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In vitro drug release and in vivo safety of vitamin E and cysteamine loaded contact lenses

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ABSTRACT

Cystinosis is an orphan disease caused by a genetic mutation that leads to deposition of cystine crystals in many organs including cornea. Ophthalmic manifestation of the disease can be treated with hourly instillation of cysteamine eye drops. The hourly eye drop instillation is tedious to the patients leading to poor compliance and additionally, significant degradation of the drug occurs within one week of opening the bottle, which further complicates this delivery approach. This paper focuses on designing a contact lens to treat the disease with improved efficacy compared to eye drops, and also exploring safety of the drug eluding contact lens in an animal model. Our goal is to design a lens that is safe and that can deliver a daily therapeutic dose of cysteamine to the cornea while retaining drug stability. We show that cysteamine diffuses out rapidly from all lenses due to its small size. Vitamin E incorporation increases the release duration of both ACUVUE®OASYS® and ACUVUE® TruEye™ but the effect is more pronounced in TruEye™ likely due to the low solubility of vitamin E in the lens matrix and higher aspect ratio of the barriers. The barriers are not effective in hydrogel lenses, which along with the high aspect ratio in silicone hydrogels suggests that barriers could be forming at the interface of the silicone and hydrogel phases. The presence of vitamin E has an additional beneficial effect of reduction in the oxidation rates, likely due to a transport barrier between the oxygen diffusing through the silicone channels and drug located in the hydrogel phase. Based on this study, both Acuvue®OASYS® and ACUVUE® TruEye™ can be loaded with vitamin E to design a cysteamine eluting contact lenses for effective therapy of cystinosis. The lenses must be worn for about 4–5 hr. each day, which is less than the typical duration of daily-wear. The vitamin E and cysteamine loaded lenses did not exhibit any toxicity in a rabbit model over a period of 7-days.

1. Introduction

Cystinosis is a metabolic disease caused by a defect in the *CTNS* gene—also known as cystinosin or lysosomal cystine transporter gene. Patients with cystinosis appear normal at birth but suffer from retarded growth and many other complications including renal tubular Fanconi syndrome, which can lead to kidney failure. The underlying cause for these symptoms is the loss of cystine efflux pathways in lysosomes, allowing for cystine crystal formation inside of cells (Gahl et al., 1982, 2000; Nesterova and Gahl, 2008; Tsilou et al., 2007). Cystinosis is a systemic disease, but its impact is seen mostly in the liver, kidneys, brain, and eyes (Tsilou et al., 2007; Tavares et al., 2009; Dufier et al., 1987). With the exception of the eyes, cystinosis can be treated with an oral dose of cysteamine (β-mercaptoethylamine or 2-aminoethanethiol) (Thoene et al., 1976; Kimonis et al., 1995). Cysteamine reacts with intra-lysosomal cystine to produce a cysteine-cysteamine complex that can be removed from the cell via lysine transport. The oral dosage of cysteamine does not provide therapeutic drug levels in the cornea and thus patients need hourly eye drops to manage the ocular symptoms (Gahl et al., 2000; Jones et al., 1991; Simpson et al., 2011). The frequent need for eye drop instillation is due to the low ocular residence time of only a few minutes for drugs instilled in eye drops which leads to a low corneal bioavailability (Bourlais et al., 1998). The drug delivery regimen for treating cystinosis is further complicated by the high rates of drug oxidation which necessitates shipping under frozen conditions and disposal a week after thawing and opening the bottle

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Table 1
List of Commercial Lenses.

Commercial Name (manufacturer)	Material	Diopter	Listed Water Content (%)	Listed oxygen permeability (barrer/mm)
1-DAY ACUVUE® TruEye™(Johnson&Johnson Vision Care, Inc., Jacksonville, FL)	Narafilcon A (silicone hydrogel)	−8.00	46	147
1-DAY ACUVUE® Oasys® (Johnson&Johnson Vision Care, Inc., Jacksonville, FL)	Senofilcon A (silicone hydrogel)	−3.50	38	107
ACUVUE® MOIST® (Johnson&Johnson Vision Care, Inc., Jacksonville, FL)	Etafilcon A (p-HEMA hydrogel)	−6.50	58	25.5

storage (Tsilou et al., 2003; Biaglow et al., 1984; Svensson and Lindvall, 1988). The degraded form of cysteamine, cystamine, is not therapeutically effective because the reactive thiol group has been replaced with a disulfide which cannot participate in the interchange with cystine. The high frequency of administration also risks low patient compliance (Jones et al., 1991; Kaiserkupfer et al., 1987, 1990; Bradbury, 1991), which in turn can limit the therapeutic benefits (Tsilou et al., 2007).

The therapy for managing ocular cystinosis can potentially be considerably improved by using contact lenses to deliver the drug (Creech et al., 2001; Li and Chauhan, 2006). While unmodified commercial contact lenses have short releases, risking toxicity effects, recent developments by Chauhan et al. have shown soft contact lenses to be a viable alternative for cysteamine ocular delivery. Vitamin-E nanoparticles integrated into silicon hydrogel lenses have been shown to extend the release period for various ocular drugs, reducing toxicity concerns while achieving a higher bioavailability than eye drops (Peng et al., 2010). Contact lenses loaded with 20% Vitamin E have been shown to maintain all critical lens properties, including adequate ion and oxygen permeability, while also having a minimal diameter increase of less than 8% at 40% Vitamin E loading for most commercial lenses; these loaded lenses have been shown to be effective in animal studies in a Beagle dog model of glaucoma (Peng et al., 2010; Peng and Chauhan, 2011; Peng et al., 2012a,b,c).

