SHAPE MEMORY POLYMER (SMP) FOAMS FOR BONE DEFECT REPAIR

An Undergraduate Research Scholars Thesis

by

OLIVIA J. GEORGE

Submitted to Honors and Undergraduate Research
Texas A&M University
In partial fulfillment of the requirements for the designation as an

UNDERGRADUATE RESEARCH SCHOLAR

Approved by:
Research Advisor: Dr. Melissa A. Grunlan

May 2014

Major: Biomedical Engineering
Mathematics

TABLE OF CONTENTS

ABSTRACT

Shape Memory Polymer (SMP) Foams for Bone Defect Repair. (May 2014)

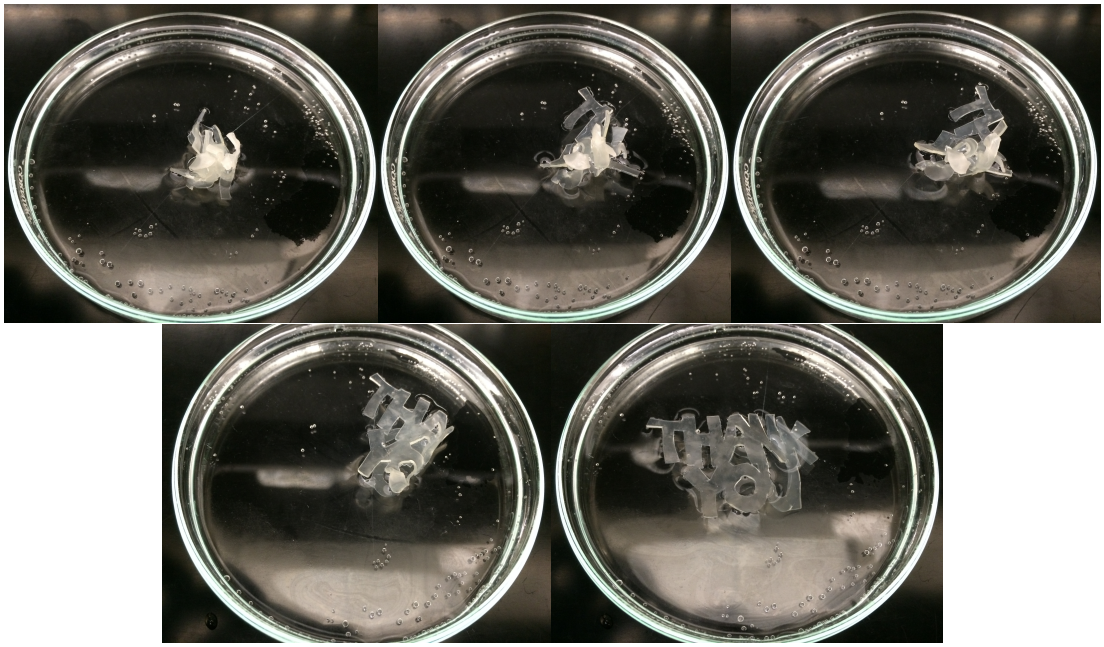
Olivia J. George
Department of Biomedical Engineering
Texas A&M University

Research Advisor:
Dr. Melissa A. Grunlan
Department of Biomedical Engineering

Thermoresponsive shape memory polymers (SMPs) are stimuli-sensitive materials that return to their permanent shape from a fixed temporary shape in response to heat. Porous SMP foams exhibit distinct properties that make them well suited for certain applications in the biomedical field. However, current SMP foams are restricted to a limited group of organic polymer systems. Inorganic-organic foams containing polydimethylsiloxane (PDMS) and poly(ε-caprolactone) (PCL) segments prepared from diacrylated PCL_n-*block*-$PDMS_m$-*block*-PCL_n have recently been reported by our research group. These SMPs exhibit excellent biological, morphological and mechanical properties that may be attractive for "self-fitting" scaffolds to heal cranio-maxillofacial (CMF) bone defects whereby application of warm saline triggers the SMP to expand and conformably fit into a defect before cooling and hardening at body temperature. To enhance the resorption capacity of the scaffolds, the PDMS component may be substituted with a degradable poly(silyl ether fumarate) (PSEF) segment. Herein, two synthetic strategies toward PCL_n-*block*-$PSEF_m$-*block*-PCL_n were explored. Synthetic approaches toward PSEF-diacrylate (i.e. without PCL shape memory ability) are also investigated.

DEDICATION

To David



ACKNOWLEDGEMENTS

I thank my research advisor, Dr. Melissa Grunlan, for her guidance throughout my undergraduate studies. It is a result of her patience and generosity that I have been able to participate in undergraduate research and write this thesis.

I thank many gentle mentors, especially David Zhang and Jenny Robinson, who have contributed indispensably toward my understanding of the project and positive experiences in undergraduate research.

I thank my lab mates for putting up with me on a daily basis.

Finally, I thank family and friends for their unconditional support.

