Published in final edited form as:
Adv Mater. 2013 February 25; 25(8): 1209–1215. doi:10.1002/adma.201203824.

A highly tunable biocompatible and multifunctional biodegradable elastomer

Maria José Nunes Pereira,
Division of Biomedical Engineering, Department of Medicine, Center for Regenerative Therapeutics, Brigham and Women's Hospital, Harvard Medical School, Harvard Stem Cell Institute, Harvard-MIT Division of Health Sciences and Technology, 65 Landsdowne St., Cambridge, MA 02139, USA. Biocant- Biotechnology Innovation Center, CNC-Center of Neurosciences and Cell Biology, University of Coimbra, 3004-517 Coimbra, Portugal

Ben Ouyang,
Division of Biomedical Engineering, Department of Medicine, Center for Regenerative Therapeutics, Brigham and Women's Hospital, Harvard Medical School, Harvard Stem Cell Institute, Harvard-MIT Division of Health Sciences and Technology, 65 Landsdowne St., Cambridge, MA 02139, USA

Dr. Cathryn A. Sundback,
Center for Regenerative Medicine, Massachusetts General Hospital, Harvard Medical School, 55 Fruit St., Boston, MA 02114, USA

Dr. Nora Lang,
Departments of Cardiac Surgery, Children's Hospital Boston, Harvard Medical School, 300 Longwood Av., Boston, MA 02115, USA

Dr. Ingeborg Friehs,
Departments of Cardiac Surgery, Children's Hospital Boston, Harvard Medical School, 300 Longwood Av., Boston, MA 02115, USA

Shwetha Mureli,
Division of Biomedical Engineering, Department of Medicine, Center for Regenerative Therapeutics, Brigham and Women's Hospital, Harvard Medical School, Harvard Stem Cell Institute, Harvard-MIT Division of Health Sciences and Technology, 65 Landsdowne St., Cambridge, MA 02139, USA

Dr. Irina Pomerantseva,
Center for Regenerative Medicine, Massachusetts General Hospital, Harvard Medical School, 55 Fruit St., Boston, MA 02114, USA

Jacob McFadden,
Center for Regenerative Medicine, Massachusetts General Hospital, Harvard Medical School, 55 Fruit St., Boston, MA 02114, USA

Dr. Mark C. Mochel,
Department of Pathology, Massachusetts General Hospital, 55 Fruit Street, Boston, MA 02114, USA

Olive Mwizerwa,
Center for Regenerative Medicine, Massachusetts General Hospital, Harvard Medical School, 55 Fruit St., Boston, MA 02114, USA

Correspondence to: Lino S. Ferreira, lino@biocant.pt; Jeffrey M. Karp, jkarp@rics.bwh.harvard.edu.

Dr. Pedro del Nido,
Departments of Cardiac Surgery, Children's Hospital Boston, Harvard Medical School, 300 Longwood Av., Boston, MA 02115, USA

Dr. Debanjan Sarkar,
Division of Biomedical Engineering, Department of Medicine, Center for Regenerative Therapeutics, Brigham and Women's Hospital, Harvard Medical School, Harvard Stem Cell Institute, Harvard-MIT Division of Health Sciences and Technology, 65 Landsdowne St., Cambridge, MA 02139, USA. Department of Biomedical Engineering, University at Buffalo, State University of New York, Buffalo, NY 14260, USA

Dr. Peter T. Masiakos,
Center for Regenerative Medicine, Massachusetts General Hospital, Harvard Medical School, 55 Fruit St., Boston, MA 02114, USA

Prof. Robert Langer,
Department of Chemical Engineering and the David H. Koch Institute for Integrative Cancer Research, Massachusetts Institute of Technology, 500 Main Street, Cambridge, MA 02139, USA

Dr. Lino S. Ferreira, and
Biocant- Biotechnology Innovation Center, CNC-Center of Neurosciences and Cell Biology, University of Coimbra, 3004-517 Coimbra, Portugal

Prof. Jeffrey M. Karp
Division of Biomedical Engineering, Department of Medicine, Center for Regenerative Therapeutics, Brigham and Women's Hospital, Harvard Medical School, Harvard Stem Cell Institute, Harvard-MIT Division of Health Sciences and Technology, 65 Landsdowne St., Cambridge, MA 02139, USA

Lino S. Ferreira: lino@biocant.pt; Jeffrey M. Karp: jkarp@rics.bwh.harvard.edu

Keywords

elastomer; biodegradable polymer; biocompatible; drug delivery; biomacromolecules

Biodegradable elastomers have emerged as promising materials for their potential to mimic the viscoelastic properties of several tissues and exhibit compliance with dynamic environments without damaging the surrounding tissue.[1, 2] Several elastomers have been recently proposed;[3–8] however, the development of highly tunable biodegradable elastomers that can effectively and controllably present biological and physical signals and withstand repeated cycles of physiologic loads, has remained elusive. Such materials should be useful for a broad range of clinically-relevant applications, such as cardiac therapy. For example, following myocardial infarction, the local controlled delivery of bioactive cues[9] or the physical support of the left ventricle wall[10] have been shown to improve cardiac function. The synergistic therapeutic effect of biochemical and biophysical cues has not yet been explored using degradable materials given the absence of materials that can simultaneously deliver bioactive cues and maintain mechanical integrity in a dynamic environment such as the beating heart. Here, we describe a novel biocompatible and mechanically tunable elastomer, poly(glycerol sebacate urethane) (PGSU), suitable for efficient encapsulation and controlled delivery of bioactive macromolecules and with the potential to be applied to cardiac drug delivery.

