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Surface-eroding Elastomer Exhibits Zero-order Release in Highly Loaded LAIs

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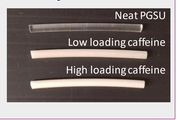
PURPOSE

Commonly used materials for long-acting implantables (LAI) comprise non-biodegradable polymers that rely on diffusion-mediated drug release. These LAIs lack the ability to achieve controlled release kinetics for multi-month therapies that require high drug loadings (>40 wt%). This affects both water-soluble drugs, where rapid diffusion occurs, and water-insoluble drugs, where slow diffusion leads to insufficient release. While biodegradable polymers exhibit benefits over non-biodegradables, bulk-degrading biodegradables similarly suffer from the inability to achieve steady release at high loadings. Surface-eroding biodegradables such as Hydralese™ (PGSU) (poly(glycerol sebacate) urethane) (Secant Group), a synthetic biodegradable elastomer for controlled drug release,[1] offer a superior polymeric delivery system able to provide zero-order release at high drug loadings over many months. Using caffeine as a model drug, *in vitro* and *in vivo* studies demonstrate Hydralese (PGSU) implants exhibit minimal burst release followed quickly by steady-state release kinetics.



OBJECTIVE(S)

Demonstrate the effectiveness of surface-eroding Hydralese (PGSU) loaded at high percentages of caffeine to maintain controlled release kinetics over many months using *in vitro* and *in vivo* analyses, as well as its manufacturability using a solvent-free room temperature extrusion technology.

METHOD(S)

Formulation

- Target Hydralese (PGSU) crosslink density selected using inverted film cup method adapted from ASTM E96.
- Various loaded-Hydralese (PGSU) formulations were tested using apparatus depicted in Figure 1.
- Depth of water penetration through matrix determined using SEM after four weeks at 37.0°C.

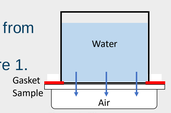


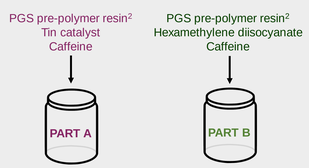
Figure 1: Film cup apparatus

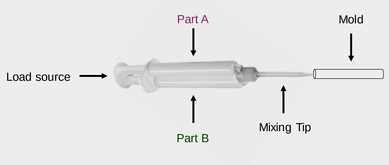
Caffeine-loaded Hydralese (PGSU) Implant Manufacture

- Hydralese (PGSU) implants were synthesized using a two-part chemistry paired with dual-barrel syringe extrusion technology.
- Methodology was optimized to eliminate common obstacles like air pockets, uneven mixing, and short working time.
- Rods were filled into molds and complete crosslinking of the urethane polymer was achieved at room temperature.

Step 1: Materials combined separately using dual-asymmetric centrifugal mixing

Step 2: Two parts combined and extruded using dual-barrel syringe fitted with a static mixing tip into mold





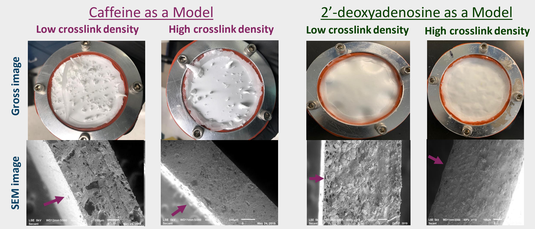
Benchtop, *In Vitro* and *In Vivo* Analyses

- Final 0, 40, and 60 wt% caffeine-loaded rods were analyzed for caffeine dispersion, content uniformity, crosslink density, compressive modulus, and chemical functionality using SEM, HPLC, TGA, MTS, and FTIR, respectively.
- *In vitro* release was monitored using a flow-through cell dissolution apparatus under physiological pH and temperature with 0.1M phosphate buffered saline.
- HPLC was used to quantify caffeine concentration in weekly collected media to generate a release profile over a two-month period (study still underway).
- *In vivo* release was assessed using a subcutaneous implantation rat model and LCMS to generate pharmacokinetic profiles from weekly plasma collections over two months (study still underway).
- Histology was performed on explanted tissue to evaluate Hydralese (PGSU) biocompatibility and degradation.

RESULT(S)

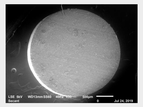
Target Crosslink Density Determined by Film Cup Experiments

- Cross-sectional SEM images of 60 wt% caffeine-loaded Hydralese (PGSU) after film cup analysis demonstrate Hydralese's (PGSU) ability to reduce water permeation by increasing crosslink density.
- Additionally, permeation is reduced in a highly loaded Hydralese (PGSU) film containing another hydrophilic API that does not exhibit agglomerations as is commonly seen with caffeine.
- Penetration of water into a polymer/drug matrix is a direct factor in burst release and dose-dependent release kinetics. Therefore, it can be extrapolated that high crosslink density will reduce burst release and achieve steady release kinetics *in vitro* and *in vivo.* This is a direct result of Hydralese (PGSU) alone exhibiting impermeability and only 2-3% swelling in water.



