Quantifying Performance of a Bi-functional Tissue Adhesive for Internal Wound Repair

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Statement of Purpose: With laparoscopic and robotic surgical techniques advancing, the need for an injectable surgical adhesive is growing[1]. For use on internal organs, the tissue adhesive must provide not only biocompatibility, but proper strength, compliance and durability to last over the wound healing process. Previously, we demonstrated that bi-functionalization of PEO-PPO block co-polymer, Tetronic with acryloyl chloride and N-Hyrdoxysiccinminide (NHS), and chemical cross-linking led to formation of a hydrogel with adhesive strengths higher than those of other similar formulations[2,3]. In the present study we quantified the compliance and strengths of the tissue adhesive under cyclic loading using a custom ex vivo pressure device.

Methods: *Preparation of tissue adhesive:* Bi-functional Tetronic adhesive was prepared through multi-step process. Acrylation was first performed in dicholormethane using published methods[3]. Briefly, four-arm Tetronic T1107 (MW: 15,000) with Triethlyamine (TEA) and acryloyl chloride was stirred for 24 hours. Triethlyammonium precipitate was filtered out and the product was neutralized to pH 7.0, then washed with ethyl either. By adjusting the initial ratios of reagents, all 4-arm acrylate Tetronic (NHS-) and 2-arm acrylate formulations were prepared. The partially acrylated T1107 was then, modified with NHS (NHS+) through reactions with 4-Dimethylaminopyridine (DMAP), Succinic Anhyride and TEA in Tetrahydrofuran (THF) for 12 hours and NHS and Dicyclohexylcarbodimide (DCC) in THF for 4 hours. Chemical crosslinking of acrylate-ends was achieved by addition reaction with appropriate amount of thiol-group donor, dithiothreitol (DTT) as previously described[3].

Mechanical testing of tissue adhesive: Two blend ratios (100:0, 75:25) of T1107-acrylate (NHS-) and T1107-acrylate-NHS (NHS+) were prepared, and pressure testing on rat bladders (Pel-Freez Biologicals) was performed using a custom ex vivo device to evaluate the performance of the adhesive under hydrated condition. Prior to testing, a small, approximately 2 mm puncture was made on the dome of the bladder using an 18 gage needle. Modified Tetronic/DTT (25 µl, pH=7.4) was applied to cover the hole and allowed to cure under hydrated condition at 37°C for 1 hr. Using a syringe pump (Harvard Apparatus) and a 60 ml syringe, the specimen was subjected to either single loading (at a flow rate of 0.8 ml/min until failure) or cyclic loading (0-40 cmH_2O at a flow rate of 0.5 ml/min for loading, and 2 ml/min for unloading, 5-hr duration or until failure). The device was controlled and pressure data were recorded using PC with a custom LabView code (National Instruments). Results were compared to a non-punctured rat bladder.

Results: Acrylation percent and product yield for T1107-acrylate (NHS-) were 93% and 63%, respectively. Acrylation percent and NHS conversion rate for NHS+ were 65% and 26%, respectively with 64% product yield. In burst tests, bladders that were sealed with 100:0 and 75:25 blends withstood average pressures of 100 cmH_2O (Figure 1). An abrupt pressure loss due to sudden separation of the adhesive from the tissue sealed with the 100:0 blend was observed. In contrast, the bladder sealed with the 75:25 blend exhibited a slow leak, which indicated that the adhesive sheared away from the tissue gradually. When compared to the non-punctured bladder (control), the bladders sealed with the adhesive did not show a steep rise in pressure, which indicates the characteristic tissue mechanical property of the bladder, high compliance (low stiffness), was not compromised.

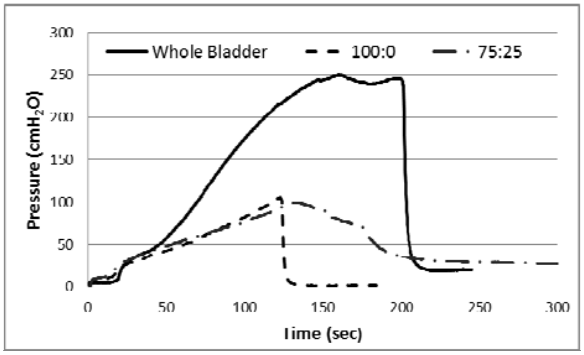

Figure 1. Maximum pressures held for various Tetronic hydrogel blends (NHS-:NHS+) sealing punctures in rat bladders. Data are representative trends, n=3.

The results of cyclic pressure (0-40 cmH_2O) testing provided evidence that Tetronic adhesive with 75:25 blend sealed the puncture for hundreds of cycles with over 24 h of testing, while the 100:0 blend was intact for only 4 cycles before the adhesive site failed (data not shown).

Conclusions: The results of the present study demonstrated that the bi-functionalized Tetronic adhesive exhibited high compliance that matches that of soft tissues and durability needed for wound repair. Further testing is needed, however, to demonstrate the actual utility of our bi-functional Tetronic tissue adhesive for various internal organ applications in vivo.

Acknowledgement: Mr. Robert Teague, Department of Electrical & Computer Engineering, Clemson University for assistance with LabView programming; Source of funding NIH EB008785

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