Synthesis and Analysis of a Novel Biodegradable Polyester Fiber Scaffold Derived from Poly(glycerol sebacate)

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Abstract

Poly(glycerol sebacate) (PGS) is a biodegradable elastomer with elastic properties advantageous for use as a scaffold in soft tissue engineering. However, it has been unable to be electrospun into fibrous scaffolds—uncured PGS is a viscous liquid at room temperature and is therefore unable to hold any fiber shape, while cured PGS, though solid at room temperature, isn't easily dissolved, a requirement for electrospinning—and requires copolymerization that confers undesirable properties on the copolymer. The molecular weight of PGS has been shown to be $1.11x10^3$ g/mol, but fibrous structures are formed in other polymers above over $1.3x10^4$ g/mol.

The aim of this study was to increase the molecular weight of PGS by modification of the synthesis reaction in order to allow for electrospinning. PGS was copolymerized with 1,8-octanediol in monomer ratios of 1:1:2, 1:3:4, and 1:4:5 (glycerol:1,8-octanediol:sebacic acid) and catalyzed by the enzyme Novozym 435. The resulting poly(1,8-octanediol-glycerol sebacate) (POGS) polymers exhibited molecular weights 46 to 74.5 times greater and melting temperatures greater than PGS and above body temperature. POGS was electrospun but did not form fibers visible to the naked eye under the first set of parameters used. Altering applied voltage, the solvent, polymer concentration, or other parameters may form definitive fibers.

The improvement in molecular weight and thermal properties demonstrates potential, and as properties varied with monomer ratio, this approach could be used to fine tune the properties of the resulting polymers for the formation of elastic tissue scaffolds.

Introduction

Tissue engineering is a scientific field that studies the growth of new tissue in order to restore, maintain, or improve tissue function; most commonly new tissue is grown using the "tissue engineering triad" of cells, a scaffold, and growth factors (Khademhosseini & Langer, 2016). Therapies using engineered tissue could treat millions: for example, bone tissue engineering treating osteoporosis or skin tissue treating burns (Furth & Atala, 2014). Engineered tissue can also be used in research. For example, a tissue engineering cancer model emulates the microenvironment better than cell cultures, which regulates cell growth and differentiation, of a tumor (Yang & Burg, 2015).

Three dimensional (3D) tissue scaffolds made of biocompatible materials have been used to create the appropriate environment in which cells will proliferate. Scaffolds therefore mimic the extracellular matrix (ECM) of the desired tissue in order to create this environment: scaffolds must provide physical support for cells and confer the mechanical properties of the tissue (Chan & Leong, 2008), and must also facilitate intercellular and cell-scaffold communication (Stratton, Shelke, Hoshino, Rudraiah, & Kumbar, 2016). Additionally, scaffolds must be biodegradable into nontoxic monomers in order to allow cells to produce their own ECM to replace the scaffold (O'Brien, 2011).

Synthetic polymers, human-made polymers like poly(lactic acid) (PLA), are popular scaffold biomaterials due to their wide range of properties and ability to be modified. These polymers hold a number of advantages over other scaffold materials—natural polymers, decellularized ECM, or self-assembled hydrogels (Chang & Leong, 2008). They inherently have better functionality, cost-efficiency, manipulability, and mechanical properties than natural polymers (Stratton et al., 2011), don't run the risk of immune reactions that decellularized ECM does, and hydrogels have poor mechanical properties (Chan & Leong, 2008).

Furthermore, through the process of electrospinning, synthetic polymers can be spun into fibers micrometers to nanometers in diameter: Electrostatic forces create a jet of polymer solution and as the jet travels, the solvent evaporates, leaving a fiber mat. These 3D fiber mats can mimic ECM well, with a high surface to volume ratio, high porosity, strong mechanical properties, and pore size distribution (Stratton et al., 2011). The electrospinning process can additionally be manipulated to modify the properties of the resulting structure (Sill & Recum, 2008).

