Coefficient of Friction Between Carboxymethylated Hyaluronic Acid-Based Polymer Films and the Ocular Surface

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Submitted: June 16, 2017
Accepted: November 2, 2017
Citation: Colter J, Wirostko B, Coats B. Coefficient of friction between carboxymethylated hyaluronic acid-based polymer films and the ocular surface. Invest Ophthalmol Vis Sci. 2017;58:6166–6174. DOI:10.1167/iovs.17-22414

Biodegradable films using a carboxymethylated, hyaluronic acid–based polymer (CMHA-S; Jade Therapeutics, Salt Lake City, UT, USA) are proving to be a safe and an effective means of local drug delivery for treatment of ophthalmic conditions.1–4

Previous studies have shown that careful control of the surface interaction of the film with the eye is critical for improved retention.

PURPOSE. Hyaluronic acid–based polymer films are emerging as drug-delivery vehicles for local and continuous drug administration to the eye. The highly lubricating hyaluronic acid increases comfort, but displaces films from the eye, reducing drug exposure and efficacy. Previous studies have shown that careful control of the surface interaction of the film with the eye is critical for improved retention.

METHODS. In this study, the frictional interaction of a carboxymethylated, hyaluronic acid–based polymer (CMHA-S) with and without methylcellulose was quantified against ovine and human sclera at three axial loads (0.3, 0.5, and 0.7 N) and four sliding velocities (0.3, 1.0, 10, and 30 mm/s).

RESULTS. Static coefficients of friction significantly increased with rate (P < 0.005), ranging between 0.18 ± 0.08 and 0.46 ± 0.13 for 0.3 to 30 mm/s, respectively. Friction became more rate-dependent when methylcellulose was added to CMHA-S. Kinetic coefficient of friction was not affected by rate, and averaged 0.15 ± 0.1. Methylcellulose increased CMHA-S static and kinetic friction by 60% and 80%, respectively, but was also prone to wear during testing.

CONCLUSIONS. These data suggest that methylcellulose can be used to create a friction differential on the film, but a potentially increased degradation rate with the methylcellulose must be considered in the design.

Keywords: ophthalmology, drug delivery, hydrogel, tribo-rheometry, biotribology

Biodgradable films using a carboxymethylated, hyaluronic acid–based polymer (CMHA-S; Jade Therapeutics, Salt Lake City, Utah, United States) are proving to be a safe and an effective means of local drug delivery for treatment of ophthalmic conditions.1–4

One existing challenge with the development of CMHA-S films for clinical use is its inability to stay on the eye in the lower fornix for extended periods of time. This limited retention hinders drug treatment and healing capacity of the film for use in ophthalmic conditions.

Computational simulations of the films have indicated that displacement of the CMHA-S films from the eye is dependent on the surface and friction interactions between the film and the eye.5 Most notably, improved retention required at least a 1.5 times greater friction interaction of the film with the eyelid than with the globe. Several methods exist to selectively increase the coefficient of friction on one side of the CMHA-S film, including micropatterning, surface roughening, or layering a second material into the polymer. Micropatterning and/or surface roughening would require careful consideration of manufacturing challenges, and may lose effectiveness with hydrogel swelling or degradation. Conversely, material layering is a relatively straightforward process and the effect of the new material would be maintained during swelling. A good candidate for this second material is methylcellulose. Methylcellulose, a polymer chemically modified from cellulose, has reported bioadhesive capabilities6,7 and can be easily added into CMHA-S prior to curing. However, the frictional interactions of CMHA-S and methylcellulose with the eye have never been measured. Therefore, it will be important to quantify the frictional properties of the CMHA-S film with and without methylcellulose to determine if an adequate increase in friction can be achieved using a layered material approach.

