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Drug-loaded Hydralese™ Poly(Glycerol Sebacate) Urethane Elastomers as Intra-vitreal Microdevices for Ocular Drug Delivery Applications

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PURPOSE

Rationale for Hydralese (PGSU)

Long-acting implantables (LAIs) have become increasingly important in providing novel formulations for active pharmaceutical ingredients (APIs). Traditionally, these systems have utilized polymers such as poly(lactic-co-glycolic acid) (PLGA), polycaprolactone (PCL), and ethylene vinyl acetate (EVA). To provide sustained release, these polymers often rely on diffusion-based mechanisms, and PLGA and PCL exhibit bulk degradation that can cause high burst release and less predictable mass loss and drug delivery. Biodegradable poly(glycerol sebacate) urethane—Hydralese™ (PGSU)—is a novel elastomer under exploration in the next generation of LAIs. PGSU is unique in its ability to provide linear release kinetics, high drug loading (often >60% w/w), and a surface-eroding degradation mechanism that minimizes burst release. Furthermore, PGSU maintains excellent mechanical properties such as high flexibility, shelf stability under ambient conditions, and biocompatibility.

OBJECTIVE(S)

Ocular therapeutics can benefit from controlled release dosage forms, specifically improved implants.

Patient compliance is often low with the frequent dosing regimens prescribed for many ophthalmic medications - often several times per day for eyedrops, or weekly or monthly injections, depending on disease and indication. Patient tolerability and safety are especially important considerations for repeat dosing. From a manufacturing perspective, these intraocular devices must be made small enough to be delivered using appropriate gauge needles (often requiring diameters of 200-450µm) and must be mechanically robust enough to be handled during manufacturing and applicator assembly. From a therapeutic perspective, intraocular devices must provide sufficient duration of treatment, must not negatively impact vision or physiological function, and must eventually biodegrade.

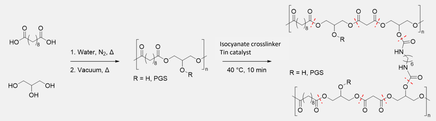
The following benefits of PGSU motivated the investigation of PGSU intravitreal implants:

- Moldable microdevices with **10-70% w/w drug** payload
- Controlled release lasting **3-6 months**
- **Non-swelling** throughout duration of implant
- **Flexible** elastomer easily assembled into applicators
- **Biocompatible** via intravitreal and episcleral implantation

This work describes the development and characterization of PGSU microdevices intended for intravitreal administration.

METHOD(S)

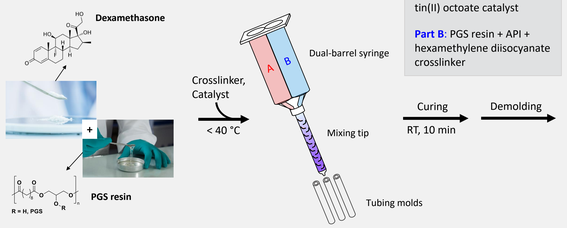
PGS Synthesis and PGSU Crosslinking



Red lines indicate hydrolysis site during bioerosion

Two-part Process for Implant Fabrication

Dexamethasone is used to treat diabetic macular edema and uveitis



Part A: PGS resin + API + tin(II) octoate catalyst

Part B: PGS resin + API + hexamethylene diisocyanate crosslinker

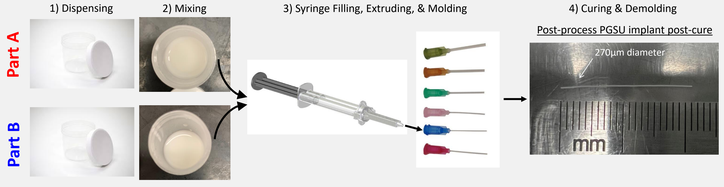
Dexamethasone-loaded PGSU implants

RESULT(S)

In-process Part A / Part B formulations pre-cure

Table 1: 3 different Part A / Part B formulations were compared for uniform mixing, yielding 10% w/w dexamethasone-loaded PGSU implants

	PGS	Dexamethasone	Tin	PGS	Dexamethasone	Isocyanate
Formulation 1	3 g	0 g	constant	7 g	1.5 g	constant
Formulation 2	2.8 g	0.2 g	constant	7.2 g	1.3 g	constant
Formulation 3	2.7 g	0.3 g	constant	7.3 g	1.2 g	constant



