Article

Release of Moxifloxacin from Contact Lenses Using an In Vitro Eye Model: Impact of Artificial Tear Fluid Composition and Mechanical Rubbing

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Purpose: The aim of this study was to evaluate and compare the release of moxifloxacin from a variety of daily disposable (DD) contact lenses (CLs) under various conditions using a novel in vitro eye model.

Methods: Four commercially available DD conventional hydrogel (CH) CLs (nelfilcon A, omafilcon A, etafilcon A, and ocufilcon B) and three silicone hydrogel (SH) CLs (somofilcon A, narafilcon A, and delefilcon A) were evaluated. These lenses were incubated in moxifloxacin for 24 hours. The release of the drug was measured using a novel in vitro model in three experimental conditions: (1) phosphate buffered saline (PBS); (2) artificial tear solution (ATS) containing a variety of proteins and lipids; and (3) ATS with mechanical rubbing produced by the device.

Results: Overall, CH CLs had a higher drug release than SH CLs ($P < 0.05$) under all conditions. Typically, a higher drug release was observed in PBS than ATS ($P < 0.05$). For CH, drug release was found to be higher in ATS with rubbing than PBS or ATS ($P < 0.05$). For most lens types, ATS with rubbing produced higher drug release than ATS alone ($P < 0.05$). Generally, the release kinetics for all conditions were sustained over the 24-hour testing period, and no burst release was observed ($P < 0.05$).

Conclusions: Moxifloxacin release from a CL into ATS is lower when compared to release into PBS. When mechanical rubbing is introduced, the amount of drugs released is increased.

Translational Relevance: Results suggest that sophisticated in vitro models are necessary to adequately model on-eye drug release from CL materials.

Introduction

Ocular drug delivery using contact lenses (CLs) is an interesting concept, and if successful, could change the paradigm of treating ocular surface diseases. The conventional treatment of using eye drops is problematic, and often ineffective, due to precorneal drug loss through tear dilution,[1–3] blinking,[4] drainage,[1,3] and nonspecific absorption.[1,3] Consequently, the average residence time for most eye drops on the ocular surface is only 2 to 5 minutes.[5] The majority of the medication is drained into the nasolacrimal duct and absorbed into the bloodstream,[6] which can then lead to undesirable systemic side effects.

Many of these barriers to ocular surface delivery of drugs can be overcome by using a CL as the drug delivering device. Drugs that are released from the CL into the postlens tear film that sits between the lens and the cornea have longer precorneal residence time.[7] Thus, in theory, a drug-delivering CL would improve a treatment regimen by significantly improving corneal drug absorption and consequently reducing the dosing frequency and concentration required to obtain therapeutic levels. The idea of using a CL for drug delivery dates back to the 1960s,[8,9] and considerable research has been conducted since that time to develop a viable commercial product.[10–15] Unfortunately, despite extensive efforts, there are still no commercial devices on the market, in part due to a limited understanding of how these devices would

Table 1. Properties of CHs Used in the Study[22]

	BioMedics 1 Day	1-Day Acuvue Moist	Proclear 1 Day	Dailies AquaComfort Plus
United States adopted name (USAN)	Ocufilcon B	Etafilcon A	Omafilcon A	Nelfilcon A
Manufacturer	CooperVision	Johnson & Johnson	CooperVision	Alcon
Water content (%)	52%	58%	60%	69%
FDA group	IV	IV	II	II
Centre thickness (mm)	0.07	0.08	0.09	0.10
Oxygen permeability ($\times 10^{-11}$)	16.8	28	33	26
Principal monomers	HEMA, PVP, MA	HEMA, PVP, MA	HEMA, PC	PVA, FMA, HPMC, PEG

EGDMA, ethylene glycol dimethacrylate; FMA, N-formylmethyl acrylamide; HPMC, hydroxypropylmethylcellulose; MA, methacrylic acid; PC, 2-methacryloyloxyethyl phosphorylcholine; PEG, polyethylene glycol; PVP, polyvinyl pyrrolidone.

perform in vivo, resulting in skepticism on their potential effectiveness.

