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Analysis of polyvinyl alcohol release from commercially available daily disposable contact lenses using an *in vitro* eye model

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Abstract: The purpose of this work was to determine the release of polyvinyl alcohol (PVA) from etafilcon A, omafilcon A, and nelfilcon A daily disposable hydrogel contact lenses using a novel *in vitro* model. PVA is an ocular lubricant that can be found in multiple formulations of artificial tears. Nelfilcon A innately contains PVA, so only the release of PVA from this lens was evaluated. Etafilcon A and omafilcon A lenses were incubated in a PBS solution containing PVA. The release of PVA was evaluated using a novel *in vitro* blink platform with Milli-Q water and PBS under various blink conditions and flow rates. Nelfilcon A lenses significantly released more PVA than other lenses at 0.5 and 1.5 h in both PBS and Milli-Q water ($p < 0.001$). For nelfilcon A, there was no statistical significance between the release profiles of PVA between the blink and no-blink conditions, or for the various flow rates ($p > 0.05$). All tested groups and lenses showed a burst release within the first 4.5 h and rapidly plateaued thereafter. The current study demonstrates that releasable PVA (whether through uptake or through being inherently available from the material) is loosely bound on hydrogel lenses, and the majority is released within 4.5 h. © 2018 The Authors. *Journal of Biomedical Materials Research Part B: Applied Biomaterials* published by Wiley Periodicals, Inc. J Biomed Mater Res Part B: Appl Biomater 107B:1662–1668, 2019.

Key Words: PVA, polyvinyl alcohol, contact lenses, uptake, release

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INTRODUCTION

Contact lenses (CLs) are one of the most successful biomedical devices, with an estimated 140 million wearers worldwide.[1] Despite their success, cessation of CL wear remains a pressing concern, with dropout rates being approximately 16% in the United States and as high as 30% in Europe and Asia.[2] A primary reason for CL dropout remains discomfort with the lenses, particularly toward the end of the day.[1–5] Not surprisingly, there has been a significant push in CL research to develop solutions to reduce CL discomfort (CLD).[6]

Although there are various approaches to tackle the problem of CLD, one that has relatively recently emerged relates to the release of "comfort" or wetting agents over time from the CL material into the tear film.[7–14] Although several of these studies report the release of agents from theoretical "drug-delivery" materials,[11–14] the release of polyvinyl alcohol (PVA), a wetting agent, has been reported from the commercially available daily disposable CLs material nelfilcon A (Dailies Aqua Comfort Plus [DACP]).[7–10,15,16] According to the manufacturer (Alcon, Fort Worth, TX), PVA is slowly released from the CL throughout the day through a blink-activated mechanism to improve end-of-day comfort.[10]

The concept of a drug delivering CL material that can slowly release wetting agents, like PVA, could also be applied to develop other CL materials to address CLD. However, to-date, there are a very limited number of studies that have experimentally examined the release kinetics of PVA from nelfilcon A.[8,10,15] There are two key challenges with regards to studying the release of PVA from CLs. The first problem is finding a suitable analytical assay that has a high sensitivity

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and selectivity for detection of PVA, as PVA does not contain a UV chromophore, so a straightforward spectrophotometric detection is not possible.[17] The detection of PVA from the nelfilcon A material was previously achieved by measuring the RI (refractive index) of the solution.[10] However, while RI is considered to be very sensitive, it is also nonspecific. An alternative colorimetric method for detecting PVA using iodine and borate has been previously published for PVA detection in waste water samples.[18] This method produces a dark blue color change in the presence of PVA, which can be monitored at 630 nm, with a high degree of sensitivity and specifcity.[18]

