

Effect of Contact Lens Solutions in Stabilizing the Activity of Tear Lysozyme

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Purpose: Interactions between tear proteins and the interfaces of contact lenses can be complex and can influence contact lens wear success. Tear proteins, including lysozyme, function to maintain the balance of ocular surface homeostasis, as evidenced by the effects of its conformation relative to stabilizing the tear film and its potential impact on corneal epithelial cells. Contact lens manufacturers include components in lens care and blister package solutions to help stabilize the tear film and preserve homeostasis. This in vitro study was performed to evaluate the ability of daily disposable contact lens package solutions to stabilize lysozyme and preserve its native conformation under denaturing conditions.

Methods: Lysozyme was added to contact lens solutions sampled from kalifilcon A, etafilcon A, senofilcon A, narafilecon A, nelfilcon A, verofilcon A, delefilcon A, somofilcon A, and stenfilcon A blister packages, then mixed with the protein denaturant sodium lauryl sulfate. Lysozyme activity was evaluated by adding test solutions to a suspension of *Micrococcus luteus*. Native lysozyme lyses the *Micrococcus luteus* cell wall, which decreases suspension turbidity. Stabilization of lysozyme activity was determined by comparing suspension turbidity before and after exposure to test solutions.

Results: Lysozyme stabilization was 90.7% for kalifilcon A solution, a statistically significant improvement ($p < 0.05$) compared to phosphate buffered saline (PBS, negative control). No significant improvement was observed with any other contact lens solution (all lysozyme stabilization $< 5.00\%$).

Conclusion: The representative tear protein lysozyme was significantly more stable in the novel kalifilcon A contact lens solution containing multiple moisturizers and osmoprotectants than in PBS or other daily disposable contact lens solutions. The lysozyme activity assay provides mechanistic evidence that the kalifilcon A contact lens solution can stabilize proteins under conditions that typically denature proteins, which may contribute to maintaining ocular surface homeostasis.

Keywords: kalifilcon A, silicone hydrogel, homeostasis, protein stabilization

Introduction

In biology, homeostasis is defined as,

the ability or tendency of the body or a cell to seek and maintain a condition of equilibrium - a stable internal environment - as it deals with external changes.¹

Ocular surface homeostasis is complex, as multiple cellular and anatomical constituents including cornea, conjunctiva, lacrimal glands, and tears must work together to maintain and restore a condition of equilibrium. The introduction of a contact lens (CL) onto the eye can represent a change that alters the equilibrium of the ocular surface.²

Tears cover the ocular surface not as a homogenous static film, but rather as a more complex, dynamic, layered construct. The tear film was traditionally modeled as a tri-layered film comprising the mucin layer in contact with the cornea, the central aqueous layer, and the lipid layer in contact with air,³ but it may be even more complex,⁴ both chemically and physically. A CL perturbs the natural tear film by splitting it into two distinct films that differ chemically and physically, the pre-lens (in contact with the lens and ambient air) and post-lens (in contact with the lens and cornea)

tear films.^{4,5} While the pre-lens film is reformed and replenished with each complete blink, the post-lens film is more stagnant, which can result in an osmolarity gradient between the anterior and posterior lens surfaces.⁶

Normal human tears comprise an aqueous solution of proteins (including mucins), enzymes, lipids, metabolites, and electrolytes that maintain osmolarity and pH.^{7,8} Lipidomic methods were used to identify over 600 lipids in human tears, metabolomic methods to identify 85 metabolites, and proteomic methods to identify 1543 proteins.⁴ Of the latter, 4 key proteins (lysozyme, lactoferrin, lipocalin, and secretory immunoglobulin A [sIgA]) are produced in relatively large amounts.⁷ Lipid-protein interactions play a role in the tear film lipid layer. Lysozyme and other lachrymal origin proteins contribute to tear film stability by adsorbing to and penetrating the tear film lipid layer, reducing surface tension.⁸ Mathematical modeling suggests that restructuring of the tear film upon blinking leads to incorporation of lysozyme (a hydrophilic protein) into the lipid film as inverse lipid micellar structures.⁹

The tear film serves as the eye's innate defense system, as well as performs other important functions, including lubrication and protection of the eye, and delivery of nutrients and growth factors to the corneal epithelium.¹⁰ Functions of major tear film components and their contributions to ocular surface homeostasis are described in the literature.¹¹ The lipid layer retards water evaporation and stabilizes the tear film at the air interface, primarily by reducing surface tension. Tear proteins in the aqueous layer perform various functions, including contributing to tear film stability and clearing microbial contamination at the ocular surface.