In the past, drug-delivering CLs were typically assessed in vitro using a vial containing 2 to 5 mL of phosphate buffered saline (PBS).[10–13,16–19] This vial-based model fails to adequately simulate the natural flow and volume of the tear film environment.[20,21] In a previous study, we showed, using an in vitro eye model to simulate tear volume and flow, that the release profile of two antibiotics (ciprofloxacin and moxifloxacin) from CLs can be sustained for 24 hours.[22] These results contrast those obtained from the same materials in a static vial, where the release followed the traditional burst-plateau profile for drug release from CLs.[22] These results suggest that the parameters of the in vitro release system play a significant role in determining the release kinetics of drugs from CLs. Thus, to better understand and assess how CLs release drugs in vivo, the effects of other key ocular parameters should also be investigated in vitro.

The composition of tear fluid and the mechanical rubbing produced by the lids are two important factors that may influence ocular drug delivery. The composition of the elution solution has been noted previously to impact the release of phospholipids from CLs.[23] The effects of eye blinking on drug release from hydrogels has been noted in only one study.[24] To our knowledge, no studies have examined the combined effects of an artificial tear solution (ATS) that mimics the composition of the human tear film and mechanical wear on drug release from CLs. The aim of this study was to evaluate and compare the release of moxifloxacin from a variety of daily disposable (DD) CLs in an ATS when exposed to mechanical rubbing using a novel in vitro eye model.

Moxifloxacin is an important antimicrobial agent used in the treatment of a wide range of ocular surface diseases.[25,26]

Materials and Methods

CLs and Drug Incubation

Four conventional hydrogel (CH) CLs (nelfilcon A [Alcon, Fort Worth, TX], omafilcon A [CooperVision, Pleasanton, CA], etafilcon A [Johnson & Johnson, New Brunswick, NJ], and ocufilcon B [CooperVision]) and three silicone hydrogel (SH) lenses (somofilcon A [CooperVision], narafilcon A [Johnson & Johnson], and delefilcon A [Alcon]) were evaluated in this study. All lenses had a dioptric power of −3.00 with a base curve of 8.6 mm. The properties of the lenses are detailed in Tables 1 and 2. Nine lenses of each type were incubated in 1.0 mg/mL moxifloxacin (Selleckchem, Houston, TX) solution in PBS (pH 7.4) for 24 hours.

Experimental Setup

The in vitro eye model, Ocuflow, previously developed in our lab was used in this study to evaluate the drug release from CLs.[22,27–29] The setup of the eye model with attachment to a microfluidic system is shown in Figure 1. The humidity was maintained using a humidifier and hygrometer to a minimum of 50% air moisture.

After the drug incubation period, the lenses were partially dried on lens paper and then placed into the eye model. For all testing conditions, the flow rate of the fluid that bathed the lens while in the Ocuflow was set to 2.1 µL/minute (3 mL/24 hours). The flow-through fluid was collected in a 12-well plate. At the

Table 2. Properties of SHs Used in the Study[22]

	Dailies Total 1	1-Day Acuvue TruEye	Clariti 1 Day
United States adopted name (USAN)	delefilcon A	narafilcon A	somofilcon A
Manufacturer	Alcon	Johnson & Johnson	CooperVision
Water content (%)	33% (surface >80%)	46%	56%
FDA group	V	V	V
Centre thickness (mm)	0.09	0.09	0.07
Oxygen permeability ($\times 10^{-11}$)	140	100	60
Oxygen transmissibility ($\times 10^{-9}$)	156.0	118.0	86
Principal monomers	Not disclosed	MPMDSM, DMA, HEMA, siloxane macromer, TEGDMA, PVP	Not disclosed