Cysteamine-loaded contact lenses could be a viable alternative for patients as young as 8 years of age (Soni et al., 1995; Walline et al., 2004; Cho et al., 2005; Walline et al., 2007). A previous paper by Hsu et al. examined using vitamin-E modified contact lenses to extend the delivery of cysteamine (Hsu et al., 2013) to about two hours with a 22% vitamin E loading in ACUVUE® TruEye™ (narafilcon B). The paper also showed that cysteamine remains stable while inside a contact lens on a time scale of its release. These results showed the viability of vitamin-E contact lenses as a device platform for treatment of the ocular complications of cystinosis. It is however not clear whether a 2-h release duration may be sufficient, since the current therapy utilizes 8–10 eye drops distributed throughout the day. Our goal here is to increase the release duration further and also to demonstrate the safety of the lenses in an in vivo study. Our recent studies with other hydrophilic drugs have shown that the narafilcon A ACUVUE® TruEye™ exhibits longer release duration compared to narafilcon B. Many studies have shown that vitamin E incorporation increases the release duration, but many fundamental questions remain unanswered regarding the mechanisms for the increase in duration. In addition to designing the lenses for cystinosis therapy, we explore other issues including likely mechanisms for drug transport, and impact of lens properties on the barrier effect of vitamin E. To achieve our goals, we compare two different types of contact lenses (narafilcon A and senofilcon A), both with and without vitamin E. By comparing the release from the two lenses, we can gauge how small differences in the composition can make large differences in the drug transport, both in control and vitamin E loaded lenses. In addition to narafilcon A and senofilcon A, we also explore the effect of vitamin E incorporation in p-HEMA hydrogel contact lens. By comparing the results from the pHEMA and silicone hydrogel lenses, we hope to gain an improved understanding of how vitamin E barriers form in the lenses. The dependency of the release durations on the vitamin E loadings are fitted to a mathematical model to characterize the properties of the vitamin E aggregates. The results are expected to improve our understanding of how the vitamin E aggregates impact drug transport. We also model the release of cysteamine loaded in contacts after insertion of the lens in the eye. The model is used to explore whether the lens can deliver sufficient amount of cysteamine to the cornea. Finally, we report the first-ever in vivo studies with cysteamine releasing contact lenses in rabbits. Since a cystinosis model is not available in rabbits, we explore only the toxicity from the optimized lenses in the animal model.

2. Materials and methods

2.1. Materials

The type of commercial contact lenses used in this study are listed in Table 1. Cysteamine (98%) was purchased from Fischer Scientific. Ethanol (200 proof) and Vitamin E (DL-alpha tocopherol, > 96%) were purchased from Sigma-Aldrich. Phosphate buffered saline (PBS), 1x, without calcium and magnesium, was purchased from Mediatech, Inc. (Hydroxyethyl)methacrylate and Ethylene glycol dimethylacrylate were also purchased from Sigma-Aldrich. All chemicals were used as supplied without further processing. Quartz cuvettes (3.5 mL, 10 mm) were purchased from Science Outlet.

2.2. Vitamin E loading procedure

Commercial lenses were rinsed, then soaked in deionized water for 15 min, and then rinsed again with deionized water. Next, lenses were soaked in a 3mL vitamin E-ethanol solution for 24 h, which was determined to be adequate for equilibrium to be reached between the lens and the solution. There is a linear relationship between the final vitamin E loading in the lens and the vitamin E-ethanol solution concentration (Peng et al., 2010). For ACUVUE® TruEye™, a concentration of 0.022, 0.044, 0.066, and 0.077 g/mL in the vitamin E – ethanol solution yields loadings of 9.9%, 19.8%, 29.6%, and 34.6% (w/w on dry basis), respectively. For ACUVUE®OASYS®, a solution concentration of 0.024, 0.043, 0.063, and 0.074 g/mL yield loadings of 10.5%, 20.6%, 30.1%, and 35.4%, respectively. After the 24 h in vitamin E-ethanol solution, the lenses are withdrawn and placed in 300 mL of DI water to extract ethanol. After an additional 24 h, the lenses are removed, gently blotted with a Kim wipe, and then transferred to PBS for at least an additional 24 h to remove the residual alcohol.

2.3. Drug loading procedure

To minimize the oxidation of the drug cysteamine, we sparged the PBS with nitrogen for two hours to reduce the dissolved oxygen concentration. Cysteamine was then added to the purged PBS to create a 50 mg/mL cysteamine solution. Hydrated lenses—both controls directly from commercial packaging and modified lenses from Section 2.2—were then placed into 3 mL of the drug solution in a vial, followed by further nitrogen purging for 1 min. The vials were then capped,

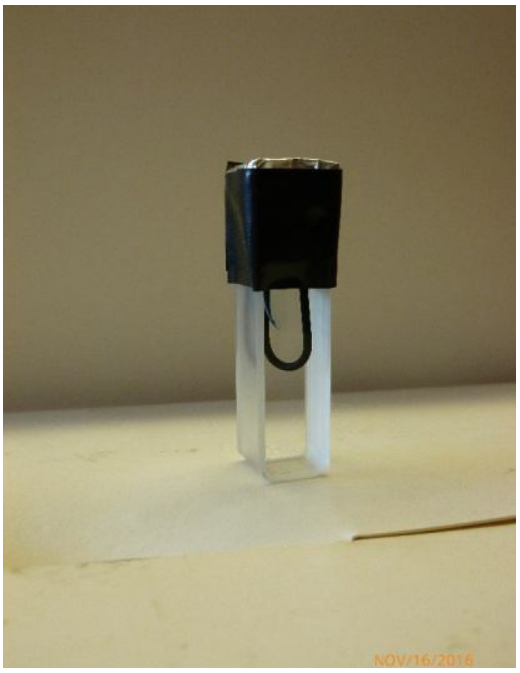

Fig. 1. Lab made sealed cuvette with a submerged contact lens to measure transient absorbance in the solution without exposure to oxygen.

wrapped with aluminum foil and duct tape, and then stored for 24 h in a refrigerator at 4 °C.