NOMENCLATURE

BDSB	1,4-bis(dimethylsilyl)benzene
$CaSO_4$	calcium sulfate
CMF	cranio-maxillofacial
CSD	critically sized defect
DCM	methylene chloride
DMAP	4-dimethyl amino pyridine
KOH	potassium hydroxide
N_2	nitrogen
Na_2SO_4	sodium sulfate
NaOH	sodium hydroxide
PCL	poly(ε-caprolactone)
PDMS	polydimethylsiloxane
PPF	poly(propylene fumarate)
PSEF	poly(silyl ether fumarate)
rbf	round bottomed flask
RT	Room Temperature
SCPL	solvent casting-particulate leaching
TE	Tissue Engineering
T_g	glass transition temperature
T_m	melting transition temperature
T_{trans}	transition temperature

CHAPTER I

INTRODUCTION

Cranio-maxillofacial bone defects

Neurocranium and facial bones comprise the cranio-maxillofacial (CMF) skeleton that supports and protects the brain, nerves, vasculature, and soft cephalic tissues [1]. According to the National Institute of Dental and Craniofacial Research, craniofacial injuries motivate 20 million visits to emergency departments each year [2]. CMF damage may be the result of congenital deformity, trauma, infection or tumorectomy, and can produce permanent disfigurement and dysfunction if healing does not occur properly [1]. In particular, critically sized defects (CSD) above a threshold wound size will not heal spontaneously during the lifetime of the patient and thus require surgical intervention to guide new bone formation [3]. Repair of CSDs typically involves use of autologous bone grafts harvested from the patient's fibula, iliac crest, scapula or radius [1, 4 - 6]. However, this approach is associated with significant drawbacks, including limited availability, donor site morbidity, and complex grafting procedures [1, 5]. Failure to appropriately shape the autograft to match defect topology can result in graft resorption [6]. Thus, alternative strategies that can overcome these limitations are of primary interest.

Tissue engineering

Tissue engineering (TE) represents a promising alternative to treat CMF bone defects [7]. An ideal bone scaffold candidate should conform intimately to edges of the defect to permit osseointegration, be osteoconductive (i.e. allowing the infiltration of bone tissue) and be bioactive (i.e. promoting bonding with the surrounding bone tissue and permitting osteogenic

cell attachment and differentiation) [4]. Many current tissue engineering systems fail to fully address these design criteria. For example, *in situ* forming hydrogels and bone ceramics have been widely explored for their ability to fill irregular defect geometries [8]. However, they lack the structural and mechanical characteristics necessary for bone defect applications. In particular, bone cements are brittle and often demonstrate poorly controlled porosity [4]. Hydrogels often exhibit variable cure times and lack sufficient mechanical strength [8].

Shape memory polymers

Shape memory polymers (SMPs) are stimuli-responsive materials that can undergo reversible shape change in response to an external stimulus [9]. Their unique dual-shape capability has prompted their investigation in a variety of biomedical applications including intelligent sutures for wound closure, self-deploying stents to prevent stroke, and embolic sponges for aneurysm treatment [9 - 12].

The shape memory effect is attributed to "netpoints" and "switching segments" that work together. The netpoints may be physical (intermolecular) or chemical (covalent) crosslinks that define the permanent shape, while the switching segments impart shape memory ability, allowing the SMP to fix a temporary shape and subsequently recover a permanent shape upon heating [9, 13 - 14]. In the case of thermoresponsive SMPs, the external stimulus is heat. Upon cycling through a transition temperature (T_{trans}), the SMP is temporarily deformed ($T > T_{trans}$) and fixed into a rigid temporary shape ($T < T_{trans}$) before recovering a permanent shape upon heating ($T > T_{trans}$) [13]. This process is represented in **Figure 1**.

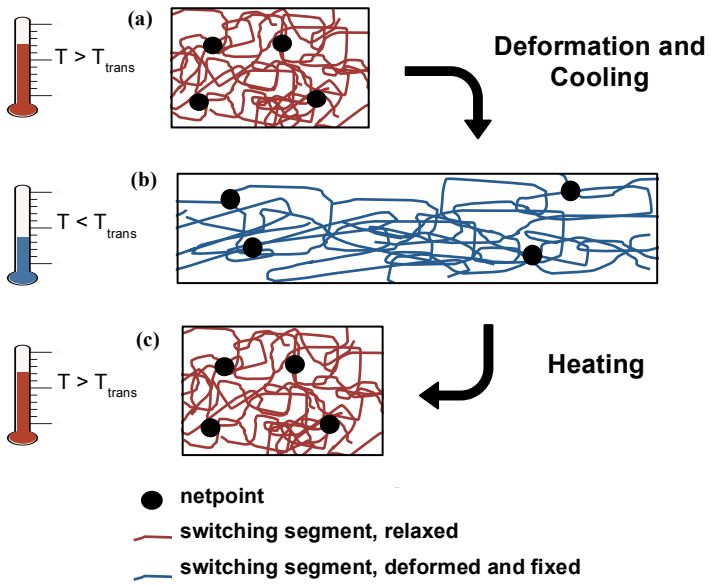


Figure 1: The entropically driven shape memory process: **(a)** polymer switching segments are easily deformed and fixed into a temporary elongation, **(b)**, upon cooling. The switching segments permit recovery of the permanent shape **(c)** upon heating. Adapted from [15].

The use of SMPs in self-fitting bone defect scaffold applications has recently been proposed [16]. Porous, thermoresponsive SMPs with sharp, tunable transition temperatures are of particular interest as these could also provide a minimally invasive alternative to current grafting approaches and as well as overcome significant limitations of hydrogel or ceramic TE scaffold designs. In this capacity, a porous SMP could be implanted into a defect in a confined volume and triggered to expand and conformably fit with the surrounding tissue upon application of warm saline. Once cooled to body temperature, the scaffold would become relatively hardened, "locking" with the osseous environment to form a tight junction necessary for defect healing (**Figure 2**).

