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Reaction Injection Molding Scale-up of Hydralese™ (PGSU) Rods for Controlled Drug Delivery

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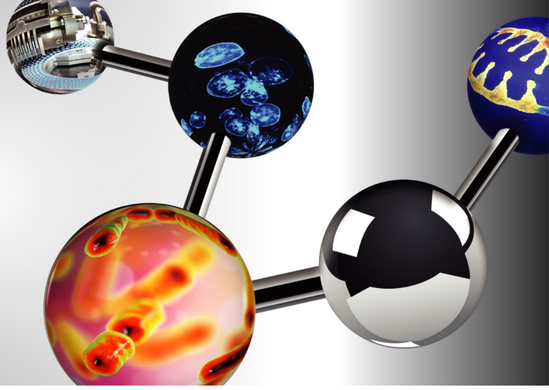


PURPOSE

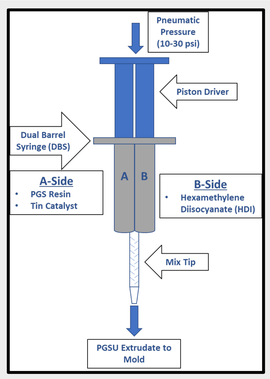
Secant Group is developing long-acting implantable and gastroretentive devices manufactured from Hydralese™ (PGSU) (poly(glycerol sebacate) urethane) for controlled drug release over a multi-month time period. Secant Group has developed a pilot scale system to scale up the production of Hydralese (PGSU) using reaction injection molding (RIM). Secant's RIM unit provides temperature control, vacuum degassing, dynamic mixing, and precise component ratio metering. In combination with a cGMP grade 316 stainless steel mold, 40mm-long by 3mm-diameter implantable rods can be produced by reaction injection molding at mild (<100 psi) pressure and mild (20-40°C) temperature.

OBJECTIVES

1. Manufacture unloaded Hydralese (PGSU) implants by a reaction injection molding process, and
2. Characterize the morphology, chemical structure, and crosslinking density of Hydralese (PGSU) implants.

METHODS

LABORATORY SCALE – DUAL BARREL SYRINGE METHOD

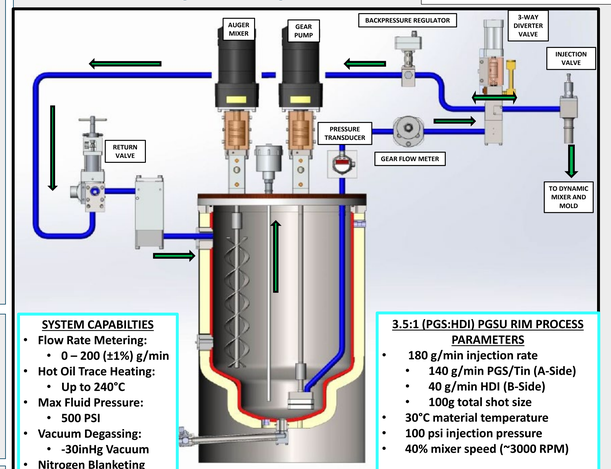


Hydralese (PGSU) devices and implants are currently fabricated at the laboratory bench scale by crosslinking drug-loaded poly(glycerol sebacate) (PGS) resin via polyol-isocyanate urethane chemistry using a dual barrel syringe (DBS). The DBS extrudes the drug-polyol blend and the isocyanate crosslinker 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.

However, batch sizes are limited to ~50g, material is subject to ambient temperature effects, and high viscosity materials can be difficult to extrude. Secant Group pursued the development of a Reaction Injection Molding (RIM) to overcome these limitations. The RIM unit provides tight material metering, high-speed mixing, temperature and pressure control, and repeatable processing.

METHODS (CONT.)

PILOT SCALE – PGSU REACTION INJECTION MOLDER

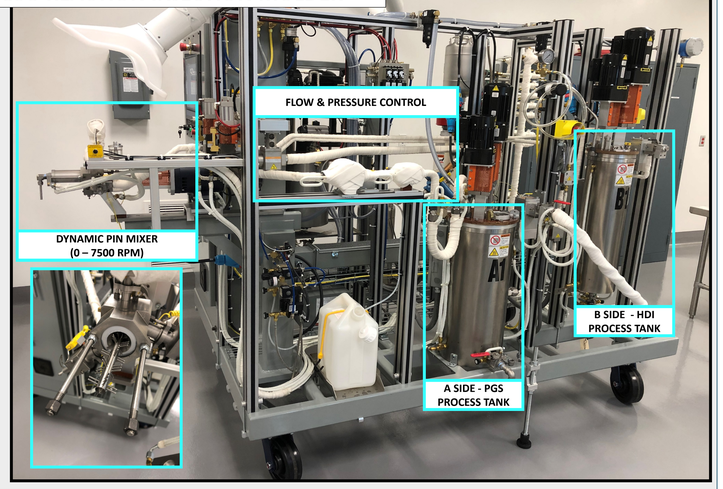


SYSTEM CAPABILTIES

- Flow Rate Metering:
  - 0 – 200 (±1%) g/min
- Hot Oil Trace Heating:
  - Up to 240°C
- Max Fluid Pressure:
  - 500 PSI
- Vacuum Degassing:
  - -30inHg Vacuum
- Nitrogen Blanketing

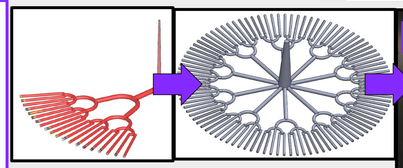
3.5:1 (PGS:HDI) PGSU RIM PROCESS PARAMETERS

