

# Development of Smart Tissue Adhesive for Treatment of Intra-operative Bladder Injury

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## Statement of Purpose:

An estimated 22 million women in the United States have undergone hysterectomy; in 2004, 617,000 of these procedures were performed. Accidental laceration of the bladder during surgery is the most common (incidence of up to 8.3%) complication of hysterectomy. Most of these bladder injuries are repaired by suturing, and the bladder is drained with a catheter. Scar formation is among the complications that can interfere with recovery of normal bladder function. Biomechanically, the use of sutures and scar formation are especially undesirable because either can compromise the proper distension of the bladder during storage of urine. In addition, the use of catheters and collecting bags can severely diminish patients' quality of life. To address these issues, we are developing a compliant tissue adhesive that will eliminate the need for suture and will minimize scar formation by release of nucleic acid-based therapeutics. For this purpose, we have recently begun investigating the physical properties of a new class of hydrogels comprised of crosslinked Tetronics®, 4-arm block copolymers of poly (ethylene glycol), and poly (propylene glycol).

## Methods:

### Synthesis and characterization of Tetronic-based hydrogels

Aqueous solutions (30% w/v) of Tetronics T1107, T904, and various blends (100/0, 75/25, 50/50, 0/100 T1107 / T904 ratio) were prepared at 4 °C. First, thermal gelation properties of each Tetronic formulation were evaluated by a tube inversion method and rheometry. In addition, to achieve stable chemical crosslinking, Tetronics were reacted with acryloyl chloride to form terminal acrylate groups. Acrylate-terminated Tetronics were crosslinked with a model thiol-containing compound (dithiothreitol, DTT) at a 1:1 molar ratio (acrylate:thiol) by Michael-type conjugate addition. Immediately following mixing, the samples were subjected to oscillatory shear deformation at 1% strain amplitude and 10 Hz frequency at 37 °C. The gelation time was measured as the point where the storage modulus crossed over the loss modulus. The mass swelling ratio ( $Q_m = \text{mass swollen gel} / \text{mass dried polymer}$ ) and mechanical properties were evaluated at both the application temperature, 37 °C; and 4 °C, where the effects of hydrophobic interactions underlying physical crosslinking are significantly reduced. Hydrogel degradation was assessed by mass loss during incubation in PBS at 37 °C.

## Results and Discussion:

At 4 °C, T1107 and T904 both formed low viscosity solutions. T1107-containing solutions exhibited thermal gelation between 20-30 °C, while T904 did not exhibit thermal gelation at any concentration or temperature within the physiological range. The gelation times for homogeneous acrylated T1107 and T904 in the presence of DTT were approximately 30 seconds and 4 minutes, respectively. The results provided evidence that both hydrogel formulations exhibited significantly greater swelling at 4 °C compared to that at 37 °C, consistent with reduced crosslinking due to the inhibition of hydrophobic interactions at reduced temperature.

In addition, the elastic modulus, UTS, and elongation at break of T1107 hydrogels were significantly greater at 37 °C compared to 4 °C, and significantly lower than T904. The most interesting aspect of these data is that T904 hydrogels were able to withstand approximately 100% elongation prior to failure. Moreover, T1107 hydrogels exhibited reproducible stress-strain response from cycle to cycle. These results demonstrate that Tetronic-based hydrogels provide substantially improved mechanical properties compared to a variety of existing hydrogel systems, which are attributable at least in part to their combination of physical and chemical crosslinking. Hydrogel degradation times ranged from 4-7 weeks depending on the Tetronic ratio.

## Conclusions and Future Work

These studies demonstrate that acrylated Tetronic hydrogels offer a tissue adhesive formulation capable of near instantaneous thermally-induced gelation combined with slower subsequent chemical crosslinking. All formulations exhibit thermosensitive swelling and mechanical properties indicating that both chemical and physical crosslinking mechanisms contribute to their physical properties. On-going studies are evaluating tissue bond strength in an ex vivo urinary bladder model and controlled release of shRNA-encoding plasmids targeting the TGF beta signaling pathway implicated in fibrotic scarring.