The second analytical problem is to develop an appropriate *in vitro* model capable of simulating the blink, as PVA release from nelfilcon A is reportedly dependent on a blink-activated mechanism.[10] The action of the eyelid "squeezes" the lens and produces the necessary force to transport the PVA into the tear film.[10] In addition, the model also ideally needs to simulate physiological tear volume (7 ± 2 μL)[19] and tear flow (0.95–1.55 μL/min) [20] to correctly simulate physiological conditions on the ocular surface. Our laboratory has previously developed an *in vitro* eye model (OcuFlow) that is able to test CLs under conditions of physiological tear flow, tear volume, and a blink-actuated mechanism that mimics the action of blinking and air exposure. In addition, it also allows any elute from the CL to be captured and subsequently analyzed.[21–24]

The aim of the current study was to measure the release of PVA from nelfilcon A, and the uptake and release of PVA from two other commercially available hydrogel daily disposable CL materials, using the OcuFlow platform.

MATERIALS AND METHODS

CLs and lens preparation

The lenses tested in the current study were 1-Day Acuvue Moist (etafilcon A, Johnson & Johnson, Jacksonville, FL), Proclear 1 Day (omafilcon A, CooperVision Pleasanton, CA), and Dailies AquaComfort Plus (nelfilcon A, Alcon, Fort Worth, TX). Table I details the reported properties of the three CLs materials examined in the current study. As can be noted, the nelfilcon A material is the only one that contains PVA. The etafilcon A and omafilcon A lenses were loaded with PVA before extraction as described below, such that the release of PVA from these materials could be compared to nelfilcon A. All lenses were obtained in their original packaging with a dioptric power of −3.00 and base curve of 8.6 mm. The blister pack solution of etafilcon A and omafilcon A were used as negative controls, and the blister pack for nelfilcon A was used as a positive control for PVA.

Reagents

Polyvinyl alcohol (PVA) MW of 13–23 kDa (average MW = 18 kDa), iodine, phosphate buffered saline (PBS), and boric acid were purchased from Sigma-Aldrich (St. Louis, MO).

PVA incubation

To compare the release of PVA from nelfilcon A, the etafilcon A and omafilcon A lenses were soaked in a solution of PVA to model the uptake and release of PVA from these materials. Etafilcon A and omafilcon A lenses were removed from the blister pack and soaked in 5 mL of PBS solution for 24 h to remove any blister pack components. These lenses were then incubated in 1 mL of PBS solution containing 1.8 mg/mL of PVA for 24 h on an orbital shaker at room temperature to "load" the lenses with PVA.

OcuFlow set-up

The set-up for the *in vitro* blink platform (OcuFlow) is shown in Figure 1. The standard flow rate for the current study was set to 6.9 μL/min (10 mL/day). This input flow rate translates to approximately 3.45 μL/min (5 mL/day) of collectable elute when accounting for evaporation under our laboratory conditions. This flow rate allows enough sample to be collected (100 μL/30 min) for analysis, which was collected using a 12-well plate. The collection time interval points were as follows: 0–0.5, 1–1.5, 4–4.5, 8–8.5, 12–12.5, and 23–23.5 h (n = 6 for each time point). The cycle for air exposure and mechanical rubbing (to simulate blinking) on the OcuFlow was set to 6.5 times/min. The spacing between the eyeball and eyelid pieces is approximately 250 μm.

Detection of PVA using iodine-borate assay

The following iodine-borate assay procedure was adopted from Prochazkova et al.[18] The color reaction of PVA was performed under laboratory conditions at 22–26 °C. A volume of 0.100 mL of sample was added to 0.375 mL of boric acid (40 g/L) and 0.075 mL of iodine solution (25 g KI and 12.7 g I_2 in 1 L of Milli-Q water). The sample was allowed to

TABLE I. Properties of Daily Disposable Contact Lenses Used in the Study

	1-Day Acuvue Moist	Proclear 1 Day	Dailies AquaComfort Plus
USAN	etafilcon A	omafilcon A	nelfilcon A
Manufacturer	Johnson & Johnson	CooperVision	Alcon
Water content (%)	58	60	69
FDA group	IV	II	II
Center thickness (mm)	0.08	0.09	0.10
Oxygen permeability ($x10^{-11}$)	28	33	26
Principal components	HEMA, PVP, MA	HEMA, PC	PVA, HPMC, PEG, FMA

FMA, N-formylmethyl acrylamide; HEMA, hydroxyethyl methacrylate; HPMC, hydroxypropylmethylcellulose; MA, methacrylic acid; NVP, N-vinyl pyrrolidone; PC, 2-methacryloyloxyethyl phosphorylcholine; PEG, polyethylene glycol; PVA, polyvinyl alcohol; PVP, polyvinyl pyrrolidone.