Interactions between tear proteins and the CLs can influence lens wear success. Upon contact with the tear film, a CL placed on eye rapidly sorbs proteins present within the tears.¹² Once sorbed, a protein can diffuse from the lens surface into the bulk, desorb back into the medium, or rearrange and change its conformation, becoming more tenaciously bound to the surface.¹² The composition of the protein layer adsorbed at the surface is dynamic, driven by the respective concentrations and surface affinities of the individual tear proteins, with the most abundant proteins adhering first, and those with lower surface affinity later displaced by those with higher affinity.¹³ Proteins sorbed on CLs can either support or disturb ocular surface homeostasis, depending upon the composition and nature of the protein layer. In general, conventional hydrogel CLs sorb more total protein than do silicone hydrogel CLs.^{14,15} The affinity of each individual tear protein for the lens surface is highly dependent upon lens material. Lysozyme is of particular interest due to its abundance in natural tears,³ its antimicrobial properties,^{3,16} and its tendency to sorb in high quantity on anionic lenses due to its positive charge.^{14,17} This protein represents a significant fraction of the total protein sorbed on many conventional poly(2-hydroxyethyl methacrylate) (pHEMA)-based hydrogel CLs and silicone hydrogel CLs;¹⁴ it accounts for up to 90% on average of the total protein deposited on clinically worn etafilcon A lenses,¹⁸ and up to 50% on balafilcon A lenses.¹⁵

Over the years, CL manufacturers have developed new lens materials and designs, as well as provided affordable, frequent replacement lens options to help reduce changes to the ocular surface, such as occur when tear film components accumulate on and within the lens. Protein deposits on CLs participate in lens fouling, and denatured proteins including lysozyme (along with other degraded proteins and lipids) may elicit an immune response,^{19–21} promoting the release of inflammatory cytokines that adversely affect human corneal epithelial cell (HCEC) viability.²² Several researchers proposed that preventing tight protein binding and denaturation, and preserving the native conformation (and thus activity) of proteins that deposit on lenses during wear should be a goal in CL development,^{14,23} as such CLs may be less likely to promote ocular inflammation and more likely to support ocular surface homeostasis.

Studies of lysozyme interaction with etafilcon A, an FDA Group IV material (high water, ionic) are illustrative, as this protein retains its activity once associated with this lens. Both in vitro^{12,16,24} and clinical^{23,25,26} studies report relatively high amounts of lysozyme sorbed on this material, the majority preserving its activity and presumably its native state, as disruption in protein conformation and structure alter protein function.²⁴ Thus, the total amount of protein sorbed on a lens is not predictive of lens discomfort.²³ Unlike etafilcon A, many silicone hydrogel CLs sorb relatively little total lysozyme, with much of it losing its biological activity, coinciding with a higher fraction of denatured lysozyme.¹⁴

With the goal of stabilizing tear proteins, CLs can be infused with isotonic buffered saline solution containing additional components to help maintain homeostasis. Numerous in vitro studies of the effects of contact lens multi-purpose solution (MPSs) upon protein in solution are published,^{19,27} as are the effects of MPSs^{25,28,29} and CL rewetting drops³⁰ upon clinically sorbed protein. In contrast, there exists little published literature describing the effects of daily

disposable CL blister package solutions upon proteins in general or lysozyme in particular. Therefore, the purpose of this study was to measure tear lysozyme stabilization in daily disposable CL blister package solutions under denaturing conditions to determine if any of the solutions can help maintain the protein in its native state.

