Zero-order Release of Hydrophilic Drugs at High Loadings Using Novel Biodegradable Elastomer Hydralese™ (PGSU)

Carissa Smoot, BS; Dennis Shull, BS; Stephanie Reed, PhD

Secant Group, LLC Telford, PA

aaps PharmSci 360

ADVANCING PHARMACEUTICAL SCIENCES, CAREERS, AND COMMUNITY

PURPOSE

Long-acting implantables (LAIs) continue to gain interest in the development of new drug delivery systems. Historically, LAIs have utilized polymers such as EVA, PCL, and PLGA. However, non-degradable polymers such as EVA have limitations in drug delivery because they must rely on drug diffusion out of the polymer, making sustained release from highly loaded implants containing hydrophilic drugs difficult to achieve. Most biodegradable polymers such as PCL and PLGA also rely on diffusion alongside their bulk degradation, and they are unable to be loaded at high concentrations without resulting in a high burst release and short duration of delivery.

Secant Group's Hydralese™ (PGSU) (poly(glycerol sebacate) urethane) provides a more attractive drug delivery system due to its surface-erosion release mechanism, which allows for near zero-order release kinetics, even at high hydrophilic drug loadings (>60% w/w). Additionally, Hydralese (PGSU) is highly flexible, water impermeable, shelf-stable, and biocompatible.

OBJECTIVE(S)

- Demonstrate Hydralese (PGSU) implants achieve zero-order release *in vitro* across multiple loadings (10-60% w/w) over multiple months with minimal burst release using hydrophilic model API 2'-deoxyadenosine,
- Demonstrate the ability of Hydralese to resist water permeation using unloaded Hydralese sheaths applied to 60% w/w 2'-deoxyadenosine loaded rods to further reduce burst release, and
- Demonstrate the inferior *in vitro* release kinetics of 2'-deoxyadenosine loaded PCL and PLGA rods as compared to Hydralese.

METHOD(S)

Due to its thermoset chemistry, 2'-deoxyadenosine-loaded Hydralese (PGSU) implantable rods were manufactured using reactive injection molding at room temperature. Loaded PCL (80kDa) and PLGA (75:25, 90kDa) were prepared using standard melt extrusion. Unloaded Hydralese sheaths were applied using an ultrasonic spray-coater fitted with a dual-chamber nozzle.

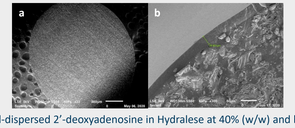

Figure 1: a) Well-dispersed 2'-deoxyadenosine in Hydralese at 40% (w/w) and b) conformal unloaded Hydralese sheath coating on 60% (w/w) 2'-deoxyadensoine-loaded Hydralese

2'-deoxyadenosine loaded rod implants (10, 20, 40, and 60% w/w in Hydralese and 40 and 60% w/w in PCL and PLGA) were analyzed for dispersion, content uniformity, assay, and mechanical properties using SEM, HPLC, and MTS, respectively.

In vitro release profiles of all implant formulations were monitored using a flow-through cell dissolution apparatus under physiological pH and temperature with 0.1M PBS with sink conditions maintained. HPLC with a UV detector was used to quantify 2'-deoxyadenosine release from the polymer matrices over 12 weeks.

RESULT(S)

Hydralese Exhibits Zero-order Release Across Multiple Loadings

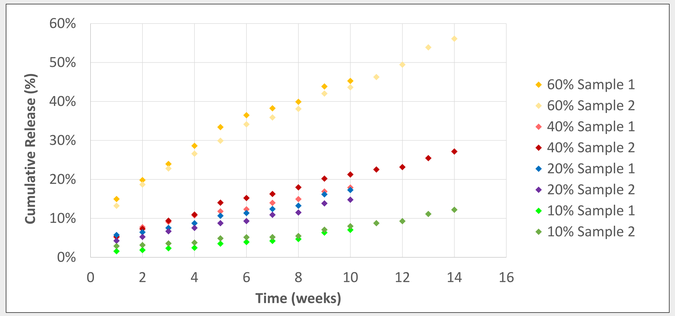

Figure 2: *In vitro* release profiles of variable-loaded 2'-deoxyadenosine Hydralese (PGSU) rods

- *In vitro* testing showed very **minimal burst** release for all Hydralese (PGSU) formulations, followed by **linear release** over the remaining time period
- Rods loaded at 60% w/w demonstrated the highest burst release and fastest release rate. This is likely due to drug particle packing density being above the percolation threshold and causing interconnectivity, leading to diffusion-driven release in combination with surface erosion-driven release

Mass and Diameter Loss During Surface Erosion

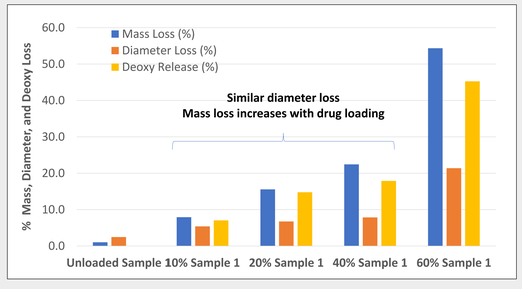

Figure 3: Dimension and mass loss data for *in vitro* dissolution samples pulled at Week 10

