Highly Tunable Degradable Elastomers for Medical Applications

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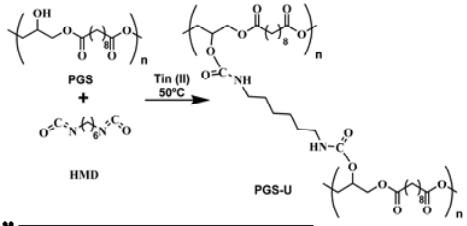
There is a clinical need for degradable elastomers that can be compliant with the dynamics of soft tissues and be resistant to withstand surgical manipulation during complex procedures. However, major challenges remain in tuning their degradation rate and mechanical properties according to the desired application. Poly (glycerol sebacate) (PGS) is a widely explored thermally crosslinked polyester elastomers, given its excellent biocompatibility and elastic properties[1]. However, its processing conditions are relatively harsh and it has a narrow range of tunability for mechanical and degradation properties[2]. We hypothesized that the controlled addition of a second type of physical and chemical crosslink based on urethane linkages would increase tunability without requiring thermal curing.

Methods: PGS pre-polymer was synthesized through a polycondensation reaction of equimolar amounts of glycerol and sebacic acid at 120ºC in vacuum. The pre-polymer was then solubilized in dimethylformamide (10% w/v) and heated to 50ºC in the presence of stannous 2-ethyl-hexanoate (0.1%). The crosslinker, hexamethylene diisocyanate (HMD), was added drop wise to the solution. To obtain polymer films with different physicochemical properties, three molar ratios were tested - glycerol: HMD 1:1, 1:0.5, 1:0.3. The reaction flask was then purged with nitrogen, sealed and the reaction was followed during 5 h. The solution was cast and solvent evaporated to obtain PGS-Urethane (PGS-U) films. The different derivatives were characterized through FT-IR and mechanical properties determined through uniaxial tensile testing. Hydrolytic and enzymatic degradation rates were evaluated *in vitro* using sodium hydroxide (0.05M) and cholesterol esterase (40U/mL) solutions, respectively. *In vitro* compatibility was evaluated through the attachment and proliferation of human mesenchymal stem (hMSC) cells on polymer surfaces and *in vivo* biocompatibility was accessed after implantation of the materials in a subcutaneous mouse model.

Results: The reaction efficiency was evaluated through FT-IR analysis. The absence of the isocyanate group band at 2267cm^{-1} shows complete reaction of the HMD. Amide I and amide II peaks were visible at 1660 and 1570 cm^{-1} respectively and the broad peak at 3600-3200 cm^{-1} in the thermally cured PGS became sharper in the PGS-U films, as a result of the –NH stretching. Therefore, isocyanate functionality is able to react with free hydroxyl groups present in the pre-polymer (fig.1a), establishing covalent (i.e. urethane linkages) and physical (i.e. hydrogen bonding) interchain crosslinks. This allowed obtaining tunable films with a Young's modulus in the range of 0.3 to 18 MPa, ultimate tensile strength from 1.3 to 13 MPa and elongations between 100 and 400 % (fig.1b).

a)



b)

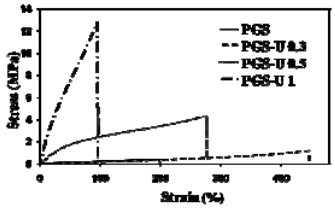


Fig. 1 a) Crosslinking reaction of PGS pre-polymer with HMD to form PGS-U derivatives and b) tunability of mechanical properties of PGS-U films in comparison with thermally cured PGS.

Degradation properties were evaluated under forced hydrolytic and enzymatic conditions as these are the main physiological mechanisms that promote polyester and polyurethane degradation. The degradation rate was proportional to the amount of HMD added to the reaction mixture. For the time range of this study, in contrast to the majority of materials tested, PGS-U with 1:1 ratio did not exhibit substantial degradation. All polymeric films supported cell attachment and proliferation to a confluent monolayer. Their subcutaneous implantation shows that they are biocompatible and exhibit a minimal inflammatory response, comparable to biocompatible materials (e.g. poly(lactic-*co*-glycolic acid).

Conclusions: We successfully synthesized a novel family of elastic biodegradable and biocompatible biomaterials that can easily be processed through a simple solvent casting method. Urethane linkage density proved to be an effective and simple control parameter to tune PGS-U over a wide range of mechanical and degradation properties. *In vitro* and *in vivo* studies showed favorable biocompatibility responses. We are currently evaluating the *in vivo* degradation properties of PGS-U and its potential use as tissue engineering scaffolds and drug delivery vehicles.

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