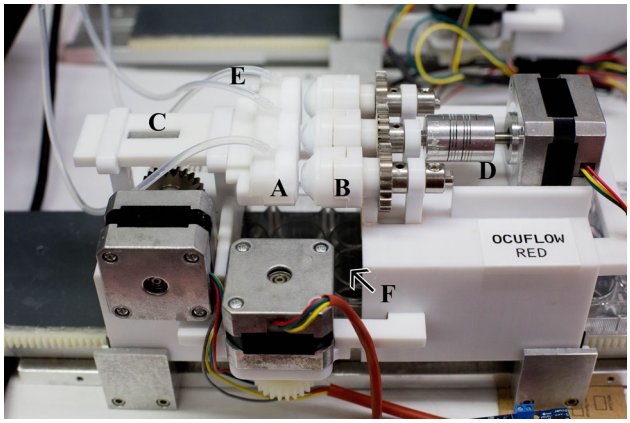

FIGURE 1. Features of the OcuFlow in vitro eye model: (A) corneal eyepiece and (B) lid housing the contact lens (C) lateral motion to simulate air exposure (D) rotational motion to generate frictional wear (E) Inlet for tear flow F 12-well collecting plate.

develop a color change for 20 min, and the absorbance of the 200 μL of sample was measured at 630 nm using a SpectraMax M5 UV–Vis Spectrophotometer (Molecular Devices, Sunnyvale, CA). Standard curves for PVA MW = 18 kDa were prepared from a stock concentration of 50 nmoL/mL in PBS and water, and then serially diluted to concentrations of 25, 12.5, 6.25, 3.125, and 1.5625 nmol/mL. The standard curves were used to calculate the concentration of PVA in the samples (n = 6).

In the current study, PVA was detected using an iodine-borate colorimetric assay.[18] The assay was able to detect PVA in the blister pack and in the CL elute with a high degree of sensitivity and specificity. As shown in Figure 2, only the nelfilcon A lenses containing PVA turned a dark green-black color, indicative of the presence of PVA. This observed color change of PVA with iodine, from orange to blue-black, was first noted by Herrmann and Haehnel, who were the first to synthesize PVA in 1927.[25]

Extraction of PVA from lenses

Six lenses of each type were placed in 1 mL of methanol contained in 2 mL vials (n = 6). The vials were capped, covered with parafilm, and placed on an orbital shaker. After 48 h, the lenses were removed and the sample was dried down using nitrogen gas. The sample was then reconstituted in 400 μL of Milli-Q water. For nelfilcon A lenses, the same methanol extraction procedure was also run for 1 min, and 24 h.

FIGURE 2. (A) etafilcon A, (B) omafilcon A, and (C) nelfilcon A in (D) 1 mL of iodine-borate solution after 1 min. The green-black color for nelfilcon A is indicative of the presence of PVA.

PVA release in MilliQ and PBS

Six lenses of each type were submerged in a rinsing solution for 1 s before mounted on the OcuFlow. The experiment was run as described in the OcuFlow section. About 100 μL of elute was collected from the wells at the specified time intervals and analyzed using the iodine-borate assay. One set of experiments was conducted with PBS, as the flow-through fluid and rinsing solution, and another set was conducted using Milli-Q water. This was undertaken as it was considered possible that the PBS and Milli-Q water flowing over the lenses may have differential impacts on lens swelling for the three lens materials. This would likely impact the release of the PVA and was considered an essential step to ensure that the lens ionicity did not impact the release rates.