Poly(glycerol sebacate) (PGS), a widely explored biodegradable elastomeric polyester, exhibits a covalently crosslinked three dimensional molecular structure that provides elastic recovery after exposure to tensile loads.[3] However, its mechanical properties are only

controllable within a narrow range (Young's modulus from 0.25 to 1.45 MPa for materials with elongations above 100%),[11] in addition to requiring high temperature (above 100°C) for long periods of time (days) during synthesis. To overcome high temperatures, PGS photocurable networks were developed.[12] While these elastomers contain functional hydroxyl groups and exhibit tunable mechanical properties, it is difficult to protect sensitive molecules from UV light (for drug delivery applications) and the elastomers obtained are typically weaker than the polyester they are derived from and require incorporation of other acrylated precursors to improve the mechanical properties. In comparison, polyurethanes have a major advantage due to the simplicity of the processing methods (e.g. solvent casting) to achieve elastomers with a broad range of mechanical properties. However, their linear nature has been associated with high creep deformation, with loss of tensile strength and elasticity when subjected to dynamic loads.[13, 14] The functionality and versatility of polyurethanes has been not only been explored in the context of biodegradable elastomers, but also as building blocks of smart nanomaterials for drug delivery applications.[15] Given the complementary advantages of thermoset polyesters and thermoplastic polyurethanes, we developed a new material, poly (glycerol sebacate urethane) (PGSU), to combine and extend the best features of existing classes of elastomers. We hypothesized that 1) the free hydroxyl groups present in partially crosslinked PGS pre-polymer would react with isocyanate-based crosslinkers, generating a three-dimensional, covalently and physically (e.g. hydrogen bonding) crosslinked network based on ester and urethane linkages (Fig. 1A), whose mechanical and degradation properties can be easily controlled through simply changing the crosslinking degree, 2) the reaction between isocyanate and free hydroxyl groups would rapidly occur under mild conditions and not require a thermal curing step.

The PGS pre-polymer used in this study had a weight-average molecular weight of 12700±1600 g/mol and a polydispersity index of 4.5±0.5, as evaluated through gel permeation chromatography. Aliphatic hexamethylene diisocyanate (HDI) was chosen as the crosslinker given its low cost and wide use in the synthesis of biodegradable and biocompatible polyurethanes.[16] Importantly, we demonstrated that PGSU can be synthesized from these components through solvent-based (PGSU-S) and solvent-free (PGSU-SF) methods (Fig. 1B). For both methods, Tin(II) 2-ethylhexanoate was used as catalyst. In the solvent-based approach the reaction occurs in an organic solvent, followed by solvent casting. After evaporation, uniform non-porous films with transparent optical properties (**SI 1A**) are obtained. To achieve a non-porous elastomer synthesized under solvent-free conditions, after mixing PGS pre-polymer with the crosslinker, the mixture was spin coated to achieve a uniform film (**SI 1B**) with a thickness dependent on the spin coating rate. Several stacked layers can be subsequently spin coated without delamination. A strong entanglement between layers is likely achieved due to the reaction of HDI with unreacted hydroxyl groups present in the underlying polymer layer. Porous scaffolds were also fabricated in the absence of organic solvents through a foaming process, well-known for polyurethanes.[17] The presence of moisture results in the reaction of HDI with water to form carbon dioxide gas, which diffuses through the polymer and creates pores during the curing process in thicker films (**SI 1C**). Free hydroxyl groups in the pre-polymer backbone can be easily crosslinked under mild conditions, while the low viscosity at temperatures below 37°C permits uniform mixing with HDI and spin coating to achieve uniform PGSU layers with controllable thickness. Importantly, PGSU-SF films can be synthesized under 36 hours, considering the time for pre-polymer synthesis and crosslinking with diisocyanate molecules, which is a major advantage compared to other elastomers that require long periods of time for complete polymerization or solvent evaporation.[1, 18]