DMA, N,N-dimethylacrylamide; MPDMS, monofunctional polydimethylsiloxane; PVP, polyvinyl pyrrolidone; TEGDMA, tetraethyleneglycol dimethacrylate.

specified time intervals, t = 0, 1, 2, 3, 4, 5, 6, 7, 8, 12, 16, and 24 hours, 100 μL of this solution was withdrawn and transferred into a 96-well plate. The fluorescence of moxifloxacin was measured using the SpectraMax M5 UV-Vis Spectrophotometer (Molecular Devices, Sunnyvale, CA) at excitation and emission wavelengths of 296 nm and 471 nm, respectively.[30]

The release of moxifloxacin from CLs was tested in three experimental conditions: (1) PBS, (2) ATS, and (3) ATS with mechanical rubbing produced by the device. ATS, containing salts, urea, glucose, proteins, mucin, and various lipids, was prepared, according to a method previously reported by our group.[31] The rate of mechanical rubbing was set to 10 rotations/min, within the average range for blink rates per minute (4.5–26 blinks/minute).[32]

Artificial Tear Solution

The composition of the ATS has been previously reported by our group.[31] In brief, it contains various salts, urea, glucose, proteins (lysozyme and hen egg albumin), mucin, and various lipids (oleic acid methyl ester, cholesterol, triolein, phosphatidylcholine, cholesteryl oleate, and oleic acid).[31] The viscosity of ATS was measured at 23°C using the Ostwald viscometer (VWR, Radnor, PA).

Statistical Analysis

Statistical analysis, repeated measures analysis of variance (RM-ANOVA) and posthoc Tukey's multi-

ple comparison tests, was performed using Statistica 8 software (StatSoft, Tulsa, OK). Unless otherwise stated, all data are reported as mean ± standard deviation. Statistical significance was considered significant for a P value of < 0.05.

Results

The total moxifloxacin released after 24 hours from seven DD CLs are summarized in Table 3 and Figure 2. The drug release profile over 24 hours for each experimental condition are shown in Figures 3 to 5. Generally, the drug release from CLs was sustained over the 24-hour testing period for all conditions, and no burst release was observed ($P < 0.05$). Overall,
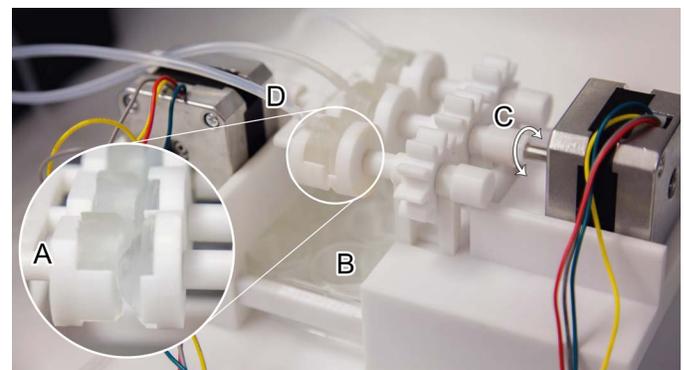

Figure 1. In vitro eye model (Ocuflow) setup: (A) corneal eyepiece and lid; (B) 12-well collecting plate; (C) rotational motion to create rubbing motion; (D) inlet for ATS tear flow.

Table 3. Release (µg/lens) Moxifloxacin after 24 Hours from CH and SH DD CLs in PBS, ATS, and ATS with Mechanical Rubbing