However, drawbacks of synthetic polymer scaffolds include a lower bioactivity, or ability to affect their biological environment. Cells interact with scaffolds via ligands on the scaffold, though natural polymers like collagen naturally have these ligands (O'Brien, 2011). Ligands can be added in synthetic polymers, but must be deliberately incorporated (Stratton et al., 2016). In addition, synthetic

polymers currently used for tissue scaffolds often have undesirable degradation times or mechanical and thermal properties. Polycaprolactone (PCL), PLA, and polyglycolic acid (PGA), some of the most commonly used synthetic polymers in tissue engineering, undergo bulk erosion (Stratton et al., 2011). Polymers undergoing this form of erosion lose mass and mechanical integrity rapidly, possibly inducing an immune response (Rai et al., 2012). Additionally, many of these polymers and their copolymers have high glass transition temperatures (Tg) above body temperature. Below Tg, at body temperature, polymers are brittle and glassy instead of elastic, and unable to be used easily for soft tissue engineering (Stratton et al., 2011).

Poly(glycerol sebacate) (PGS) is a biocompatible synthetic polymer without many of the drawbacks described above. PGS is synthesized from glycerol and sebacic acid, nontoxic monomers found naturally in the human body—a major component of triglycerides, and a metabolic intermediate of fatty acids, respectively (Wang et al., 2002). As an elastomer, or elastic polymer, with a glass transition temperature below -60 °C, PGS is elastic at body temperature and has properties suitable for soft tissue engineering. PGS degrades via surface erosion, allowing it to retain its mechanical properties for longer (Liu, Jiang, Shi, & Zhang, 2012). Similarly to vulcanized rubber or the main ECM polymers collagen and elastin, PGS has a 3D network of random crosslinked coils that lend it its elasticity. As glycerol has 3 hydroxyl groups and sebacic acid has 2 carboxyl groups, PGS has usually been synthesized from glycerol and sebacic acid in equimolar ratios, which reduces crosslinking and increases elasticity (Wang et al., 2002). Glycerol's hydroxyl groups allow biodegradation via hydrolysis, and its secondary hydroxyl allows for hydrogen bonding between backbones, hydrophilicity (and therefore biocompatibility), and crosslinking.

PGS synthesis of an equimolar mixture occurs at 120 °C under argon for 24 hours. At this point, the PGS is mostly linear. Afterwards, the uncrosslinked prepolymer undergoes a curing process, or rapidly crosslinks when sebacic acid reacts with the secondary hydroxyl groups of glycerol, at 120°C with pressure reduced from 1 Torr to 40 mTorr over 5 hours, then for 48 hours at 40 mTorr (Fig. 1) (Wang et al., 2002).

However, PGS has a few drawbacks as well. As with other synthetic polymers, it has a low bioactivity. In addition, PGS cannot be electrospun into fibers: uncured PGS is a viscous liquid at room temperature and is therefore unable to hold any fiber shape, while cured PGS, though solid at room temperature, isn't easily dissolved in organic solvents to begin electrospinning (Hu et al., 2016).

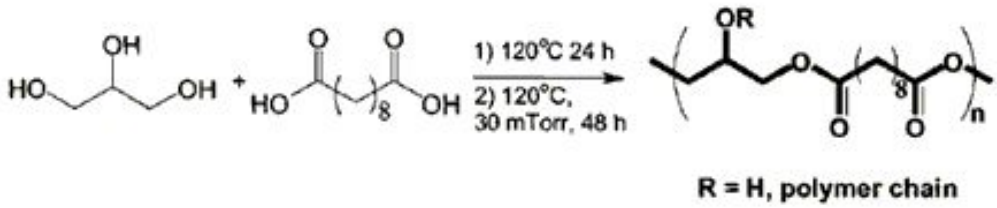

Figure 1: Overview of PGS reaction (Wang et al., 2002).

In order to improve upon these innate disadvantages, PGS has been modified in many ways. Altering the synthesis conditions and molar ratio of monomers has been shown to modify its physical properties (Fig. 2). The polymer, as the duration and temperature of the reaction increases, changes from a wax to a viscous liquid. This liquid is the prepolymer state, wherein glycerol's primary hydroxyl groups are depleted first due to the lower activation energy required. Increasing reaction time further causes sebacic acid to react with secondary hydroxyls, beginning rapid crosslinking. Additionally, glycerol loss during synthesis, not uncommon under the temperature and pressure conditions, causes the resulting PGS to be more rigid—a different molar ratio of the monomers influences Young's modulus (Li, Hong, Naskar, & Chung, 2015). Li et al. found that degree of esterification can predict Young's modulus and degradation rate. As esterification occurs initially, a PGS prepolymer is synthesized. As additional esterification, crosslinking grants PGS its elastic properties. With even further crosslinking, PGS becomes rigid. A PGS polymer synthesized from a glycerol:sebacic acid ratio of 2:3 was totally crosslinked and rigid (Wang et al., 2002).