PVA release from nelfilcon a for no-blink and low flow rate

The release of PVA from the nelfilcon A lenses has been described as being driven by the blink.[10] To examine this, the following experiments were only conducted for nelfilcon A to examine the effects of blinking and a low flow rate on the release of PVA. Both experiments were conducted using PBS as the flow-through fluid. Six nelfilcon A lenses were submerged in a rinsing solution of PBS for 1 s and tested in the no-blink condition at the regular flow rate. For the no-blink condition, the OcuFlow was set to the closed position with no mechanical actuation.

For the low flow rate condition, the flow was set to 3.45 μL/min (5 mL/day). These input flow rates translate to approximately 1.725 μL/min (2.5 mL/day), respectively, of collectable fluid when accounting for evaporation under our specific laboratory conditions. This flow rate is very similar to physiological conditions (between 0.95 and 1.55 μL/min).[20] As a result of the low flow rate, 50 μL samples were collected directly from the eyepieces. The low flow condition was tested with both blink and no-blink conditions.

Statistics

Statistical analysis was performed using Statistica 8 software (StatSoft, Tulsa, OK). All data are reported as mean ± standard deviation, unless otherwise stated. Repeated measures analysis of variance (RM-ANOVA) was performed to determine the differences across various time-points and lenses. Two-way ANOVA was performed to determine differences across testing groups. Post hoc Tukey multiple comparison tests were used when necessary. In all cases, statistical significance was considered significant for a p value of <0.05. Graphs were plotted using GraphPad Prism version 7.0 (GraphPad Software, La Jolla, CA).

RESULTS

As shown in Figure 2, nelfilcon A lenses containing PVA turn green-black when exposed to the solution of iodine-borate. This color change is indicative for the presence of PVA.

TABLE II. Total Amount of PVA in Blister pack (n = 3) and Total Amount of Extractable PVA From the lens after 48 h (n = 6) for etafilcon A, omafilcon A, and nelfilcon A

	etafilcon A	omafilcon A	nelfilcon A
Total PVA in blister pack (μg)			409.5 ± 56.7
PVA (MW = 18 kDa) in 1 mL incubation solution (μg)	1800	1800	-
PVA extracted after 48 h (μg/lens)	14.7 ± 3.5	17.8 ± 5.6	41.6 ± 9.6
PVA extracted after 24 h (μg/lens)			38.0 ± 16.0
PVA extracted after 1 min (μg/lens)			53.5 ± 10.1

Etafilcon A turned a reddish orange and omafilcon A turned orange. The color change in etafilcon A is because of the presence of polyvinyl pyrrolidone (PVP) complexing with iodine.[8,26] The iodine-borate solution is an orange color.

The total amount of PVA from the blister pack for nelfilcon A, shown in Table II, was 409.5 ± 56.7 μg, respectively ($p < 0.001$). The total amount of extractable PVA for nelfilcon A was 41.6 ± 9.6 μg/lens. Etafilcon A and omafilcon A were rinsed in PBS and incubated in a solution of 1.8 mg/mL of PVA. The extractable PVA from these lenses were 14.7 ± 3.5 μg/lens (Table II) for etafilcon A and 17.8 ± 5.6 μg/lens for omafilcon A (Table II). The amount of extractable PVA for nelfilcon A was significantly higher than etafilcon A and omafilcon B ($p < 0.001$). There were no differences in the amount of PVA extracted from nelfilcon A after extraction times of 1 min, 24 h, or 48 h ($p > 0.05$).

The release of PVA from the CLs is summarized in Table III. Nelfilcon A significantly released more PVA than etafilcon A and omafilcon A incubated with PVA at the 0.5 and 1.5 h time points in both PBS and Milli-Q water (Fig. 3). All lenses had similar PVA release after the 4.5 h time-point. The release of PVA in PBS was higher than Milli-Q water for nelfilcon A ($p < 0.05$). The release of PVA was higher in Milli-Q water than PBS for omafilcon A ($p < 0.05$), and there was no differences for etafilcon A ($p > 0.05$).