| Commercial Name	Material	Moxifloxacin in PBS (µg/lens)	Moxifloxacin in ATS (µg/lens)	Moxifloxacin in ATS + Rubbing (µg/lens)
[CH]1-Day Acuvue Moist	etafilcon A	111.26 ± 12.9	96.2 ± 4.4	164.3 ± 15.5
[CH]Biomedics 1 Day	ocufilcon B	107.5 ± 23.4	62.9 ± 9.9	158.8 ± 24.4
[CH]Proclear 1 Day	omafilcon A	95.0 ± 6.2	75.9 ± 7.7	108.4 ± 21.8
[CH]Dailies Aqua Comfort Plus	nelfilcon A	45.1 ± 3.6	24.0 ± 3.6	40.42 ± 2.6
[SH]Clariti 1 Day	somofilcon A	42.4 ± 5.1	28.0 ± 3.7	30.6 ± 11.3
[SH]Dailies Total 1	delefilcon A	27.9 ± 3.9	16.7 ± 3.7	18.07 ± 4.3
[SH]1-Day Acuvue TruEye	narafilcon A	30.2 ± 0.8	7.0 ± 3.2	28.7 ± 6.6

conventional hydroxyethyl methacrylate (HEMA)-based hydrogel CLs had a higher drug release than SH CLs ($P < 0.05$) under all conditions ($P < 0.001$).

Typically, a higher drug release was observed in PBS than ATS ($P < 0.05$). For CH CLs, drug release was found to be higher in ATS with rubbing than PBS or ATS ($P < 0.05$). For most lens types, ATS with rubbing produced higher drug release than ATS alone ($P < 0.05$). Total drug release in PBS varied between 27.9 ± 4.0 and 111.3 ± 12.9 µg/lens, in ATS drug release ranged between 7.0 ± 3.2 and 96.2 ± 4.4 µg/lens, and in ATS with rubbing the drug release ranged between 18.1 ± 4.3 and 164.3 ± 15.5 µg/lens.

To determine the components in ATS that may have led to a reduction in the observed drug release, a subsequent experiment was conducted with 2 CH (etafilcon A and ocufilcon B) and 1 SH (somofilcon A) in either ATS without proteins or ATS without lipids ($P < 0.05$). As shown in Figure 6, there were no differences for drug release from somofilcon A between the three tested solutions. For etafilcon A and ocufilcon B, there were differences in total drug release between the three solutions ($P < 0.05$), but there was no conclusive trend. The dynamic viscosity of the ATS was 1.09 ± 0.03 mPa•s, which was slightly higher than the viscosity of PBS 0.99 ± 0.01 mPa•s at 23°C ($P < 0.001$). The measured viscosity for PBS is similar to the reported viscosity of water.[33]