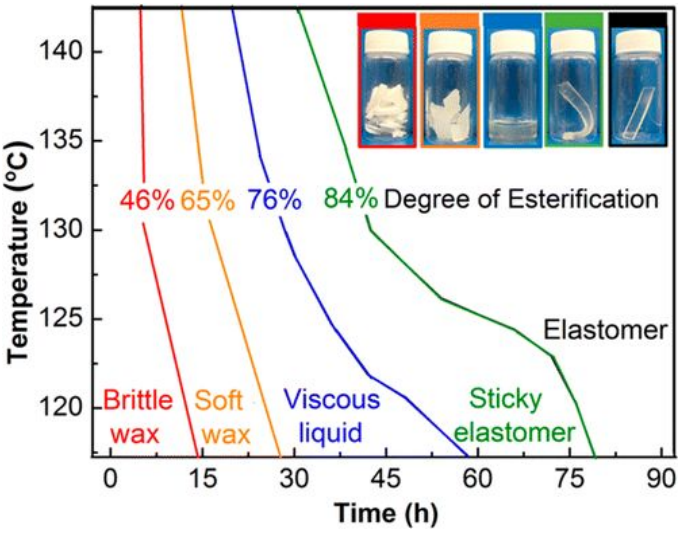

Figure 2: Diagram showing how the degree of esterification affects the physical state of PGS (Li et al., 2015).

Copolymerization, polymerization of multiple different monomers, and blending, dissolving multiple polymers in one solution, of PGS are popular modifications to achieve desired properties (Jeffries et al., 2015). In these cases, PGS's mechanical properties can be retained, while copolymerization or blending another polymer can improve the resulting thermal and bioactive properties. However, these processes can cause the copolymer to obtain undesirable properties. In one case, PGS was copolymerized with poly(methyl methacrylate), allowing the copolymer to be successfully electrospun, but Tg increased to 115°C, rendering the PGS-PMMA copolymer unable to be used for soft tissue engineering. In fact, PGS constituted less than 5% of the copolymer, and wasn't detectable in NMR—many of the copolymer's properties weren't from PGS (Hu et al. 2016).

The aim of this study was to increase PGS's molecular weight to improve mechanical and thermal properties in order to allow for electrospinning. PGS synthesized by the usual reaction has a low molecular weight (Rai et al., 2013). In general, increasing molecular weight can improve upon the mechanical properties and increase melting and crystallization temperature (Nunes, Martin, & Johnson, 1982). This was done by a modification of the synthesis reaction—copolymerization with 1,8-octanediol and the addition of Novozym 435, an enzyme catalyst. 1,8-octanediol, the largest water-soluble and nontoxic aliphatic diol, has previously been used as a monomer in a polyester elastomer (elastic polymer), poly(1,8-octanediol-*co*-citrate) (Yang, Webb, & Ameer, 2004). Novozym 435, a lipase based on immobilized *Candida antarctica* lipase B, is a commercially available biocatalyst. Novozym 435 catalyzes esterification reactions and helps increase molecular weight by aiding in esterification along glycerol's primary hydroxyls as opposed to the secondary hydroxyl group (Ortiz et al., 2019). This property of Novozym 435 and copolymerization with 1,8-octanediol were used in order to extend polymer backbone length and reduce crosslinking to retain elasticity while increasing molecular weight.

Methods

Materials

Chemicals were obtained from Sigma-Aldrich.

Synthesis of PGOS

Glycerol, 1,8-octanediol, and sebacic acid measured in ratios of 1:1:2, 1:3:4, and 1:4:5 were reacted in a parallel synthesizer (Argonaut Advantage Series 2050) and stirred at 500 rpm. There were 5 vials per ratio group, each containing a total of 5 grams. First, the monomers were mixed and melted at

150 °C, then kept at 120 °C for the next 24 hours in a N_2 atmosphere according to Wang et al. The temperature was then lowered to 90 °C and 5 g of Novozym 435 was added, still under nitrogen. After two hours, the nitrogen atmosphere was removed and pressure was reduced to 100 Torr for 4 hours. Afterwards, pressure was reduced by 25 Torr every 12 hours until the pressure reached 25 Torr. POGS prepolymers weren't crosslinked for analysis, but curing was able to be performed at 140 °C at 0.1 Torr for 48 hours.