Materials and Methods

Study Material

In this experiment, CL solutions were sampled from fifteen blister packages of each of nine different daily disposable CLs (Table 1). Variation in solution components can be observed in both legacy CLs, such as nelfilcon A and etafilcon A and more recently developed CLs such as verofilcon A, kalifilcon A, and somofilcon A, as disclosed in their respective package inserts.^{31–39} The nelfilcon A (Alcon, Ft. Worth, TX) solution contains hydroxypropyl methylcellulose (HPMC) and polyethylene glycol (PEG), as well as poloxamer 108; the delefilcon A and verofilcon A (Alcon) solutions contain copolymers of polyamidoamine and poly(acrylamide-acrylic) acid (PAO-PAAA); the kalifilcon A (Bausch & Lomb Incorporated, Rochester, NY) solution contains poloxamer 181, poloxamine 1107, glycerin, and erythritol; somofilcon A and stenfilcon A (CooperVision, Pleasanton, CA) solutions contain poloxamer 407 and polysorbate, respectively; the etafilcon A solution contains polyvinylpyrrolidone (PVP), while the narafilcon A and senofilcon A (Johnson & Johnson Vision Care, Inc., Jacksonville, FL) solutions contain methyl ether cellulose (MEC). The water-soluble phospholipid sodium coco PG dimonium chloride phosphate (Siltech, Toronto, Ontario, Canada) in phosphate buffered saline (PBS, Gibco – Thermo Fisher Scientific, Waltham, MA) was used as a positive control. Other materials used and were *Micrococcus luteus* (*M. luteus*, Sigma-Aldrich, St. Louis, MO), sodium lauryl sulfate (SLS, Fluka, Honeywell Research Chemicals, Morris Plains, NJ) denaturing agent, lysozyme (chicken egg white, Sigma), and an ultraviolet/visible spectrometer at 450 nm.

Table 1 Contact Lens Solutions Evaluated

Material	Manufacturer's Solution Description	Brand Name	Manufacturer
Nelfilcon A ³¹	Phosphate-acetate buffered saline with comfort additives hydroxy-propylmethyl cellulose (HPMC) and polyethylene glycol 400 (PEG 400) and poloxamer 108	Dailies Aqua Comfort Plus	Alcon (Ft. Worth, TX)
Delefilcon A ³²	Phosphate buffered saline solution (PBS) with approximately 0.3% of polymeric wetting agents consisting of copolymers of polyamidoamine and poly (acrylamide-acrylic) acid	Dailies Total1	
Verofilcon A ³³		Precision1	
Kalifilcon A ³⁴	Phosphate buffered saline solution with potassium chloride, poloxamine 1107, poloxamer 181, glycerin, and erythritol	Infuse	Bausch & Lomb Incorporated (Rochester, NY)
Somofilcon A ³⁵	Borate Buffered Saline Solution containing 0.005% w/v Poloxamer 407	Clariti-1 day	CooperVision (Pleasanton, CA)
Stenfilcon A ³⁶	Phosphate Buffered Saline Solution with Tween	MyDay	
Etafilcon A ³⁷	Buffered saline solution with povidone	1-day Acuvue MOIST with Lacreon	Johnson & Johnson Vision Care, Inc. (Jacksonville, FL)
Narafilcon A ³⁸	Buffered saline solution with methyl ether cellulose	1-day Acuvue TruEye with Hydraclear	
Senofilcon A ³⁹		Acuvue 1-day Oasys with HydraLuxe	