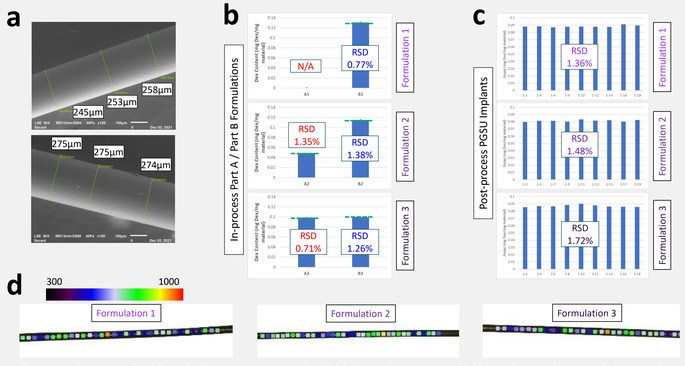


Figure 1: a) Representative SEMs of 10% dexamethasone-loaded PGSU intravitreal implants with 270µm diameter. b) Assay of in-process Part A and Part B formulations revealed drug loading was on target and formulations were well mixed. n=5 locations collected within the mixing container. Green line denotes target theoretical drug content. c) Assay of post-process PGSU implants revealed consistent drug loading across the batch. n=5 implants, each 45mm in length. b) and c) Assays were performed using DMSO solvent extraction. d) Raman spectroscopy by 785nm laser analyzed each implant surface with ~5µm depth. One peak associated with dexamethasone was selected for color mapping, illustrating content uniformity. n=3 implants, n=35 points per implant, each 10mm in length.

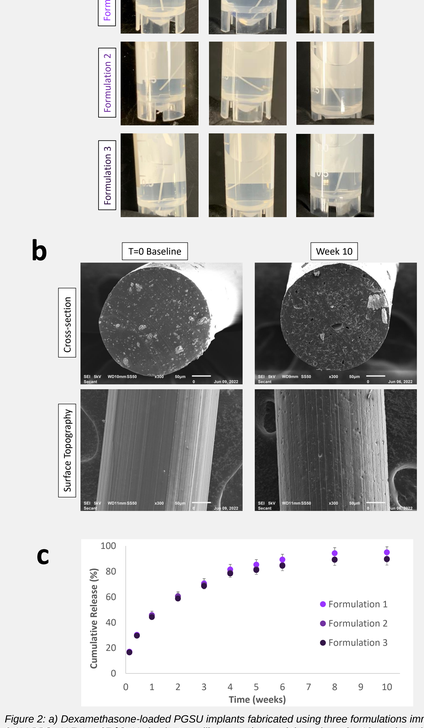
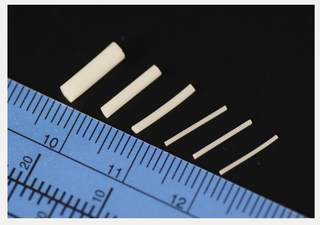


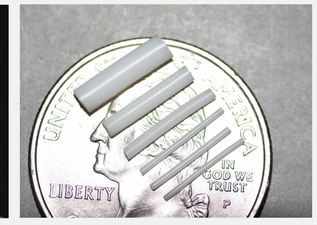
Figure 2: a) Dexamethasone-loaded PGSU implants fabricated using three formulations immersed in 0.1M PBS pH 7.4 at 37 °C. No implant swelling was observed throughout the 10-week study, as evidenced by gross images on weeks 3, 4, and 5. b) Representative SEMs of dexamethasone-loaded implants prior to and after 10 weeks of dissolution. Porosity left by released drug particles and erosion on implant surface is observed. c) Dexamethasone in vitro release showed all 3 formulations performed consistently, with PGSU sustaining release over 10 weeks. n=5 implants, each 10mm in length.

CONCLUSION(S)

Hydralese (PGSU) demonstrates promise as an intravitreal implant and deeper investigation into intraocular product translation is underway.

Hydralese (PGSU) is a useful polymer excipient in the manufacture of drug-loaded microdevices for use as intravitreal implants. Manufacturing processes for PGSU materials support the fabrication of uniform, flexible, and small diameter implants that contain **drug payloads up to 70% w/w**. PGSU implants with 270µm diameter sustain the release of dexamethasone for up to 10 weeks *in vitro* at 10% w/w drug loading. Higher loadings at 40%, 60%, and 70% w/w have been evaluated as well, at **diameters ranging from 200 to 450µm**, for ophthalmologically-relevant APIs with various aqueous solubilities. Similar processability, uniform mixing, uniform dimensions, assay, and content uniformity were observed. Release kinetics *in vitro* reveal **3- to 6-month delivery durations**, depending on implant dimensions. Analysis of biodegradation rate *in vitro* and *in vivo* is ongoing. Preliminary biocompatibility studies administering PGSU implants in various ocular compartments *in vivo* has highlighted the **non-swelling, well-tolerated, and non-immunogenic** nature of PGSU in the eye. Further analysis comparing *in vitro* release rates observed under the dissolution conditions used here to *in vivo* pharmacokinetics will prove critical for demonstrating the value of PGSU long-acting intraocular implants.





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