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Small-Scale, Rapid Prototyping of Hydralese™ (PGSU) (poly(glycerol sebacate) urethane) Microdevices for Controlled Drug Delivery in Ocular Implants

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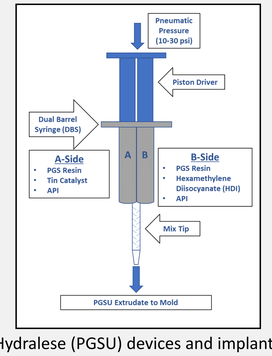
PURPOSE

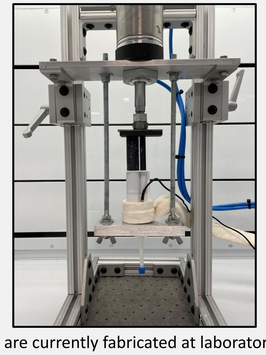
Secant is developing long-acting implantable and gastroretentive devices manufactured from Hydralese™ (PGSU) (poly(glycerol sebacate) urethane) for controlled drug release over a multi-month time period. Intraocular long-acting implantable drug delivery devices can achieve sustained delivery of active pharmaceutical ingredients (API), such as corticosteroids like dexamethasone, to the back of the eye and vitreous to treat conditions such as diabetic macular edema and uveitis. Secant has developed a low-cost, rapid prototyping method to create high drug-loading microrod implants (200-450µm diameter) for long-acting drug delivery in ocular indications using microtube bundles. The microtube bundle emulates a multilumen extrusion to reduce differential pressures and increase flow rate. Additionally, incorporating temperature control of the reactive materials within the dual barrel syringe (DBS) dispensing cartridge maintains the viscosity of high drug-loading resin blends over the course of the mold injection process.

OBJECTIVES

1) Develop a prototyping method for casting 200µm and 450µm outer diameter x 20mm long microdevices at drug loadings up to 60% w/w dexamethasone
2) Characterize the morphology, diameter, and dexamethasone loading of the loaded Hydralese (PGSU) microdevices

METHODS





Hydralese (PGSU) devices and implants are currently fabricated at laboratory bench scale by crosslinking drug-loaded poly(glycerol sebacate) (PGS) resin via polyol-isocyanate urethane chemistry using a dual barrel syringe (DBS). The DBS extrudes the drug-polyol blend and the isocyanate crosslinker through separate barrels, and the two material streams meet in a static mixing tip, after which the blended material is flowed into a mold for ambient curing.

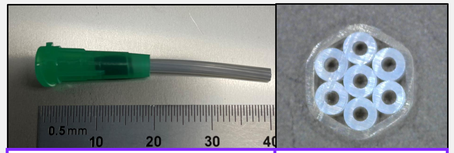
METHODS (CONT.)

Microtubing Bundle Fabrication

Polytetrafluoroethylene (PTFE) microtubing was sourced at commercially available inner diameters of 0.008" (203µm) and 0.018" (457µm) to approximate target diameters of 200µm and 450µm, respectively. Microtubes were cut to a 30mm length, and a predetermined number of microtubes were inserted into an equal length 0.09" ID PTFE heat shrink tubing. Bundles of parallel microtubes sheathed in heatshrink tubing were heated and allowed to shrink, securing the microtubing together. The bundle of microtubes was inserted through a Luer-lock dispensing tip, cut to allow passage of the bundle. The bundle was mated to the Luer-lock end of the static mixing tip of the DBS and allowed to fill with the reactive mixture and cure.

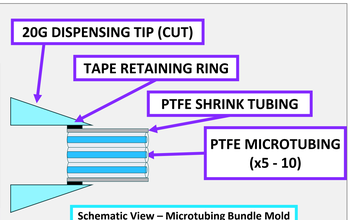
Dual Barrel Syringe Heating

After filling and curing, microtubing bundles are disassembled and the shrink tubing cut away to release the interior filled microtubes. The microtubes are scored with a blade to allow the PTFE to be peeled away, revealing the microdevice. Microdevices are trimmed to final length and inspected for quality and diameter.