The reaction efficiency and the molecular structure of the derivatives obtained were evaluated by FTIR (Fig. 1C). The PGS pre-polymer presents a broad peak at 3445 cm^{-1}, resulting from free hydroxyl groups (-OH stretch). With the addition of HDI, free hydroxyl

groups are replaced by urethane groups and consequently a proportional deviation of this peak to lower wavelength (PGSU-S 1:0.3 at 3359 cm^{-1}, PGSU-S 1:0.5 at 3337 cm^{-1}, PGSU-S 1:1 at 3329 cm^{-1}) is observed, corresponding to the –NH group stretch. This shift also reveals the increase in hydrogen bonding forces with the isocyanate linker content. The peak near 1735 cm^{-1} is attributed to the carbonyl group stretching from ester groups in PGS pre-polymer and PGSU derivatives. Amide I and amide II bands at 1630 and 1580 cm^{-1} are only observed in PGSU derivatives, further confirming the establishment of urethane linkages in the polymer backbone. The absence of the characteristic isocyanate group band at 2270 cm^{-1} reveals the complete reaction of the isocyanate groups in all PGSU derivatives. Similar spectra were obtained for films prepared through the solvent-free approach, indicating no major chemical differences in the polymeric network established. All derivatives synthesized were insoluble in a variety of organic solvents (e.g. tetrahydrofuran, dimethylsulfoxide, dioxane, DMF, and dichloromethane), further confirming the establishment of an interchain chemically crosslinked network resulting from the reaction between the free hydroxyl groups in the PGS pre-polymer and the isocyanate crosslinker.

Thermal properties were evaluated for PGSU-S films, with all derivatives showing glass transition temperature (T_g) values below 0°C (−11.8 °C for PGSU-S 1:0.3, −7.3 °C for PGSU-S 1:0.5, −4.2 °C for PGSU-S 1:1). The material's amorphous nature at room and body temperature assures its' elastomeric properties. In addition, the lack of significant swelling of PGSU films in physiological solutions (**SI 2**) also contributes to its mechanical integrity once exposed to a wet environment (e.g. *in vivo*). The high degree of swelling in ethanol (**SI 2**) facilitates the removal of any unreacted monomers (sol content) entangled in the crosslinked network.

Several strategies have been previously reported to improve the mechanical properties of PGS elastomers, including the addition of micron-size fillers (e.g. Bioglass), or the introduction of functional groups (e.g. amide groups) to improve the polymer crosslinking.[8, 16, 19] Despite considerable improvements in the range of properties achieved, high curing temperatures are still required. Through simply changing the degree of crosslinking by the introduction of urethane groups, PGSU films can be tailored to achieve a broad range of mechanical properties (Young's modulus from ~0.1 to 20 MPa), mimicking the stiffness of a diverse range of tissues, such as the myocardium, pericardium, skin, aorta, or cartilage (Fig. 1D and 1E).[18] The crosslink density (Fig. 1D), was calculated using the formula:

$$n = E_o/(3RT)$$

where Eo is the Young's modulus, R the gas constant, and T temperature. Also of interest is the improved tensile strength of PGSU films compared to thermally cured PGS. For example, both PGSU-S and -SF 1:0.3 and PGS show a Young's modulus below 1 MPa yet, the urethane crosslink improves the tensile strength (1.35±0.76MPa for PGSU-S 1:0.3 compared to 0.38±0.06MPa for PGS) and elongation (516±109% for PGSU-S 1:0.3, compared to 200±30 % for PGS) of the material (Fig. 1E). The improved properties likely derive from the fact that urethane provides a covalent crosslink and increases hydrogen boding between polymer chains.[8, 16] These features may be exploited in load-bearing applications where strength and elasticity are essential. Furthermore, biomaterials are often significantly manipulated prior to proper placement and thus must maintain their integrity following transplantation and during surgical implantation. While aliphatic polyurethanes have been associated with permanent deformation once exposed to tensile forces, [14] PGSU shows minimal creep deformation and minimal loss of tensile strength after 100 tensile

cycles (Fig. 1F). The presence of covalent crosslinks between the polymeric chains likely prevents them from sliding past one another, therefore improving their stability under dynamic environments.