Many techniques have been developed to quantify the coefficients of friction of hydrogel-based contact lenses in the eye. Roba et al.8 created a consistent and physiologically-relevant in vitro test setup to measure the coefficient of friction of a wide range of contact lenses against mucin-coated glass. The reported range of coefficient of friction values was 0.02 to 0.5. Using a glass slide resulted in consistent protein adsorption onto the glass, but this study did not take into account the unique surface morphology or the nonlinear and time-dependent material properties of soft ocular tissues. More recently, researchers have tested the coefficient of friction of hydrogel-based contact lenses against a human corneal interface. They report coefficients of friction ranging between 0.1 and 0.6.9,10 The difference in values between the studies indicates that using a realistic interaction surface, such as the cornea or sclera is important to obtaining realistic values.

The frictional qualities of hydrogel polymers are dependent on their material characteristics, such as molecular structure and water content. Liu et al.11 reported a coefficient of friction range of 0.05 to 0.3 for polyacrylic acid hydrogels against a glass
sphere, and found the coefficient of friction decreased in hydrogels with higher water content. Higher values (0.3–0.9) were reported for polyvinyl alcohol hydrogel formulations. Therefore, any friction testing of hydrogel polymers must be performed in the fully hydrated state of the polymer.

Previously, researchers have used a rotational test method to test the coefficients of friction of cartilage-on-cartilage and cornea-contact lens interfaces. Typically, tribometers are used to quantify the coefficients of friction; however, rheometers have also proven to be sufficient for tribometric experiments as the experiments can be performed under various loading conditions and precise environmental controls that are unique to rheometers.

In this study, we modified and validated a stress- and rate-controlled rheometer with custom fixtures designed to quantify the coefficient of friction of CMHA-S on the eye. Specifically, the objectives of this research were to (1) quantify the coefficient of friction of the CMHA-S polymer film with the sclera at a range of sliding velocities representative of eyelid and globe movement in the eye, and (2) compare the effects of methylcellulose on the friction of CMHA-S. These data will be used to inform innovative multilayered designs to improve retention of hyaluronic acid–based hydrogel films in the eye.

METHODS

Materials

The coefficient of friction between sclera and CMHAS was quantified for three biointerfaces: ovine sclera and CMHAS (n = 7), ovine sclera and CMHAS with methylcellulose (n = 5), and human sclera and CMHAS (n = 8). Dried CMHAS film sheets with and without methylcellulose were received from Jade Therapeutics. The methylcellulose was added into the CMHAS solution before the crosslinking agent of poly(ethylene glycol) diacrylate (PEGDA) was added. The dried sheets were cut into 1 × 1-cm strips and rehydrated with PBS until fully swelled.

Adult sheep eyes (N = 5) were donated by the Neonatal Chronic Lung Disease and Development Lab (Kurt Albertine, University of Utah), and stored en bloc in PBS until testing (<5-hours postmortem). At the time of testing, sclera was dissected from the eye, and an annulus punch (outer radius R_o = 4 mm, and inner radius R_i = 2 mm) was taken from anterior sclera. One to four samples were acquired per eye. Adult human eyes (N = 4, aged 30–60 years) were collected from the Utah Lions Eye Bank (Murray, UT, USA) within 24-hours postmortem and placed in PBS. The human eyes were prepared similarly to the sheep eye, and 1 to 3 annulus samples were acquired from each eye. All testing with human sclera occurred within 50 hours of death.

Blink Tears Lubricating Eye Drops (Abbott Laboratories, Inc., Abbott Park, IL, USA) was selected as the lubrication fluid as its formulation is an appropriate approximation of the tear fluid. Its active ingredient is polyethylene glycol, which mimics the lubricating and viscoelastic properties of mucin in tear fluid. Sodium hyaluronate, a derivative of hyaluronic acid, exists in the solution (<0.4%) and is thought to increase tear film stability by approximating the flow and deformation properties of the tear aqueous layer. Rate-dependent viscosity of Blink Tears was measured using cone and plate geometry on a DHR-2 rheometer (TA Instruments, New Castle, DE, USA). Shear thinning of the lubrication fluid was observed (n = 4), with a zero-shear viscosity of 16.72 ± 0.08 mPa.s, and a high-shear viscosity of 10.10 ± 0.06 mPa.s (Fig. 1). A study by Tiffany quantified the viscosity of human tears from three subjects as a function of shear rate (2–160 s^-1). Shear thinning was reported similar to our lubricant measurements, but the viscosity ranged 5 mPa/s for the lowest shear rate and fell to 1.5 mPa/s at the highest shear rate. This suggests that the lubricant used in this study replicates the non-Newtonian properties of human tears, but has slightly higher viscosities.