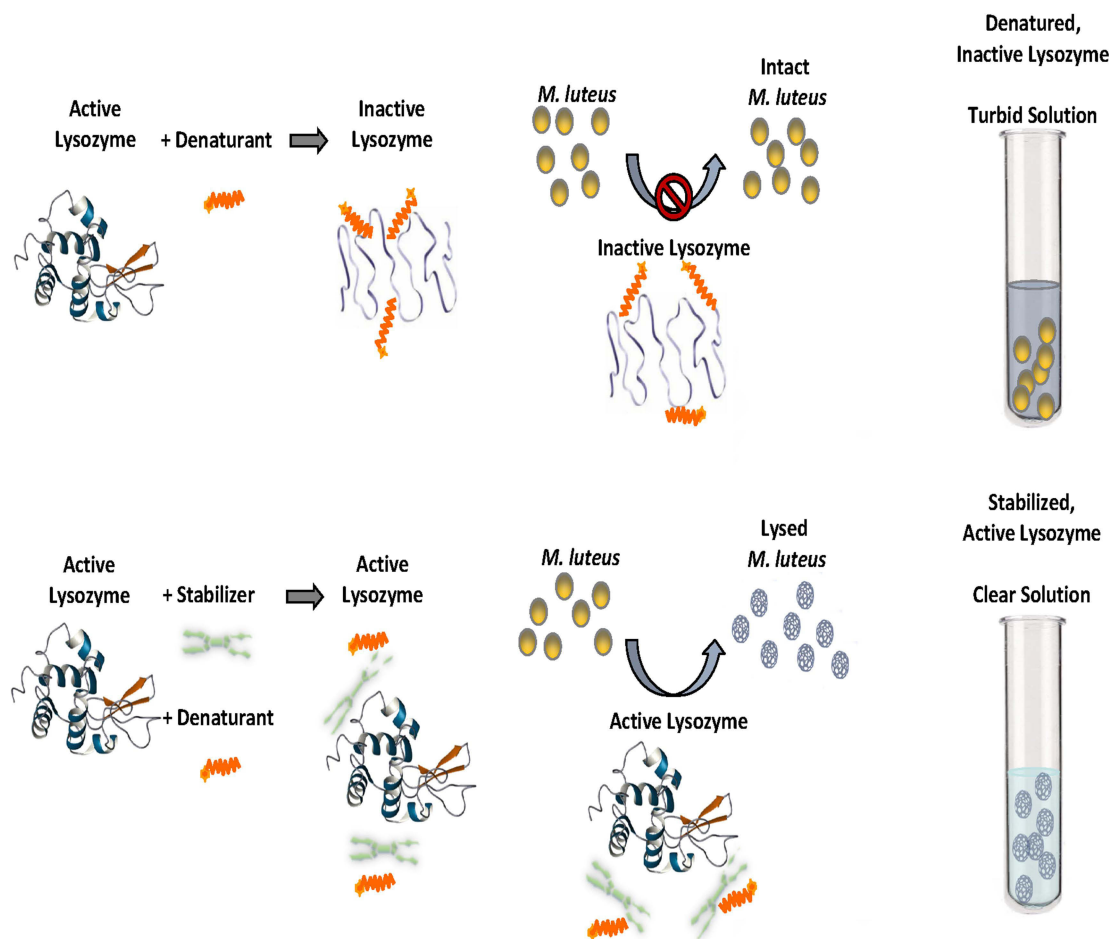


Figure 1 Lysozyme activity assay.

Notes: Active native lysozyme image courtesy of Biological Magnetic Resonance Data Bank (2020, October 7). BMRB Featured System: Lysozyme. <https://bmr.io/featuredSys/Lysozyme/>, used with permission. CC0 1.0 Universal (CC0 1.0) Public Domain Dedication.⁴²

Lysozyme Activity Assay

The assay is based on lysozyme's enzymatic cleavage of peptidoglycan, resulting in the digestion of the cell wall of *M. luteus* in a suspension. *M. luteus* is sensitive to active lysozyme and is highly susceptible to lysozyme-mediated killing. Native lysozyme attacks *M. luteus* cells, which decreases suspension turbidity as the cell walls are lysed by the enzyme.⁴⁰ The decrease in optical density (OD) is a relative indicator of enzymatic activity and can be measured by following the decrease in absorbance at 450nm (OD450) over time using a spectrophotometer. When the conformation of the lysozyme changes, the enzymatic activity decreases.⁴¹ Therefore, enzymatic activity against *M. luteus* was used to assess changes in the conformation of the lysozyme from the active native form to the inactive denatured form (Figure 1).

