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Retrievability, IVIVC, and Biocompatibility of a 2'-deoxyadenosine-loaded Hydralese™ (PGSU) Implant

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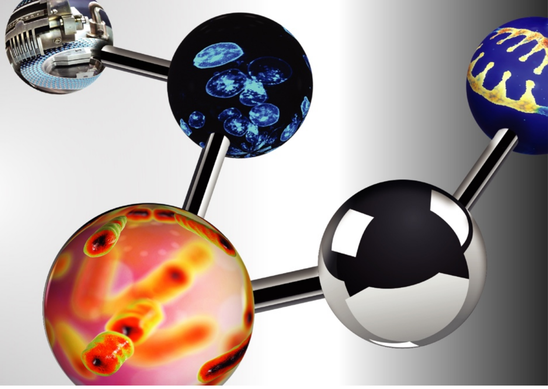

PURPOSE

Biodegradable polymers traditionally used in long-acting implantable (LAI) formulations, such as polycaprolactone (PCL) and poly(lactic-co-glycolic acid) (PLGA), rely on diffusion and bulk-erosion to release their payload. During swelling and bulk-erosion, some of these stiff polymeric implants become soft and pulpy, losing mechanical integrity. Some become brittle and stiff, prone to breaking, increasing inflammation in the surrounding tissue and preventing the implant from retrieval if desired or necessary.

Previous work has shown that the novel surface-eroding bioresorbable polymer, Hydralese™ (poly(glycerol sebacate) urethane) (PGSU) (Secant Group), can be loaded with high drug loadings (≥60% w/w) with minimal burst release followed by sustained linear, multi-month cumulative release, and good biocompatibility per ISO 10993 testing.[1,2] The surface-erosion degradation mechanism also results in the structural integrity of the implant remaining intact throughout degradation, allowing for retrieval of the implant if necessary.

OBJECTIVE

In this work, the retrievability of Hydralese (PGSU) polymer implants loaded with 2'-deoxyadenosine (2'dA) at 40% and 60% (w/w) was assessed in beagle dogs. The explanted rods were analyzed and an *in vitro-in vivo* correlation (IVIVC) was prepared using previous USP IV dissolution data. Unloaded Hydralese (PGSU) implants were analyzed for inflammatory response by histopathology as part of the dog study, and the complete suite of ISO 10993 biocompatibility testing was performed on unloaded implants.

METHODS

- **Implant Production:** Hydralese (PGSU) implants were made as previously described using bench scale reaction-injection molding.[1]
  - Cylindrical rod implants, 3mm by 40mm
- **Beagle Dog Study:** Beagle dogs were implanted with 0%, 40%, or 60% loaded 2'dA implants
  - 0% implants were retrieved at six months
  - 40% and 60% 2'dA loaded implants were retrieved at three, four, five, and six months
- **Explant Analysis:** Explants were analyzed by dimensional change and mass loss, and the remaining 2'dA
  - Remaining 2'dA determined by extraction and HPLC quantification
  - Cumulative release was inferred based on remaining 2'dA
- **IVIVC:** IVIVC was made by comparing cumulative release with previously collected *in vitro* dissolution data
- **Histopathology:** Inflammatory response and biocompatibility of unloaded Hydralese (PGSU) implants were assessed using histopathology on cryo-sections collected following implant site excision from dogs post-mortem
- **ISO 10993:** Biocompatibility testing was separately performed following ISO 10993 standard guidelines

RESULTS

- *In vitro* release @ 18 wks[1]
  - Surface-erosion observed
  - Linear release from Hydralese (PGSU) observed
- 40%-loaded implant
  - 31% diameter loss
  - 33% 2'dA released
- 60%-loaded implant
  - 41% diameter loss
  - 78% 2'dA released