To determine the potential of PGSU derivatives in biomedical applications, we assessed their biodegradation profiles and cytocompatibility *in vitro*. In the presence of cholesterol esterase, PGSU-S films exhibited a degradation profile dependent on the degree of crosslinking (**SI 3**). The ester groups in the polymer backbone are highly sensitive to enzymatic degradation; however, with increased urethane content the accessibility to ester bonds is hindered resulting in slower degradation rates. Human mesenchymal stem cells were used to test the cytocompatibility of PGSU-S materials. While fewer cells adhered to PGSU-S than to tissue culture polystyrene (TCP) (day 1); cells proliferated on PGSU-S and at day 8 their metabolism, as assessed by a MTT assay, was not statistically different from cells on TCP (**SI 4**). Given the positive preliminary data, we examined the *in vivo* acute and chronic inflammatory response in a subcutaneous rat animal model and compared it to poly(lactic-co-glycolic acid) (PLGA), a degradable material that has been FDA-approved in several products for intended internal use.[20] PGSU-S samples can be autoclaved without major changes to their physical properties. No adverse reactions to the implants or complications were noted during the implantation period of 40 weeks. H&E and anti-CD68 macrophage stainings were employed to characterize the inflammatory response to the implants (Fig. 2A). The inflammatory responses to the PGSU-S polymers were similar when comparing all derivatives, and characterized as mixed lymphohistiocytic reaction with the predominance of histiocytic at 1 and 4 week time points, and lymphocytic reactions at all later time points. No giant cells could be identified in any material group at any time point. All PGSU sample groups exhibited mild to moderate infiltration by CD68-positive macrophages at 1 week post implantation; at all later time points, CD68-positive infiltration was characterized as minimal. The inflammatory reaction to PLGA was significantly higher ($p<0.1$) than the reaction to the PGSU-S at 1 and 4 weeks (Fig. 2A and 2B). Capsule thickness did not vary significantly among all PGSU samples (Fig. 2B) and was comparable to PLGA at 1 week. PLGA capsule could not be measured at later time points as all samples were nearly fully degraded at 4 weeks post-implantation. Previous reports describe that PLGA derivatives generate a fibrotic capsule between 150 and 1000 μm for implantation periods between 1 and 12 weeks.[7, 21]

Following 20 weeks of implantation, all samples maintained their circular shape, with PGSU-S 1:0.3 and 0.5 exhibiting a gradual decrease in sample diameter and thickness, with a remaining weight of 59.9±3.9 and 68.2±1.5%, respectively (Fig. 2C). At week 40, explanted PGSU-S 1:0.3 and PGSU-S 1:0.5 samples were fragmented and therefore not considered for weight loss evaluation. The degradation rate observed for all the derivatives was generally slower than what has been described for other elastomers, such as PGS, whose degradation rate cannot substantially be tuned. [11] SEM evaluation of PGSU-S 1:0.3 following 20 weeks showed minimal morphological changes on the micron-scale suggesting that the degradation mechanism is based on surface erosion (Fig. 2D). No significant weight loss or morphologic changes were observed for PGSU-S 1:1 samples during the 40 week study.

Biodegradable elastomers are gaining significant attention in cardiac therapy, with potential applications ranging from reconstructive procedures, tissue engineering to localized drug delivery [10, 22–25]. The mechanical compliance and degradation properties of biomaterials applied to the heart have been shown to strongly influence cardiac function and the material's integration with the host tissue.[2] However, clinically-used materials (e.g. Dacron) are stiff, non-degradable and are associated with long-term fibrosis and calcification, compromising regional function.[26] Porous PGSU-SF 1:0.3 exhibits similar

mechanical properties to native heart tissue[23] and the mild synthetic conditions used to formulate the solvent-free PGSU should permit localized delivery of bioactive macromolecules. Such an approach could provide new therapeutic options for cardiac disease given that many biomolecules exhibit short half-lives and/or present systemic toxicity. Towards potential cardiac applications, we performed a preliminary *in vivo* biocompatibility study to evaluate how porous PGSU-SF 1:0.3 interacts with myocardial tissue. The sol content was not extracted to simulate applications for drug delivery of bioactive agents. Specifically, PGSU-SF films could be easily manipulated and sutured, showing excellent tear-resistant properties. Cardiac acute and chronic inflammatory responses to PGSU-SF 1:0.3 films were evaluated one and four weeks after implantation, respectively, through H&E staining (Fig. 2E). While diffuse granulation tissue and infiltrated lymphocytes were visible surrounding the implant, the myocardial surface did not show signs of a significant inflammatory response and no major fibrotic response or collagen deposition was observed. The presence of sol content does not seem to impact the biocompatibility profile of PGSU-SF. Importantly, no changes in cardiac function were observed via echocardiography analysis (Fig. 2F). Moderate chest adhesions, commonly found after thoracotomy procedures, were observed during heart excision at both time points.

Given the possibility of preparing PGSU-SF elastomers under mild conditions, we evaluated their applicability as a controlled delivery system for bioactive molecules. While the use of biodegradable polyurethane foams for the delivery of therapeutic proteins has been previously reported, [27] the mechanical properties of the materials obtained have been limited to tensile moduli below 0.12 MPa. In contrast, proteins could easily be loaded directly into the highly tunable PGSU-SF, without interfering with the curing process or final properties of the elastomer. To evaluate the bioactivity of the released biomolecules, lysozyme was used as a model protein given the availability of simple and cost-effective assays to quantify its activity. The protein was encapsulated in porous PGSU-SF with approximately 1 mm thickness, and exhibited a small initial burst followed by sustained protein release for at least 2 days (Fig. 3A i). Importantly, the majority of the protein released was bioactive (Fig. 3A ii).