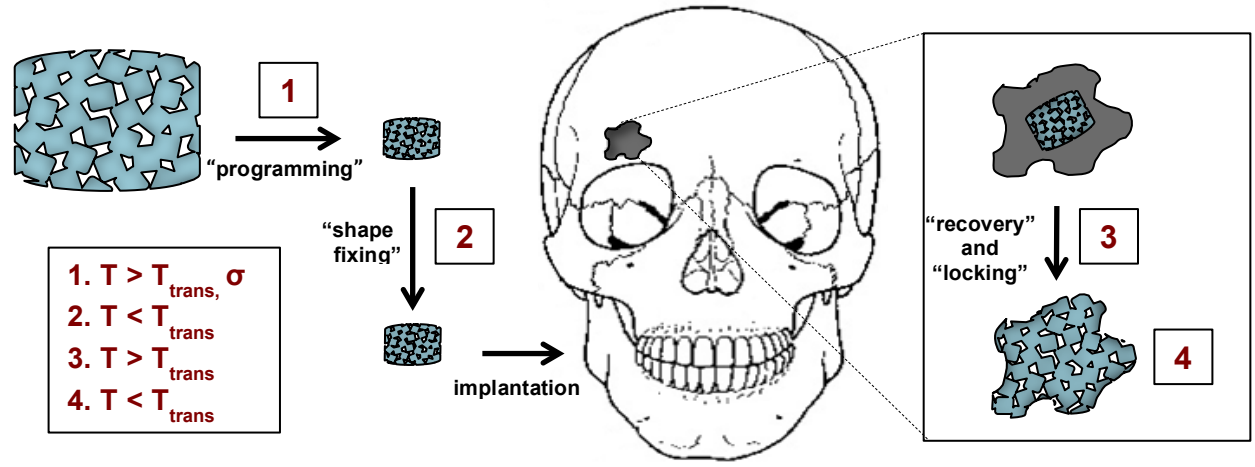


Figure 2: The SMP is "programmed" into a temporary shape and implanted into the defect at $T < T_{trans}$. Heating with warm saline ($T > T_{trans}$) triggers deployment. Upon cooling to body temperature ($T < T_{trans}$), the scaffold hardens and "locks" with the surrounding tissue.

Hybrid SMPs

Poly(ε-caprolactone) (PCL)-based SMP systems have gained recent attention in biomedical applications due to PCL's degradability, elasticity, and biocompatibility [12]. PCL crystalline domains act as switching segments with a melting transition temperature (T_m) serving as the T_{trans} of the SMP. The T_m of PCL can be tuned from 43-60 °C with adjustments in molecular weight, rendering the polymer effective in *in vivo* applications that require minimal heating. Incorporation of additional polymeric segments, including polyurethanes and poly(n-butyl acrylate), in the polymer backbone has been investigated as a route to tune SMP scaffold properties [12]. However, these designs are largely limited to organic-only SMP systems. To realize the potential of SMPs, hybrid systems that incorporate both organic and inorganic components should be considered, as these tend to impart superior control of physical properties versus homopolymer systems [5, 17]. In particular, inclusion of a silicon-containing polymer segment could afford unique degradation, thermal and mechanical properties useful in bone defect applications.

Innovation

We recently prepared porous thermoresponsive SMP "foams" based on macromers containing poly(ε-caprolactone) (PCL) and polydimethylsiloxane (PDMS) segments, diacrylated PCL_n-*block*-$PDMS_m$-*block*-PCL_n, using a revised solvent casting-particulate leaching (SCPL) approach that includes salt fusion and photocrosslinking [13 – 14, 18]. By tailoring salt particle size, degree of salt fusion and macromer concentration, SMP foams with excellent shape fixity (R_f), shape recovery (R_r) and highly tunable pore interconnectivity, pore size, and modulus were achieved. Furthermore, addition of a mussel-inspired polydopamine coating was shown to increase hydroxyapatite formation (i.e. bioactivity [19]) and enhance the capacity of the SMP to support osteoblast adhesion, proliferation and osteogenesis [18].

These properties align well with the requirements of an effective TE bone substitute. Yet, modifications in backbone structure could further improve scaffold degradation [20]. In particular, substitution of a degradable poly(silyl ether fumarate) (PSEF) segment for the non-degradable PMDS softening segment could enhance the scaffold's capacity for resorption *in vivo*. While PSEF's exhibit low glass transition temperatures (T_g's) similar to PDMS, these segments possess labile silyl ether (Si-O-C) functionality that degrades within weeks to months. Added hydrophilicity and crosslinking potential afforded by fumarate groups make PSEF particularly versatile [21]. Herein, routes to achieve diacrylated PSEF as well as diacrylated PCL_n-*block*-$PSEF_m$-*block*-PCL_n were developed and initial syntheses executed.

CHAPTER II

METHODOLOGY

Polymer synthesis

Two synthetic routes to prepare **AcO-PCL$_n$-*block*-PSEF$_m$-*block*-PCL$_n$-OAc** and **AcO-PSEF$_m$-OAc** macromers were developed and are shown in full in **Figures 3** and **4**.

