PSeD were enabled by virtue of its more defined polymer structure than that of PGS. Initial evaluation using nonimmortalized cells showed PSeD to be cytocompatible *in vitro*. The synthetic strategy is general and can be used to synthesize other glycerol-based linear polyesters. We are currently investigating modification of PSeD with oligopeptides, optimizing the curing conditions, and expanding the application of this synthetic platform to other diacids. We expect this new design platform will lead to a diverse family of biodegradable and bioactive polymers with versatile mechanical, physical, chemical, and biological properties tailored for a wide range of biomedical applications.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Fig. 1.

The newly designed synthetic strategy of PSeD leads to a biodegradable polymer that retains the biocompatibility of PGS but with a more defined structure that is advantageous for subsequent functionalization.

Fig. 2.

Direct esterification under optimized conditions produced the monomer diglycidyl sebacate in one step with simpler procedure and higher yield than the previous two-step route.[33]

Fig. 3. (A) The ^1H NMR spectrum of PSeD is consistent with the proposed structure with glyceryl moiety at δ from 3.55-4.54 ppm, sebacoyl moiety at δ 1.31, 1.62, and 2.35 ppm, and -OH group at δ 2.89 ppm. (B) The ^{13}C NMR spectrum of PSeD corroborates well with the ^1H NMR. The resonance of the glyceryl moiety occurs at δ 61.31-72.08 ppm, the sebacoyl moiety at δ 24.78, 28.95, and 34.05 ppm, and the ester group at δ 173.94 ppm.

Fig. 4.

(A) ^{13}C DEPT 135 NMR spectrum of PSeD was used to distinguish the different carbons of PSeD. The positive peaks and negative peaks correspond to CH and CH_2 groups, respectively. (B) The ^1H - ^{13}C HETCOR NMR spectrum revealed the correlation of protons and carbons in PSeD. The strong peaks '*' represented most NMR signals of the glyceryl moiety, which displayed at the normal chemical shift region of a diglyceride and indicated a mostly linear structure of PSeD. The weak signal '#' revealed that the proton at 5.09 and 5.28 ppm was attached to the carbon at 72.06 ppm, which corresponded to the CH group of the glyceryl unit in the ester form (d'). (C) According to the relative chemical shifts and the results of ^{13}C DEPT 135 and ^1H - ^{13}C HETCOR NMR spectra, the protons from 5.09-5.28 ppm were deduced to be the secondary hydrogen d', which corresponds to the triglyceride, branched part of PSeD. Thus, the relative integration (0.1) of protons from 5.09 to 5.28 ppm revealed the low crosslinking of PSeD (approximately 10%).

Fig. 5. The FTIR spectrum of PSeD displayed the signal of expected functionalities: O-H bonds at 3461 cm^{-1} and ester C=O bonds at 1740 cm^{-1} .

Fig. 6.

A model reaction for the conjugation of biomolecules to PSeD.

Fig. 7.

A model reaction for further derivatization of PSeD. Maleic monoester derivative of PSeD was readily synthesized by microwave-assisted esterification, which yielded a polymer with free α , β -unsaturated carboxylic groups and provided more approaches to further functionalization.

Fig. 8. Typical tensile stress vs. strain curve of cured PSeD elastomer. (A) Simple tensile test to failure. (B) Cyclic tensile test at 50% for 5 cycles. Note the reversibility of the deformation after the first cycle.

Fig. 9.

Baboon smooth muscle cells cultured on PSeD surface exhibited normal morphology, similar to that on TCPS. Representative phase contrast photomicrographs of baboon smooth muscle cells at day 3 after seeding in PSeD-coated wells (A) and TCPS wells (B) (magnification 100 $\times$, scale bar = 300 μ m). (C) MTT assay of baboon smooth muscle cells in PSeD wells and TCPS wells showed that there were more metabolically active cells on PSeD than on TCPS in the first three days. Data represent mean $\pm$ SD. * Statistical significance ($p < 0.05$). Normalized values shown.

Table 1

Optimization of polymerization between diglycidyl sebacate and sebacic acid.

Entry	<i>n</i> Bu ₄ NBr	Solvent	Temperature	Time	<i>M_n</i>	PDI	Yield ^a
1	none	DMF	90 °C	50 h	11.5 kDa	6.5	60%
2	3.4 mol %	Dioxane	100 °C	114 h ^b	Crosslinked	–	75%
3	1.4 mol %	Dioxane	80 °C	160 h ^b	12.7 kDa	5.9	78%
4	0.1 mol %	Dioxane	95 °C	174 h	16.6 kDa	2.5	90%

^aUnoptimized.

^bThe final reaction mixture formed a resin and could not be stirred.

Table 2

Comparison of the properties of PSeD and PGS prepolymer.

Compound	M _n (kDa)	PDI	Crosslinking (%) ^a	T _m (°C)	T _c (°C)	T _g (°C)	T _d (°C)
PSeD	16.6	2.5	10	26.4, 52.3	1.2	None ^b	382.9
PGS	9.0	9.3	55	-3.4, 15.0, 33.3	-12.0	None ^b	^c

^a According to the analysis of NMR spectra. For PSeD please see Figure 4C. For PGS please see Figure S1 in supporting information.^b No glass transition temperature was observed above -100 °C.^c Not measured.

Table 3

Solubility of PSeD in various solvents.

Solvent ^a	Hexane	Et ₂ O	CH ₂ Cl ₂	THF	CHCl ₃	Ethyl acetate
Solubility ^b	–	–	+	+	+	+
Solvent ^a	Dioxane	Acetone	MeOH	EtOH	DMF	H ₂ O
Solubility ^b	+	+	+	+	+	–

^aRanked according to the polarity.

^binsoluble; +: soluble

Table 4

Mechanical properties of cured PSeD and PGS.

Elastomer	Young's modulus (MPa)	Tensile strength (MPa)	Elongation (%)
PSeD	1.57 ± 0.48	1.83 ± 0.06	409 ± 29
PGS ^a	0.282 ± 0.025	0.5	267 ± 59.4

^aRepresentative data of PGS is shown [1]. PGS and PSeD were cured via different mechanisms; the crosslinking density were both low, but unlikely to be identical.