Figure 4 shows the release of PVA over time in PBS under different blink conditions and flow rates for nelfilcon A. There was no statistical significance between the release profiles of PVA between the blink and no-blink conditions ($p > 0.05$). In addition, there were no differences in the PVA release profiles between the different flow rates in either the blink condition or no-blink condition ($p > 0.05$).

DISCUSSION

Both etafilcon A and omafilcon A inherently do not contain any PVA. To compare the release of PVA from these daily disposable hydrogel lenses with that from nelfilcon A, they were incubated in a PBS solution containing PVA to "load" the lenses with PVA. This solution had approximately four to five times more PVA than the blister pack for nelfilcon A. Despite this, the amount of inherently extractable PVA for nelfilcon A (41.6 ± 9.6 μg/lens) was significantly higher than both etafilcon A (14.7 ± 3.5 μg/lens) and omafilcon A (17.8 ± 5.6 μg/lens). These results clearly demonstrate that the nelfilcon A material does indeed deliver a significant level of PVA from the lens material, and that that level was greater than that which was achieved by merely "passively" loading hydrogel lenses even at a higher PVA concentration.

For nelfilcon A, the lenses were also extracted after 1 min and 24 h to compare the data with the 48 h extraction. The rationale behind the different extraction time points was to evaluate whether more PVA could be extracted from the lens over time. However, there were no differences in the amount of PVA extracted from the nelfilcon A lenses at any of the three time points (see Table II), with between 38 and 53 μg/lens being extracted ($p > 0.05$). Nelfilcon A lenses are synthesized from PVA, and so there could potentially be non cross-linked PVA within the bulk of the lens material. PVA could also be added in excess during the manufacturing process. Previous studies hypothesized that these non cross-linked PVA molecules within the CL bulk could leach out over time, to provide sustained release of PVA from the lens.[8,10]

The release of PVA from etafilcon A, omafilcon A, and nelfilcon A was investigated in both PBS and Milli-Q water using the OcuFlow platform. The release of PVA for all tested lens types and conditions followed a burst release within the first 4.5 h and plateaued thereafter. After 4.5 h, the amount of released PVA was similar between all lenses and conditions. For the OcuFlow release studies, nelfilcon A released significantly higher amounts of PVA at 0.5 and 1.5 h compared to etafilcon A and omafilcon A. These results are in agreement with the methanol extraction studies, where nelfilcon A had the highest amount of extractable PVA. There are two notable differences with the data in the current study and that previously published.[16] The first relates to the burst release of PVA observed in the current study,

TABLE III. PVA Released Fom etafilcon A, omafilcon A, and nelfilcon A (μg) in PBS versus Milli-Q water (mean ± SD) n = 6

	etafilcon A (μg/lens)		omafilcon A (μg/lens)		nelfilcon A (μg/lens)	
Time (h)	PBS	MilliQ	PBS	MilliQ	PBS	MilliQ
0.5	5.1 ± 2.7	6.7 ± 3.3	2.7 ± 2.6	4.6 ± 2.0	31.9 ± 11.5	16.9 ± 6.0
1.5	1.4 ± 0.8	1.6 ± 0.9	1.2 ± 1.7	1.8 ± 0.3	5.6 ± 2.2	4.2 ± 2.3
4.5	0.5 ± 0.2	0.2 ± 0.2	0.3 ± 0.6	1.5 ± 0.3	0.3 ± 0.1	0.0 ± 0.0
8.5	0.2 ± 0.1	0.4 ± 0.5	0.2 ± 0.4	0.1 ± 0.1	0.3 ± 0.1	0.1 ± 0.2
12.5	0.1 ± 0.1	0.0 ± 0.3	0.0 ± 0.1	0.0 ± 0.0	0.3 ± 0.0	0.0 ± 0.0
23.5	0.0 ± 0.1	0.4 ± 0.5	0.0 ± 0.1	0.0 ± 0.2	0.2 ± 0.0	0.0 ± 0.0