Tribo-Rheometry Device and Test Setup

The tribo-rheometry device was designed based on the test setup used by Morrison et al. to measure the coefficients of friction of contact lenses with the eyelid and cornea. Custom top and bottom attachment pieces were designed and manufactured to modify an AR-G2 stress- and rate-controlled rheometer into a tribo-rheometer (Fig. 2; TA Instruments). The AR-G2 has a torque sensor resolution of 0.1 μN.m, and a load cell range from 0.005 to 50 N. It is able to apply an angular velocity while simultaneously enforcing a constant normal load (within a prescribed tolerance window), and measure torque resistance due to the relative motion between articulating surfaces.

The sclera annulus was affixed with cyanoacrylate adhesive to the upper rheometer head. The CMHAS hydrogel film was sandwiched between a rubber washer and neoprene sheet using a custom lower grip fixture. The top of the grip fixture was carefully threaded onto the bottom piece in a manner that did not tear the hydrogel film or trap air bubbles underneath. The grip fixture was affixed to the AR-G2 using a keyhole slot that aligned all the components concentrically.

Friction Test Protocol

After the hydrogel film samples were mounted in the testing system, the lubrication fluid was applied to the reservoir of the grip fixture until the hydrogel was submerged. Before each test, the inertia of the rheometer head was calibrated, the axial load was zeroed, and the gap between the sclera and hydrogel was zeroed.

The test protocol was carried out at axial loads of 0.3, 0.5, and 0.7 N. A ±0.1-N tolerance was allowed for each load. Using an assumed contact area of 37.7 mm² (π(R_i^2 − R_o^2)), normal pressures at each load were calculated to range from 8 to 18 kPa during the duration of the test. This is similar to the
reported range of physiological pressures on the eye during blinking (1–15 kPa).\textsuperscript{21–25}

For each axial load (starting at 0.3 N and incrementing upward), four revolutions in each positive and negative directions were applied at increasing effective sliding velocities, $v_{\text{eff}}$, of 0.3, 1.0, 10.0, and 30.0 mm/s, with a 12-second relaxation time between each set of four revolutions. Effective sliding velocities were selected from reported eyelid blink speeds,\textsuperscript{24} and are related to angular frequencies, $\omega$, by $v_{\text{eff}} = \omega R_{\text{eff}}$, where $R_{\text{eff}}$ is the effective radius equal to $2/3\left[(R_o^3 - R_i^3) / (R_o^2 - R_i^2)\right]$. A relaxation time of 12 seconds was selected to match other studies measuring friction of hydrogel-based contact lenses against the cornea.\textsuperscript{9,14} A fast sampling method was used that acquires data on a logarithmic time scale (up to a 2-kHz sampling rate) over each velocity step, and allows for the static coefficient of friction to be captured at the step onset. Every friction test was carried out on a new scleral tissue annulus and CMHA-S film sample.

**Tribo-Rheometry Test Validation**

The synthetic material polytetrafluoroethylene (PTFE), commonly known as Teflon, was selected to validate the accuracy of the custom tribo-rheometry device and testing protocol. PTFE was chosen because it has a well-known and reproducible coefficient of friction with a similar order of magnitude to the anticipated CMHA-S friction values. Teflon-on-Teflon kinetic coefficient of friction is reported to be 0.04, and the expected CMHA-S values were between 0.02 and 0.20. Therefore, validating the tribo-rheometer test device on Teflon surfaces with a low-magnitude of friction would validate the ability of the system to capture the lower limits of the torque sensor (0.1 $\mu$Nm).