Characterization of PGS prepolymer

Gel permeation chromatography (GPC, Waters, ResiPore column) was used to measure number average molecular weight (Mn) and weight average molecular weight (Mw). Approximately 2 mg of POGS from each sample was dissolved in 1 mL anhydrous tetrahydrofuran. Samples were calibrated against polystyrene.

Differential scanning calorimetry (DSC, TA Instruments Modulated DSC 2920) was used to measure the melting temperature (Tm) and crystallization temperature (Tc). Analysis was done on 10-20 mg of each sample. Each underwent a heat-cool-heat procedure: the sample was heated to 250 °C, cooled to -60 °C when Tc was measured, then heated back to 250 °C when Tm was measured. Measuring Tm on the second heating ensured that polymer chains would be uniformly amorphous or crystalline.

Proton nuclear magnetic resonance (NMR, Bruker) at 500 mHz was used to confirm the ratios of monomers in the product. Approximately 2 mg of POGS from 3 samples of each ratio was dissolved in 0.3 mL deuterated tetrahydrofuran. The 3 samples closest to average, as determined from GPC and DSC, were chosen for NMR analysis. The resulting spectra were processed and analyzed using Mestrenova software. The peaks integrated to find ratios of 1,8-octanediol and sebacic acid were 4.0-4.09 and 2.23-2.38, respectively; peaks of protons from glycerol and sebacic acid were according to Li et al., 2013.

Electrospinning process

Electrospinning was performed on the highest molecular weight ratio. 2 grams from the best sample of the ratio (determined by proximity to mean of both GPC and DSC) was dissolved in a 5 mL solution of 9:1 chloroform:ethanol. The 40% POGS solution was fed at a rate of 1 mL/hr into a 17.5 kV electric field. The distance between the needle and the collector, a rotating mandrel of aluminum foil that aligns the fibers into a parallel sheet, was approximately 20 cm.

Statistical analysis

All the data presented are expressed as mean ± standard deviation of the mean. Student's t-test and one-way ANOVA were used to find significance, and differences between the groups are considered statistically significant at $p < 0.05$.

Results

In order to increase molecular weight and allow for electrospinning of PGS, 1,8-octanediol was copolymerized with glycerol and sebacic acid monomers in ratios of 1:1:2, 1:3:4, and 1:4:5 (glycerol:1,8-octanediol:sebacic acid). The reaction was catalyzed by the enzyme catalyst Novozym 435, and with an extended reaction time and reduced temperature (compared to Wang et al.) inside a parallel synthesizer with five 5 g vials.

Analysis by GPC measuring number average molecular weight (Mn), weight average molecular weight (Mw), and dispersity (Đ), was performed on all five samples of each polymer. Mn is the total weight of all polymer molecules divided by the number of molecules, while Mw is an average weighted by weight fractions. Đ is calculated from the ratio of Mw/Mn.

Mn values are in the 6000-9000 g/mol range while the Mw values are between 50000 and 85000 g/mol. The 1:3:4 polymer has the highest Mn. The Mn of this medium octanediol ratio is 47.5% greater than the low octanediol and 31.9% greater than the high octanediol. Medium octanediol's Mn value was significantly different from these two ratios ($p = 0.02$ and $p = 0.04$, respectively), while there was no significant difference in Mn between low and high octanediol ($p = 0.47$). The Mw of low octanediol was highest, but only negligibly higher than medium; but low octanediol had Mw 59.6% greater than high octanediol (Fig. 3). The Mw of high octanediol was significantly different from both other ratios ($p = 0.01$ between medium and high, $p = 0.03$ between low and high), but there was no significant difference between low and medium octanediol ratios ($p = 0.78$). High octanediol has the lowest dispersity at 7.75, with the low octanediol being 9.125, and medium being 14.3.