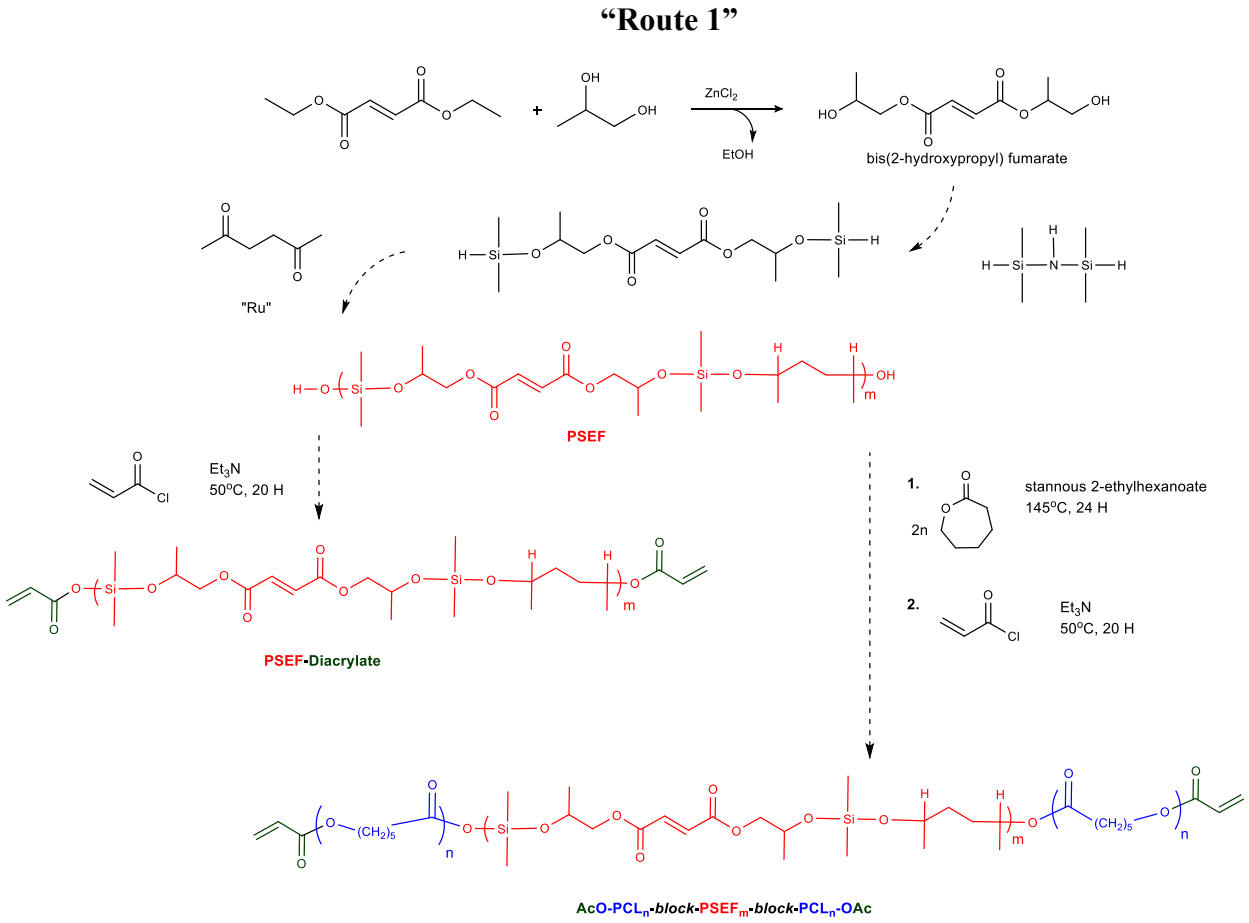


Figure 3: First proposed strategy toward **AcO-PSEF-OAc** and **AcO-PCL$_n$-*block*-PSEF$_m$-*block*-PCL$_n$-OAc** macromer syntheses.

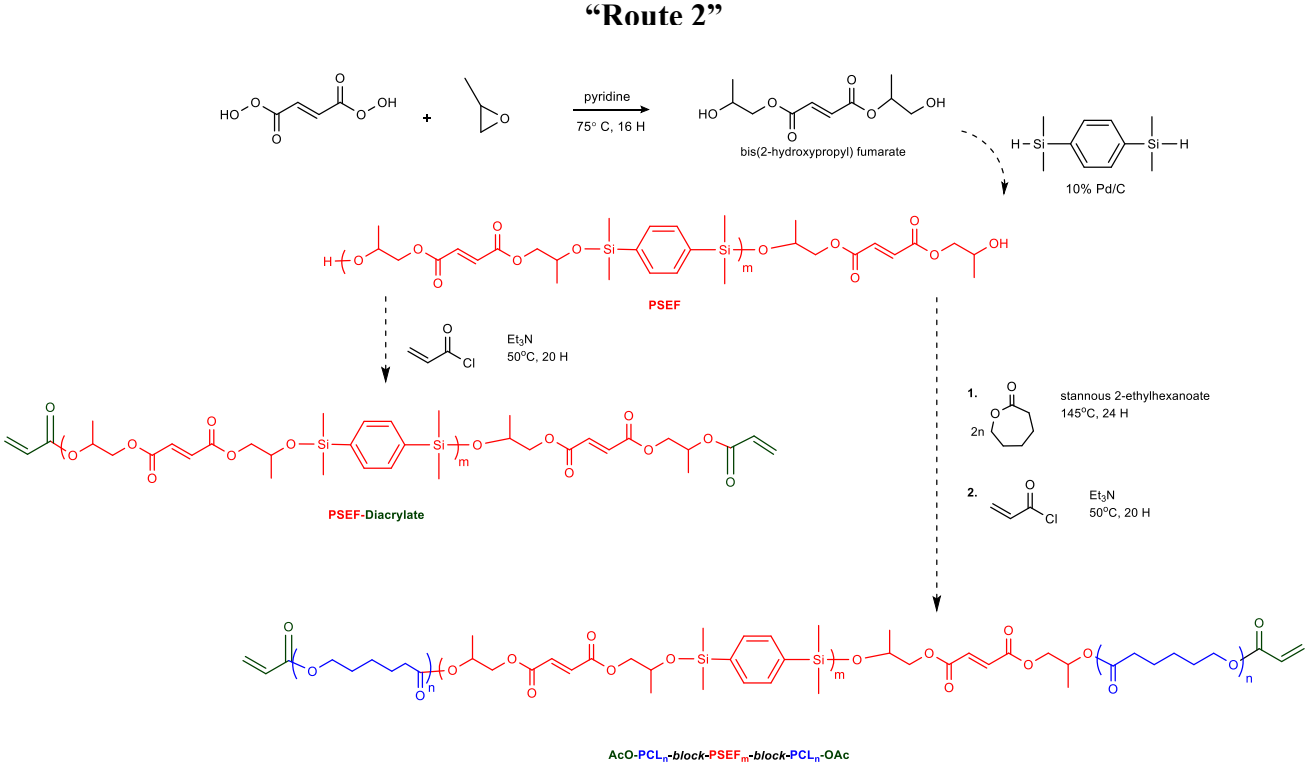


Figure 4: Second proposed strategy as an alternative route toward **AcO-PSEF-OAc** and **AcO-PCL$_n$-*block*-PSEF$_m$-*block*-PCL$_n$-OAc** macromer syntheses.