Overall, materials that released the highest amounts of moxifloxacin were etafilcon A (1-Day Acuvue Moist) and ocufilcon B (Biomedics 1 Day), which are both HEMA-based, Food and Drug Administration (FDA) group IV materials with a high water content and are negatively charged. Omafilcon A (Proclear 1 Day), a HEMA-based, FDA group II material with a high water content but overall neutral charge, also showed high drug release. The CLs releasing the lowest amount of drug for each testing condition were nelfilcon A (Dailies AquaComfort Plus), a polyvinyl alcohol (PVA)-based, FDA group II material with a high water content and neutral charge, as well as all SH lenses. All lenses containing moxifloxacin were visually clear throughout the entire duration of the study.
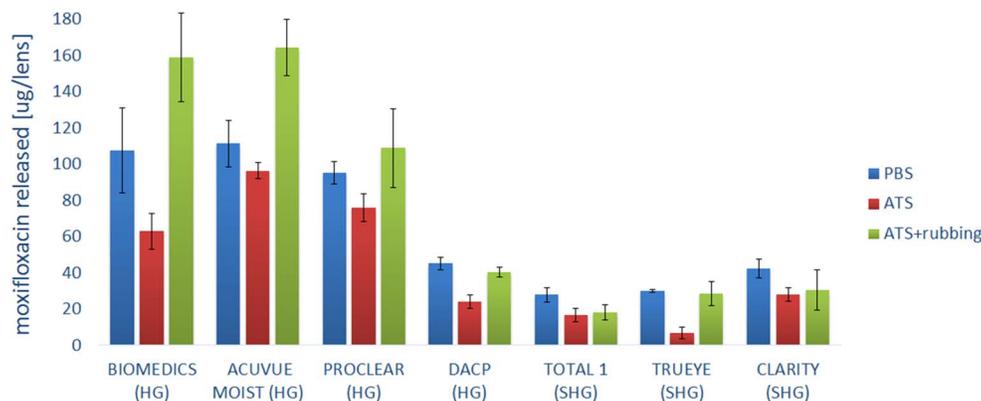
Figure 2. Total release of moxifloxacin (µg/lens) from DD commercial CLs in PBS, ATS, and ATS with mechanical rubbing. The values plotted are the mean ± standard deviation for three trials.
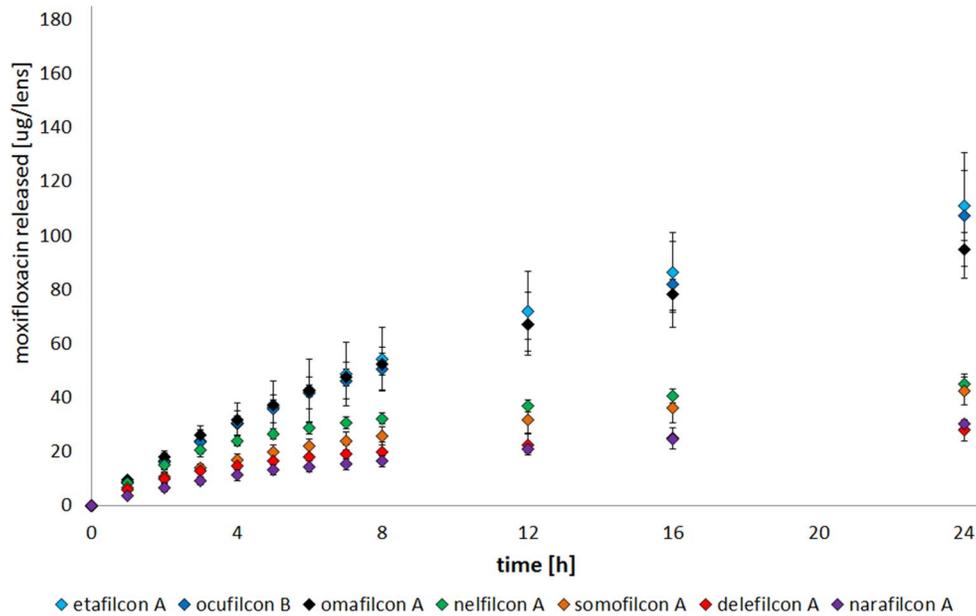
Figure 3. Release of moxifloxacin (μg/lens) in the eye model with a flow rate of 2.1 μL/minute PBS over 24 hours. The values plotted are the mean ± standard deviation for three trials.