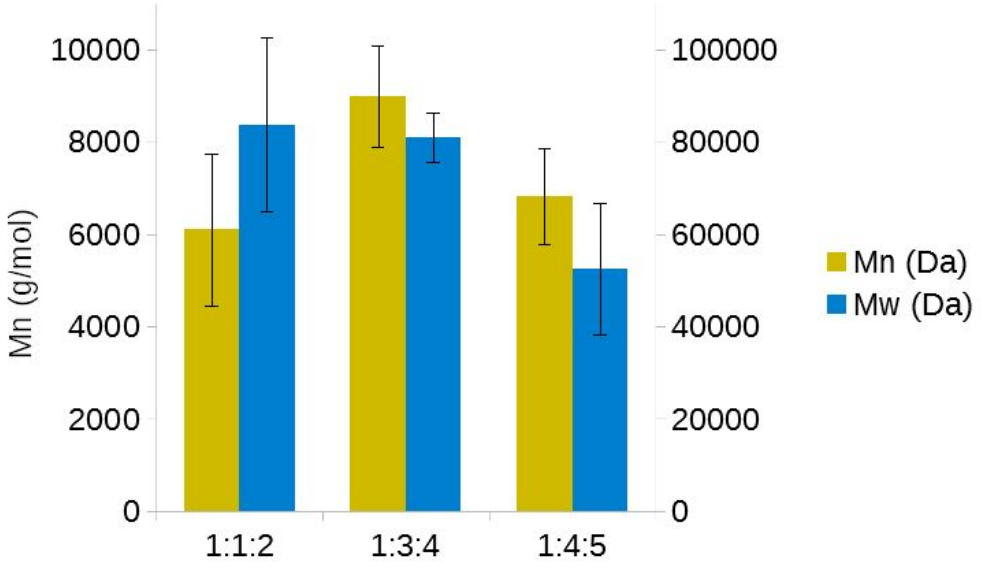

Figure 3: Mean (± SD) Mn and Mw of POGS polymers as measured by GPC. POGS polymers referred to by ratio of monomers (glycerol:1,8-octanediol:sebacic acid). ANOVA was performed to find significance, and equal variance two tailed t-tests were performed between groups to find which specific groups were significantly different.

Analysis by DSC showed that both melting temperature (Tm) and crystallization temperature (Tc) increased statistically significantly with increased ratio of octanediol. High octanediol has a Tm = 65.03 °C, 11.6% greater ($p = 0.00007$) than medium octanediol; and a Tc = 46.85 °C, 4.4% greater than medium ($p = 0.01$). Medium octanediol has a Tm 30.9% greater than low ($p = 0.00009$), and Tc 72.3% greater than low ($p = 0.000004$) (Fig. 4). Tm and Tc were also significantly different between low and high octanediol ratios ($p = 0.000006$, $p = 0.000002$ respectively).

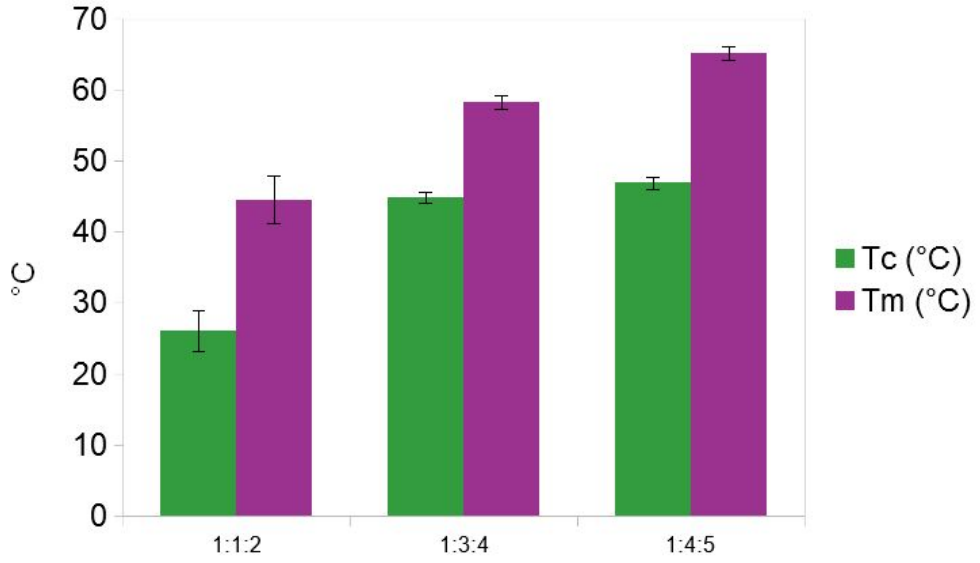

Figure 4: Mean (± SD) Tm and Tc of POGS polymers as measured by DSC in comparison to PGS (Wang et al., 2002). Statistical analysis was the same as with GPC.

