Thin, elastic polymer films for preventing unwanted soft tissue attachments

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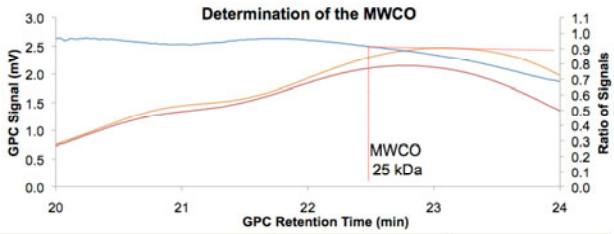
Statement of Purpose: Unwanted scar tissue attachments plague up to 95% of all surgical procedures including abdominopelvic, facial reconstruction, and tendon repair.[1] Synthetic barrier devices are mechanically robust but remain beyond the critical healing period, often causing fibrotic response. Naturally based devices degrade quickly but have poor handling. We have developed unique processing that produces hyaluronic acid/alginate-blended thin membranes that are mechanically robust and degrade quickly. Furthermore, our liquid tissue anchor (LTA) triggers mucoadhesivity of the membranes, precluding the use of sutures or tacks. The LTA relaxes the membrane by disrupting crosslinks, affording tunable degradation. The device is permeable to necessary proteins and repair molecules and thus does not interrupt the normal healing process.

Methods: Modified hyaluronic acid (HA) and alginate films were prepared according to our previously reported method.[2] Briefly, HA and alginate are cast from an aqueous solution. Films are exposed to UV to facilitate crosslinking of the HA component. All films are exposed to calcium chloride to gel the alginate, and washed excessively with ddI water. Permeability studies were conducted on a Franz diffusion cell and analyzed by GPC. Dextran of varying molecular weights was used as model molecules and data is presented as a molecular weight cut off. A rat peritoneal abrasion model was conducted in compliance with protocols approved by The University of Texas at Austin IACUC committee. Animals received no barrier or the HA/alginate film to separate injured tissues. The cecum and abdominal wall were abraded, with injuries proximal. Films were placed between these abraded tissues in test groups. Animals were sacrificed at 7 days and tissue attachments or lack of tissue attachments was observed. Statistical inferences were made using Mann-Whitney U tests, with a p-value < 0.05 considered statistically significant. Tissues recovered from the necropsy were fixed in formalin, sectioned, and stained with hematoxylin and eosin for histological examination using standard techniques. Handling properties were assessed by surgeons in the field, both during *in vivo* application and in a comparison study. HA/Alginate films were handled wet and dry, and assessed for practical use.

Results: HA/alginate films significantly permit molecules of Stokes radius of 3.6 nm. HA/alginate films effectively prevented unwanted soft tissues attachments compared to animals that did not receive any barrier treatment (p-value = 0.04). The films degraded within 7 days and significantly reduced inflammation of local tissue when compared to untreated animals. Independent surgeon assessment validated the HA/alginate films offered a great improvement in handling capabilities as compared to currently available devices. HA/Alginate films were found to feel like a biological tissue with appropriate elasticity and strength.

Group	# of animals free of scarring (N = 10)	p-value
Control (untreated)	3	--
Alafair Membrane + LTA	8	0.04

Fig 1. Application of Alafair's membrane and LTA in the rat cecal abrasion model showing strong mucoadhesion. Results of rat cecal abrasion model show successful and statistically significant prevention of unwanted soft tissue attachment when compared to untreated animals.



Molecule	MW (Da)	Rs (nm)
IgG	150000	5.1, 5.5
Bovine serum albumin	66000	3.48
bFGF	17000	1.45
Vancomycin	1485.71	-
Tobramycin	467.51	-

Fig 2. Alafair's membrane prevents dextran molecules above 100,000 molecular weight from permeating. Molecules of Stokes radius greater than 7.0 nm (log Rs = 0.470 x log MW – 1.513) do not permeate. Dextran molecules below 25,000 molecular weight significantly permeate. Molecules of Stokes radius less than 3.6 nm significantly permeate the membrane. All tests were conducted at 6 hours. Growth factors such as bFGF, water soluble drugs, such as Vancomycin and Tobramycin should permeate the membrane easily. Large molecules such as antibodies are not expected to permeate the membrane.

Conclusions: We successfully created safe, biodegradable, effective anti-adhesion films to prevent unwanted soft tissue attachments in the rat peritoneal model.[3,4] HA/alginate films demonstrate superior handling characteristics when assessed by surgeons in the field. Furthermore, HA/alginate membranes permit permeation of molecules relevant to proper healing, further suggesting that the technology does not interfere with normal healing processes.

References: 1.Ward and Panitch. J of Surg Res, 2011;(165):91-111. 2. Zawko and Schmidt. Acta Biomaterialia, 2010;(6);2415-2421. 3.Mayes S et al. BMES Annual Meeting, Oct 2013; Seattle, WA. 4.Mayes S et al. Polymers in Medicine ACS Conference, Oct 2013; Sonoma, CA.