Development of Therapeutic Hydrogels for Traumatic Optic Neuropathy

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Statement of Purpose: Traumatic optic neuropathy (TON) is either a temporary or permanent loss of function of the optic nerve as a result of head injury. The more common form of TON, indirect TON, arises when force from an impact to the surrounding bones or the eye globe is transferred to the optic nerve [1]. Recently, a physiologically relevant animal model was developed for indirect TON. Rats were subjected to varying levels of unilateral torsion generated by a novel apparatus designed to induce torsional indirect TON. Functional visual testing and histological analysis demonstrated that this approach reliably reproduced clinically relevant TON. We hypothesized that an injectable hydrogel cast with the ability to form and contract (with minimal compression) around the damaged optic nerve could locally deliver neuroprotective agents to the site of TON injury, preventing further axonal degeneration.

Methods: Alginate blends of Protanal LF 10/60 and Manucol (FMC BioPolymer, Philadelphia, PA), with calcium chloride as the crosslinker, were prepared and evaluated for gel formation under physiological conditions and the ability to contract upon formation. Viscoelastic properties of the hydrogels were determined using a Kinexus ultra+ rheometer (Malvern Instruments Ltd, Worcestershire, UK). Methylene blue (MB) was incorporated into the hydrogels at 0.01 and 0.1% w/w to be evaluated as a neuroprotective agent. Release rate of methylene blue over time was measured using a SpectraMax M5 microplate reader (Molecular Devices, LLC, Sunnyvale, CA) at wavelength 609 nm. COMSOL Multiphysics v5.2 was used to determine contractility of the hydrogel.

Results: Formulations prepared with a blend of the two alginates form hydrogels with the ability to contract. These hydrogel formulations were tailored to have mechanical properties in the range optimal for nerve regeneration (Figure 1). Methylene blue was incorporated into the hydrogels and release profiles varied with composition (Figure 2). The finite element model shown in Figure 3 was used to demonstrate the operating principle of the hydrogel cast, which is designed to force the injured ends of axons together within the casted region while maintaining tension on the uninjured portions of the axons. While this model is based on an oversimplification of the optic nerve, it is a first approximation of the expected mechanical performance of the developed injectable hydrogel system.

Conclusions: Combinations of Protanal and Manucol produced hydrogels that contract slightly with controlled release of methylene blue. Future research aims to evaluate these hydrogels using the validated animal model of TON with magnetic resonance imaging to analyze the efficacy of methylene blue as a neuroprotective agent.

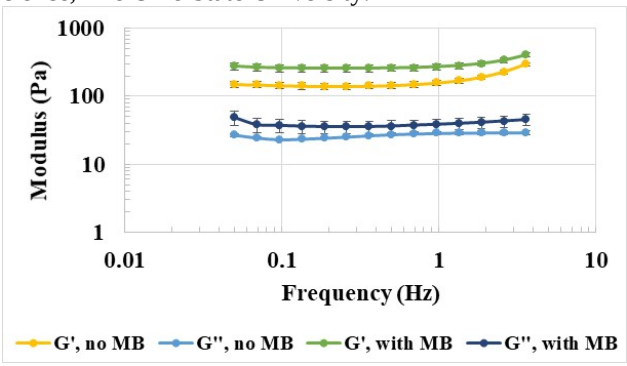

Figure 1. Rheology experiments (frequency sweep from 0.05 Hz to 5 Hz at 1% strain) showed the storage moduli (G') and loss moduli (G") were higher with MB incorporation.

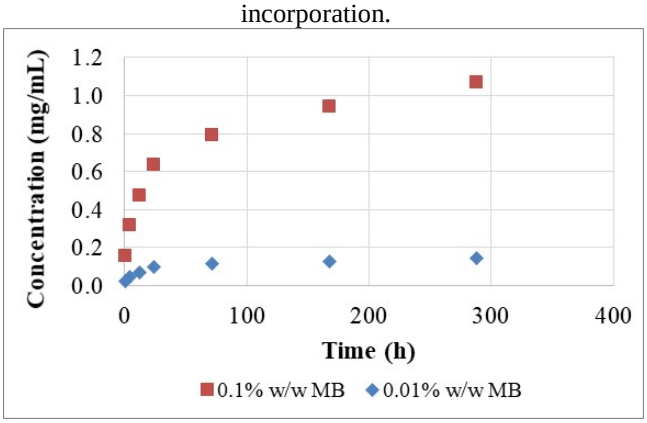

Figure 2. Release rate of MB over time could be controlled by loading different amounts of MB or modifying the affinity of MB to alginate polymers.

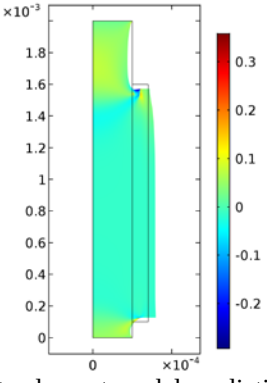

Figure 3. Finite element model prediction for the axial strain distributions within the optic nerve following 4% contraction of hydrogel cast. This is an axisymmetric model where the optic nerve was modeled as a cylinder and the hydrogel as an annular cylinder. The axial strain is slightly positive outside the casted region and slightly negative within the region, implying the injured region would be under axial compression while the axons beyond the cast would be under axial tension.

References:

1. Steinsapir KD. Surv Ophthalmol. 1994;38:487-518.