Discussion

The rate of drug release into an aqueous media is determined by its solubility, and the rate at which the drug reaches equilibrium between the solution and the lens. The release of moxifloxacin, which is highly hydrophilic,[34] would therefore be dependent on the rate of tear flow. In a previous study measuring the release of moxifloxacin from the same eye model, drug release from CLs was sustained for 24 hours for etafilcon A and ocufilcon B.[22] Omafilcon A reached a plateau within 12 hours, while narafilcon A and all SHs released moxifloxacin within 4 hours.[22] In the previous study, the flow rate was set at 3.33 μL/minute (4.8 mL/day). However, in this study, the flow
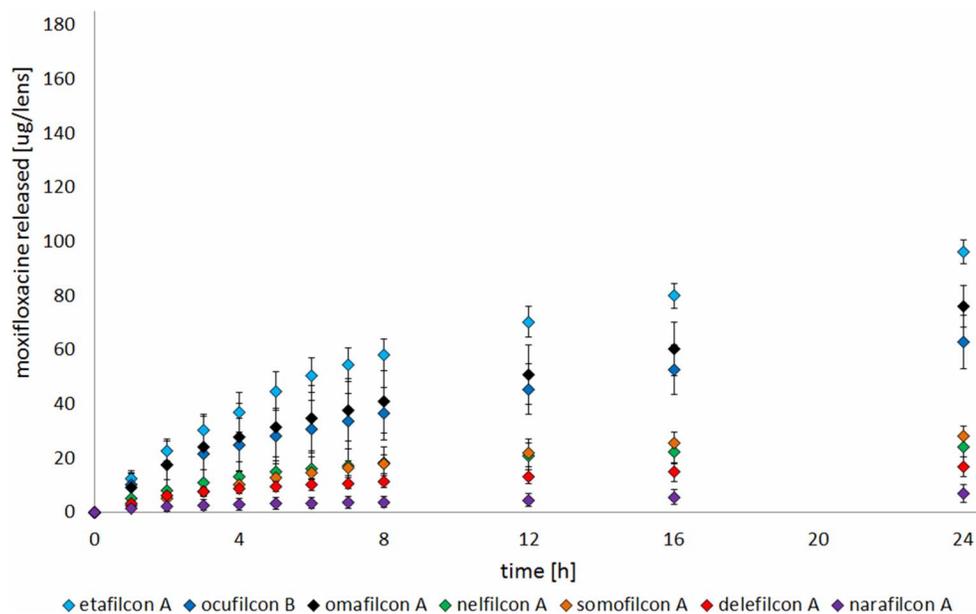
Figure 4. Release of moxifloxacin (μg/lens) in the eye model with a flow rate of 2.1 μL/minute ATS over 24 hours. The values plotted are the mean ± standard deviation for three trials.

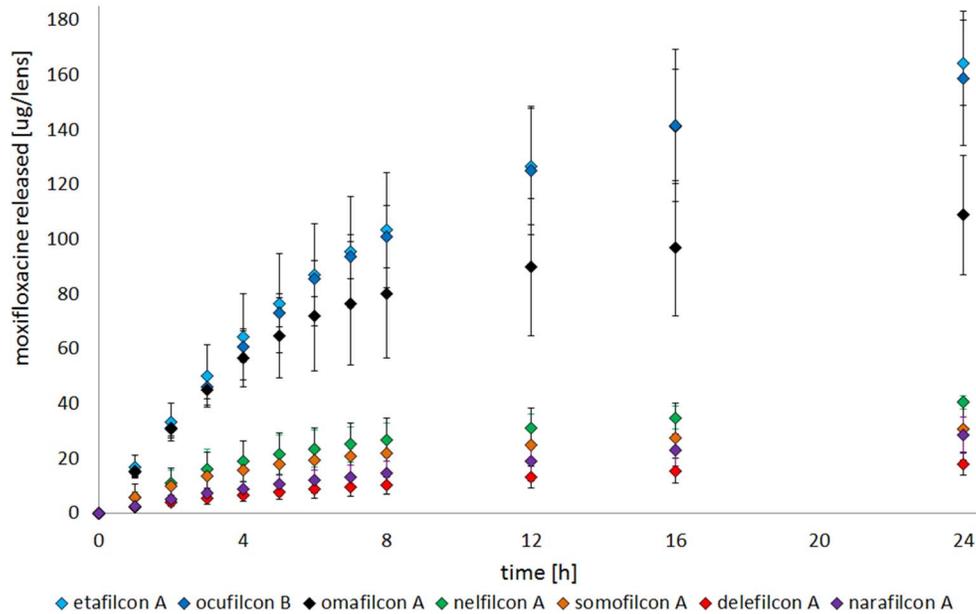**Figure 5.** Release of moxifloxacin (μg/lens) in the eye model with a flow rate of 2.1 μL/minute ATS and mechanical rubbing over 24 hours. Mechanical rubbing was set to 10 rotations/minute. The values plotted are the mean ± standard deviation for three trials.

rate was decreased to 2.08 μL/minute (3.0 mL/day), closer to physiological tear turnover rates,[21] and the release of moxifloxacin from CLs into PBS was sustained over the 24 hours for all lens types ($P < 0.05$). In a vial, the release of moxifloxacin follows more closely to a burst-plateau profile within 1 hour.[22]