For the validation testing, an annulus sample (outer radius $R_o = 4$ mm, and inner radius $R_i = 2$ mm) and a circle with larger radius ($R = 15$ mm) were punched out of a Teflon sheet ($n = 3$). The annulus was glued with cyanoacrylate adhesive to the rheometer head, and the circular sheet was held in place in the grip fixture. After the two Teflon surfaces were aligned concentrically and placed in contact with each other, the test protocol described in the Friction Test Protocol section above was applied. The entire protocol was performed for positive sliding velocities only.

**Data Analysis**

**Static Coefficient of Friction.** A static coefficient of friction ($\mu_{\text{static}}$), which represents the friction between two nonmoving surfaces, was calculated by $\tau_{\text{static}} / (R_{\text{eff}} \times N)$, where $\tau_{\text{static}}$ was found to be the maximum torque measured within the first 10° of rotation, $N$ was the instantaneously measured axial load, and $R_{\text{eff}}$ was the effective radius as defined in the Friction Test Protocol section above.\textsuperscript{25} Another static coefficient of friction ($\mu_{\text{static,eq}}$) was calculated by using the equalized axial load, $N_{\text{eq}}$, instead of the instantaneous load. $N_{\text{eq}}$ was defined as the axial load reading after the contacting surfaces had undergone stress-relaxation for 12 seconds.

Despite inertial calibration prior to each test, an increasing inertial effect due to the weight of the rheometer head was observed within the first 0.1 seconds of test time, and with increasing $v_{\text{eff}}$. For the slowest two velocities, $\tau_{\text{static}}$ occurred after the inertial effect, and were easily identifiable. However, the inertial effect provided challenges in extracting $\tau_{\text{static}}$ for the two faster velocities (Fig. 3). To approximate $\mu_{\text{static}}$ at these velocities, an average inertial curve was produced for each sliding velocity and was subtracted from the raw torque data. The inertial curve was produced by running the test without specimens or contact between the upper and lower fixtures of the device. To correct for inertial ringing, a low-pass finite impulse response filter was applied to the subtracted torque traces. A representative example of the original and corrected torque data can be seen for each tested velocity in Figure 4.

**Kinetic Coefficient of Friction.** Two kinetic coefficients of friction ($\mu_{\text{kinetic}}, \mu_{\text{kinetic,eq}}$) were calculated to observe the resistance of the sclera-CMHA-S biointerface to steady-state motion. The first friction coefficient was calculated by $\mu_{\text{kinetic}} = \tau / (R_{\text{eff}} \times N)$, where $\tau$ and $N$ were the instantaneous torque and axial load measurements from the rheometer. The second kinetic coefficient was calculated by $\mu_{\text{kinetic,eq}} = \tau / (R_{\text{eff}} \times N_{\text{eq}})$, using the equalized axial load, $N_{\text{eq}}$. Average kinetic
coefficients of friction were calculated from the last two revolutions of the test.

**Statistical Analysis.** All coefficients of friction are reported as the mean ± SD from the mean for each sliding velocity, \( v_{\text{eff}} \). Statistics were performed using JMP software (v11.0.0; SAS Institute, Inc., Cary, NC, USA). Teflon-on-Teflon tests were said to be significantly different from the validation parameter if 0.04 was not within the 95% confidence interval of the tests. Significant differences between CMHA-S with and without methylcellulose and the effects of \( v_{\text{eff}} \) were evaluated using a 2-way ANOVA with repeated measures. This statistical test was also used to identify significant effects of CMHA-S against human and ovine sclera with rate. A significance level of \( P < 0.05 \) was used for all analyses.

