Controlled Release of Hyaluronic Acid from Molecularly Imprinted Hydrogel Contact Lenses

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Statement of Purpose: Ocular dryness and resulting discomfort has been reported by over 75% of contact lens users, with over 25% reporting frequent-to-constant symptoms that impact quality-of-life and may lead to discontinuation of contact lens use. It is presently treated by the frequent instillation of comfort molecule eye-drops, but frequent multiple administration, and short residence time limit the efficacy of such measures. We have rationally designed hydrogel contact lenses that can deliver the comfort agent hyaluronic acid (HA) to the ocular epithelium at a constant therapeutic rate of approximately 6μg/hour for 24 hours, and demonstrate, for the first time, the control over reptation of a long-chain molecule by molecular imprinting strategies. We augment the hydrogel structure of nelfilcon A (CIBAVISION, Duluth, GA), a commercial daily-wear contact lens material, with multiple complexation points comprising acrylamide, N-vinyl pyrrolidone, and 2-(diethylamino) ethyl methacrylate, thereby mimicking the binding site of the naturally occurring HA-binding protein CD44 [1]. There is an inverse correlation between the percent functional monomers in the hydrogel and the HA diffusion coefficient. Also, increasing the variety of functional monomers lowers the HA diffusion coefficient. The hydrogel lenses produced in this work could serve dual roles as a comfort and therapeutic contact lens, since HA has been shown to have therapeutic properties in corneal wound healing and epithelial cell migration [2].

Methods: *Synthesis of Hydrogel Lenses* nelfilcon A macromer (CIBA VISION, Inc.) was mixed with hyaluronic acid sodium salt (*Streptococcus equi*, Fluka, MW~1.2 million Dalton) and functional monomers acrylamide, 2-(diethylamino) ethyl methacrylate (Aldrich, Milwaukee, WI) and N-vinyl pyrrolidone (Polysciences, Warrington, PA) until homogeneous. Hydrogels ~125 μm thick were synthesized with free-radical UV photopolymerization and cut into disks of 14 mm diameter. *In vitro Hyaluronic Acid Release Studies* Kinetic release studies were conducted in artificial lacrimal fluid. The disks from the synthesis step were immediately placed in 5 mL of lacrimal fluid at 35°C, continuously agitated with an orbital shaker (Stovall Life Sciences, Greensboro, NC) at 30 rpm. Care was taken to assure perfect sink release conditions. Release of HA was monitored with a HA ELISA assay kit (Corgenix, Denver, CO). *Dynamic Mechanical Analysis Studies* Hydrogel lenses were dried in air, then in a vacuum oven, until the weight change was less than 0.1%. The gels were then weighed in air and in heptane, a non-solvent, using a microbalance. The lenses were equilibrated in DI water and the fully swollen lenses were weighed in air and in heptane. The equilibrium swelling ratios were calculated by Archimedes' principle. Stress-strain data was obtained by performing tensile studies on a dynamic mechanical analyzer (TA Instruments, Wilmington, DE). Hydrogels prepared in strips (in triplicate) were mounted on a dynamic mechanical analyzer at a gauge length of 30 to 35 mm, and extended at a constant rate of 4 mm/min. The gels were fully hydrated through the experiment.

Results: We hypothesized that by adding functional monomers similar to amino acids found in the binding site of CD44, we can tailor the binding affinity, and hence the release characteristics of HA from nelfilcon A hydrogel. Equilibrium swelling studies and mechanical studies confirm that change in diffusion coefficients is independent of the hydrogel mesh size.

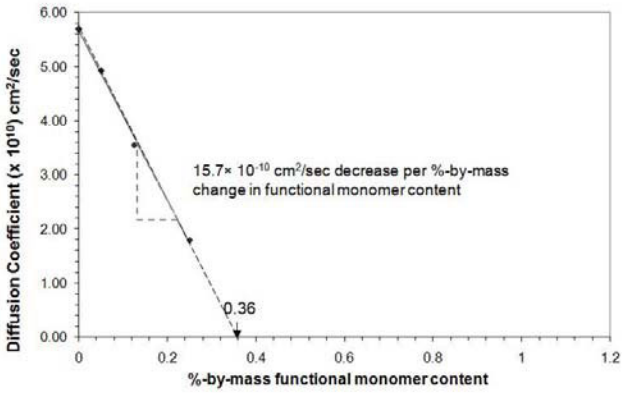

Figure 1: HA Diffusion Coefficient From Lens versus Percent Functional Monomer Content

The results show that there is a clear inverse correlation between the percent functional monomer content in the hydrogel and the diffusion coefficient of HA. Diverse functional monomer content decreases the diffusion coefficient by a factor of 1.5compared to single monomer content, and there is no correlation between the diffusion coefficients and the normalized mesh sizes of the hydrogels.

Conclusions: This is the first demonstration in the literature of imprinting a large molecular weight polymer within a hydrogel and delayed reputation, and the technique can be applied to other gel systems. By changing the mass content and relative proportions of the monomers within the hydrogel, we can dramatically vary the diffusion coefficients and release profiles of the HA, without altering the mesh size The nelfilcon-based imprinted hydrogels can deliver hyaluronic acid comfort molecules to the eye in therapeutic amounts, and may lead to a dramatic improvement in the comfort of contact lens wearers.

References:

[1] Bajorath J. *J Biol Chem*. 1998; 273:338-343.
[2] Camillieri G. *J Ocul Pharmacol Ther* 2004; 20:548-553.

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