Integration of peaks of 1H NMR confirmed the ratios of the octanediol to sebacic acid of the product as approximately equal to the monomer ratio in the reactants (Figure 5). Low octanediol with a ratio of octanediol:sebacic acid of 1:2 had a ratio in NMR of approximately 0.92:2. Medium octanediol with a ratio of octanediol:sebacic acid of 3:4 had a ratio in NMR of approximately 2.98:4. High octanediol with a ratio of octanediol:sebacic acid of 4:5 had a ratio in NMR of approximately 3.72:5. Other peaks were assigned to protons as expected (Li, Cook, Moorhoff, Huang, & Chen, 2013).

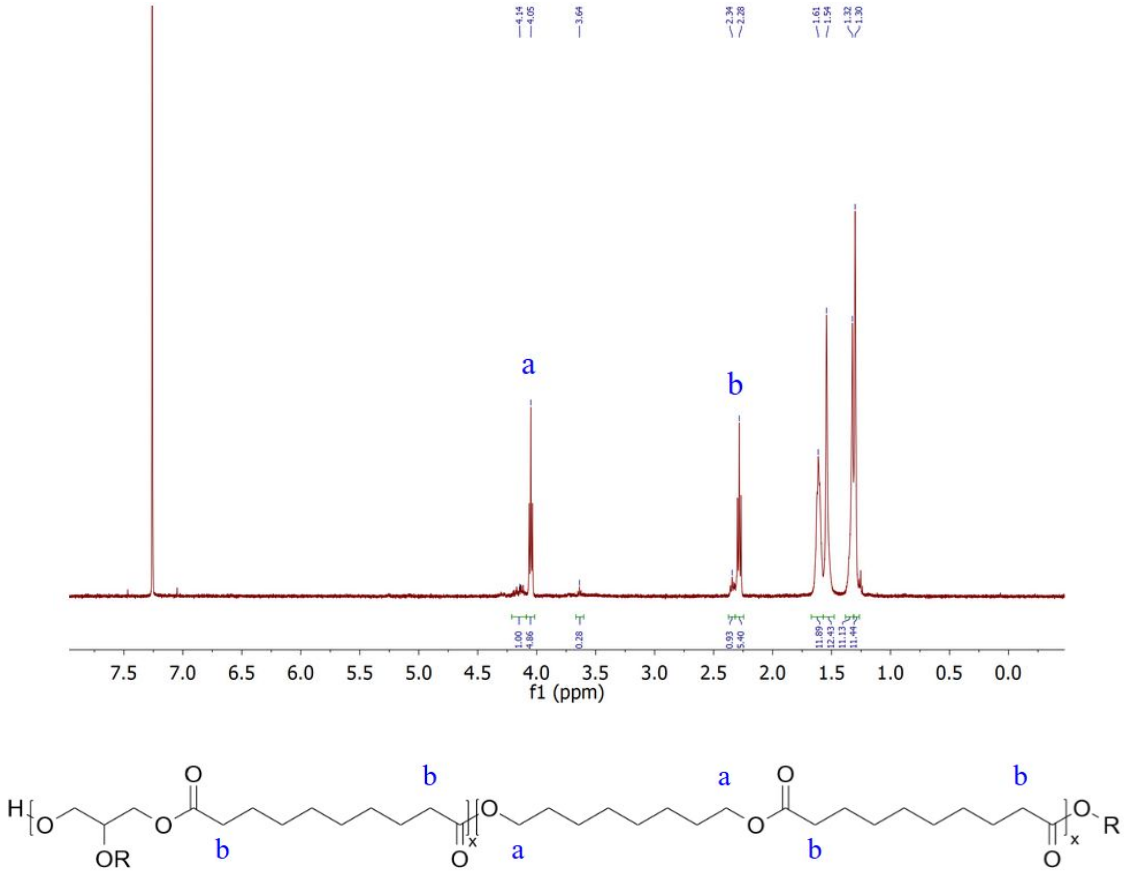

Figure 5: 1H NMR spectrum of a 1:4:5 POGS prepolymer. Peaks a and b correspond to protons a and b on the POGS structural formula. Integral of peak a determined ratio of 1,8-octanediol, and integral of peak b determined ratio of sebacic acid.

