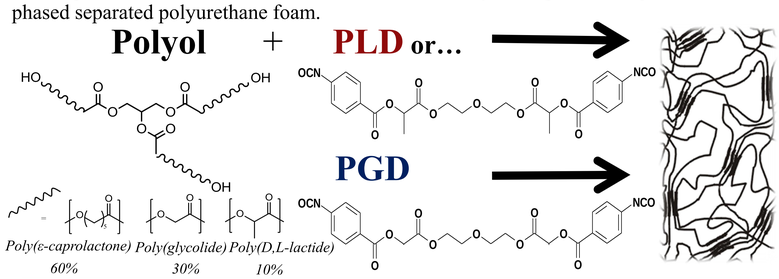
Biodegradable, Injectable, Micro-Phase Separated Polyurethane Foams

[a] Albert W. Hinman, [b] Jonathan M. Page, **and Scott A. Guelcher*[b]**

[a] Department of Biological Sciences, Virginia Tech [b] Department of Chemical and Biomolecular Engineering, Vanderbilt University, 2301 Vanderbilt Place, VU Station B #351604, Nashville, TN 37235, USA. Tel.: +1 615 322 9097; Fax: +1 615 343 7951; E-mail: scott.guelcher@vanderbilt.edu

Introduction

Injectable, polyurethane foams are a promising candidate in soft tissue regenerative medicine to replace skin graft therapy: alleviating the expensive costs and invasive procedures that skin grafts employ. Two novel, liquid isocyanates were tested in various foam formulations for this purpose. The isocyanates, PLD (para-amino benzoic acid-**lactide**-diethylene glycol) and PGD (para-amino benzoic acid-**glycolyde**-diethylene glycol), are synthesized from non-toxic precursors and should degrade hydrolytically. Degradable polyurethanes typically need chemical cross linking in order to maintain structural integrity. PGD polyurethane foams were found to form physical cross links via hydrogen bonded hard segments. There is also evidence of micro-phase separation of the hard segment. PGD formulations are one of the first fully biodegradable, injectable, micro-phased separated polyurethane foam.



Objective

To synthesize, characterize, and optimize an injectable polyurethane foam formulation for the use of soft tissue repair application.

Methods

Foam Synthesis
- Foams were synthesized through hand –mixing the water (hard segment blowing agent), diisocyanate (hard segment), polyol (soft segment), sucrose filler beads (porosity booster), turkey red oil (stabilizer), and blowing catalysts (triethylene diamine, TEDA).

Mechanical Analysis
- Mechanical analysis completed through using a dynamic mechanical analyzer on a TA Q800 for static compression at 37º C to measure stress-strain curves. Elastic modulus data was obtained from the resulting plots.

Thermal Analysis
- Thermal analysis tested for the glass transition temperature, crystallization temperature, and degradation temperature with differential scanning calorimetry (DSC) and thermogravimetric analysis (TGA). Degradation studies were tested through a heat bath, which expedited degradation for analysis by a magnitude of four (57ºC).

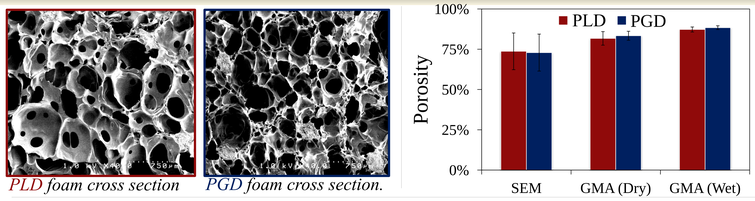
Wide Angle X-Ray Diffraction
- WAXD spectra's were obtained for each of the foams on a range of 5-40º 2θ.

Attenuated Total Reflectance-Fourier Transform Infrared Spectroscopy
- ATR-FTIR spectra's were obtain for each of the foams and changes in hydrogen bonding were analyzed by a curve fitting algorithm.

Porosity Analysis
- Porosity was analyzed though SEM images through ImageJ and gravimetric analysis (GMA). GMA: uses volume, theoretical density, and mass of foam to obtain porosity.

Scanning Electron Microscopy
- Foam sections (approx. 0.5cm^3) were cut and placed onto a SEM stub, and then coated through gold sputtering for image analysis. SEM images were utilized to obtain insight into pore size and structure.

Results



PLD foam cross section *PGD foam cross section.*

Figure 1. *Foam porosities were measured through GMA and SEM analysis. PLD and PGD had similar average pore sizes, 253±27 and 347±77 µm respectively. Foams were injected underwater, which simulates wound fluid in vivo, and analyzed for porosity via GMA. Both foams maintained stability even in the presence of an excess of water.*

Results

Static Mechanical Analysis

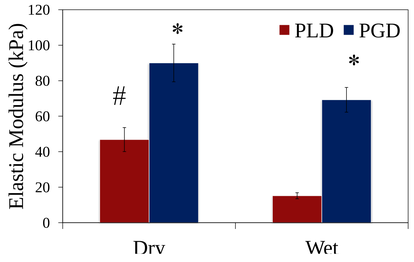


Figure 2. *Foams were run through static mechanical analysis to determine their elastic modulus when dried and wet. Interestingly, PGD behaved similarly within both of these conditions. Both foams have elastic moduli in the range of soft tissues in the body.*

* p<0.05 Statistically significant to PLD dry and wet values
# p<0.05 Statistically significant to PGD wet

