Simultaneous Release of a Wetting and a Therapeutic Agent from model Silicone Hydrogel Materials used for Extended Ocular Drug Delivery.

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Introduction:

Topically administered ocular formulations, representing 90% of the ophthalmic medication, are a well-accepted and convenient method for drug delivery used for the treatment of diseases of the anterior segment of the eye. However 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 that drug delivering contact lenses might have the potential to overcome. Silicone hydrogel (SH) contact lenses have been proposed as an alternative ocular drug delivery system, capable of replacing topically administered ocular formulations, due to their high oxygen permeability [1] allowing for extended wear and potential for targeted delivery to the corneal surface [2]. 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.

Materials and 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 weights (MW) and concentrations and PVP (10 kDa) of different concentrations were used as 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 range of 400-750 nm. Drug release was monitored and quantified by UV spectroscopy.

Results:

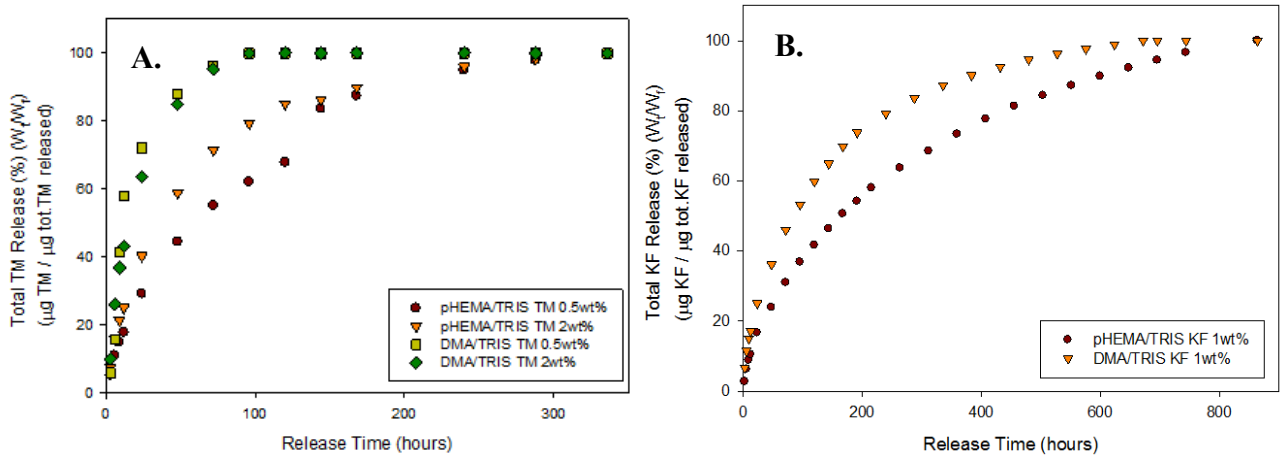

Figure 1: A. Timolol maleate and **B.** Ketotifen fumarate release kinetics of pHEMA/TRIS and DMA/TRIS hydrogels. Data are shown as mean (±SD) with n=4.

Discussion:

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 9 day period for pHEMA/TRIS SH. However, KF release lasted 24 days in DMA/TRIS SH and 36 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, possibly 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.

Conclusions:

The development of SH 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.

References:

1. Kunzler, J.F., Silicone Hydrogels for Contact Lens Application, *Trends in Polymer Science*, Elsevier. (1996); 52-59.
2. Peng, C.C., Chauhan A., Extended cyclosporine delivery by silicone–hydrogel contact lenses, *Journal of Controlled Release* (2011); 154.3: 267-274.