Preclinical Evaluation of Sprayable In-Situ Crosslinking Hydrogel Coatings

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Statement of Purpose: Surgical procedures in the peritoneal cavity typically result in the formation of post-surgical adhesions.[1] Commercial barriers such as Seprafilm® have demonstrated clinical efficacy in preventing post-surgical abdominal adhesions by separating tissue planes during healing.[2] However, Seprafilm® is not indicated for laparoscopic procedures. A sprayable, *in situ* crosslinked hydrogel that forms a tissue adherent adhesion barrier would be better suited for laparoscopic surgical techniques. FocalSeal-S is an amphiphilic poly(oxyethylene) (PEO)-based macromer core with hydrolytically degradable oligo-ester flanks and acrylate ester termini. The material can be photopolymerized *in situ* to form tissue adherent, resorbable hydrogels with sealant and adhesion reduction properties.[3,4] More recently we have discovered a related macromer, Pluronic F127L5A2 (PluronicL5A2) derived from a poly(oxyethylene-oxypropylene-oxyethylene) (PEO-PPO-PEO) block copolymer using a similar synthesis process that provides hydrogels with thermoreversible swelling properties. This abstract describes preclinical studies aimed at utilizing these macromer materials as sprayable, *in situ* crosslinked hydrogel adhesion barriers that do not require photochemistry or a primer step.

Methods: Focalseal-S and PluronicL5A2 were formulated into two-part systems (Parts A and B) each with 2-7 % solids in water. Ferrous gluconate (0.6 wt %) was added to part-A and t-butyl hydroperoxide (0.035-0.070 wt %) was added to part-B. Hydrogels were prepared by spraying or mixing component A with equal amounts of component B using a dual syringe applicator. A rat cecal abrasion model was utilized to determine efficacy. Naive Sprague Dawley rats weighing ~275g were anesthetized and subjected to laparotomy and standardized mechanical abrasion of the cecum. Gel was applied using a Micromedics air-assist sprayer with CO_2 as the accelerant. The cecum was coated with ~ 1.8mL of test material. Animals were evaluated postmortem at 7 days for the presence/absence of adhesions to the cecum.

Results: *In vitro* swelling studies at 37°C in phosphate buffered saline showed the FocalSeal-S hydrogels increased in mass whereas the PluronicL5A2 gels decreased in mass (Figure 1). Both gels were degraded within 2 weeks under these conditions. When sprayed onto a collagen membrane, gel concentrations of 4-7% solids where shown to adhere well to the membrane and required peeling or scraping to remove. A rat cecal abrasion model showed the presence of both FocalSeal-S and PluronicL5A2 formulations attached to the cecum after 7 days. FocalSeal-S gels decreased the incidence of adhesions to the cecum while PluronicL5A2 gels were observed to have adhesions formed to the gel itself (Table 1). These adhesions did not resolve at later time points (data not shown).

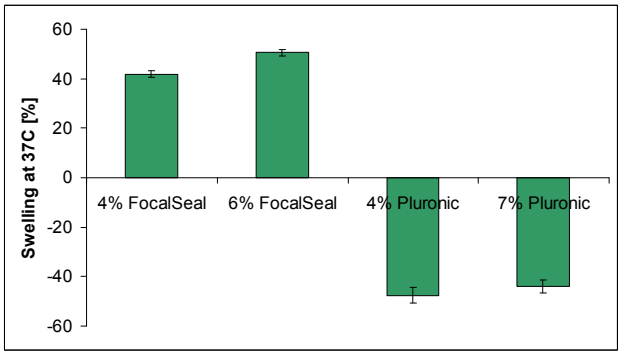

Figure 1. Effect of macromer selection and concentration on swelling

Group	% with No Adhesions	Mean Incidence of Adhesions ± SEM
4% FocalSeal-S (n=19)	74	0.3 ± 0.2
6% FocalSeal-S (n=10)	60	0.5 ± 0.2
7% PluronicL5A2 (n=10)	0	3.1 ± 0.4
5% PluronicL5A2 + 2% FocalSeal-S Blend (n=9)	33	1.0 ± 0.3
Historical Surgical Control (n=10)	10	2.2 ± 0.3

Table 1. Results from rat cecal abrasion studies at day 7

Conclusions: A sprayable adhesion barrier is required to adhere well to tissue, not interfere with normal wound healing, and resorb shortly after preventing post-surgical adhesions. *In vitro* assays showed FocalSeal-S and PluronicL5A2 macromers can be crosslinked using redox chemistry and demonstrated good tissue adherence. FocalSeal-S increased in mass, typical of most hydrogels, while PluronicL5A2 decreased in mass due to its thermoreversible properties. Degradation rate for both formulations was a function of macromer concentration, where gels with higher solids degraded slower. While both macromers demonstrated adequate *in vitro* properties for an adhesion barrier, they performed quite differently in the rat cecal abrasion model. Both FocalSeal-S and PluronicL5A2 hydrogels formed a barrier and were well adhered to the cecum at 7 days; however, PluronicL5A2 did not show efficacy in preventing adhesions to the cecum. The PluronicL5A2 appears to be adhesiogenic where FocalSeal-S shows efficacy as a barrier hydrogel. Additional preclinical studies will be conducted to further investigate and optimize the adhesion prevention properties of the FocalSeal-S hydrogels.

References:

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