Next, to achieve improved control over the delivery profile, we developed a strategy based on the sequential layering of PGSU-SF that permits controlled localization of encapsulated molecules (Fig. 3B). When the pre-polymer was spin coated at 3000RPM and without protein powder, the size of each layer was 33.5±0.1 μm. Given that the release is based on both diffusion and polymer degradation mechanisms, controlled release could be achieved through altering the stacking order of the loaded and unloaded layers, the size of the encapsulated protein powder, and the presence of osmotic agents. As a proof of concept, the lyophilized model protein bovine serum albumin (BSA) was sieved to particle sizes of either below 32 μm, similar to the thickness of each layer, or to below 75 μm. These particles were encapsulated in internal layers of PGSU-SF 1:0.3 films. Given the low degree of swelling that PGSU films exhibit in aqueous environments, the diffusion of water to solubilize and release the entrapped protein is limited. As a result, the majority of the protein remains entrapped within the polymeric network, especially when the particle size is smaller than the layer thickness (Fig. 3C). The use of larger protein particles results in increased protein release at earlier time points given the proximity to the liquid/substrate interface. Dissolution of the protein likely leads to a porous structure that further contributes to sustained release for longer periods of time. The release can be accelerated through the co-encapsulation of protein with an osmotic agent such as trehalose that increases water uptake into the PGSU-SF films (**SI 5**). The encapsulation of BSA and trehalose sieved to particle size below 32 μm within the internal PGSU-SF layer resulted in the sustained protein release for more than 18 days, with approximately 50% of the protein content released during this time period (Fig.

3D). The encapsulation of the same protein formulation in external polymer layers resulted in faster release of the protein loaded. Protein diffusion may occur in multiple directions from the prepared disks and this is dependent on the spatial localization of the encapsulated biomolecule and relevant surface areas exposed to water. For example, if the biomolecule is encapsulated in an internal layer, it is likely that radial diffusion will play a significant role, while if encapsulated on external layers, axial diffusion may be most prevalent. These results demonstrate the versatility of PGSU-SF materials that can be selectively modulated to achieve specific release kinetics of proteins through simple changes in the methods used to prepare the polymer films.

PGSU is an easy-to-process elastomer that can be synthesized under mild conditions through solvent-based or solvent free methods. We demonstrated that PGSU derivatives are biocompatible, show a biodegradation rate dependent on the degree of crosslinking, and can be tuned to exhibit a broad range of mechanical properties that are compliant with several biological tissues, including cardiac tissue. Furthermore, PGSU-SF derivatives can encapsulate and release biomacromolecules in their bioactive forms. Towards next generation biomaterials and drug delivery platforms, we envision that PGSU polymers with highly tunable properties will be useful for multiple therapeutic applications.

Experimental

The detailed experimental procedures are available in the supporting information.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

We would like to thank Admet Inc. for generously providing an eXpert 7601 mechanical tester that was instrumental for this work. This work was supported by National Institutes of Health grant GM086433 to JMK, and National Institutes of Health grant DE013023 to RL. MJP acknowledges the Portuguese Foundation for Science and Technology (fellowship SFR/BD/43013/2008.) and the MIT-Portugal program (bioengineering focus area).

References

1. Serrano MC, Chung EJ, Ameer GA. Adv Funct Mater. 2010; 20:192.
2. Stuckey D, Ishii H, Chen QZ, Boccaccini A, Hansen U, Carr C, Roether J, Jawad H, Tyler D, Ali N, Clarke K, Harding S. Tissue Eng Part B. 2010; 16:3395.
3. Wang YD, Ameer GA, Sheppard BJ, Langer R. Nat Biotechnol. 2002; 20:602. [PubMed: 12042865]
4. Guan J, Sacks M, Beckman E, Wagner W. Biomaterials. 2004; 25:85. [PubMed: 14580912]
5. Yang J, Webb AR, Ameer GA. Adv Mater. 2004; 16:511.
6. Bruggeman JP, Bettinger CJ, Nijst CLE, Kohane DS, Langer R. Adv Mater. 2008; 20:1922.
7. Bettinger C, Bruggeman J, Borenstein J, Langer R. Biomaterials. 2008; 29:2315. [PubMed: 18295329]
8. Cheng H, Hill PS, Siegwart DJ, Vacanti N, Lytton Jean AKR, Cho SW, Ye A, Langer R, Anderson DG. Adv Mater. 2011
9. Ruvinov E, Leor J, Cohen S. Biomaterials. 2011; 32:565. [PubMed: 20889201]
10. Fujimoto K, Tobita K, Merryman W, Guan J, Momoi N, Stolz D, Sacks M, Keller B, Wagner W. J Am Coll Cardiol. 2007; 49:2292. [PubMed: 17560295]
11. Pomerantseva I, Krebs N, Hart A, Neville CM, Huang AY, Sundback CA. J Biomed Mater Res Part A. 2009; 91A:1038.
12. Nijst C, Bruggeman J, Karp J, Ferreira L, Zumbuehl A, Bettinger C, Langer R. Biomacromolecules. 2007; 8:3067. [PubMed: 17725319]

