Tribology International 89 (2015) 27–33

Contents lists available at ScienceDirect

Tribology International

journal homepage: www.elsevier.com/locate/triboint

In vitro friction testing of contact lenses and human ocular tissues: Effect of proteoglycan 4 (PRG4)

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ARTICLE INFO

Article history:
Received 15 June 2014
Received in revised form
25 September 2014
Accepted 26 November 2014
Available online 4 December 2014

Keywords:
Biotribology
Contact lens
PRG4

ABSTRACT

Contact lens friction was recently shown to correlate with *in vivo* comfort, with lower friction lenses providing improved comfort. Proteoglycan 4 (PRG4) is a recently discovered ocular surface boundary lubricant. The objectives of this study were to measure the friction of commercially available silicone hydrogel (SiHy) contact lenses against human cornea and eyelid tissues, and evaluate the ability of PRG4 to lubricate, and adhere to, SiHy contact lenses. The *in vitro* friction test employed here effectively measured and distinguished the SiHy contact lens friction coefficients against human eyelid and cornea tissues, and PRG4 functioned as an effective boundary lubricant.

1. Introduction

Approximately 135 million people wear contact lens worldwide, and among them, approximately 50% complain of dry eyes, particularly at the end of the day [1]. The primary reasons for contact lens intolerance, resulting in 25% of wearers discontinuing use and 26% decreasing the frequency and duration of use, are irritation, discomfort and dryness [2]. The causes of dryness and discomfort during contact lens wear are complex, multi-factorial, and remain to be fully appreciated.

Modern soft contact lenses are made from hydrogels, which are highly hydrated 3D polymer structures. As oxygen transport has been widely shown to impact physiological performance [3–5], silicone hydrogel (SiHy) materials were developed. SiHy materials include the addition of a siloxane macromer that greatly increases material oxygen permeability [6]. Since discomfort is the primary reason for discontinuation of lens wear, a better understanding of the factors that contribute to comfort may provide insight into the design of better lenses and dry eye treatments. Interestingly, despite the introduction of these new materials and wetting agents that have been incorporated into and released from them, discomfort levels remain broadly similar to 10 years ago [7]. This suggests that current material variables being used to guide the development of new lenses may not correlate strongly with *in vivo* comfort.

The Tear Film & Ocular Surface Society's recent report of the impact of contact materials, design and solutions on contact lens discomfort [8] reported that friction is currently the only material variable to correlate well with *in vivo* comfort scores, based upon data from two studies [9,10]. This work strongly suggests that superior frictional properties of lens materials are a key parameter that significantly correlates to contact lens comfort. Peer-reviewed contact lens coefficient of friction data from over 700 one-month wearing trials demonstrated significant correlations to both end of day comfort and 2-h mean comfort data [9]. Another group, using an alternative method of determining friction coefficients, demonstrated statistically significant relationships between the coefficient of friction of 5 soft contact lens materials and subjective data for insertion comfort, overall comfort, and end of day comfort from a database of clinical trials [10]. The clinical relevance of ocular surface friction and damage clinically is further supported by 74% of symptomatic wearers presenting with a condition termed "lid wiper epitheliopathy" (LWE) [11]. LWE is characterized by "wear marks" on the leading edge of the eyelid, and is possibly due to increased friction between the leading edge of the palpebral conjunctiva of the eyelid and a dry lens surface [11,12].

Currently, a number of SiHy lenses on the market employ a variety of strategies attempting to improve lubrication and enhance in-eye comfort. For example, Acuvue Oasys® (senofilcon A), includes a high molecular weight polyvinylpyrrolidone (PVP) monomer in the bulk material. Acuvue TruEye® (narafilcon A) is a daily disposable version of Acuvue Oasys® and has a similar composition that contains PVP. The recently available Dailies Total 1® (delefilcon A) lenses are made from a "bioinspired material" that has a ~5 μm

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http://dx.doi.org/10.1016/j.triboint.2014.11.022
0301-679X/

thick polymer brush layer of covalently linked hydrophilic monomers at its surface [13–18].

One potentially promising method of decreasing contact lens friction, and therefore possibly improving their *in vivo* comfort, is to employ natural lubricants found at the ocular surface. Proteoglycan 4 (PRG4), also known as lubricin, is a mucin-like glycoprotein that is present at the surfaces of articulating ocular tissues [19]. PRG4 has been shown to lubricate both human cornea – polydimethylsiloxane (PDMS) and human cornea – eyelid tribopairs in an *in vitro* test [19,20]. PRG4 is thought to function by physically adsorbing to surfaces *via* a hydrophobic interaction of its C-terminal domain and the surface [21], allowing its mucin domain, which is composed of chains of negatively charged sugars, to create a low friction "polymer brush-like" lubricant layer [22]. This layer is able to lubricate in the absence of a thick fluid film and has therefore been called a boundary lubricant. PRG4 is known to interact and lubricate synergistically with other molecules such as with the negatively charged polysaccharide polymer hyaluronan [19,20,23,24]. This is thought to occur through a non-covalent, entanglement [25]. It is possible that PRG4 may interact with ocular mucins in a similar way, though peer reviewed literature examining the nature of such an interaction does not currently exist. Considering these data, PRG4 is an ideal candidate for reducing ocular friction at the surface of a contact lens and possibly even maintaining low friction coefficients in the case of compromised tear films. PRG4 is not effective at all surfaces, since as a boundary lubricant it must be able to adhere to the surface in a functional confirmation. Surface force apparatus experiments have shown that PRG4 can in fact increase friction compared to saline against surfaces treated to be hydrophilic [25]. The friction reducing properties of PRG4 in a boundary mode of lubrication on commercially available contact lenses and human ocular tissues remain to be evaluated.

