Extended Ocular Drug Delivery using Hyaluronic Acid-containing model Silicone Hydrogel Materials

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Statement of Purpose: Topically administered ocular formulations, such as ophthalmic solutions, suspensions and ointments, represent the 90% of the ophthalmic medication used to treat the anterior segment of the eye. While eye drops are a well-accepted and convenient method for ocular drug delivery, they exhibit significant limitations such as poor drug bioavailability, low residence time, pulsatile delivery profiles in the tear fluid as well as the need for patient compliance. Silicone hydrogel (SH) contact lenses have been proposed as potential alternative ocular drug delivery systems, capable of replacing eye drops, due to their high oxygen permeability and potential for targeted delivery to the corneal surface. The ability of novel hyaluronic acid (HA)-containing SH materials to release timolol maleate (TM), a β-blocker widely used for glaucoma treatment, or ketotifen fumarate (KF), an anti-histamine administered for ocular allergies was studied. HA is a highly hydrophilic glycosaminoglycan widely used in ophthalmic applications due to it lubricating and mucoadhesive properties. Polyvinylpyrrolidone (PVP), a polymer used as internal wetting agent in conventional and silicone hydrogels, was used for comparative studies.

Methods: The model SH used consisted of a hydrophilic monomer, either 2-hydroxyethyl methacrylate (HEMA) or N,N-dimethylacrylamide (DMA), a hydrophobic silicone monomer of methacryloxypropyltris (trimethylsiloxy) silane (TRIS) and the cross-linker ethylene glycol dimethacrylate (EGDMA). HA of different molecular weight (MW) and concentration or PVP (10 kDa) of different concentrations was used as a wetting agent. The wetting and the therapeutic agent were added to the polymer mixture during synthesis through direct entrapment. The reaction was performed by UV induced free-radical polymerization, using a custom designed acrylic mold. The compositions of focus are pHEMA/TRIS (90/10 wt%) and DMA/TRIS (50/50 wt%). The impact of the wetting agent on the swellability, the surface wettability, optical transparency and *in vitro* drug release was studied. Surface wettability was determined through the contact angles using the captive bubble technique, optical transparency was assessed through a measurement of transmittance of the SH in the rage of 400-750 nm. Drug release was monitored and quantified by UV spectroscopy.

Results: The non-covalent entrapment of the wetting agent into the SH led to materials with releasable wetting agent. Simultaneous drug and wetting agent incorporation resulted in modified SH with increased water content and significantly improved surface wettability ($p<0.05$). DMA/TRIS materials exhibited higher surface wettability and swellability compared to pHEMA/TRIS. In addition, the optical transparency of these materials was not affected by drug loading. However direct entrapment of HA decreased their optical clarity. *In vitro* release of TM and KF showed that TM was released within 4 days for DMA/TRIS and over a 14 day period for pHEMA/TRIS SH. However, KF release lasted 14 days in DMA/TRIS SH and 25 days in pHEMA/TRIS materials respectively. For both therapeutic agents used in the current research, non-covalent entrapment of wetting agent and its MW did not significantly change the release kinetics, however the release rate of TM was slowed and controlled by the release of the HA for both SH, due to electrostatic interactions between protonated TM and anionic HA. This relatively low alteration in release kinetics may be attributed to the low amount of wetting agent added as well as to the fact that it is also released through the matrix of the materials along with the drug. Generally, pHEMA/TRIS SH showed a higher and more controlled release profile than DMA/TRIS, due to differences in the degree of swelling as well as different interactions developed between the silicone hydrogel matrix and the therapeutic agent.

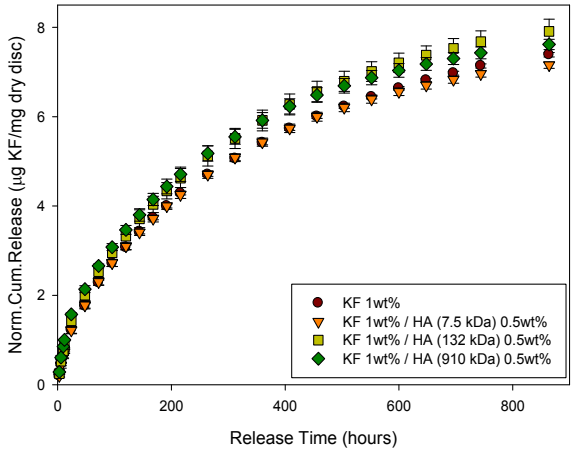

Figure 1: Cumulative release of KF-loaded pHEMA/TRIS hydrogels containing HA of different MW. Data are shown as mean (±SD) with n=4.

Conclusions: The development of silicone hydrogel materials capable of simultaneously releasing a therapeutic and a wetting agent for an extended period of time may have promise as extended drug delivery systems for the treatment of front of the eye ailments while also providing comfort during wear.