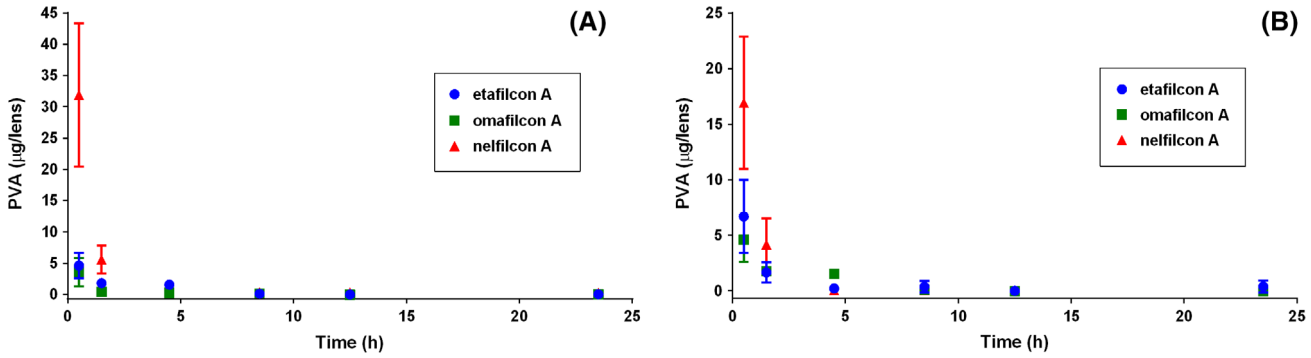

FIGURE 3. Release of PVA (μg/lens) from contact lenses in (A) PBS and (B) Milli-Q water over 24 h (mean ± SD) n = 6.

which was not reported in the previous study.[16] The second difference is the time it took the lens to equilibrate in the previous work, which occurred approximately after 20 h.[16] For the current study, the equilibrium was reached much faster, after 4.5 h for both the standard OcuFlow flow rate of 10 mL/day (6.9 μL/min) and a slower flow rate at 5 mL/day (3.45 μL/min). The faster flow rate in the current study compared to the 5 mL static incubation volume, or the 100 μL/h exchange rate previously used, could result in the observed differences in equilibration time.[16]

We initially hypothesized that the differences in rate between these two studies could be due to the continuous rubbing mechanism from the OcuFlow platform, which could accelerate the release of PVA. As a blink activation is reported to be necessary to force PVA release from the lens and too much force could hypothetically accelerate PVA release.[10,16]

However, there were no differences in the amount of PVA released in the blink and no-blink condition using the OcuFlow, appearing to remove this as being a potential source of the differences in the data derived. These results suggest that the blink rate and/or force from the OcuFlow device did not have any significant effect on the release kinetics of PVA from nelfilcon A.

The release of PVA in PBS was higher than in Milli-Q water ($p < 0.05$) for nelfilcon A, despite the lenses swelling more in Milli-Q water than PBS.[27] The mechanisms underlying the higher release in PBS for nelfilcon A are not clear. We hypothesize that it could be because of the interactions of the phosphate ions with the hydroxyl groups of PVA, which helps stabilize the molecule in aqueous solution, and therefore facilitates its release from the lens. A previous study has reported degradation of PVA in PBS from hydrolytic cleavage of hydrogen bonding among hydroxyl groups of PVA chains.[28] The different lens preparation step, rinsing with PBS versus MilliQ, may also play a role.