13. Guelcher S. Tissue Eng Part B. 2008
14. Theron JP, Knoetze JH, Sanderson RD, Hunter R, Mequanint K, Franz T, Zilla P, Bezuidenhout D. Acta Biomater. 2010; 6:2434. [PubMed: 20080215]
15. Ding M, Li J, He X, Song N, Tan H, Zhang Y, Zhou L, Gu Q, Deng H, Fu Q. Adv Mater. 2012; 24:3639. [PubMed: 22689222]
16. Jagannath D, Hao X, Jinhui S, Paul T, Sudershan RG, Kytai TN, Brent SS, Liping T, Jian Y. Biomaterials. 2008:29.
17. Guelcher S, Patel V, Gallagher K, Connolly S, Didier J, Doctor J, Hollinger J. Tissue Eng. 2006; 12:1247. [PubMed: 16771638]
18. Liu QY, Jiang L, Shi R, Zhang LQ. Prog Polym Sci. 2012; 37:715.
19. Liang SL, Cook W, Thouas G, Chen QZ. Biomaterials. 2010; 31:8516. [PubMed: 20739061]
20. Mainil-Varlet P, Gogolewski S, Nieuwenhuis P. J Mater Sci Mater Med. 1996; 7:713.
21. Bruggeman J, Bettinger C, Langer R. J Biomed Mater Res Part A. 2010; 95:92.
22. Fujimoto K, Guan J, Oshima H, Sakai T, Wagner W. Ann Thorac Surg. 2007; 83:648. [PubMed: 17258002]
23. Chen Q-Z, Bismarck A, Hansen U, Junaid S, Tran M, Harding Sn, Ali N, Boccaccini A. Biomaterials. 2008; 29:47. [PubMed: 17915309]
24. Bouten C, Dankers P, Driessen-Mol A, Pedron S, Brizard A, Baaijens F. Adv Drug Deliv Rev. 2011; 63:221. [PubMed: 21277921]
25. Chen QZ, Ishii H, Thouas G, Lyon A, Wright J, Blaker J, Chrzanowski W, Boccaccini A, Ali N, Knowles J, Harding Sn. Biomaterials. 2010; 31:3885. [PubMed: 20153041]
26. Robinson K, Li J, Mathison M, Redkar A, Cui J, Chronos N, Matheny R, Badylak S. Circulation. 2005; 112:43.
27. Li B, Davidson JM, Guelcher SA. Biomaterials. 2009; 30:3486. [PubMed: 19328544]