Route 1: Synthesis and purification of bis(2-hydroxypropyl) fumarate

Bis(2-hydroxypropyl) fumarate intermediate may be prepared as described in [21]: Diethyl fumarate (196.6 g) and propylene glycol (259.4 g) are combined (1:3 molar ratio) in a 1L three-necked round bottom flask (rbf) equipped with a Teflon-coated stir bar. The system is purged under nitrogen (N_2) at a stir rate of 150 r.p.m. Hydroquinone (0.25 g, 2.3 x 10^{-3} mol) and $ZnCl_2$ (1.55 g, 1.1 x 10^{-2} mol) are added to the reaction flask connected to a condenser and the stir rate increased to 300 r.p.m. The flask is heated in a silicone oil bath at 110 °C for 30 min. After 30 min, the temperature is increased to 120 °C for 30 min, then to 130 °C. The reaction is allowed to proceed until approximately 90 % of the theoretical yield of ethanol (95 g) has been collected

in the receiving flask before cooling to room temperature (RT) under N_2. **Figure 5** depicts the setup for this reaction.

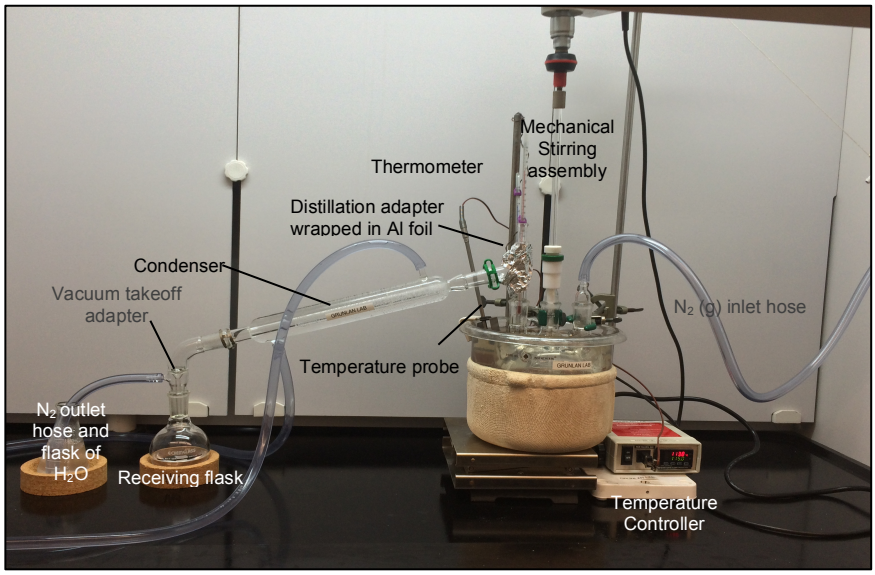


Figure 5: The setup for bis(2-hydroxypropyl) fumarate synthesis.

To purify bis(2-hydroxypropyl) fumarate, methylene chloride (DCM) is added to the crude product for a total solution volume of 800 mL. The solution is transferred to a 2-liter separatory funnel and 1.85 % HCl added such that the acid and macromer solutions are at a volume ratio of 1:1. The mixture is agitated several times before allowing the phases to separate. After 10 min, the polymer phase is collected. This procedure is repeated twice with double-distilled water replacing the 1.85 % HCl; and twice with brine solution.

To dry bis(2-hydroxypropyl) fumarate, sodium sulfate is slowly added while stirring with a magnetic Teflon stir bar until sodium sulfate aggregates become apparent. Stirring is maintained for 30 min followed by filtration through a Büchner funnel (ashless filter paper). The filtrate is transferred into a 1-liter rbf and DCM is removed under reduced pressure.

Ethyl ether washes are performed in a 2 liter Erlenmeyer flask by slowly pouring the bis(2-hydroxypropyl) fumarate solution into 1 liter ethyl ether over ice while stirring. The ether phase is decanted and the product is dissolved in 300 mL DCM. Solvents are removed under reduced pressure at 40 °C and the purified product is achieved upon drying under high vacuum at RT for 8 h and subsequent N_2 purging.

Route 1: Preparation of PSEF from bis(2-hydroxypropyl) fumarate

[Protocol to be finalized]

Route 1: Preparation of OH-PCL_n-block-$PSEF_m$-block-PCL_n-OH macromers

Attachment of PCL-diol to PSEF is achieved via a ring opening polymerization similar to [22]: PSEF and ε-caprolactone are combined in a m:2n molar ratio in the presence of a tin catalyst (0.11 mmol). The reaction is then stirred in a rbf equipped with a rubber septum and magnetic Teflon stir bar for 24 h at 145 °C under N_2. After cooling to RT, the crude product is dissolved in a minimal amount of chloroform ($CHCl_3$) and precipitated twice in excess cold (~10 °C) methanol before drying under vacuum at 45 °C for 20 h.

