An *in situ* Forming Hydrogel for the Controlled Intra-Articular Delivery of Losartan

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INTRODUCTION: Arthrofibrosis, a debilitating condition characterized by excessive scar tissue formation in and around a joint, can occur following trauma or surgery. It is believed that TGF-β1 driven differentiation of fibroblasts into myofibroblasts contributes to development of arthrofibrosis through excessive collagen production. Local pharmacologic inhibition of myofibroblastogenesis may prove effective in preventing arthrofibrosis following injury or surgery, but to date, no such interventions have been implemented in the clinical setting. Losartan, an FDA-approved antihypertensive, has been shown to be antifibrotic in multiple animal models and we hypothesized that intra-articular delivery of losartan may prevent arthrofibrosis without risk of hypotension from systemic delivery. Preliminary studies proved that losartan (.2mg/ml) inhibits myofibroblastogenesis and total collagen deposition when directly applied to human fibroblasts *in vitro*. However, a minimum of 72 hours losartan exposure is required for long-term antifibrotic effects, indicating the need for a biocompatible carrier that allows for sustained intra-articular losartan release. We hypothesized that a thermosensitive, *in situ* forming hydrogel comprised of FDA-approved Pluronic F127 (PF127) and Hyaluronic Acid (HA) could be utilized for this purpose. PF-127, a triblock polymer of poly(ethylene glycol) (PEO), poly(propylene glycol) (PPG) and poly(ethylene oxide) (PEO), forms a thermosensitive gel that represents an injectable liquid solution at room temperature and transitions to a gel (sol-gel transition) at temperatures between 30-37ºC. Addition of HA, a shear thinning hydrogel, increases the strength of the hybrid hydrogel, extending medication release duration without decreasing injectability. The goal of this study was to evaluate the physical characteristics, ease of synthesis, and losartan-release rate of a PF127/HA hydrogel.

METHODS: Hydrogels of varying concentrations of PF127 (10-40%) and HA (.5-2%) were synthesized via a simple stirring technique. PF127 was first added to water and stirred for 1 hour at 4ºC. Once a clear liquid was achieved, HA powder was added to the mixture and stirred at 4ºC for 1 hour. Once a clear mixture was again achieved, sol-gel transition temperatures were determined using a vial test in which 5 ml of each gel was placed in a glass vial and was slowly warmed in a water bath until sol-gel transition occurred, as determined by inverting the vial. (**Figure 1**) Gels of 20% PF127 and 1% HA were identified as the most promising with a sol-gel temp of 32ºC. Gels of this composition were then synthesized with 1 mg/ml or 2mg/ml losartan. To load losartan into the gel, lyophilized losartan was dissolved in water and mixed with PF127 and HA as described above.

To determine the release rates, losartan-loaded gels (2ml) were injected into a dialysis cassette which was sealed and warmed to 37ºC for gel formation. The cassette was then immersed in a specimen cup filled with phosphate buffered saline (PBS, pH 7.4) and sealed. Gels were then incubated at 37ºC with continuous gentle rotation for 28 days. (**Figure 2**) A sample of PBS was collected daily, and PBS was replaced with fresh PBS after each sample collection. Losartan concentration was determined by High Pressure Liquid Chromatography (HPLC) and release rates were calculated from the concentrations measured from each collection.

RESULTS: A hydrogel of 20% PF127 and 1% HA is easily synthesized and loaded with losartan via a simple stirring technique and undergoes sol-gel transition at 32ºC. Losartan loaded PF127-HA hydrogels release losartan continuously for at least 28 days. Approximately 50% of the losartan is released within the first 10 days with a plateau in release rate between days 10 and 28. (**Figure 3**)

DISCUSSION: Our results suggest the feasibility of a sustained intra-articular delivery of losartan from a single injection via a losartan-loaded thermosensitive hydrogel. Upcoming *in vivo* studies in an animal model of arthrofibrosis will further delineate efficacy in prevention of arthrofibrosis.

SIGNIFICANCE/RELEVANCE: This study is the first to investigate the feasibility of sustained intra-articular delivery of losartan via a thermosensitive drug-loaded hydrogel.

IMAGES AND TABLES:

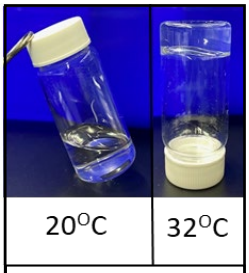

Figure 1. Images of 20% PF-1% HA hydrogel as a liquid at 20C and after sol-gel transition at 32C.

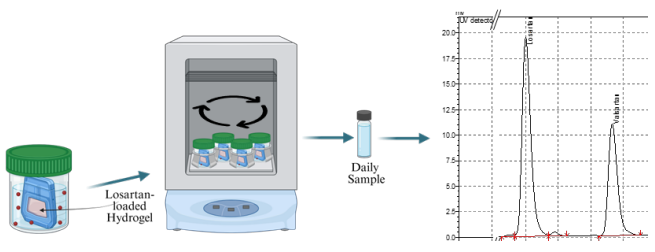

Figure 2. Release Rate Study
Losartan-loaded hydrogels injected into dialysis cassette and immersed in PBS containing specimen up. Gels incubated wit gentle rotation. PBS samples daily and losartan concentration measured by HPLC.

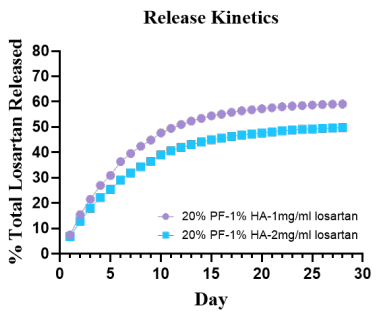

Figure 3. Cumulative % Drug Release of Losartan-Loaded Hydrogels
% of Total losartan released over 28 days from 20% PF127-1% HA gels with either 1mg/ml or 2mg/ml losartan concentrations.