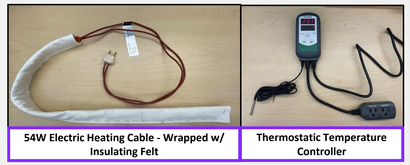


Fully Assembled | Cross Section

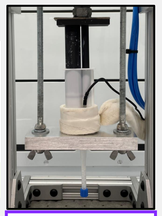
7x457µm Microtubing Bundle Mold



Schematic View – Microtubing Bundle Mold



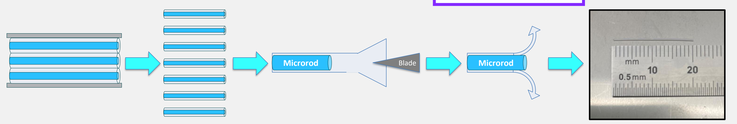
54W Electric Heating Cable - Wrapped w/ Insulating Felt | Thermostatic Temperature Controller



Dual Barrel Syringe Cartridge with Heating Wrap

Microdevice Demolding

After filling and curing, microtubing bundles are disassembled and the shrink tubing cut away to release the interior-filled microtubes. The microtubes are scored with a blade to allow the PTFE to be peeled away, revealing the microdevice. Microdevices are trimmed to final length and inspected for quality and diameter.



Remove Shrink Tubing | x7 Filled Microtubes | Flatten and Score End of Tube | Peel Away Tubing | 60% w/w API Loaded 457µm x 20mm Microimplant

RESULTS

60% w/w dexamethasone Hydralese (PGSU) microrods were successfully made using microtube bundles at 203µm and 457µm nominal outer diameter. Optical microscopy images show the rods were cylindrical with a smooth finished exterior. Microdevice outer diameter, measured by calibrated optical microscopy, demonstrated dimensional tolerances within ± 10µm. Drug loading was measured by extraction and HPLC and found to be on target. Dexamethasone Hydralese (PGSU) microrods exhibited morphology, diameter, and loading consistent with industry expectations and tolerances.

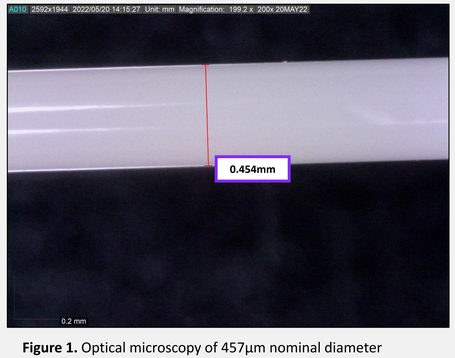


Figure 1. Optical microscopy of 457µm nominal diameter Hydralese™ (PGSU) microrod with 60% w/w dexamethasone loading showing in tolerance (±10µm) diameter and smooth surface finish.

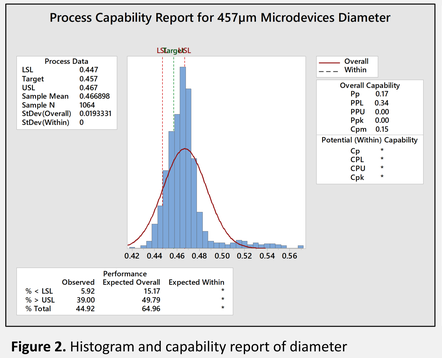


Figure 2. Histogram and capability report of diameter measurements of nominal 457µm microdevice diameters, n=1064. Microdevice outer diameter is directly correlated with microtubing mold inner diameter. Manufacturer tubing ID tolerance 0.018"+0.003"/-0.002" (457 +76/-50 µm).

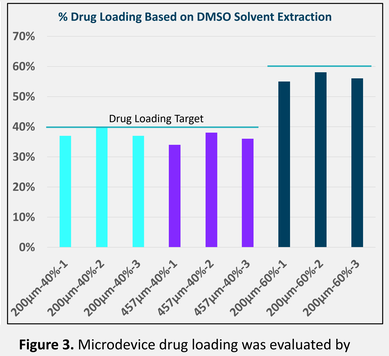


Figure 3. Microdevice drug loading was evaluated by solvent extraction with DMSO and quantified by HPLC at 200µm and 457µm device diameters and 40% and 60% w/w loading.

CONCLUSIONS

1. The microtube bundle process is an effective prototyping method for high drug-loaded Hydralese (PGSU) formulations and corresponding microdevice fabrication.
2. The microtube bundle process allows for increased production volumes while maintaining control over microdevice product quality and finish.
3. This process can be adapted for scale-up to support production of drug-loaded PGSU intravitreal implants for ocular drug delivery.

Hydralese™ Biodegradable Elastomers

REFERENCES

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- Nicholson, C. B., Harris, J. J., Gabriele, P. D. "Water-mediated preparations of polymeric materials" (2016). *U.S. Patent No. 9,359,472*.

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