**RESULTS**

**Tribo-Rheometry Test Validation**

The results of the Teflon-on-Teflon tribological measurements showed good validation of the custom tribo-rheometry test setup (Fig. 5). For 0.3- and 1.0-mm/s sliding velocities, coefficients of friction were validated with the largest discrepancy being only 0.01 higher than the expected value of 0.04, and all confidence intervals including 0.04. For faster sliding velocities (10 and 30 mm/s), \( \mu_{\text{static}} \) and \( \mu_{\text{static, Neq}} \) were found to be higher than the expected value. The largest error, which was 0.017 higher than 0.04, was \( \mu_{\text{static, Neq}} \) at 10 mm/s. This was caused by a single data point that had a much higher measured torque than the other specimens. No specific reason was identified for the increased value, so it was kept in the data set. Small deviations of \( \mu_{\text{kinetic}} \) and \( \mu_{\text{kinetic, Neq}} \) from 0.04 were due to minor imperfections in the surface alignment, which

![Figure 3](http://arvojournals.org/)  
**FIGURE 3.** Average inertial effects found within the first 0.1 seconds of test time for each positive tested velocity (0.3, 1.0, 10, and 30 mm/s). As velocity increases, the inertial amplitude also increases.

![Figure 4](http://arvojournals.org/)  
**FIGURE 4.** Inertial effects to the torque curves are shown for each positive tested velocity (solid line). These inertial effects are damped out of the torque curve (×) so that static coefficient of friction can be observed.
resulted in inconsistent contact and spikes in the normal load readings, especially for faster velocities.

**CMHA-S Film Static Friction**

As expected, average torque for both $\tau_{\text{static}}$ and $\tau_{\text{kinetic}}$ increased as the applied load increased (Fig. 6). Occasionally, the CMHA-S film tore during the test protocol. When this happened, the step at which the film tore and all consecutive velocity steps were eliminated from analysis.

There was no observable difference between $\mu_{\text{static}}$ and $\mu_{\text{static,Neq}}$ as the instantaneous axial load measured at $\tau_{\text{static}}$ was very similar to the equalized axial load measured after a 12-second stress-relaxation period (Fig. 7). For ovine sclera, static coefficients of friction significantly increased with sliding velocity ($P < 0.003$). Specifically, $\mu_{\text{static}}$ increased from $0.18 \pm 0.08$ to $0.46 \pm 0.13$ and from $0.25 \pm 0.14$ to $0.73 \pm 0.17$ for CMHA-S and CMHA-S with methylcellulose, respectively. There was also a significant interaction effect between rate and CMHA-S material ($P = 0.0014$). This is because $\mu_{\text{static}}$ of CMHA-S with methylcellulose was closer to $\mu_{\text{static}}$ of CMHA-S at the slowest velocity (39% increased), but differed at quicker velocities (51%-107% increased). CMHA-S against human sclera was also rate dependent and not significantly different from CMHA-S tested against ovine sclera.

**CMHA-S Film Kinetic Friction**

Instantaneous normal load readings oscillated around the tolerance window throughout the test; therefore, calculations for $\mu_{\text{kinetic}}$ and $\mu_{\text{kinetic,Neq}}$ produced different results for kinetic friction (Fig. 8). For $\mu_{\text{kinetic}}$ calculations, CMHA-S was on average $0.12 \pm 0.06$ for all sliding velocities, while CMHA-S with methylcellulose ranged from $0.15 \pm 0.06$ to $0.32 \pm 0.36$, and peaked at a sliding velocity of 1 mm/s. Normal loads that exceeded the upper enforced load limit caused calculations for $\mu_{\text{kinetic}}$ to be artificially low. This was especially evident at faster sliding velocities for CMHA-S with methylcellulose, as $\mu_{\text{kinetic}}$ decreased at the two faster velocities. Sliding velocities of 1 and 30 mm/s were significantly different for CMHA-S with methylcellulose, and there was a significant material effect at 1 mm/s.