Experimental Procedure

A 20% solution of SLS detergent in distilled water and a 25mg/mL solution of lysozyme in PBS were prepared. A 0.03% *M. luteus* suspension in PBS was prepared from lyophilized cells and mixed for at least 1 hour before use. The initial time point absorbance (T=0 OD450) of the *M. luteus* suspension was determined by obtaining the average of at least 9 samples of absorbance OD450 of the suspension. Solution was removed from 15 CL blister packages to ensure an adequate volume of solution to prepare 2.5mL solution aliquots, and 2.5mg solubilized lysozyme was added to triplicate samples to achieve a final concentration of 1mg/mL lysozyme in test solutions, which is within the range of its reported 0.7 to 4.6 mg/mL concentration in normal tears.⁴³ To the test sample/lysozyme solution were added 20 μ L of SLS denaturant solution, and the mixture was vortexed and incubated at room temperature. After 5 minutes, 0.5mL of this

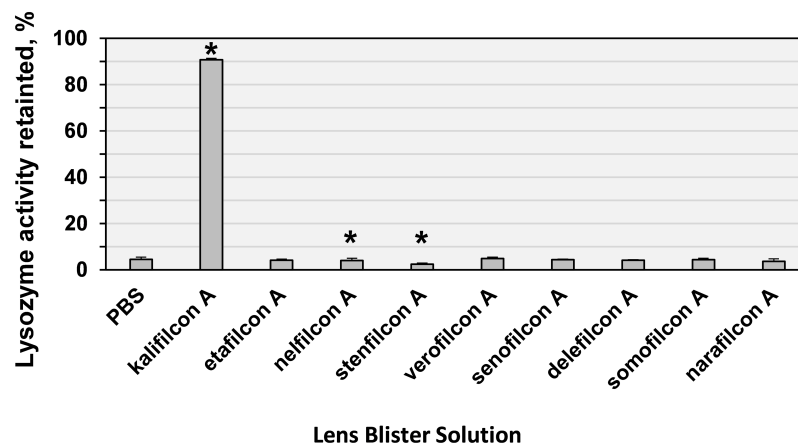


Figure 2 Lysozyme activity retained after addition of detergent in the presence of contact lens blister package solutions. Lysozyme stabilization expressed as percentage of activity retained after exposure of the protein to sodium lauryl sulfate in the presence of the respective CL solutions. *Significantly different from PBS control at $p < 0.05$.

solution were added to 4.5mL aliquots of *M. luteus*, and the mixture was vortexed and incubated at room temperature. After 5 mins, approximately 1mL of the resulting suspension was measured at OD450. (As the assay reaction is time-dependent, a consistent reaction time for each sample is essential for comparison. In pilot experiments, 5 minutes were determined to be sufficient for cell lysis to occur.) The percentage of lysozyme maintained in native form was determined by calculating the ratio of the difference of suspension turbidity before and after exposure to test solutions ($T=0$ OD450 – $T=5$ OD450) relative to the initial turbidity ($T=0$ OD450).

Statistical Analysis

The differences in lysozyme stabilization between each test lens solution ($n=3$) and the PBS control were tested for significance using a two-sample Student's *t*-test; a significance level of $\alpha = 0.05$ was utilized.

Results

The PBS control solution retained 4.5% of lysozyme activity. Lysozyme stabilization was 90.7% for kalifilcon A solution, a statistically significant improvement ($p < 0.05$) compared to PBS (Figure 2).

All other solutions provided $<5.0\%$ stabilization. The etafilcon A, verofilcon A, senofilcon A, delefilcon A, somofilcon A and narafilecon A solutions retained lysozyme activity that was not significantly different than that of the PBS control ($p > 0.05$). Both nelfilcon A and stenfilcon A solutions had significantly less retained lysozyme activity when compared to the PBS control ($p < 0.05$).

Discussion

Ocular surface homeostasis is complex. The placement of a CL on the surface of the eye changes the state of homeostasis, and lens materials, lens designs, and solutions integrated into the lens material can play a role in helping to maintain ocular surface homeostasis. The state of tear proteins plays a key role in preserving homeostasis, and it remains an area to be explored further. The solutions supporting daily disposable CL materials can play an important role in stabilizing tear proteins.