To determine the efficacy of ocular lubricants and novel contact lens materials, a method of determining the friction associated with these lenses and lubricants is needed. *In vitro* contact lens friction coefficients are a system parameter, and its measurement can be affected by the test system scale and contact area, surfaces, parameters (*e.g.* applied load and sliding velocity), and lubricants [20,26–33]. In the presence of a contact lens, a numerical fluid model estimated that the eyelid exerts pressures of 12–18 kPa for sliding speeds of 10–100 mm/s [34]. The *in vitro* test setup used previously by Morrison et al. [20] and Schmidt et al. [19] is one method that has proved useful in assessing friction of contact lens biomaterials and ocular surfaces. This macroscale test uses a rotational test setup to maintain a fixed area of contact, to prevent an entraining fluid film to enter between the articulating surfaces and therefore allow for a boundary mode of lubrication to be dominant, so that material surface properties can be assessed. This test setup uses human ocular tissues to allow for physiological interactions of natural lubricants, since PRG4 must be able to adhere to a surface to impart lubrication function [25], and employs physiologically relevant loads and articulating velocities. However, this test setup has yet to be employed to evaluate the lubricity of commercially available contact lenses, and the potential friction reducing effect of PRG4 on these lenses. The objectives of this study were therefore to:

(1) Measure the *in vitro* friction of commercially available SiHy contact lenses against human cornea and eyelid tissues.
(2) To evaluate the ability of PRG4 to lubricate, and adhere to, SiHy contact lenses.

2. Experimental

2.1. Materials

Human corneas (age: 45–79) were obtained from the Southern Alberta Lions Eye Banks. The corneas were stored in Optisol-GS at 4 °C and used within 2 weeks of harvest. Human eyelids (age: 80–91) were excised from fresh cadavers from the University of Calgary body donation program. Approval for use and appropriation of these tissues was obtained from the University of Calgary Conjoint Health Research Ethics Board. Two-weekly replaced SiHy contact lenses Acuvue Oasys® (senofilcon A) and daily disposable SiHy contact lenses Acuvue TruEye® (narafilcon A) and Alcon Dailies Total 1®, (delefilcon A) lenses were purchased. PDMS control samples were purchased as a 2-component kit (Sylgard 184, Dow Corning, Toronto, Canada) and a base to curing agent mass ratio of 10:1 was used.

PRG4 was obtained by purifying media conditioned by bovine articular cartilage explant culture, as described previously [20,35]. Purification was done using diethylaminoethyl cellulose anion exchange chromatography and centrifugal unit filtration. Purity was confirmed to be ~85% by SDS-PAGE and protein stain, and the concentration of the purified solution of PRG4 was determined by bicinchoninic acid (BCA) assay [36]. For the saline control in this study, Bausch and Lomb Saline Plus® (Bausch and Lomb, Rochester, NY, USA) was used. PRG4 was resuspended in this saline at a concentration of 300 μg/mL.

2.2. In vitro friction measurement: Test setup

The *in vitro* ocular friction tests used to evaluate the boundary mode friction of contact lenses, and friction reducing ability of PRG4, were adapted from previously described methods [19,20]. Tissue samples were mounted on a BOSE ELF3200 with axial and rotational actuators, and axial load and torque sensors (Fig. 1). In the case of a contact lens—cornea test, the resected cornea was fixed to the end of a semi-spherical silicone rubber plug (radius = 6 mm) by applying cyanoacrylate adhesive (superglue) to the sclera. A silicone rubber sleeve was fitted around the cornea-plug apparatus, which served to hold the lubricant fluid. This apparatus was then attached to the rotational actuator of the BOSE ELF3200, thus forming the bottom-articulating surface. A contact lens was thoroughly washed with saline to remove substance from the blister pack. An annulus (outer radius $r_o = 3.2$ mm, inner radius $r_i = 1.5$ mm) was punched from the contact lens and immediately glued to an annulus holder using cyanoacrylate adhesive. This annulus holder was then attached to the linear actuator, thus forming the upper-articulating surface. Upon articulation between the upper and lower sample, an annular contact area was formed. It is assumed that the contact area was a flat annulus *i.e.* outer radius $r_o = 3.2$ mm, inner radius $r_i = 1.5$ mm and that it remains stationary throughout rotation. In the case of an eyelid—contact lens test, the contact lens was washed with saline then fixed to the end of a semi-spherical silicone rubber plug (radius = 6 mm) by applying cyanoacrylate adhesive to the edge of the lens. A silicone rubber sleeve was fitted around the lens-plug apparatus to hold lubricant solutions. An annulus (outer radius $r_o = 3.2$ mm, inner radius $r_i = 1.5$ mm) was punched from an eyelid and glued to an annulus holder. This annulus holder was then attached to the linear actuator, thus forming the upper articulating surface.

2.3. In vitro friction measurement: Test protocol

After mounting the samples on the BOSE ELF 3200, 0.3 mL of saline control solution or a 300 μg/mL PRG4 solution was placed in the bath formed by the silicone rubber sleeve on the bottom holder to form a lubricant bath. The articulating surfaces were then allowed to equilibrate with the test lubricant for a minimum of 5 min. The tissue samples were brought into contact at three manually determined axial positions to correspond with axial loads of 0.3 ± 0.03, 0.5 ± 0.03, and 0.7 ± 0.03 N (normal pressures: 10.1–27.3 kPa based on an apparent contact area of 24.6 mm^2). Once in contact at a given axial position, a 12 s dwell time preceded four revolutions in both positive and negative directions at four different effective linear