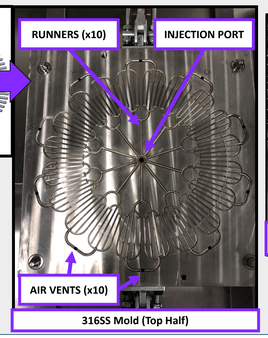
- 180 g/min injection rate
  - 140 g/min PGS/Tin (A-Side)
  - 40 g/min HDI (B-Side)
  - 100g total shot size
- 30°C material temperature
- 100 psi injection pressure
- 40% mixer speed (~3000 RPM)

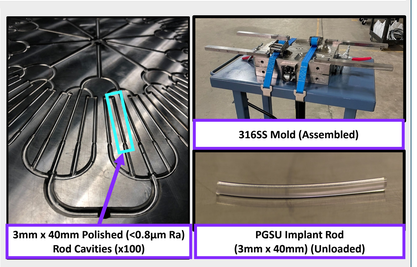


Computational Fluid Dynamics (CFD) Analysis & Design of Mold

- Mold flow simulated to determine runner, gate, vent, and cavity design
- Mold injection pressure: 100 psi
- Fluid temperature: 40°C
- Fluid viscosity: 90,000 – 100,000 cP
- Density: 1200 kg/m^3
- Surface tension: 0.04 n/m
- Hex and tet elements: 250,000 Total
- 1/5 simulation for simplified calculation



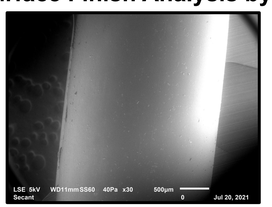




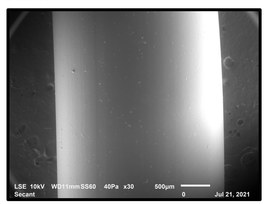
PGSU implants were made by a reaction injection molding method. The polyol (A-side) was comprised of pre-polymer PGS resin and a tin catalyst. The isocyanate (B-side) was comprised of hexamethylene diisocyanate (HDI). The components were brought up to temperature (30°C each) and degassed with vacuum and a vertical auger shaft. Using a submerged gear pump, each material was pumped in recirculation through a pressure transducer and a gear flow meter until steady state pressure and flow was achieved. The programmable logic controller (PLC) of the RIM unit metered polyol and isocyanate components into a high-speed dynamic pin mixer at a ratio of 3.5:1 PGS:HDI w/w.
The mixture was injected at low-velocity laminar flow to reduce injection backpressure (<100 psi) and prevent demixing of the disparately viscous A/B material. To meet the low velocity flow limits of the high viscosity materials, mold runner design was simulated and optimized through computational fluid dynamics (CFD) analysis. The final design of the mold was machined from 316 stainless steel and included 100 mold cavities 40mm long by 3mm diameter, polished to cGMP grade surface finish (<0.8µm R_a). Material was cured in the mold for 24 hours at 23°C before opening, ejecting material, and recovering product rods.

RESULTS

Surface Finish Analysis by SEM



316SS Mold



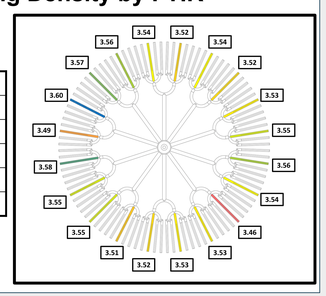
3mm PE Tube Mold

SEM imaging of 3mm-diameter rod sample outer surface at 30x magnifications to compare surface finish of new 316 stainless steel mold and laboratory scale polyethylene tube molds. Note part line present on stainless steel mold rod.

Mixing Uniformity and Crosslinking Density by FTIR

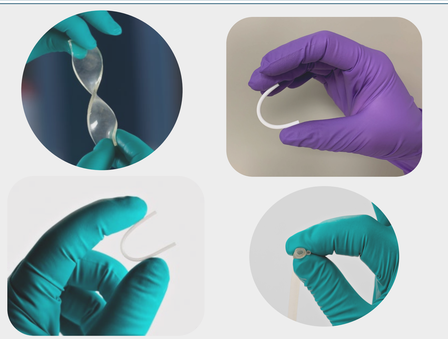
Chemical structure was characterized by Fourier-transform infrared spectroscopy (FTIR). Crosslinking density of the rods was determined by a trained macro comparing characteristic FTIR peaks linearly related to PGS:HDI weight ratio. Heat map of rod samples is presented, demonstrating A-side (PGS) : B-side (HDI) mix uniformity. All rods fall within PGSU crosslink density specification of 3.4:1 to 3.6:1 PGS:HDI.

USL	3.40
LSL	3.60
Mean	3.54
RSD	0.88%
Min	3.46
Max	3.60



CONCLUSIONS

- Reaction injection molding of Hydralese (PGSU) is an excellent commercial scale production process that allows for increased production volumes while maintaining control over product quality and finish.
- Results are comparable to current laboratory scale production methods.
- Precise metering of component ratios allows for repeatable production of low variability crosslink densities for controlled drug-release profiles.
- With strong process control and the capability to produce various shapes, sizes, and formulations of product at cGMP conditions, reaction injection molding of Hydralese (PGSU) is an exceptional choice for commercial scale production of drug-loaded long-acting implantable and gastroretentive devices.



Hydralese™ Biodegradable Elastomers

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