In this study, lysozyme was incubated with respective solutions sampled from the blister packages of nine daily disposable CL models, two of which were traditional hydrogels (nelfilcon A and etafilcon A) and the remaining seven silicone hydrogels, as well as with PBS as control. Retained lysozyme activity after incubation of the test solutions with SLS was greater with the kalifilcon A solution compared with PBS control, and less with the stenfilcon A and narafilecon A solutions compared with PBS control (all $p < 0.05$; Figure 2); activity with the etafilcon A, verofilcon A, senofilcon A, delefilcon A, somofilcon A and narafilecon A solutions did not differ from PBS control (all $p \geq 0.05$).

Lysozyme was selected as the model protein in this study for three reasons. First, along with lipocalin and lactoferrin, it is abundant in natural tears;⁷ second, it is known to deposit on soft CLs;²⁹ third, an assay of the enzyme's biological activity provides an indicator of native versus denatured protein conformation.²⁹ As a model protein, the results can be indicative of outcomes associated with other proteins found in tears.

Denatured lens-bound protein can affect homeostasis by changing CL surface wetting characteristics or the coefficient of friction (COF) between the lens and the ocular surface, dependent upon both the specific adsorbed proteins and their conformational state, as well as the specific lens. For example, model pHEMA and polymethyl methacrylate (PMMA) lens surfaces became more hydrophobic (less wettable) upon adsorption of albumin.⁴⁴ COF increased concomitantly at high surface coverage but was not significantly different at lower coverage when the protein denatured.⁴⁴ In comparison, when lysozyme sorbed on CLs, COF increased at high surface coverage of ocufilcon D and helfilcon A but not nelfilcon A lenses.⁴⁵ The researchers proposed that increased COF might be related to denatured lysozyme rather than total lysozyme sorbed. Increased friction can elicit cytokine and chemokine mediated ocular surface inflammation, perpetuating a vicious cycle of hyperaemia and dryness.²⁰

Comparison of the publicly disclosed solution formulations of the lenses evaluated suggests that not all surfactants are effective in this lysozyme stabilization model system. All of the daily disposable CL blister packages evaluated in this study contain phosphate or borate buffered saline, and each contains one or more additional ingredients intended to improve lens performance. These include surfactants such as poloxamers and poloxamines, and humectants such as PEG and HPMC. The kalifilcon A solution also contains glycerol and erythritol osmoprotectants, which are used as protein stabilizers in the pharmaceutical industry.⁴⁶ Because surfactants are known to mediate protein refolding,⁴⁷ surfactant-containing solutions might potentially help prevent tear protein denaturation. However, neither the poloxamer 108 in the solution for nelfilcon A lenses, nor the poloxamer 407 in the solution for somofilcon A lenses at their respective concentrations did so for lysozyme in this study ($4.0\% \pm 1.0\%$ and $4.4\% \pm 0.6\%$ retained activity, respectively). Only the kalifilcon A lens solution, which includes dual surfactants/moisturizers and dual osmoprotectants largely retained lysozyme activity.

Studies of the interactions between surfactants and proteins reported in the literature offer some clues as to how surfactants in kalifilcon A might contribute to protection of tear film protein. As molecules of globular lysozyme denature, they tend to aggregate with neighboring molecules. In one study, poloxamer and poloxamine multi-block surfactant copolymers, but not the humectant PEG, were reported to suppress aggregation of heat-denatured lysozyme, with poloxamine 1107 more effective than either poloxamer 108 or poloxamer 188.⁴⁸ This observation is believed to be due to steric effects, illustrating the importance of the relative sizes of the hydrophobic regions of the protein and the poloxamine 1107 surfactant.⁴⁹ It was also proposed that this surfactant mimics naturally occurring small heat shock proteins to prevent irreversible aggregation.⁵⁰ In the case of the kalifilcon A solution, highly hydrophilic poloxamine 1107 (hydrophile-lipophile balance, HLB = 18–23)⁴⁷ may work in conjunction with hydrophobic poloxamer 181 (HLB = 3)⁴⁷ to stabilize different parts of the lysozyme molecule.