2.4. In vitro drug release experiments

The in vitro release was measured in PBS that was purged with nitrogen for 2 h. The vial for the drug loading was removed from the refrigerator and placed at room temperature for half an hour. The lens was then removed, gently wiped with a Kim-wipe and placed in a lab-made holder (Fig. 1) that included a harness attached to the lid of a quartz cuvette. The cuvette was filled with 4 mL of purged PBS, and the lid was then placed on the cuvette, which led to submerging of the harness and the lens into the purged PBS, initiating the release of the drug. The lid of the cuvette was then covered with a parafilm followed by two layers of aluminum foil and two layers of duct tape to minimize the possibility of oxygen diffusing into the cuvette. In between measurements, the cuvettes were placed in a nitrogen blanket to further reduce the possibility of oxygen diffusing in and reacting with the drug. The cuvette was periodically inserted into the spectrophotometer (Thermospectronic Genysys 10S UV–vis) to measure the spectra from 190 to 290 nm. The spectra of cysteamine and its oxidized form cystamine are significantly different so concentrations of both components can be determined by fitting the measured spectra to a linear combination of the reference spectra for both components, as described by Ref. Kim and Chauhan (2008). At high enough concentrations, the absorbance of the peak can be too high to accurately be described by Beer-Lambert's law. This violation can be shown upon fitting the spectra over the entire measured range to the calibration. In order to stay within the range of Beer-Lambert, the fitted spectra could be taken at higher spectra ranges (250–290 nm), neglecting wavelengths with too high an absorbance. The release data was fitted to a sink model, which is a good approximation due to the very high solubility of cysteamine in aqueous solutions. With this assumption, the percent released, or the mass released at time t divided by the total mass released after infinite time, is calculated to be (Kim et al., 2008):

$$Percent\ Released = 1-\frac{8}{\pi^2}\sum_{n=0}^{\infty}\frac{1}{(2n+1)^2}\exp\left(-\frac{(2n+1)^2\pi^2}{4h^2}Dt\right) \quad (1)$$

where h is half the lens thickness (~40 μm) and D is the diffusion coefficient of the drug in the lens. The experimental data for the entire release duration was fitted to the model through a least square fit to determine the diffusion coefficient. Also, the partition coefficient of drug in the lens was calculated using the following equation, which also assumes sink conditions during release,

$$K = \frac{V_{release}}{V_{lens}}\frac{C_{release}}{C_{loading}} \quad (2)$$

where $V_{release}$ and V_{lens} are the volume of the release medium and the lens, $C_{release}$ is the final concentration of the drug during release, and $C_{loading}$ is the concentration of drug in the loading solution.

For release at a larger volume, 20 mL of PBS was pipetted into a 22 mL glass scintillation vial (Fisher Scientific). This solution was purged for 2 h with nitrogen. At this point, a lens was placed into the solution, and the vial was sealed with a septum. At specific time intervals, 2 mL of solution were withdrawn from the vial and placed into a cuvette and measured. The 2 mL of solution was then returned to the vial.

2.5. In vivo drug release model

The mass of drug delivered to the cornea through contact lens wear is calculated using a mass transport model originally proposed by Hsu et al. (2013),Zhu and Chauhan (2005). The model treats POLTF, lens, and cornea as a flat, two-dimensional films of constant thickness. The curvature can be neglected as the thicknesses of these sections, or the order of 10–100 μm, are much smaller than their length, of the order of 1 cm. This gives a simplified equation for the concentration of cysteamine, C_{tear}, in the POLTF

$$V_{tear}\frac{dC_{tear}}{dt} = j_{lens}A_{lens} - K_{cornea}A_{lens}C_{tear} \quad (3)$$

where V_{tear} is the volume of the POLTF, A_{lens} is the surface area of a normal contact lens, K_{cornea} is the permeability of the cornea for the drug, j_{lens} is the mass flux of cysteamine from the contact lens into the POLTF. It should be noted that $t = 0$ occurs when the lens is inserted into the eyes, so C_{tear} is zero initially. A detailed derivation of this equation is available in Li and Chauhan (2006). By assuming that the POLTF concentrations are small relative to the lens, the system can be assumed to operate under sink conditions, where the j_{lens} can be modeled by

$$j_{lens=}\sum_{n=0}^{\infty}\frac{2C_iD}{h}\exp\left(-\frac{(2n+1)^2\pi^2}{4h^2}Dt\right) \quad (4)$$

where C_i is the concentration of cysteamine loaded into the lens, h is half the lens thickness, and D is the effective diffusivity. Using the initial condition of zero concentration in the POLTF, Eq. (3) can be solved to predict the dynamic concentration of drug in the tears in between the lens and the cornea. The mass entering the cornea, M_{cornea} is estimated by

$$M_{cornea} = \int_0^{\infty} K_{cornea}A_{cornea}C_{tear}\,dt \quad (5)$$

where K_{cornea} is the overall permeability of the drug in the cornea, A_{cornea} is the surface area of the cornea available for diffusion and C_{tear}(t) is the time-dependent concentration of drug in the tear film.