ATR-FTIR

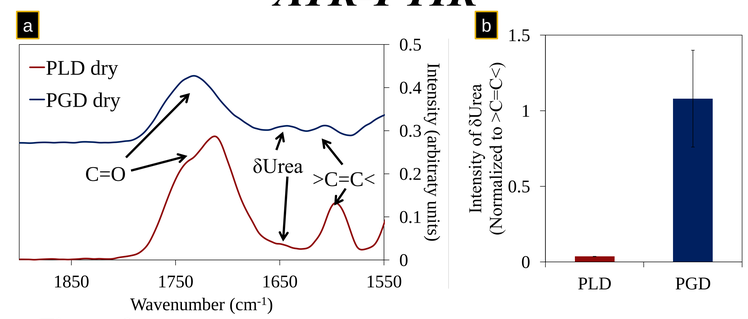


Figure 3. *Evidence of hydrogen bonding was measured through ATR-FTIR. (a) Spectral plots over the region of interest for PLD and PGD foams. (b) Results of curve fitting for δUrea (1645 cm^{-1}) normalized to benzene ring stretching (1600 cm^{-1}). PGD foams held a much larger intensity of the aggregate urea hydrogen bonding.*

X-Ray Diffraction

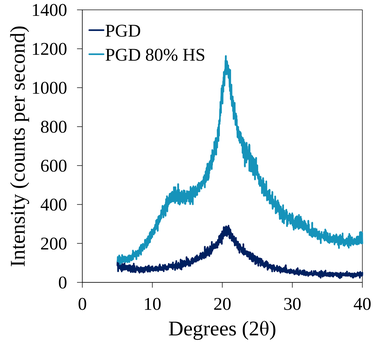
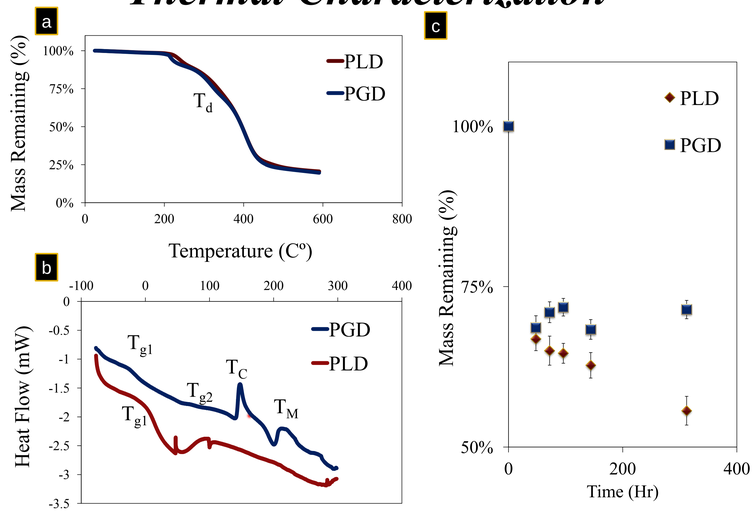


Figure 4. *PGD Foams were analyzed with wide angle x-ray diffraction to qualitatively determine the presence of hard segment crystallinity through observing the amount of molecular crystallization (indicator of hard segment partition). Increasing the amount of PGD in the foam greatly increased the intensity of crystallization of the hard segment, illustrating greater separation of the hard and soft segments. PLD foams showed no evidence of crystallinity.*

Thermal Characterization



Thermal Characterization Data (d)

Sample	T_d (Cº)	T_{g1} (Cº)	T_{g2}(Cº)	T_C(Cº)	T_M(Cº)
PLD Foam	335.7	14.8	-	-	-
PGD Foam	330.2	-16.5	99.3	147.4	200.1
PGD Foam-80% HS	332.5	-68.8	134.8	146.8	193.9
Polyester Polyol	-	*-45.9*	-	-	-
PGD Foam-Polyether	338.1	-67.7	138.4	153.5	197.0
Polyether Polyol	-	*-67.8*	-	-	-

Figure 5. *Foams were analyzed with (a) thermogravimetric analysis for degradation temperature (T_d); (b) differential scanning calorimetry for glass transition (T_g) and crystallization (T_C) and melting (T_M) of hard segment; and (c) in vitro degradation analysis. (d) Relevant thermal transistions from TGA and DSC. The PGD foams were found to have two glass transitions representing the soft (T_{g1}) and hard (T_{g2}) segments. The soft segment T_g occurs near the T_g of the pure polyester polyol, indicating phase separation. Two methods were attempted to induce further phase separation, increasing the hard segment and utilizing a polyether polyol. Both methods produced depressed T_{g1}. Polyether polyols, composed of a 4,800 g/mol polypropylene glycol triol, produced near perfect micro-phase separation without increasing the hard segment content. The PLD foams did not show the presence of hard segment crystallization or phase separation even with polyether soft segments. In vitro degradation shows that PGD remains stable up to 60 days at 37º C (adjusted for temperature) , while PLD foams degrade over the same timeframe.*

Conclusions & Future Work

PGD and PLD are both able to produce a stable foam with >80% porosity, PGD foams were found to have more stable mechanical and degradation properties. Thermal analysis, ATR-FTIR and WAXD illustrated that these properties were caused by micro-phase separation of the hard segment. It was also shown that the micro-phase separation can be enhanced by increasing the hard segment or using a polyether soft segment. For future works, *in vitro* cytotoxicity and *in vivo* testing can elucidate the biostability of the foams.

Acknowledgements

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