Homogeneous Rod Implants Successfully Formed Using Dual-barrel Syringe Method

- Resultant crosslink density, content uniformity, and compressive moduli were consistent across a representative 40% and 60% caffeine-loaded Hydralese (PGSU) rod batch (Figures 2 and 3).
- Scanning electron microscopy images depicted good dispersion of the caffeine within the Hydralese (PGSU) matrix.
- Within multiple rod batches, tight selection criteria were applied to implants for their use *in vitro* and *in vivo.*



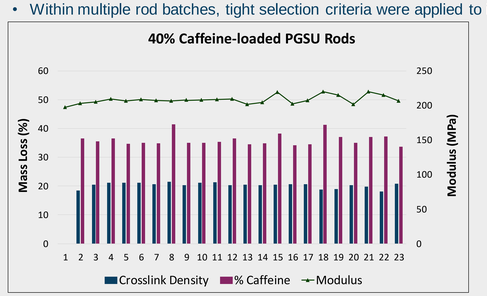


Figure 2: Crosslink density, % caffeine, and moduli results for a representative 40% caffeine-loaded Hydralese (PGSU) rod batch

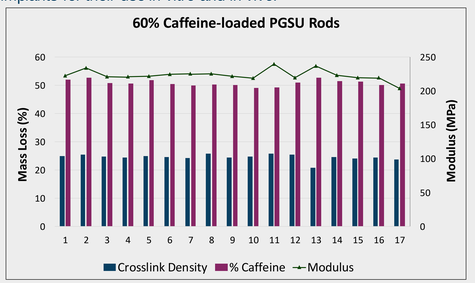


Figure 3: Crosslink density, % caffeine, and moduli results for a representative 60% caffeine-loaded Hydralese (PGSU) rod batch

In vitro Release Kinetics of Highly Loaded Hydralese (PGSU)

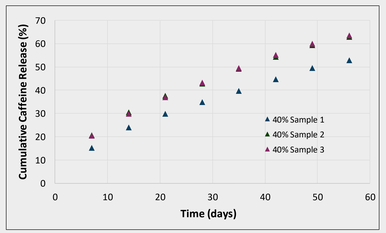


Figure 4: *In vitro* release kinetics of 40% caffeine-loaded Hydralese (PGSU) rods quantified by LCMS

- No lag observed in reaching zero-order release from onset through two-month time period with minimal burst release.
- Data demonstrates the ability of Hydralese (PGSU) to resist water permeation and swelling, generating a true surface erosion-dependent release mechanism.
- Release rate is consistent across the manufactured rod batch.

In Vitro and *In Vivo* Higuchi Modeling

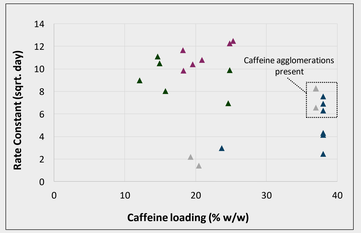


Figure 5: Higuchi modeling comparison between *in vitro*, *in vivo* high crosslinked rods and *in vitro*, *in vivo* of low crosslinked rods

- Highly crosslinked rods show similar rate constants across 20-40% loadings, demonstrating release rate is independent of caffeine content.
- Calculated rate constants for high crosslinked rods are significantly lower than is commonly observed for EVA, PCL, and PLGA.

In vivo Release Kinetics and Histology of Highly Loaded Hydralese (PGSU)

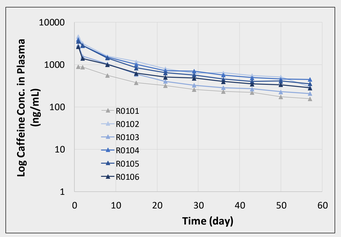


Figure 6: Pharmacokinetic curve of 40% caffeine-loaded Hyrdalese (PGSU) rod implants in rats

- Highly loaded Hydralese (PGSU) showed minimal burst release *in vivo* and sustained zero-order kinetics for two months.
- Expected duration of delivery 6-10 months based on clearance rate of 45 mL/hr.[3]
- Release rates consistent across the six implants.

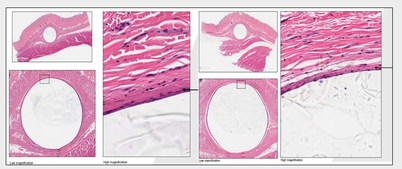


Figure 7: Histology staining on control animal (left) and animal containing drug-loaded implant (right). Arrows indicate minimal fibroplasia.

- Histology three months post-implantation showed little to no inflammation or fibroplasia for all animals.
- No macrophages, lymphocytes, or fibrous encapsulation observed in both control and drug-loaded Hydralese (PGSU).

CONCLUSION(S)

For numerous treatments being studied today, LAIs capable of delivering a steady dose over months to years are needed. Current materials on the market rely on diffusion-based release kinetics, whether degradable or non-degradable, and therefore have difficulty being loaded at high percentages and still exhibit zero-order release for multiple months. Hydralese (PGSU) behaves as a true surface-eroder demonstrated *in vitro* and *in vivo*, and paired with its low swellability and water permeability, can be loaded at high concentrations and still exhibit low burst release and zero-order release. Furthermore, challenges in manufacturability regarding API and crosslink density homogeneity have been overcome in conjunction with the development of reliable analytical techniques. Ultimately, Hydralese (PGSU) implants are an attractive carrier providing efficient pharmacokinetics, longer-lasting treatment at higher API loadings, and enhanced patient comfort via improved implant flexibility, when compared to traditional polymers.

REFERENCES

[1] Reed, S., inventor; Secant Group, assignee. Tunable, controlled-release, urethane-containing elastomers and processes of forming the same. US patent application 16/547,175. Filed August 21, 2019.
[2] Nicholson, C.B., inventor; Secant Group, assignee. Water-mediated preparations of polymeric materials. US patent 9,359,472. Issued June 7, 2016.
[3] Welch, R.M., Hsu, S.Y., DeAngelis, R.L. (1977). Effect of Aroclor 1254, phenobarbital, and polycyclic aromatic hydrocarbons on the plasma clearance of caffeine in the rat. *Clinical Pharmacology & Therapeutics,* 22, doi: 10.1002/cpt1977225part2791.

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