2.6. Degradation of cysteamine in contact lens inside humidification chamber

The drug loaded into the contacts will oxidize during wear due to diffusion of oxygen into the lens. To determine the extent of degradation, contact lenses loaded with drug were exposed to ambient oxygen levels. The drug loaded lenses were removed from the vials and placed

inside of a humidified chamber that was open to atmosphere to allow oxygen diffusion and maintained at a temperature of about 27 °C. The humidity kept the lenses hydrated and the exposure to the ambient conditions allowed oxygen diffusion into the lens at rates that may be comparable to the in vivo conditions. The lenses were kept in the chamber for 5 h, and then subjected to the procedures described in Section 2.4 to measure the amount of cysteamine and cystamine in the lens after 5 h of exposure to oxygen. In addition to the commercial contact lenses, degradation rates were also measured for 200 μm thick pHEMA films. The poly(hydroxyethyl methacrylate) were prepared by mixing 2.7 ml of monomer 2-hydroxyethyl methacrylate (HEMA) and 10 μL of ethylene glycol dimethacrylate (EGDMA) with 2 ml of deionized water (Kim and Chauhan, 2008). The solution was then purged by bubbling nitrogen for 10 min. Six mg of photoinitiator (Darocur® TPO) was added to the monomer mixture with stirring for 5 min and the resulting solution was immediately injected into a mold composed of two 5 mm thick glass plates separated by a 0.2-mm thick plastic spacer. The mold was then placed on Ultraviolet transilluminator UVB-10 (Ultra·Lum, Inc.) and the gel was cured by irradiating by UVB light (305 nm) for 40 min. The lenses were cut into 1 cm by 1 cm squares, and then loaded with cysteamine as described by Section 2.3 and then used for degradation rate measurements by the procedure described above.

2.7. Scanning electron microscopy imaging

The microstructure of the vitamin E barriers in ACUVE® Moist® and ACUVUE® TruEye™ lenses was explored by SEM imaging on a FEI Nova NanoSEM 430. Samples were prepared by drying the hydrogel at ambient conditions for one day. Dried samples were then cut with a precision blade to expose the cross-section and placed onto carbon tape. The samples were then coated with a single pass of gold-palladium and imaged.

2.8. In vivo safety studies

All studies were performed with prior permission from the Institutional Animal Ethics Committee and in agreement with tenets of ARVO for research in vision and ophthalmology. The study was conducted in five healthy New Zealand White Rabbits of either sex. A preliminary examination was performed to rule out any pre-existing ocular anomalies. The safety studies were conducted with ACUVUE®OASYS® lenses loaded with 20% (w/w) vitamin E on dry basis. The lenses were equilibrated with 6 mg/mL cysteamine resulting in drug loading of 120 μg. The lenses were packaged in 6 mg/mL solution of cysteamine prior to in vivo use to ensure that drug does not diffuse out of the lens prior to insertion in the eyes. Additionally, 5 mg/mL levofloxacin was added to the packaging solution as a preservative to prevent growth of any micro-organisms. It is noted that benzalkonium chloride (BAK) is used as a common preservative but it is known that contact lenses take up substantial amounts of BAK, which in turn may cause toxicity when the lenses are placed on the eyes. The vitamin E and drug loaded lenses were placed in one eye of each of the five rabbits for 24 h and replaced daily with a fresh lens for seven days consecutively. The eyes were evaluated on 24 h and 7 day post treatment and compared with pre-treated normal eyes. The animals were euthanized with an overdose of anesthetic and the eyes were enucleated and fixed in 10% formaline for histopathological examination.

2.8.1. Gross clinical examination

Gross examination was performed to evaluate any sign of opacity, irritation, congestion, blepharospasm.

2.8.2. Slit lamp biomicroscopy

The pre-treated and treated eyes of each animal were observed under slit lamp biomicroscope at 24 h, on 7th day for any sign of inflammation.

2.8.3. Flourescein dye test

Standard flourescein dye test was performed to record any defect in corneal surface following daily use of cysteamine loaded contact lens for 7 days. One drop of flourescein dye was instilled on the corneal surface and washed with normal saline and observed under slit lamp bio microscope prior to implantation, further at 24 h and on 7th day post treatment.

2.8.4. Schirmer tear test

To evaluate any change in tear formation Schirmer tear test I was performed placing standard test papers in the culdesac of medial canthus for one minute and the wetting length at one minute were recorded. Readings were taken pre treatment, at 24 h and on 7th day post treatment.

2.8.5. Cochet bonnet aesthesiometer

To evaluate if daily use of cysteamine loaded lens influences the corneal sensation; corneal sensitivity was recorded using cochet bonnet aesthesiometer. The thread in various deceasing lengths was used to stimulate the cornea mechanically and the response in form of blink reflex to each touch was recorded. Sensitivity was measured by using a Cochet-Bonnet aesthesiometer (LuneauOphtalmologie, Chartres, France), which had a 0.12 mm-diameter nylon filament with lengths ranging from 0 to 6 cm. Sensitivity was assessed in the centre of the cornea by decreasing the length of the filament in 0.5 cm steps until blink reflex was obtained after three consecutive stimulus. Cochet-Bonnet aesthesiometry was reported as filament length (cm) and also converted to pressure (g/mm^2) against the cornea by using a conversion table provided by the manufacturer (6 cm corresponded to 0.4 g/mm^2, and 0.5 cm corresponded to 15.9 g/mm^2).