Route 1: Acrylation of HO-PCL$_n$-block-PSEF$_m$-block-PCL$_n$ –OH and PSEF

HO-PCL$_n$-block-PSEF$_m$-block-PCL$_n$-OH (or PSEF) polymer end groups may be converted into photosensitive acrylate groups in the presence of acryloyl chloride. The macromer (20 g) is dissolved in DCM (120 mL) in a 250 mL rbf equipped with a Teflon stir bar. "1 piece" of 4-dimethyl amino pyridine (DMAP) is added to the reaction flask and the solution is purged under N_2 for 5 min at 260 r.p.m. Triethylamine and acryloyl chloride are slowly added to the reaction flask in a molar ratio of 2:4:1 to HO-PCL$_n$-block-PSEF$_m$-block-PCL$_n$-OH (or PSEF), and the flask is stirred under N_2 for 30 min. The system is then taken off N_2, positioned under a condensation tube and heated to 50 °C. Reaction conditions are maintained for 20 h.

DCM is removed under reduced pressure and the product is washed with ethyl acetate (135 mL) to remove triethylamine hydrochloride salts. The mixture is gravity filtered through ashless filter paper. Solvents are removed from the filtrate under reduced pressure. The polymer is then re-dissolved in DCM (140 mL) and washed with (13.5 mL) 2 M K_2CO_3 (aq). Following separation, the organic layer is collected, dried with anhydrous $MgSO_4$, and gravity filtered. DCM is removed under reduced pressure to achieve the purified product.

Route 2: Synthesis and purification of bis(2-hydroxypropyl) fumarate

Alternatively, bis(2-hydroxypropyl) fumarate may be synthesized from propylene oxide and fumaric acid in a reaction modified from [23]. The setup for this reaction is shown in **Figure 6.**

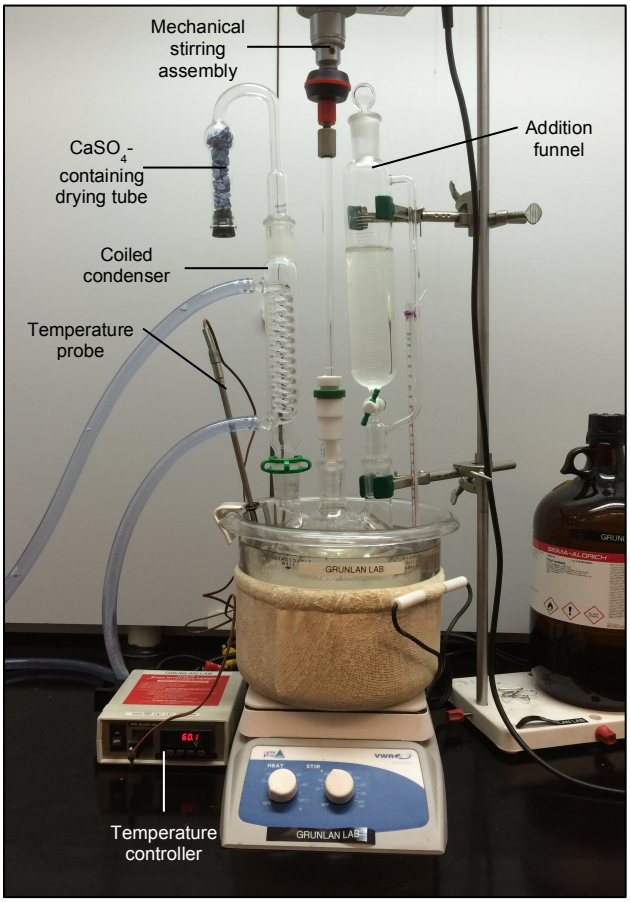


Figure 6: Apparatus for "Route 2" bis(2-hydroxypropyl) fumarate synthesis.

The day before starting the reaction, pyridine is dried over KOH, and 2-butanone and propylene oxide are dried over 4Å molecular sieves. Dry 2-butanone (200 mL) and 0.0016 mol hydroquinone are added to a 1L 3-neck rbf and stirred at 300 rpm. Fumaric acid (116 g, 1 mol) is added to the reaction vessel via funnel before attaching a coiled condenser and drying tube. Dry pyridine (2.7 mL) is added directly to the reaction mixture via micropipette. Propylene oxide (160 mL, 2.29 mol) in 160 mL dry 2-butanone (1:1 vol) is carefully added to an addition funnel

clamped to the rbf. The reaction vessel is sealed with Keck clips and heated to 75 °C for approximately 1 h. The addition funnel is then carefully opened such that propylene oxide enters the vessel at a drop rate of 1 drop/s. Reaction conditions are maintained for 16 h before cooling to RT for purification. After the reaction has cooled, the dropping funnel and coiled condenser are detached from the flask and the distillation apparatus shown in **Figure 7** is assembled while stirring is maintained.

