Shape Memory Polymer Hydrogels with Cell-Responsive Degradation for Crohn's Fistula Healing

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Statement of Purpose: Crohn's disease is an extremely common form of inflammatory bowel disease. Often Crohn's disease is associated with the formation of tunneling wounds, known as fistula, between portions of the urinary, reproductive, and/or digestive systems.[1] Fistula are often associated with pain, infections, and abscesses. 83% of Crohn's patients with fistula formation undergo surgical intervention to either drain or bypass the fistula openings, and ~23% of these patients ultimately require bowel resections.[2] Current treatments options such as setons and anti-inflammatories, are effective in initial closer but involve multiple surgical operations and long-term immunosuppression. Recently, bioprosthetic plugs, composed of lyophilized porcine intestinal submucosa, have been used to seal and heal fistula. Yet, these materials are subject to dislodging and infections. Thus, a fistula-filling material that degrades with the healing window of fistulas would be useful for a single procedure Crohn's fistula treatment.

To that end, we have developed a low-cost water responsive shape memory polymer (SMP) hydrogel foam containing polyvinyl alcohol (PVA) and cornstarch (CS) with a disulfide polyurethane crosslinker. The shape memory properties allow for low profile facile delivery and rapid expansion back to the permanent shape for wound filling. These hydrogels undergo dual degradation by amylases and reducing thiol species, such as glutathione/dithiothreitol (DTT).

Methods*: Synthesis:* SMPs were synthesized using an isocyanate terminated disulfide crosslinker containing hexamethylene diisocyanate and hydroxyethyl disulfide. Different polyol ratios (CS:PVA) of 0:1, 1:2, 1:1, and 2:1 were combined and crosslinked at 50°C in DMSO. Hydrogels were synthesized with PVA of 6 or 25 kDa to examine effects of PVA molecular weight. Foams were synthesized using NaCl porogen (300-500 µm) leaching, **Fig. 1a**. *Characterization:* Resulting hydrogels were characterized in terms of gel fraction, swelling, shape memory properties, surface chemistry, pore structure/size, mechanical properties, cytocompatibility, and cell attachment. *Degradation:* Foam wet masses were measured each day during incubation in solutions of PBS, DTT (10 mM), amylase (100 Units), and DTT+amylase.

Results: Hydrogel formulations all exhibited successful crosslinking indicated by gel fractions > 70 %. Swelling rates were affected by starch content, showing increased swelling with higher starch content with all formulation achieving equilibrium swelling near 60 minutes **(Fig. 1b)**. Shape recovery in all formulations was achieved within 3 minutes (**Fig. 1c**). Tensile moduli of synthesized hydrogels were between 0.1-0.5 MPa. Foam showed compressive moduli between 20-40 kPa. All synthesized materials showed cytocompatibility of > 85%. Increased degradation rates were seen with increased starch content in solutions containing amylase and/or DTT (**Fig. 1d-e)**.

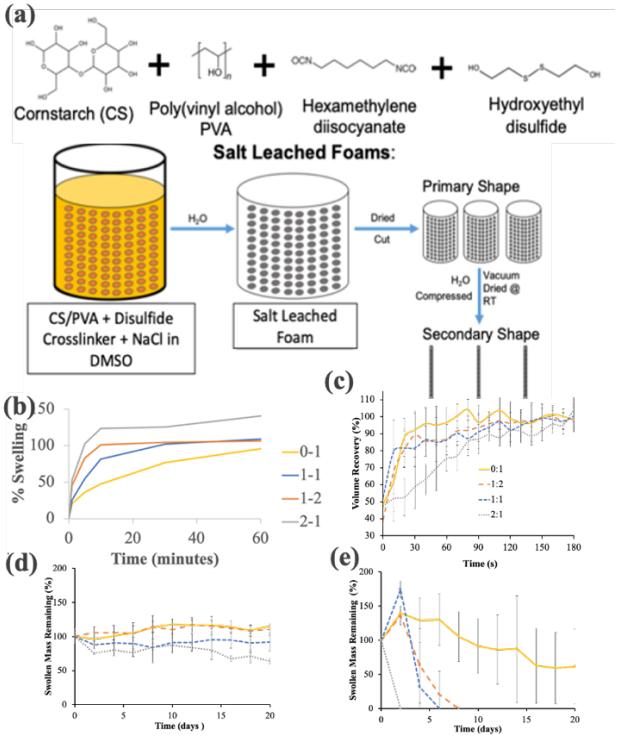

Figure 1. (a) Schematic of foam synthesis and shape programing. (b) Swelling profiles of hydrogels containing 25kDa PVA. (c)Shape memory profiles of 25k foams. (d) Enzymatic degradation profiles in amylase (e) Disulfide reduction-based degradation profile of 6k formulations hydrogel in DTT.

Conclusions: Materials showed excellent water responsive shape memory, which allows for application via a low-profile catheter. Degradation rates are responsive to both starch content and molecular weight of PVA. This allows for degradation rates to be easily tuned to relevant healing times. These porous hydrogel foams show tunable properties with an easy method of synthesis for the treatment of Crohn's fistula.

References:

1. Park KT, Ehrlich OG, Allen JI, et al.. *Inflamm Bowel Dis*. 2020;26(1):1-10.
2. Andreou C, Zeindler J, Oertli D, Misteli H. L*Sci Rep*. 2020;10(1):1-7