Medium octanediol was electrospun but even with a rotating collector, no visible parallel fibers were formed (Fig. 5). Scanning electron microscopy was not performed, however, and the formation of fibers cannot be concluded.

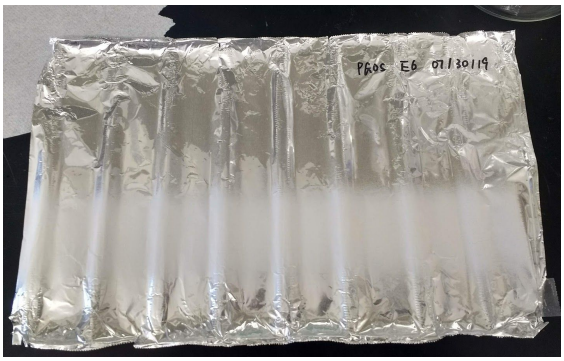

Figure 6: Electrospun 1:3:4 POGS. Fibers parallel to each other aren't visible to the naked eye.

Discussion

The modification of PGS synthesis increased molecular weight successfully. 1,8-octanediol was used as a result of its long chain length, increasing molecular weight substantially with each additional reaction (Yang et al., 2004). Novozym 435 was used as a catalyst to increase molecular weight as it shows specific acylation of primary, as opposed to secondary, alcohols (Ortiz et al., 2019). The molar ratios of monomers (1:1:2, 1:3:4, and 1:4:5 glycerol:1,8-octanediol:sebacic acid) were chosen so that the ratios of hydroxyl-containing and carboxyl-containing monomers are equal. In PGS, glycerol and sebacic acid are reacted in a 1:1 ratio. This reaction is much simpler than previous PGS copolymerization attempts for electrospinnability (Hu et al., 2016).

The GPC results indicate that the method described successfully increased molecular weight. Although the molecular weight of PGS varies among different research groups (Li et al., 2015; Hu et al., 2016; Rai et al., 2012), POGS maintained molecular weights much higher than PGS. Mw of POGS was 46 to 74.5 times greater than one group's Mw of PGS ($1.11x10^3$) (Rai et al., 2012). Mn of POGS was 2.2 to 1.5 times greater than one group's Mn of PGS (4080) (Hu et al., 2016). The measured Mn or Mw of one sample from both the lowest and highest octanediol ratios were drastic outliers and excluded from all GPC analysis. Low and medium POGS had similarly high Mw, and medium POGS clearly had the highest Mn. However, adding more octanediol (and reducing glycerol) didn't see Mw or Mn increase directly with it. Instead, a medium glycerol:1,8-octanediol:sebacic acid ratio balanced octanediol's chain regularity with glycerol's additional functional groups to allow for esterification in additional ways and increase molecular weight.

Low octanediol with a monomer ratio of 1:1:2 has a ratio of 5 hydroxyls to 4 carboxyls (ratio of 1.25), while medium octanediol with monomer ratio of 1:3:4 has 9 hydroxyls for every 8 carboxyls (ratio of 1.125) and high octanediol with a monomer ratio of 1:4:5 has 11 hydroxyls for every 10 carboxyls (ratio of 1.1). While increasing the ratio of octanediol as much as possible would increase molecular weight by a greater amount for every reaction between two molecules, it also reduces the amount of free hydroxyl groups for carboxyl groups to be reacted with. Therefore, as octanediol was added, it first increased molecular weight, but when octanediol was added further, molecular weight began to decrease as a result of the smaller hydroxyl:carboxyl ratio.

DSC results show that all ratios of POGS have Tc and Tm temperatures greater than those of PGS, with Tc and Tm increasing with increasing ratio of octanediol. The crystallization temperature of PGS was shown to be -18.5 °C, and melting temperature was shown to be 5.23 °C (Wang et al., 2002). Crystallization temperatures of POGS were all above room temperature, more than 40 °C greater than

PGS's Tc. Melting temperatures of POGS were 39 to 60 °C greater than Tm of PGS. However, notably, at room temperature, medium and high octanediol prepolymers were solid, while low octanediol was a viscous liquid—a marginal variance from DSC results that show Tc slightly greater than room temperature even in low octanediol. Its Mn isn't significantly different from high octanediol, and its Mw isn't significantly different from medium octanediol; therefore, its physical state isn't explained by molecular weight, but by octanediol itself. Octanediol's linearity provides additional regularity, allowing chains to pack more tightly and crystallization to occur more easily (Flory, 1981). Again, increased ratio of octanediol reduced the ratio of glycerol and therefore hydroxyl groups available for crosslinking. Therefore, additional octanediol increased the linearity of polymer chains; Tc and Tm increased with additional octanediol and the polymers with greater amounts of octanediol were solid.