2.8.6. Intraocular pressure (IOP)

The change in intraocular pressure following daily use of cysteamine loaded contact lens was evaluated at 24 h and 7 days following treatment The corneal surface was desensitized using topical anesthesia and the IOP was recorded using Tonopen (Reichet, USA) and compared to pre treatment value.

2.8.7. Specular microscopy

To evaluate if use the cysteamine contact lenses adversely influenced the corneal endothelial cell count, corneal endothelial cell count prior to treatment and at various time points after treatment i.e. 24 h and 7 days were evaluated with specular microscopy (Topcon, Japan).

2.8.8. Histology of the tissue

The cornea, iris and retina from the treated eyes were harvested and processed for histopathology. Standard protocol was followed for histopathology and staining. In brief, the tissues were dehydrated in graded alcohol, cleared in xylene and embaded in paraffin. Sections of 5 μm thickness were cut in a microtome and mounted on L lysine coated glass slides and stained with haematoxylin and eosin (H&E) using standard procedure. Stained sections were examined under microscope and imaged (Leica, Germany).

2.8.9. Pharmacokinetics

The dynamic concentrations in tears and aqueous humor were not measured in this study.

2.9. Statistical analysis

Data has been analysed using Microcal Origin software and expressed as mean ± SD. Non-paired t-test performed the comparison between groups.

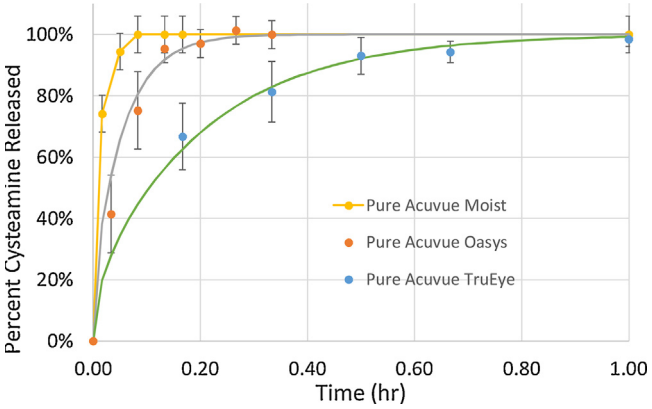

Fig. 2. Cysteamine release profiles from control contact lenses.

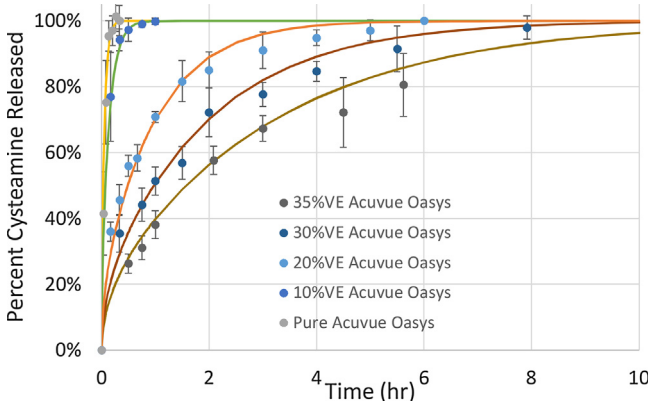

Fig. 3. Cysteamine release profiles from ACUVUE®OASYS® Vitamin E loaded lenses.

3. Results

3.1. In vitro drug release from unmodified commercial contact lenses

The release profiles for the three commercial lenses are shown in Fig. 2. The term *release duration* is defined here as the time for release of 90% of the loaded drug. All lenses exhibit rapid drug release, which is expected due to the hydrophilicity and small size of the drug cysteamine. ACUVUE® Moist® (etafilcon A) andACUVUE®OASYS® (senofilcon A) release the drug in less than 10 min, while ACUVUE® TruEye™ (narafilcon A) has a longer release duration of 35 min. The solid lines in the figures are model fits based on sink model. The values of diffusivity obtained from the fits are listed in Table 2.

3.2. Effect of vitamin E on release

All three lenses were loaded with different amounts of vitamin E to explore the dependency of the drug release durations on vitamin E loadings. ACUVUE® TruEye™ and ACUVUE®OASYS® were loaded with 10%, 20%, 30%, and 35% vitamin E (w/w on dry basis). ACUVUE® Moist® was loaded with only 20% vitamin E. Vitamin E incorporation does not significantly increase the release duration for ACUVUE® Moist® lenses (results not shown). The release duration for these lenses loaded with 20% vitamin E remains about 15 min. All prior studies with vitamin E incorporation have been conducted with silicone-hydrogel materials. ACUVUE® Moist® was explored here to determine whether the approach is effective for hydrogel lenses. The results suggest that vitamin E does not form barriers in the hydrogel lenses. Vitamin E incorporation in ACUVUE® TruEye™ lenses significantly increased the release durations to 0.90, 2.0, and 4.0 h for loadings of 10%, 20%, and 30%, respectively. For ACUVUE®OASYS®, the release durations increased to 0.89, 2.15, and 4.25 h for 10, 20 and 30% loadings, respectively. The release profiles for these two lenses can be seen in Figs. 3 and 4 . Vitamin E incorporation also affected the mass of cysteamine loaded into the lens. As seen in Table 2, both mass loaded and partition coefficients decreased for increasing Vitamin E loadings for both ACUVUE®OASYS® and ACUVUE® TruEye™. The solid lines in the figures are model fits based on sink model. The values of diffusivity obtained from the fits are presented in Table 2. Also relative increase in release durations, i.e., the ratio of release time from the vitamin E loaded lens (τ) and the control lens (τ_0) are plotted in Fig. 5 for both ACUVUE® OASYS® and ACUVUE® TruEye™ lenses.