For all biointerfaces, $\mu_{\text{kinetic,Neq}}$ was constant with sliding velocity (Fig. 8B). Average $\mu_{\text{kinetic,Neq}}$ for CMHA-S was $0.15 \pm 0.1$, while average $\mu_{\text{kinetic,Neq}}$ for CMHA-S with methylcellulose was higher with a value of $0.27 \pm 0.12$. Although the addition of methylcellulose increased $\mu_{\text{kinetic,Neq}}$ on average by 80%, no statistically significant differences were found between the materials. One notable difference between the materials was the increased wear in CMHA-S with methylcellulose. This wear occurred during application of the 0.5-N normal load at higher velocities, resulting in very few data points evaluated at higher sliding velocities, and zero data points for a normal load of 0.7 N (Fig. 6). CMHA-S against human sclera had kinetic coefficients of friction that were also constant with velocity. No significant differences were found between CMHA-S against human and ovine sclera.

**DISCUSSION**

The objective of this study was to measure the coefficients of friction of CMHA-S films with and without methylcellulose against sclera for the purpose of offering insight into designs to improve retention of hydrogel films in the eye. The static coefficients of friction of the CMHA-S films significantly increased with sliding velocity. This rate dependence is likely due to the viscoelastic adhesion properties of the lubricant.
and/or the viscoelastic mechanical properties of the CMHA-S films and sclera. Static friction is defined by a critical shear that is required to initiate sliding between the two surfaces. This point is affected by the amount of overlap of surface asperities, and the stiffness of these asperities to resist shearing. Thus, at the onset of shearing, the overlapping asperities undergo a time-dependent relaxation suggesting that the critical shear, and also the static coefficient of friction, is dependent on rate. The inability of the lubricant to displace quickly at high rates would increase the rate dependence further. The differences in the viscoelastic properties of CMHA-S with and without methylcellulose likely explain why the materials were not equally affected by rate. Material characterizations of both materials in our lab have shown that CMHA-S with methylcellulose has a slower rate of stress relaxation than CMHA-S. Therefore, the stress and resistance to shearing of CMHA-S with methylcellulose is more time dependent, and will be more strongly affected by sliding rate.

A limitation of the static coefficient of friction measurements for the two quicker sliding velocities is the large rheometer inertial effects seen within the first 0.1 second of the test. Subtracting out the inertial effects from the raw torque measurements worked well for 0.3- and 1.0-mm/s sliding velocities, but overestimated \( \mu_{\text{static}} \) and \( \mu_{\text{static,Neq}} \) for Teflon-on-Teflon by 0.007 to 0.017 at 10- and 30-mm/s sliding velocities. The coefficients of friction of the CMHA-S films were an order of magnitude higher than the Teflon; therefore, the inertial effects will be smaller. This suggests that the CMHA-S static coefficients of friction measured in this study are less affected by the error. In fact, trends and ranges of static coefficients of friction reported in the literature for cornea and hydrogel contact lens biointerfaces\(^9,10,14\) are similar to those reported for CMHA-S in this study. Thus, we believe the measured static
coefficients of friction of CMHA-S films are realistic approximations, despite the errors seen during validation.