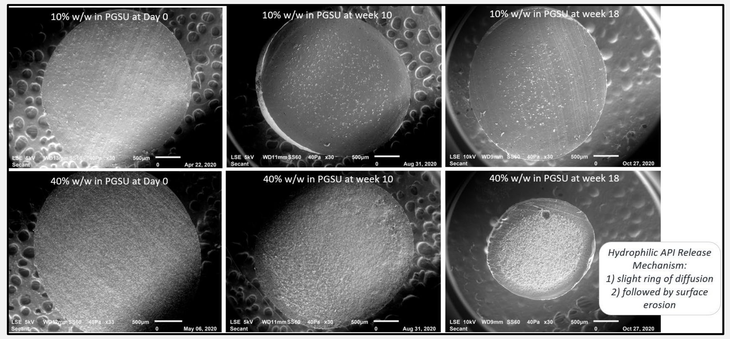

Figure 1. SEM images of 10% and 40% 2'dA-loaded Hydralese (PGSU) implants at three *in vitro* timepoints, Day 0, Week 10 and 18. At 18 weeks *in vitro,* a similar diffusive ring is observed to a 40%-loaded implant at 6 mos. *in vivo*.[1]

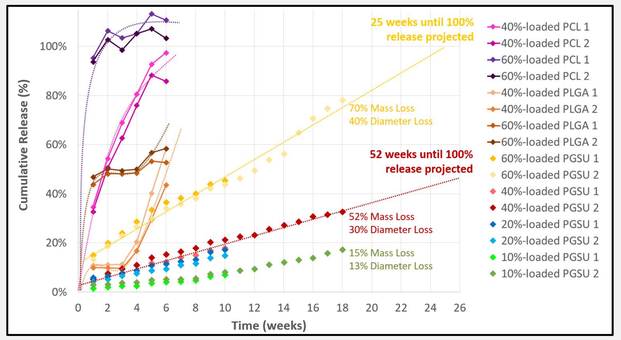

Figure 2. *In vitro* release curves of various 2'dA loadings from PCL (80kDa), PLGA (75:25, 80kDa), and Hydralese (PGSU).[1]

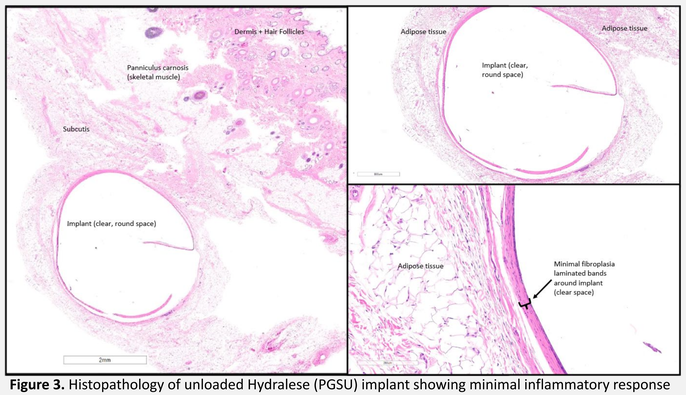

Figure 3. Histopathology of unloaded Hydralese (PGSU) implant showing minimal inflammatory response and minimal fibroplasia. No chronic inflammatory cells or foreign body giant formations were observed.

Table 1. Results of ISO 10993 testing

ISO 10993 Test	Scoring
Cytotoxicity	0/0/0
Irritation: Intracutaneous Injection	0/0, 0/0, 0/0, 0/0, 0/0
Systemic Toxicity: Systemic Injection	0/0/0/0/0
Systemic Toxicity: Material Mediated Pyrogen	0/0/0
Hemocompatibility: Complement Activation	Like negative control
Hemocompatibility: Partial Thromboplastin Time	Like negative control
Hemocompatibility: Platelet & Leukocyte Count	Like negative control
Hemocompatibility: Hemolysis	Like negative control
Genotoxicity: Ames	Like negative control
Genotoxicity: Chromosomal Aberration	Like negative control
Sensitization	Like negative control
Implantation: Subcutaneous 4 week	0/0/0, no reaction

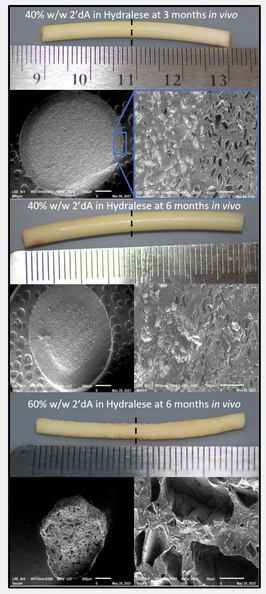

Figure 4. Gross and SEM images of 2'dA-loaded Hydralese (PGSU) implants explanted at 3 and 6 months. Cross-sections analyzed by SEM shown as dotted lines.