The ability of the surfactants in the kalifilcon A solution to contribute to stabilized lysozyme activity observed in this study is consistent with other studies of surfactants and lens care products. In one study, MPS formulations that included poloxamine 1107 preserved 90% of lysozyme activity in the presence of sodium dodecyl sulfate (aka SLS), while formulations that included poloxamine 1304, poloxamer 407, or poloxamer 237 preserved no more than 6%.²⁷ In addition, the use of an eye drop containing lauryl ether carboxylic acid and poloxamine 1304 surfactants in conjunction with wear of silicone hydrogel CLs only marginally decreased denaturation of lysozyme sorbed on lenses.³⁰ These studies support the differential performance of solutions containing poloxamine 1107 and 1304 at promoting retention of native lysozyme structure. This difference may reflect differences in relative surfactant concentration in the products studied, as well as the relative difference in HLB between the two surfactants, poloxamine 1107 being highly hydrophilic (HLB = 18–23) and poloxamine 1304 being medium hydrophilic (HLB = 12–18).⁴⁷ Poloxamine 1107 was reported to be able to disaggregate lysozyme and preserve its secondary structure after exposure to dithiothreitol.⁵¹ While not specifically exploring lysozyme stabilization, one study reported that poloxamine 1107 sorbed on etafilcon A lenses increased lens wettability that persisted over the first four hours of wear and was retained by the lens over a full eight-hour wearing period.⁵² Wettability and subjective comfort were improved compared with the untreated control lens and highlight that various ingredients can have a sustained benefit over the course of the wearing period.

Retaining tear protein structure and function by the kalifilcon A solution supports the possibility of clinical benefits. Contact of the kalifilcon A lens solution that includes protein stabilizing agents with the CL wearer's ocular surface may help stabilize tear proteins within the tear film and therefore may help to maintain ocular surface homeostasis. Future studies to determine the relative contributions of the components of the solution and effects of potential contributors to protein stabilization versus denaturation are warranted, including studies to determine if the in vitro lysozyme stabilization demonstrated in this study occurs during lens wear.

Conclusion

The representative protein lysozyme, in the presence of a novel CL solution containing dual moisturizers and dual osmoprotectants, was significantly more stable when compared to PBS and other daily disposable CL solutions intended to support various lens materials. The lysozyme activity assay provides mechanistic evidence that the kalifilcon A CL solution can stabilize proteins under conditions that typically denature proteins. While the clinical significance of small amounts of denatured lysozyme remains to be established, native proteins contribute to tear film stability and protects the ocular surface from microbial colonization. Additional research will further the understanding of the benefits of stabilizing proteins in preserving ocular surface homeostasis during CL wear.

Acknowledgment

The abstract of this paper was presented at the 2021 British Contact Lens Association (BCLA) Virtual Clinical Conference and Exhibition held June 13–14, 2021. (Scheuer C, Barniak V, Rah M, Reindel W. Effect of daily disposable contact lens solutions in stabilizing the activity of a tear film protein. *Cont Lens Anterior Eye* 2022;45 Suppl 1: 101638.)

Funding

This work was funded by Bausch & Lomb Incorporated.

Disclosure

All authors are employees of Bausch & Lomb Incorporated. Ms Catherine A Scheuer reports a patent 17/398556 pending to Bausch+Lomb, a patent 110129328 pending to Bausch+Lomb, a patent PCT/EP2021/072140 pending to Bausch+Lomb. Ms Vicki L Barniak reports a patent 17/398,556 pending to Bausch & Lomb, a patent 110129328 pending to Bausch & Lomb, a patent PCT/EP2021/072140 pending to Bausch & Lomb. Dr William Reindel reports a patent 17/398556 pending to Bausch +Lomb, a patent 110129328 pending to Bausch+Lomb, a patent PCT/EP2021/072140 pending to Bausch+Lomb. The authors report no other conflicts of interest in this work.

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