Considering the prominent roles of proteins and lipids in the fouling of CLs,[35,36] using PBS as an elution solvent potentially overlooks key determi-

nants in drug release. The effect of the composition of the release medium on therapeutics release from CLs has been previously reported; the release of phospholipids from CLs were five times faster in ATS than water.[23] Surprisingly, in this study the release of moxifloxacin was significantly lower when released in ATS than PBS ($P < 0.05$), which markedly contrasts previous published results.[23] The differences in the observed release could be attributed to the differences in properties between phospholipids and moxiflox-
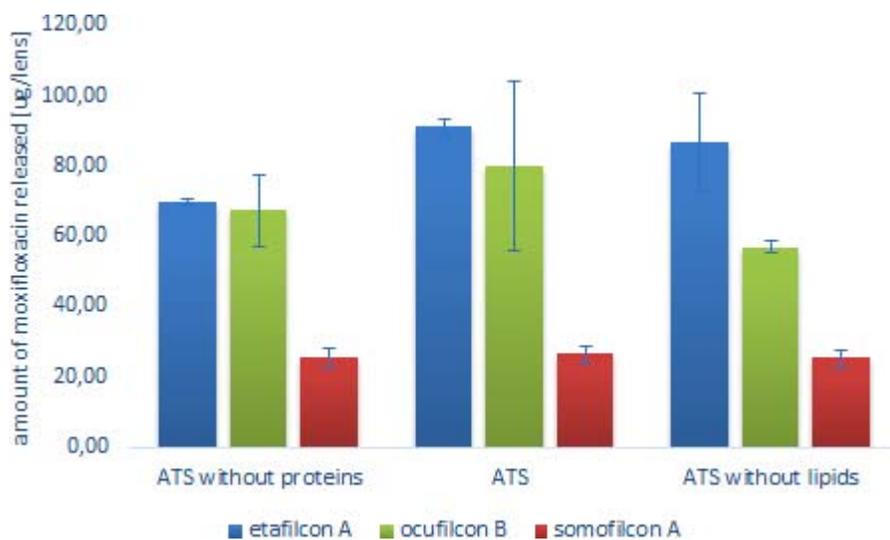

Figure 6. Release of moxifloxacin (μg/lens) in a lipid solution, protein solution, and ATS. The values plotted are the mean ± standard deviation for three trials.

acin, the composition of ATS, and the in vitro model used to measure the release. Nevertheless, the underlying mechanisms resulting in a lower drug release in ATS than a PBS solution is unclear.

Drug release from CLs into ATS is significantly more complex to describe than PBS due to the presence of various salts, proteins, mucin, and lipids within ATS.[31] Any one of these factors, or a combination of them, could interact with the drug in the lens, leading to a lower or higher drug release. Furthermore, the mechanisms of protein and lipid deposition on the CLs[37] could also alter drug–lens interactions, and consequently drug release kinetics. However, the duration of the experiment was only 24 hours, and within this time frame it is expected that tear film deposition would not have a significant impact on drug release.

To elucidate the individual effects of proteins and lipids on drug release, three lenses (etafilcon A, somofilcon A, and ocufilcon A) were tested in ATS without either proteins or lipids. For somofilcon A, there were no differences in the amount of moxifloxacin release in ATS, ATS without proteins, or ATS without lipids ($P > 0.05$). For etafilcon A, ATS without proteins released less drug than ATS ($P < 0.05$), while for ocufilcon A, ATS without lipids released less drug than ATS ($P < 0.05$). These results suggest that each lens material interacts differently with ATS, resulting in slightly different drug release kinetics. Currently, there is no obvious trend to explain for the effects of protein or lipids on drug release from CLs.