3.3. Cysteamine oxidation inside contact lens

The degradation studies in the humidified chamber open to the ambient conditions showed that 15.6 ± 3.1% of cysteamine loaded in ACUVUE®OASYS® degraded to cystamine in 5 h. The degradation was 30.9 ± 1.9% for ACUVUE® TruEye™ lenses in 5 h. For both lenses, an increase in vitamin E loading decreased the degradation rates significantly. For lenses loaded with 20%, the degradation fraction reduced to 8.6 ± 4.2% and 17.1 ± 2.6% for the OASYS® and TruEye™lenses, respectively. These results are summarized Table 5. ACUVUE® Moist®, a brand of pHEMA lenses, was also tested to determine whether lower oxygen permeability reduces the oxidation rates. These lenses yielded a degradation of 68% in 5 h, while the lab made pHEMA gel yielded a degradation of 9.6%.

Table 2
In vitro release parameters. Drug release measured by UV-vis spectrophotometry and compared to reference spectra. Released drug used to calculate partition coefficient (Eq. (2)). Effective diffusivity was calculated using fit to solution of Fick's Law of Diffusion simplified by perfect sink assumption.

Contact Lens	Total drug release amount (μg)	Partition Coefficient, K	Effective diffusivity (10^{-5} mm^2/min)	Reference diffusivity (10^{-5} mm^2/min)*
ACUVUE® Oasys®	619.7 ± 50.1	0.534 ± 0.113	18.63 ± 1.90	21.42 ± 2.92
ACUVUE® Oasys® (10% VE)	464.0 ± 8.6	0.480 ± 0.008	7.42 ± 1.42	
ACUVUE® Oasys® (20% VE)	408.1 ± 36.7	0.396 ± 0.034	1.08 ± 0.15	1.16 ± 0.33
ACUVUE® Oasys® (30% VE)	345.0 ± 33.2	0.359 ± 0.026	0.54 ± 0.14	
ACUVUE® Oasys® (35% VE)	288.2 ± 25.2	0.301 ± 0.041	0.34 ± 0.09	
1-DAY ACUVUE® TruEye™	712.4 ± 28.6	0.741 ± 0.030	3.03 ± 0.82	
1-DAY ACUVUE® TruEye™ (10% VE)	651 ± 31.2	0.695 ± 0.072	1.49 ± 0.31	
1-DAY ACUVUE® TruEye™ (20% VE)	603.1 ± 21.2	0.628 ± 0.014	0.68 ± 0.12	
1-DAY ACUVUE® TruEye™ (30% VE)	538.9 ± 17.3	0.559 ± 0.019	0.36 ± 0.06	
1-DAY ACUVUE® TruEye™ (35% VE)	498.1 ± 65.3	0.517 ± 0.058	0.21 ± 0.03	
	n = 6	n = 6	n = 6	*from. Hsu et al., 2013

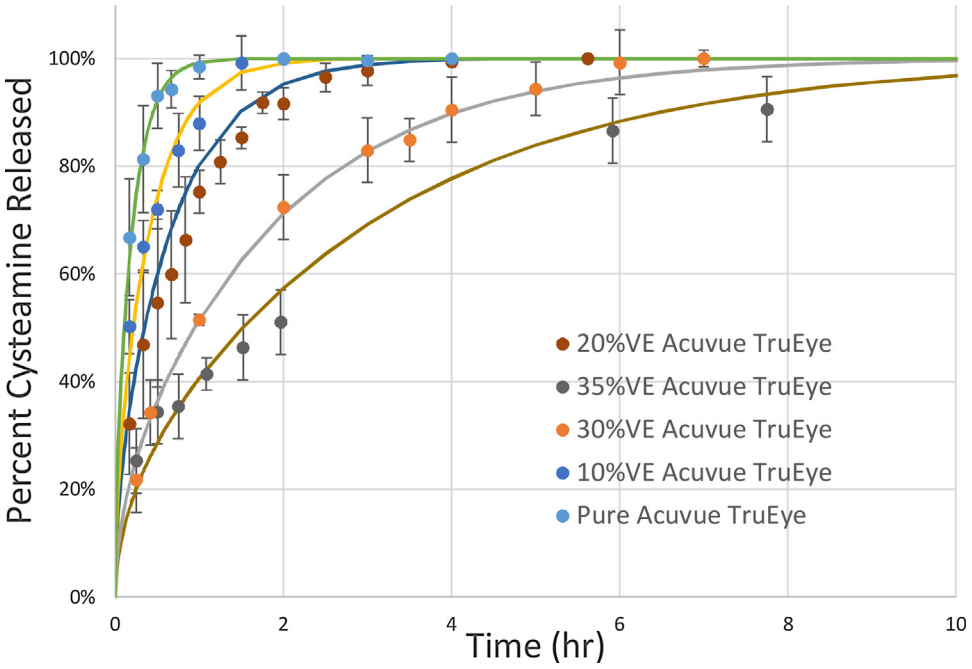

Fig. 4. Cysteamine release profiles from vitamin E loaded ACUVUE® TruEye™ lenses.