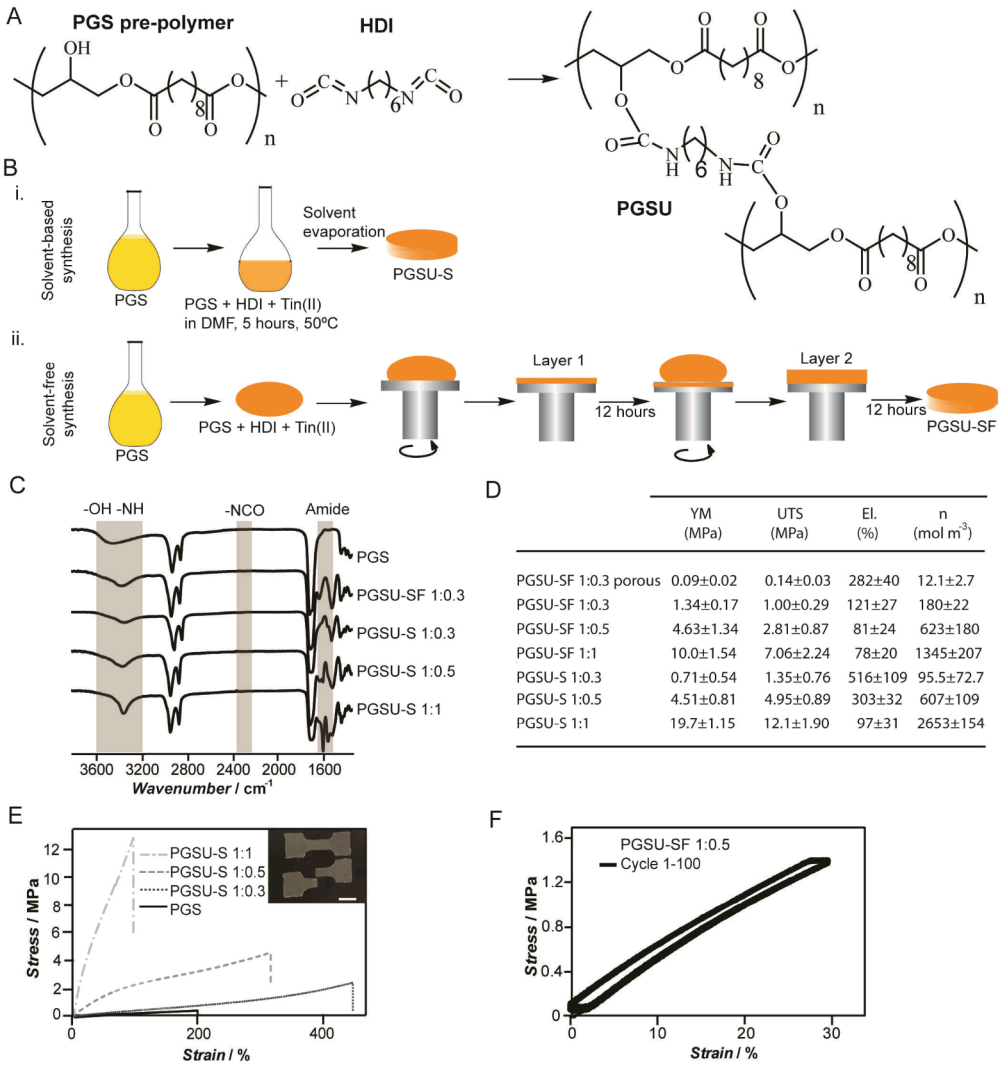

Figure 1.

Chemical and mechanical characterization of PGSU elastomers. A) Synthetic scheme for PGSU. B) Synthetic routes for PGSU synthesis under (i) solvent-based and (ii) solvent-free conditions. C) FTIR analysis of PGS pre-polymer and PGSU polymers synthesized under solvent-based and solvent free conditions. D) Summary of mechanical properties and degree of crosslinking for several PGSU derivatives (YM: Young's modulus, UTS: ultimate tensile strength, El: elongation, n: crosslinking density. E) Typical stress-strain of PGSU-S films and thermally cured PGS elastomer and representative images of PGSU-S 1:0.3 films before and after tensile testing, revealing minimal creep and size/shape changes. F) Stress-strain profile of PGSU-SF 1:0.5 films during 100 cycles of tensile loading shows that the elastomer maintains its tensile properties with minimal creep.