Another explanation for a lower drug release from CLs is the differences in viscosity between PBS and ATS. The dissolution of a drug into the media is dependent on the media viscosity, where higher viscosity leads to slower drug dissolution.[38] However, the viscosity of ATS is only slightly higher than that of PBS. So while the higher viscosity of ATS may contribute to the lower drug release, it is likely that it is not the primary factor leading to the observed trend. The viscosity of ATS in this study is lower than the viscosity of human tears (2.33 mPa•s).[33] This is likely due to the fact that our ATS does not contain many of the lipids that contribute to the viscosity of natural tears.[33]

Another important ocular parameter that can affect drug release from CLs is blinking. In this study, only the mechanical wear component of the blink was simulated. The CL sits tightly between the corneal eyepiece and eyelid piece. The rotation of the corneal eyepiece circularly causes the CL to rub against the eyelid piece. The rubbing occurred at a rate of 10 cycles every minute, which falls within the average range for blink rates, of 4.5 to 26 blinks/minute.[32] For most lens types, mechanical rubbing in ATS resulted in significantly higher drug release than ATS alone ($P < 0.05$). This observation also has been reported in another study modelling the effects of blinking on drug release from hydrogels.[24] Furthermore, the tear film is shear-thinning (non-Newtonian) in which the viscosity is not constant. We speculate that the rubbing process between the eyelid and corneal eyepiece decreases the viscosity of the ATS,[33,39] which increases the amount of drugs released from the CL.

In general, CH lenses released more drugs than SH lenses, which is similar to previously reported results.[10,16,22] Etafilcon A (1-Day Acuvue Moist) and ocufilcon B (Biomedics 1 Day), two CH materials with a high water content that are negatively charged, released the highest amount of moxifloxacin. Nelfilcon A (Dailies AquaComfort Plus) was the only CH that behaved like a SH in regards to drug release. The lowered drug release for this lens type is unclear, but could be linked to the composition of the material, which is composed of PVA instead of the traditional HEMA-based materials found in other CH. Furthermore, the lens also contains wetting agents such as PVA and PEG, which are not cross-linked to the polymer. These agents occupy space within the matrix, which could interfere with the lens ability to absorb and release drugs. The two lenses with the lowest drug release for all tested conditions were two SH, delefilcon A (Dailies Total 1) and narafilcon A (1-Day Acuvue TruEye).

An important concern in CL drug delivery is whether the amount of drugs released by the CL is comparable to eye drops for treatment. In general, the amount of drugs that can be loaded and released from a CL is significantly lower in comparison to the amount in eye drops administered over the treatment duration. That being said, the idea behind drug delivery with CL is to achieve similar or better efficacy than eye drops at lower drug dosing. Results from several in vivo studies have validated the efficacy a CL drug delivery platform, despite releasing considerably less drugs.[15,40–45] For in vitro studies, the minimum inhibitory concentrations for 90% of bacterial isolates (MIC_{90}) can be used as relative measure of efficacy for release of antibiotics. All of the CLs, in all testing conditions, released enough moxifloxacin to meet the MIC_{90} (0.047 µg/mL)[46]

against common and susceptible pathogens over the 24-hour study period.

Based on the in vitro model used in this study, the release of moxifloxacin can be sustained for up to 24 hours. The drug release profiles are dependent on the properties of the CL. The amount of drug that is released is dependent on the composition of the elution solution, with lower amounts of drug being released in ATS than PBS. When mechanical rubbing is introduced to those lenses exposed to ATS, the amount of drug released from the CLs increased compared to ATS alone. In conclusion, certain parameters such as ATS can decrease the amount of drugs released, while other parameters, such as mechanical rubbing, increases the amount of drugs released. These results underline the importance of considering various ocular parameters when determining drug release from CLs. Another key parameter affecting drug release from CLs, the properties of the drug such as molecular size, chemical structure, polarity, and solubility,[47,48] was not investigated in this study. This factor, and the complex interactions between material, drug properties, and elution system on CL drug delivery will be investigated in future studies.

Acknowledgments

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