Kinetic coefficients of friction were mostly constant across velocities; however, some discrepancy to this finding was observed in the two different calculations for kinetic coefficient of friction in CMHA-S with methylcellulose. Throughout the test, normal load readings were challenging to maintain within the enforced load limits, especially at higher rates. At the two higher velocities, the axial load feedback control was slower than the sampling rate. This caused the axial load to overcorrect or extend above the enforced load limits. Therefore, \( \mu_{\text{kinetic}} \), which was inversely related to instantaneous load, \( N \), saw erroneously low values during rotation. An example of this is seen in Figure 8A, where \( \mu_{\text{kinetic}} \) of CMHA-S with methylcellulose drastically decreases at sliding velocities of 10 and 30 mm/s. These erroneous values caused average \( \mu_{\text{kinetic}} \) calculations to be skewed from the majority of the data. Consequently, \( \mu_{\text{kinetic}} \) tended to be lower than \( \mu_{\text{kinetic, Neq}} \) which was calculated instead with an equalized load, \( N_{\text{eq}} \), recorded after 12 seconds of relaxation. Based on these observations and the results of the validation studies, it is concluded that \( \mu_{\text{kinetic, Neq}} \) calculations are more accurate. Further, the differences between \( \mu_{\text{kinetic, Neq}} \) and \( \mu_{\text{kinetic}} \) in this study mirror the differences that are seen by Schmidt and Sah. They also concluded \( \mu_{\text{kinetic, Neq}} \) more accurately measured the frictional response when fluid pressurization effects are present in a boundary lubrication method.

CMHA-S films with methylcellulose had 60% to 80% higher coefficients of friction than CMHA-S films without methylcellulose. This increase was not statistically significant, but CMHA-S with methylcellulose films also experienced notable wear during testing at higher loads and velocities. The increased friction and wear of the CMHA-S films with methylcellulose may be due to its low stiffness compared with the stiffness of the unmodified CMHA-S film material. Gong et al. developed a surface repulsion model to investigate mechanisms of frictional properties of various hydrogels. According to their model, it was found that a lower elastic moduli of the hydrogels resulted in higher predictions of friction. We have experimentally measured the elastic modulus of CMHA-S with methylcellulose and found it to be 94% lower than the elastic modulus of CMHA-S. This lower modulus decreases the ability of the surface asperities of the CMHA-S with methylcellulose to support the applied loads, thus bringing more asperities into contact. Increased asperity contact would describe the increased friction observed in the films with methylcellulose. Furthermore, the asperities of the CMHA-S with methylcellulose would be
less resistant to shear stress due to the lower modulus, and increase the wear rate as observed in this study.

The presence of wear supports that CMHA-S film friction was measured with a boundary lubrication regime versus a hydrodynamic regime. Boundary lubrication, by definition, is a mode of thin film lubrication that coats and adheres to the asperities in order to reduce penetration of the opposing surface asperities. This results in reduced shear strength at the interface. Boundary lubricants are effective in reducing asperity penetration, but they are slow to recover from displacement. Specifically, at quick sliding velocities, the regeneration of the lubrication monolayer is not rapid enough to replenish the fluid film over the asperities, therefore increasing susceptibility to wear. This may have exacerbated the wear seen at higher sliding velocities.

The increase in friction from the addition of methylcellulose to CMHA-S suggests that this may be a viable method to improve retention of hydrogel films at the ocular surface and in the inferior fornices. However, the observed wear of CMHA-S with methylcellulose must be carefully considered in design. CMHA-S with methylcellulose substantially wore down at 0.5 N at 30 mm/s. This is representative of the physiological pressure and sliding velocity seen on the eye during blinking and normal eye movement, and suggests that the formulation with methylcellulose may wear rapidly following placement into the eye. However, if the film is designed such that the methylcellulose is placed only in contact with the inner eyelid, the relative motion between the eyelid and CMHA-S with methylcellulose would be reduced, and the rate of degradation of CMHA-S with methylcellulose may be slower in vivo than what was seen in the experimental tests. Literature suggests that wear may also be reduced up to 60% by increasing the crosslinking density of hydrogel polymer. The tribological and wear effects due to changing crosslinking density of CMHA-S with methylcellulose could be evaluated in future work.