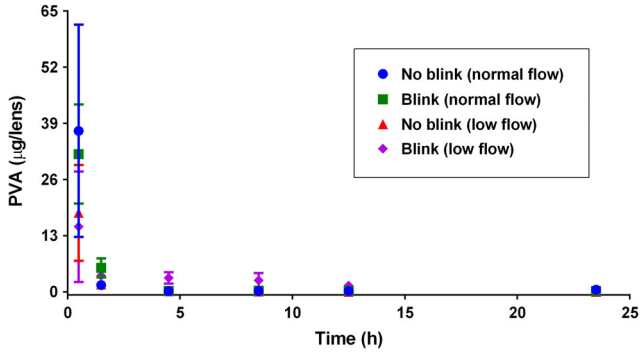

FIGURE 4. Release of PVA (μg/lens) from nelfilcon A in PBS under different blink conditions and slower flow rate over 24 h.

The results from the current study suggest that PVA release, from the PVA-loaded omafilcon A and etafilcon A materials and the PVA-based nelfilcon A material, follows a typical burst release-plateau profile. These kinetics are in agreement with typical observations for the majority of drug delivery studies with commercial CLs.[21,22,29–32]Although minute quantities of PVA leaving the lens materials were still detected after 4.5 h, the clinical significance for such small amounts of PVA release warrants further investigation. Based on the results, the clinical effect of PVA would be most apparent in the first 1.5–4.5 h. That being said, "drug delivery" with CLs is unique because the lens can entrap the released compound in the posterior lens tear film, holding it against the cornea. This area is shielded from the typical ocular removal mechanisms such as tear dilution,[33] and blinking,[33] that remove drugs from the ocular surface, Consequently, the PVA released and entrapped between the lens and the cornea could remain longer on the ocular surface than expected. However, this would not occur over the front surface of the lens, in which it would act as a lubricant between the lens and the under surface of the eyelid, potentially reducing the frictional force between the lid and lens. Furthermore, this lubricating effect may not be long lasting with PVA, as shown by a previous *in vitro* study examining wear time and coefficient of friction (CoF).[34] The CoF of nelfilcon A increased significantly after an *in vitro* aging process that simulated *in vivo* lens wear.[34]

One further point to consider is that the values reported in the current study for the amount of wetting agent released are estimates of actual concentrations, as the standard curves used to derive these values were generated using commercially available versions of PVA. The assumption is that the molecular weights of PVA are reflective of the actual wetting agents found in the nelfilcon A blister packs. The actual molecular weight of PVA in the current commercial nelfilcon A lenses and in its blister pack is proprietary. Different molecular weights of PVA will have different uptake and release profiles from lenses.

To compensate for evaporation over the course of the sampling time, the input flow rate for the OcuFlow was set at 6.9 μL/min to collect enough sample for analysis at each time point. As elution of compounds from CLs is affected by tear flow rate,[21] a faster flow rate will inevitably lead to a faster burst release. However, while the tear flow-rate *in vivo* will be slower, there are other components not simulated on the OcuFlow (such as faster blinking rates[35] and exposure to corneal and conjunctival cells) that may increase elution of the wetting agents from the CLs.[36]

CONCLUSION

The purpose of the study was to evaluate the release of PVA from commercial CLs using a novel *in vitro* blink platform. Various conditions were tested, including different rinsing media, flow rates, and blink conditions. There were no differences in the release kinetics for different flow rates or blink conditions. For all tested conditions, burst release was observed within the first 1.5 h, which plateaued rapidly after 4.5 h. The PVA-based nelfilcon A lenses released more PVA than PVA-loaded etafilcon A and omafilcon A. The results from the current study suggest that releasable PVA from nelfilcon A is loosely bound on the surface or subsurface of the lens.

CONFLICT OF INTEREST

The authors Riederer, Lau, and Lorenz are employees of J&J. Jones and Subbaraman have received research support or lectureship honoraria from the following companies: Advanced Vision Research, Alcon, Allergan, Contamac, CooperVision, Essilor, GL Chemtec, Inflamax Research, J&J Vision, Menicon, Nature's Way, Novartis, Ocular Dynamics, Oculus, Safilens, Santen, Shire, TearLab, TearScience. Jones is also a consultant and/or serves on an advisory board for Alcon, CooperVision, J&J Vision, Novartis and Ophtecs.

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