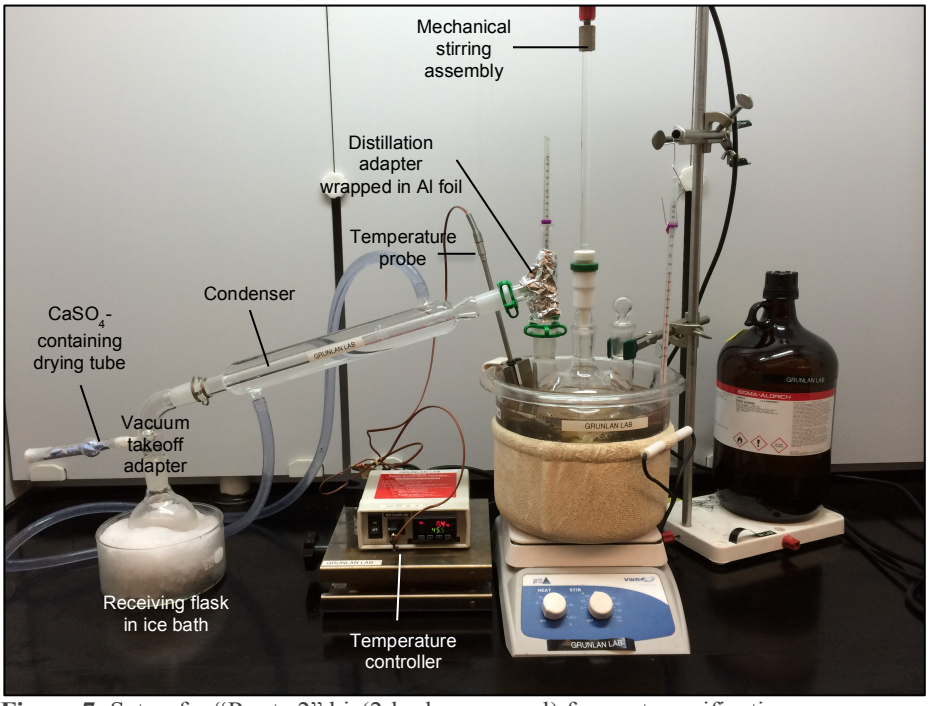


Figure 7: Setup for "Route 2" bis(2-hydroxypropyl) fumarate purification.

The reaction mixture is reheated to 85 °C and unreacted propylene oxide is allowed to vaporize for 1 h. An aspiration connection is substituted for the $CaSO_4$ drying tube, and 2-butanone is distilled (approx. 1 h). Stirring is maintained while the vessel is allowed to cool to RT for 30 min. The product is washed three times with 500 mL hexane and dissolved in DCM. Three washes with 300 mL 6:4 solution of 0.2 M NaOH:brine are performed, followed by a 300 mL brine wash. Purified bis(2-hydroxypropyl) is isolated upon drying with anhydrous Na_2SO_4, filtering through a Büchner funnel (ashless filter paper), and rotary evaporation overnight.

Route 2: Preparation of PSEF from bis(2-hydroxypropyl) fumarate

PSEF synthesis is expected to follow a cross-dehydrocoupling reaction modified from [24 - 26] whereby bis(2-hydroxypropyl) fumarate (slight excess) and 1,4-bis(dimethylsilyl)benzene (BDSB) are combined in a Schlenk flask with 0.25 mol% of 10 wt% palladium on activated carbon as a catalyst at RT. After rapid evolution of hydrogen, the temperature is raised to 100°C and maintained for 24 h. The catalyst is removed by filtration on Celite with THF as an eluent. Precipitation in cold methanol, followed by drying *in vacuo* at RT yields the purified product.

Route 2: Preparation of OH-PCL$_n$-block-PSEF$_m$-block-PCL$_n$-OH macromers

This step is expected to follow identically the procedure outlined for the corresponding step in **"Route 1"** above.

Route 2: Acrylation of HO-PCL$_n$-block-PSEF$_m$-block-PCL$_n$ –OH and PSEF

This step is expected to follow identically the procedure outlined for the corresponding step in **"Route 1"** above.

Characterization

NMR

^{1}H NMR spectra are recorded on a Mercury 300 spectrometer (300MHz) with $CDCl_3$ as an internal standard.

CHAPTER III

RESULTS

^{1}H NMR

The first step of "Routes 1" and "2" were performed. In the first attempt, "Route 1" produced a viscous oligomeric product rather than the expected bis(2-hydroxypropyl) fumarate intermediate. This may be explained by slight temperature fluctuations in the reaction vessel that allowed undesirable transesterification reactions to occur [23]. "Route 2" yielded the desired intermediate (x_n~1) with the ^{1}H NMR spectra below (**Figure 8)** that is consistent with that previously reported [23].

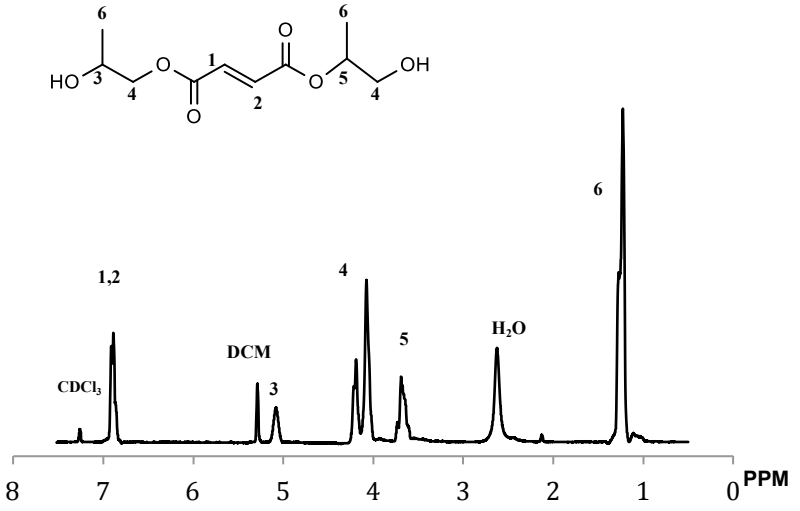


Figure 8: Nuclear magnetic resonance spectra of bis(2-hydroxypropyl) fumarate

CHAPTER IV

CONCLUSION

Exceptional biological, morphological and mechanical properties recently observed in inorganic-organic SMPs suggest their utility in bone defect repair applications. Introduction of a silyl ether-fumarate (PSEF) segment could further enhance a PCL-based SMP's resorption capacity by nature of its hydrolytically labile backbone. Moreover, tailoring the relative length of this segment would also manipulate mechanical properties of the resulting scaffolds. Herein, two independent strategies were developed toward the synthesis of a PSEF-containing SMP and the first step of each is evaluated. Diacrylated PSEF macromers may be also produced (i.e. without PCL switching segments) to yield useful macromers to produce scaffolds, albeit without shape memory behavior. "Route 1" was found to yield an oligomeric intermediate in the first step whereas "Route 2" yielded the bis(2-hydroxypropyl) fumarate intermediate as desired. The higher molecular weight intermediate observed in "Route 1" could be of interest in later stages as a method of tuning scaffold degradation properties. In future stages, the diacrylated polymers will be crosslinked to produce a library of SMPs with tunable degradation profiles.