The boundary lubricant also plays a role in the friction and wear rate of CMHA-S films. Tear film is a highly-ordered and surface-tethered fluid, containing mucins and lubricin glycoproteins that effectively reduce shear stresses secondary to eyelid blinking. Hyaluronic acid-based drops, which are a standard of care treatment for dry eye in parts of the world, help solve some of deficiencies in normal boundary lubrication that can occur at the ocular surface. Because hyaluronic acid-based drops are effective for increasing lubrication for the treatment of dry eye, we assumed the use of hyaluronic acid-based lubricating eye drops was a sufficient representation of the tear film in the eye. The lubricant exhibited non-Newtonian behavior during viscosity testing, similar to human tears, but had slightly higher viscosity magnitudes. Film degradation during testing suggests the load bearing was carried by the surface asperities and not the lubrication fluid. This is indicative of a boundary lubrication regime. In this regime, the coefficient of friction measurements of the films would not be dependent on flow properties of the lubrication. Therefore, we believe the slight measured differences in viscosity magnitude between the lubricant and human tears will not change the tribological behavior of CMHA-S measured in this study.

The sliding velocities at which the coefficients of friction were experimentally measured are representative of those reported for blinking, but much slower than saccadic eye movements, which can reach velocities up to 140 mm/s. Therefore, the question arises how the coefficients of friction for CMHA-S will change up to velocities of 140 mm/s, and how to best approximate these values. Extrapolation of $\mu_{\text{static}}$ values up to sliding velocities of 140 mm/s would push friction coefficients unrealistically close to a value of one, and is therefore not appropriate. Tribological phenomenon between lubricated surfaces is traditionally described by the Stribeck curve, in which the coefficient of friction is categorized into lubrication regimes depending on the sliding parameters such as load, sliding speed, and lubricant viscosity. However, hydrogel materials and ocular lubrication are reported to have tribological behavior that is qualitatively different than the Stribeck curve. Specifically, the parameters at which hydrogel materials transition from a boundary lubrication regime to a mixed lubrication regime are not well defined. Therefore, it is unclear how the kinetic coefficient of friction for the CMHA-S films will change for sliding speeds up to 140 mm/s, and answers will only be obtained through further experimentation.

One final consideration is how the CMHA-S films will uphold in injured or diseased eyes, in which these films are intended for use. In these eyes, it is hypothesized that the harsh, inflammation-ridden environment with elevated catabolases and enzymes will increase the degradation rate of the CMHA-S polymer. It is unknown whether this altered environment will uniformly degrade CMHA-S formulations with and without methylcellulose. Future work will need to evaluate the likely changes in degradation rate, and friction and wear properties of each CMHA-S formulation while in the presence of proinflammatory conditions.

**Conclusions**

The static coefficient of friction of the CMHA-S films with the sclera was 0.18 ± 0.08 and increased with rate to 0.46 ± 0.13. The addition of methylcellulose to CMHA-S increased the static coefficient of friction by 60% and also increased the rate dependence. Kinetic coefficient of friction was 0.15 ± 0.1 and was not rate dependent, and CMHA-S films with methylcellulose had 80% higher kinetic coefficient of friction for all sliding velocities. While the CMHA-S with methylcellulose yielded higher coefficients of friction, it was prone to wear suggesting that CMHA-S with methylcellulose may degrade more rapidly under the normal physiological conditions seen in the eye. However, this degradation may be negligible or delayed depending on the placement of the film in the fornix, or with additional crosslinking of the polymer.

**Acknowledgments**

The authors thank Jules Magda, PhD, (Department of Chemical Engineering, University of Utah, UT, USA) for his expertise and assistance in measuring the non-Newtonian flow properties of Blink Tears Lubricating Eye Drops. Supported by grants from the National Science Foundation under award number IIP-1430921 (Alexandria, VA, USA), and the Department of Defense under award number W81XWH-14-C-0025 (Washington, D.C., USA). Jade Therapeutics, Inc. is a wholly owned subsidiary of EyeGate Pharmaceuticals, Inc.

Disclosure: **J. Colter**, EyeGate Pharmaceuticals (E, R, S); **B. Wirostko**, EyeGate Pharmaceuticals (E, I), P; **B. Coats**, EyeGate Pharmaceuticals (F)

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