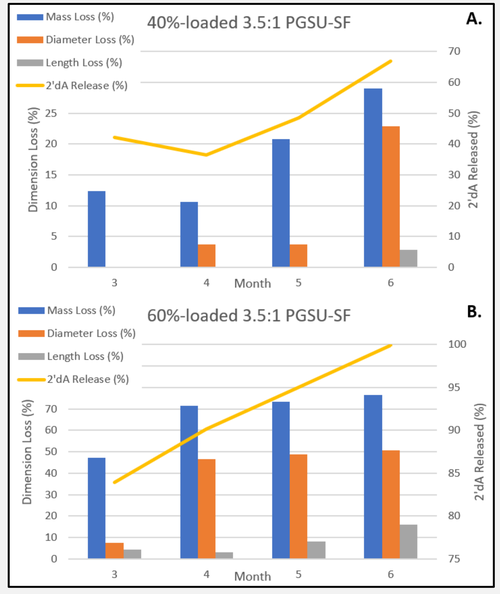

Figure 5. Dimensional change, mass loss, and inferred cumulative drug release of the 40% 2'dA (**A**) and 60% 2'dA implants (**B**).

- All implants were retrievable at each time point
- All 60%-loaded implants maintained structural integrity
  - Were not brittle and the entire rod remained retrievable
- Surface-erosion is evident in observed diameter loss and by SEM (Fig. 4)
- *In vivo* diameter loss of 23% and 50% were observed for the 40%- and 60%-loaded implants, respectively (Fig. 5)
  - Similar diameter loss to *in vitro* testing
- Cumulative release of 66.8% and 99.9% at six months, 40%- and 60%-loaded respectively (Fig. 5)
  - 60%-loaded implants expected to completely degrade within one month of total payload release

CONCLUSIONS

- Degrading by surface-erosion, Hydralese (PGSU) is retrievable up to at least six months *in vivo*. Hydralese (PGSU) provides multi-month sustained release from high loadings (≥60% w/w) while retaining structural integrity with minimal inflammatory response.
  - Fully depleted implants likely to degrade within 4 weeks
- IVIVCs have a strong correlation between the *in vivo* and *in vitro* dataset, R^2 values of 0.99
- Histopathology of Hydralese (PGSU) exhibits little to no inflammatory response
- ISO 10993 testing demonstrates excellent biocompatibility
  - All samples across all animals scoring zero or like negative control

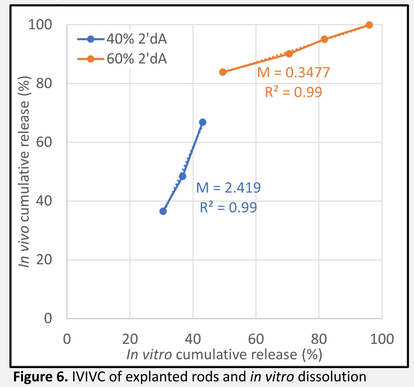

Figure 6. IVIVC of explanted rods and *in vitro* dissolution data from Figure 2.

REFERENCES

1. Smoot, C., Shull, D., Reed, S. (2020, October 26 – November 5). Zero-order Release of Hydrophilic Drugs at High Loadings Using Novel Biodegradable Elastomer Hydralese™ (PGSU) [Poster Presentation]. American Association of Pharmaceutical Scientists.

2. Reed, S., Smoot, C., Shull, D., D'Ottavio, J. (2019, July 21-24). Next Generation Long-acting Implantables Using Surface-eroding Elastomers [Poster Presentation] Controlled Release Society, Valencia, Spain.

3. Reed, S., inventor; Secant Group, assignee. Tunable, controlled-release, urethane containing elastomers and processes of forming the same. US patent 10918764B2 Granted February 16, 2021.

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