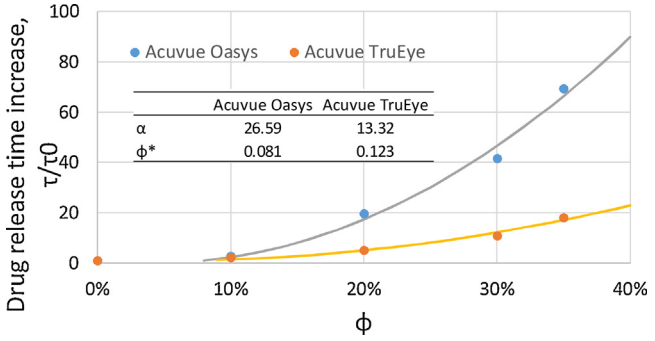

Fig. 5. Effect of vitamin E loading in silicone hydrogel contact lenses on the relative increase in drug release duration.

3.4. Modeling in vivo drug release from contact lens

The potential for cystinosis therapy by drug eluting contact lenses was tested by estimating the in vivo drug transport through a mathematical model described in Section 2.6. The parameters used in the model include geometric parameters of the lens and cornea, and transport parameters for the lens and the cornea. The geometry of both the cornea and the lens is known, so the values of the parameters are taken from literature, and listed in Table 3. The transport parameters for the contact lenses were obtained from the modeling of the in vitro release. The transport of the drug into the cornea is a complex process including both transcellular and paracellular paths, though paracellular path will likely dominate for the hydrophilic drugs such as cysteamine. Both mechanisms are lumped together into the permeability of the cornea (K_{cornea}), which is available in literature for a large number of drugs through model estimates or measurements in diffusion cells (Prausnitz and Noonan, 1998). The corneal permeability has not been measured for cysteamine, so the value was estimated based on its size and hydrophilicity to lie in the range 1.5×10^{-6} and 5×10^{-5} cm/s. For validation of these estimates, we used data of cystinosis therapy in a mouse model (Simpson et al., 2011), and used the data to estimate the corneal permeability of 1.4×10^{-5} cm/s, which lies in the estimated range. Since, there could be significant variability between mice and humans, we report our predictions for both the high and the low ends of the estimated permeability. The model for in vivo release is designed to determine the transient concentration in the tears after placing a contact lens, and to calculate the mass of the drug that reaches the cornea. Fig. 6A and B present the predicted concentration transients in the

Table 3
In vivo model parameters.

Parameter	Value	Source
A_{cornea} (surface area of cornea)	104 mm^2	Peng et al., 2012
V_{drop} (volume of each eye drop)	25 µL	Hsu et al., 2013
A_{lens} (surface area of contact lens)	230 mm^2	–
V_{tear} (volume of POLTF)	2.3 µL	Hsu et al., 2013
h (half thickness of normal contact lens)	40 µm	Creech et al., 2001

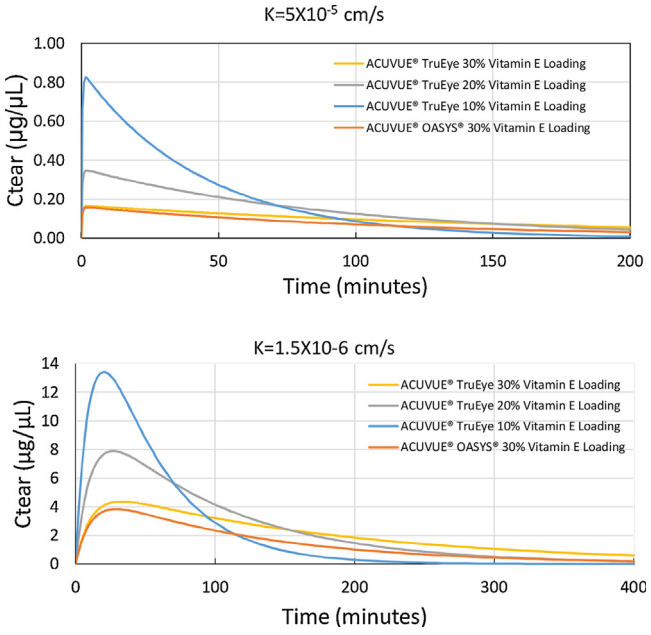

Fig. 6. Predicted concentration transients of cysteamine in the POLTF after insertion of a drug and vitamin E loaded contact lens for two different values of cornea permeability, $K = 5 \times 10^{-5}$ cm/s (A) and 1.5×10^{-6} cm/s (B).

Table 4
In vivo model results for cysteamine delivered to cornea.

Lens	Vitamin E	Predicted Mass that Reaches Cornea (μg) with respective Kcornea (cm/s)		
		1.50E-06	1.50E-05	5.00E-05
Acuvue Oasys	10%	6.97	20.86	38.06
	20%	17.93	56.97	108.16
	30%	25.55	82.65	142.55
	35%	32.18	104.96	159.58
Acuvue TruEye	10%	15.23	48.05	91.16
	20%	22.71	73.00	132.02
	30%	31.31	102.02	157.77
	35%	39.74	130.22	172.73

Table 5
Degradation results of cysteamine loaded lenses in humidification chamber with percentage degraded defined as fraction of measured drug degraded over total mass released.