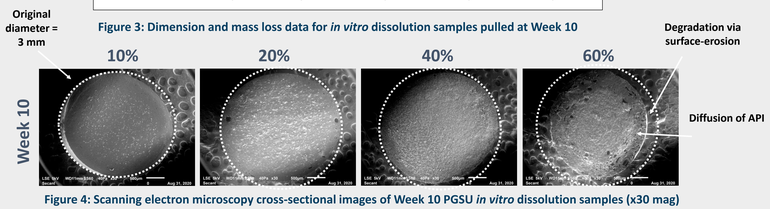

Figure 4: Scanning electron microscopy cross-sectional images of Week 10 PGSU *in vitro* dissolution samples (x30 mag)

- Some diffusion was observed for all loadings, as visualized by the ring around the implant circumference where API is absent and has diffused out.
- All loadings showed a similar diffusion distance from the implant edge, likely linked to a minor degree of implant permeability arising when drug particles are present.
- In high loadings (60% w/w), diffusion of drug results in interconnected pores, causing an increase in both surface area and **surface-erosion driven release**.

Unloaded Hydralese Sheath Successful as Diffusion Barrier

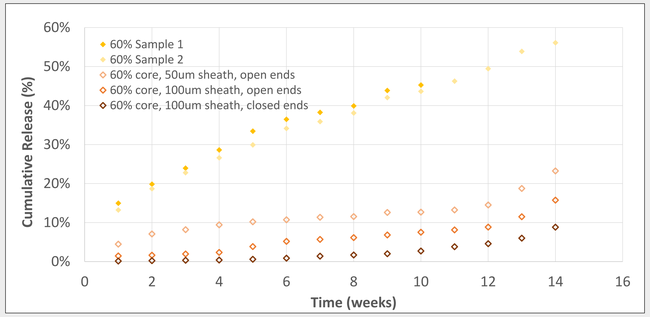

Figure 5: *In vitro* release profiles of 60% w/w 2'-deoxyadenosine in Hydralese rods with unloaded Hydralese sheaths

- Addition of a thin unloaded sheath proved effective as a **diffusion barrier** to significantly reduce initial burst release down to **0-5%.**
- Greater reduction in burst and overall release was observed with **increasing sheath thickness**, especially when the ends were coated as well.
- Sheath designs can provide **delayed or pulsatile release kinetics**.

Commercial Polymers PCL and PLGA Do Not Sustain Release

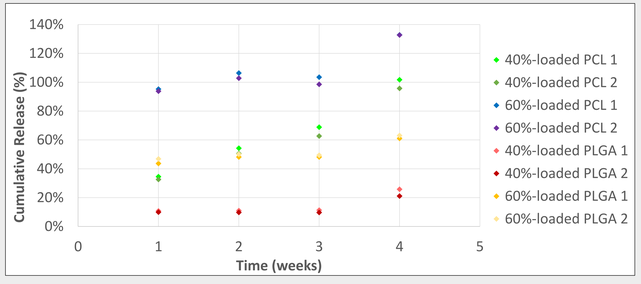

Figure 6: *In vitro* release profiles of 40% and 60% w/w 2'-deoxyadenosine in PCL and PLGA rods

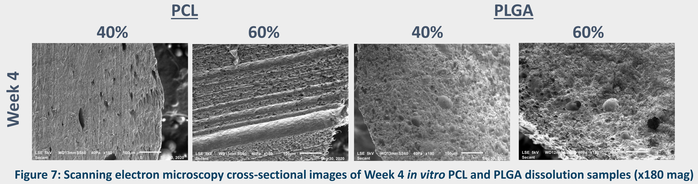

Figure 7: Scanning electron microscopy cross-sectional images of Week 4 *in vitro* PCL and PLGA dissolution samples (x180 mag)

- PCL rods demonstrated substantially faster release rates compared to PGSU, with 60% w/w reaching 100% release after just 1 week, confirmed by extensive porosity in SEM image.
- PLGA rods exhibited large burst followed by a lag phase, with the second-phase release beginning by Week 4.
- Fast release from PCL likely due to unfavorable hydrophobic environment
- High degree of swell commonly observed for PLGA drove high burst and accelerated release

CONCLUSION(S)

LAIs capable of delivering a steady drug dosage over months or years could drastically improve treatments and patient options. Materials currently used in this market, whether degradable or non-degradable, rely on diffusion-based release kinetics, and therefore have difficulty being loaded at high percentages without exhibiting high burst release. Hydralese (PGSU) outperforms commercial polymers for several reasons. First, it utilizes surface erosion as demonstrated *in vitro*. Second, it demonstrates minimal water permeability when loaded with drug. Third, it can be loaded at high drug concentrations and still exhibit minimal burst release and zero-order kinetics over 12 weeks. Additionally, the benefits of an unloaded Hydralese sheath could exhibit pulsatile release in a multi-layered construct, perhaps favorable for the delivery of vaccines. Ultimately, Hydralese (PGSU) implants are an ideal delivery vehicle even at high drug loadings, providing efficient pharmacokinetics, longer-lasting treatment, and elastomeric flexibility, when compared to traditional polymers.

REFERENCE(S)

[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.

secant group

PARTNERS FROM INSPIRATION TO REALIZATION