High octanediol POGS has a Tm almost exactly equal to that of PCL, the most popular synthetic elastomer. POGS's Tm is less than that of PGA or PLA (or copolymers), but these are used below Tg in the body and are crystalline; and often worse for soft tissue engineering (Stratton et al., 2011).

Electrospinning with the parameters described above did not create successful fibers visible to the naked eye. Although fibers are microscopic, fibers are visible in normal images of created mats (Fig. 7). However, given POGS's properties, fibers should be able to be formed under different conditions. When Mw is too low, electrospinning may fail because chain entanglement is necessary for the process. However, polymer fibers have been created with Mw = 13000 g/mol, 6 times less than the Mw of medium octanediol that was used (Koski, Yim, & Shivkumar, 2004). A PGS copolymer was successfully electrospun with Mw = 82200 g/mol, almost exactly the Mw of medium octanediol (Hu et al, 2016). Therefore, it's assumed that altering the concentration of polymer solution, distance from needle to collector, polarity, or other parameters can successfully produce aligned fibers. It seems that capillary-collector distance may have caused the electrospinning process to become electrospraying, a process similar to electrospraying, in which solid polymer droplets, not fibers, are formed (Sill & Recum, 2008). A smaller distance may have allowed for fibers to form.

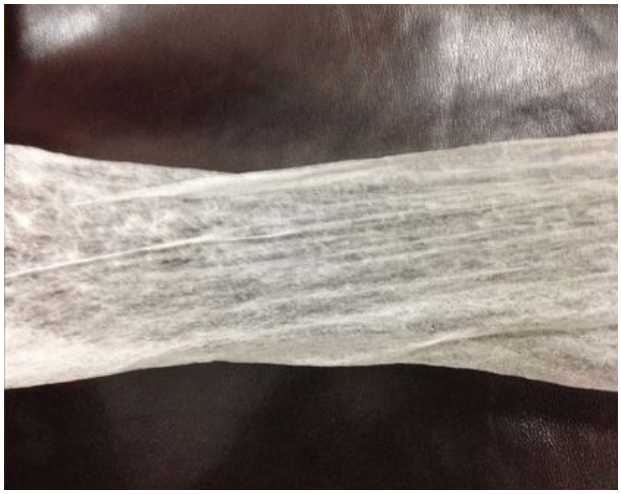

Figure 7: An electrospun fiber mat. Although not aligned by a rotating mandrel collector, fibers and pores are visible without the use of scanning electron microscopy (Moon, Gil, & Lee, 2017).

Medium octanediol had the highest Mn and shared the highest Mw, which was approximately equal to low octanediol, among all POGS ratios. Its thermal properties were not much lower than those of high octanediol, and its Tc and Tm allow for POGS to at least hold a fiber shape at room temperature. Additionally, the glycerol:1,8-octanediol:sebacic acid ratio of medium octanediol strikes a balance between hydrophobic hydrocarbon chains that promote molecular weight and hydrophilic glycerol that promotes biocompatibility. When above Tg, mechanical strength increases with molecular weight. It's possible that 1:3:4 would have the best mechanical properties and best bioactivity among all ratios. All things considered, a medium octanediol ratio improved POGS's properties most.

Conclusions and Future Research

Copolymerization of PGS with 1,8-octanediol and catalysis by Novozym 435 was effective in synthesizing POGS with higher molecular weight that could be used in soft tissue engineering. Measured thermal properties show that POGS fibers would maintain a solid form at room temperature and possibly be able to survive thermal crosslinking at a high temperature. The method described may allow for electrospinning, although no visible fibers were seen. Further analysis should be done to confirm the viability of the polymer. Electrospinning parameters, such as solvent or polymer concentration, can be changed to allow for creation of electrospun 3D fiber mats. Additionally, confirming biocompatibility and mechanical strength though *in vitro* culture and dimensional mechanical analysis would be beneficial.

However, the successfully improved molecular weight and thermal properties demonstrate potential for POGS use in soft tissue scaffolds.

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