REFERENCES

[1] Ji W, Wang H, van den Beuken J, Yang F, Walboomers XF, Leeuwenburgh S, Jansen JA. Local delivery of small and large biomolecules in craniomaxillofacial bone. Advanced Drug Delivery Reviews. 2012;64:1152-64.

[2] National Institute of Dental and Craniofacial Research, NIH CDC. Bethesda MD: Oral Health in America: A Report of the Surgeon General. 2002.

[3] Schmitz JP, Hollinger JO, The Critical Size Defect as an Experimental Model for Craniomandibulofacial Nonunions, Clin. Orthop. Relat. Res. 1986;205:299–308.

[4] Calori GM, Mazza E, Colombo M, Ripamonti C. The use of bone-graft substitutes in large bone defects: Any specific needs? Injury. 2011;42:2:56-63.

[5] Szpalski C, Barr J, Wetterau M, Saadeh PB, Warren SM, Cranial bone defects: current and future strategies. Neurosurg. Focus. 2010;29:1-11.

[6] Neovius E, Engstrand T. Craniofacial reconstruction with bone and biomaterials: Review over the 11 years. J Plastic Reconstruct Aesthetic Surg. 2010;63:1615-23.

[7] Hollister SJ et. al. Engineering craniofacial scaffolds. Orthod Craniofacial Res. 2008;8:162-173.

[8] Drury JL, Mooney DL. Hydrogels for tissue engineering: scaffold design variables and applications. Biomaterials. 2003;24:4337-51.

[9] Behl M, Lendlein A. Shape-memory polymers. Materials Today. 2007;10:20-8.

[10] Langer R, Lendlein A. Biodegradable, elastic shape-memory polymers for potential biomedical applications. Science. 2002;296:1673-6.

[11] Small W IV, Singhal P, Wilson TS. Maitland DJ. Biomedical applications of thermally activated shape memory polymers. J. Mater. Chem. 2010;20:3356-66.

[12] Sission AL, Ekinci D, Lendlein A. The contemporary role of ε-caprolactone chemistry to create advanced polymer architectures. Polymer. 2013;54:4333-50.

[13] Zhang D, Petersen KM, Grunlan MA. Inorganic–organic shape memory polymer (SMP) foams with highly tunable properties. ACS Appl Mater Interfaces. 2012;5:186-91.

[14] Zhang D, Burkes WL, Schoener CA, Grunlan MA. Porous inorganic-organic shape memory polymers. Polymer. 2012;53:2935-2941.

[15] Lendlein A, Kelch S. Shape-Memory Polymers. Angew. Chem. Int. Ed. 2002;41:2034-57.

[16] Martin I, Miot S, Barbero A, Jakob M, Wendt D. Osteochondral tissue engineering. Journal of Biomechanics. 2006;40:750-65.

[17] Judeistein P, Sanchez C. Hybrid organic-inorganic materials: a land of multidisciplinarity. J. Mater. Chem. 1996;6:511-25.

[18] Zhang D, George OJ, Petersen KM, Jimenez-Vergara AC, Hahn MS, Grunlan MA. A bioactive "self-fitting" shape memory polymer (SMP) scaffold with potential to treat cranio-maxillofacial (CMF) bone defects. In revision.

[19] Kokubo T, Takadama H. How useful is SBF in predicting in vivo bone bioactivity? Biomaterials. 2006;27:2907-15

[20] Mabry JM, Runyon MK, Weber WP. Poly(silyl ether)s by Ruthenium-Catalyzed Hydrosilylation Polymerization of Aliphatic ω-Dimethylsilyloxy Ketones and Copolymerization of Aliphatic α, ω-Diketones with α, ω-Dihydridooligodimetylsiloxanes. Macromolecules. 2002;35:2207-11.

[21] Kasper FK, Tanahashi K, Fisher JP, Mikos AJ. Synthesis of poly(propylene fumarate). Nature Protocols. 2009;4:518-525.

[22] Schoener CA, Weyand CB, Murthy R, Grunlan MA. Shape memory polymers with silicon-containing segments. J. Mater. Chem. 2010;20:1787-1793.

[23] Christenson EM, Soofi W, Holm JL, Cameron NR, Mikos AG. Biodegradable Fumarate-Based PolyHIPEs as Tissue Engineering Scaffolds. Biomacromolecules. 2007;8:3806-3814.

[24] Li Y, Kawakami Y. Efficient Synthesis of Poly(silyl ether)s by Pd/C and $RhCl(PPh_3)_3$-Catalyzed Cross-Dehydrocoupling Polymerization of Bis(hydrosilane)s with Diols. Macromolecules. 1999;32:6871-6873.

[25] Li Y, Kawakami Y. Synthesis and Properties of Polymers Containing Silphylene Moiety via Catalytic Cross-Dehydrocoupling Polymerization of 1,4-Bis(dimethylsilyl)benzene. Macromolecules. 1999;32:8768-8773.

[26] Wang M, Zhang Q, Wooley KL. Silyl Ether-Coupled Poly(ε-caprolactone)s with Stepwise Hydrolytic Degradation Profiles. Biomacromolecules. 2001;2:1206-1213.