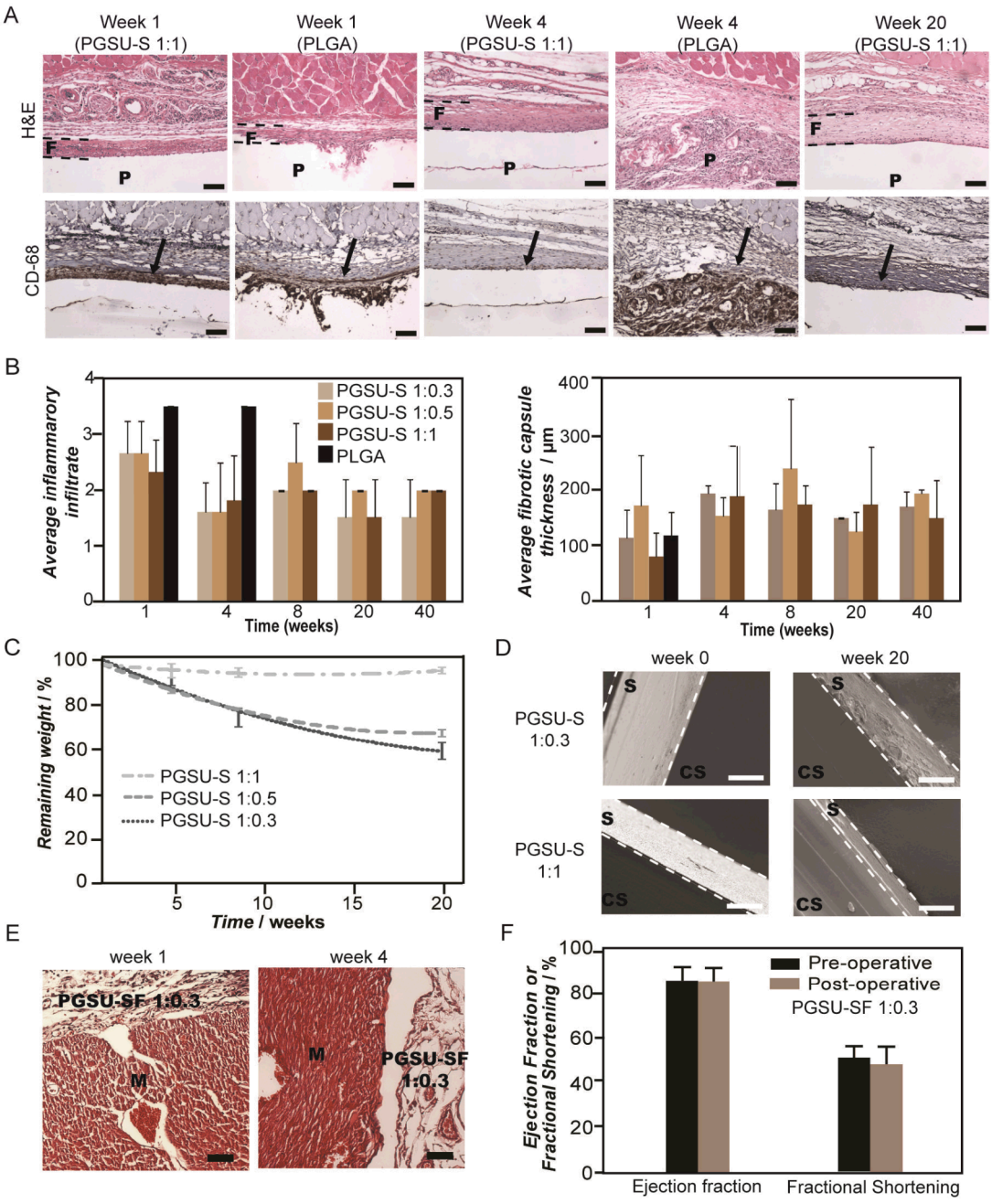

Figure 2.

In vivo subcutaneous and cardiac biocompatibility/biodegradation of PGSU elastomers. A) Representative images of H&E and anti-CD68 stained histological sections of the subcutaneous tissue surrounding PGSU-S 1:1 and PLGA polymers (P: polymer implant location, F: fibrous capsule). Scale bar represents 100 μm. B) Characterization of foreign body response to PGSU-S and PLGA implants through qualitative evaluation of the inflammatory infiltrate (from 0 representing no infiltrate, to 4 representing severe infiltrate). C) *In vivo* degradation profile of PGSU-S films implanted subcutaneously. D) Morphologic evaluation of PGSU-S 1:0.3 and 1:1 cross-sections through SEM (S: polymer surface, CS: polymer cross-section). Scale bar represents 50 μm. E) Representative images of H&E

sections of cardiac tissue in contact with PGSU-SF 1:0.3 elastomer following implantation for 1 and 4 weeks (M: myocardium tissue, P: polymer implant location). D) Cardiac function before and 4 weeks after PGSU-SF implantation.

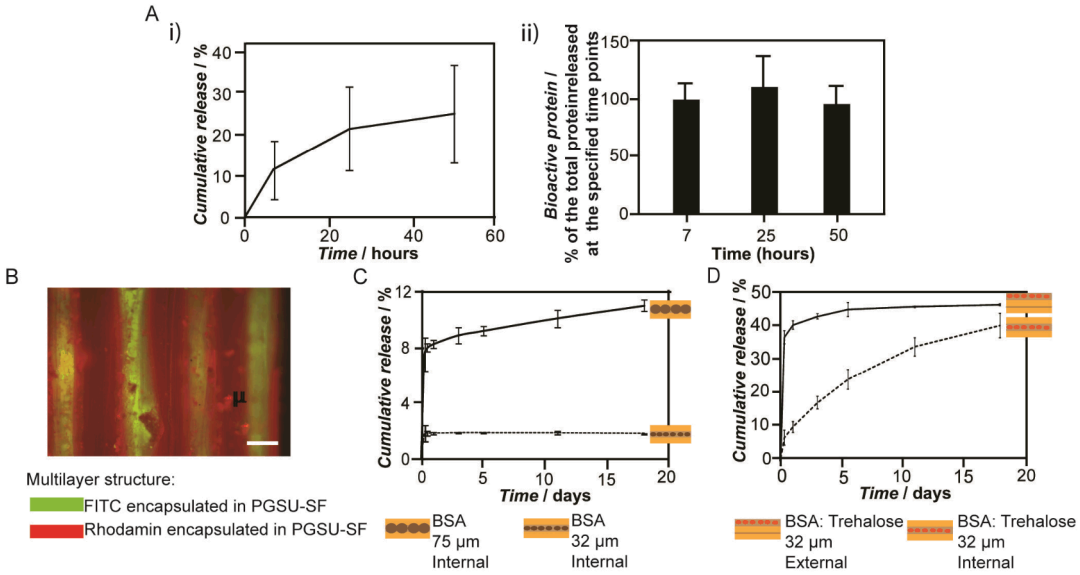

Figure 3.

Sustained release of bioactive proteins from PGSU-SF 1:0.3 films. A) Release kinetics (i) and bioactivity (ii) of the lysozyme released from PGSU-SF 1:0.3 porous patches. B) Selective encapsulation of rhodamine and FITC intercalated in PGSU-SF 1:0.3 layers using a spin coating technique. Scale bars represent 100 μm. C) Release kinetics of the model protein BSA sieved to <75 and <32 μm particle size encapsulated within the internal layer of a trilayer spin coated PGSU-SF 1:0.3 film. D) Release kinetics of BSA co-encapsulated with the osmotic agent trehalose (1:1 ratio) and sieved to <32 μm particle size from internal and externals layers of a tri-layer spin coated PGSU-SF 1:0.3 film. Trehalose accelerates protein released by promoting increased water uptake of PGSU-SF 1:0.3 polymers.