Lens	Vitamin E Loading	Percent Degraded
Acuvue Moist	0%VE	68.0% ± 9.0%
p-HEMA	0%VE	10.6% ± 2.1%
Acuvue Oasys	0%VE	15.6% ± 3.1%
	10%VE	12.5% ± 0.5%
	20%VE	8.6% ± 4.2%
	30%VE	5.3% ± 1.1%
Acuvue TruEye	0%VE	30.9% ± 6.9%
	10%VE	19.0% ± 2.0%
	20%VE	17.1% ± 2.6%
	30%VE	10.4% ± 3.1%

POLTF after placing a contact lenses loaded with the drug by soaking in a loading concentration of 50 mg/mL. Fig. 6A shows the predictions for the highest estimated corneal permeability (5×10^{-5} cm/s), while 6B is for the lowest (1.5×10^{-6}).The concentration transients can be used to calculate the mass of drug that reaches the cornea. However, it is important to determine whether the cornea will exhibit toxicity to the drug concentration in the POLTF. While in vivo model discussed later are necessary to access toxicity, the mathematical models could serve as useful preliminary steps to design a system that has a good likelihood of success in the in vivo studies. Hsu et al. modeled drug concentration transients after instillation of 0.55% eye drops and obtained a maximum concentration of 3 mg/mL, or 38 mM in the tears. We assume that contact lenses should be designed such that the maximum concentration in the tears do not exceed 3 mg/mL. The results in Fig. 6 show higher concentrations, which implies that the lenses must be loaded by soaking in solutions at concentrations lower than 50 mg/mL to reduce the risk of toxicity. The model was used to determine the loading concentration that would result in a maximum concentration on 3 mg/mL in the POLTF. For the in vivo predictions shown in Table 4, the loading concentration was adjusted so that the maximum cysteamine concentration in the POLTF would be 3 mg/mL.

3.5. In vivo safety study

3.5.1. Gross examination

There was no sign of irritation, congestion, lacrimation or blepharospasmor photophobia in any cysteamine contact lens eye at 24 h and on 7th day post implantation.

3.5.2. Slit lamp biomicroscopy

Examination under slit lamp biomicroscopy showed clear transparent anterior segment in the treated eyes without any sign of inflammatory response or signs of uveitis i.e. aqueous flare. Corneal or lens opacity was also absent. The eye resembled pretreated eyes (Fig. 9).

3.5.3. Flourescein dye test

Flourescein dye test was negative in all eyes treated with cysteamine contact lens both at 24 h, 7 days after treatment (Fig. 9).

3.5.4. Shirmer tear test

There was no significant ($p > 0.05$) change in tear volume in cysteamine lens treated eyes at 24 h (8.0 ± 1.87mm/min)and on 7th day (7.0 ± 1.87 mm/min)vs pre-treatment value (6.8 ± 2.05 mm/min).

3.5.5. Intraocular pressure

There was no significant ($p > 0.05$) change in intraocular pressure (IOP) at 24 h (8.4 ± 1.34 mm/Hg), and on 7th day (8.8 ± 0.8334 mm/Hg) compared to pre-treated value (9.0 ± 0.71 mm/Hg).

3.5.6. Corneal sensitivity

The corneal sensitivity response cysteamine lens treated eyes did not vary significantly ($p > 0.05$) at 24 h (3.5 ± 0.35) and on 7th day (3.7 ± 0.27) in comparison with pretreatment values (3.8 ± 0.84).

3.5.7. Specular microscopy

There was no significant ($p > 0.05$) change in endothelial cell count in eyes treated cysteamine lens at 24 h (2406.4 ± 154.42 cells/mm^2) and on 7th day (2377.6 ± 163.30 cells/mm^2)in comparison to pre-treatment values (2337.4 ± 143.19 cells/mm^2) (Fig. 10).

3.5.8. Histopathology

There was no adverse response to intraocular tissues following daily exposure to cysteamine loaded contact lens, the cornea, iris and retina maintained normal morphology as examined by stained sections of the tissues (Fig. 10).

4. Discussion

4.1. Effect of vitamin E on release

The effect of vitamin E incorporation is significantly different in the pHEMA lenses compared to the silicon hydrogels. The silicone hydrogel lenses (ACUVUE® OASYS® and ACUVUE® TruEye™) remain fully transparent after vitamin E incorporation (Fig. 7) while hydrogel lenses (ACUVUE® Moist®) become hazy (Fig. 8). Furthermore, a 20% vitamin E loading has negligible effect on the drug release duration for the pHEMA based lenses, while the drug release duration is considerably increased in the silicone hydrogel lenses. The SEM images show that the size of the vitamin E barriers in the ACUVUE® Moist® lenses are of the order of tens of microns, which is the cause of the loss of transparency. The barrier size in the silicone hydrogel lenses is considerably smaller, although it is not possible to discern the shape and size of the barriers because the vitamin E likely redistributes in the lens during sample preparation steps such as cracking of the lens to reveal the cross-section. In a single phase material such as ACUVUE® Moist® lenses, the vitamin E is expected to phase separate into spherical particles, which could be considerably large in size. In a bi-phasic material such as silicone hydrogel lenses, it is plausible that the presence of a continuous phase boundary within the lens impacts the formation of the vitamin E barriers to take on a shape different from a spherical form due to phase separation from a hydrophilic phase. For instance, vitamin E could be deposited on the interface of the silicone and the hydrophilic phases, which would lead to thin, high-aspect ratio barriers, consistent with all observations. The increase in release duration due to vitamin E incorporation is attributed to the barrier effect, i.e., the hydrophilic drug molecules are forced to diffuse around the barriers leading to an increase in release duration. The barrier effect is dependent on the aspect ratio of the particles, which is perhaps low for the large particles in the

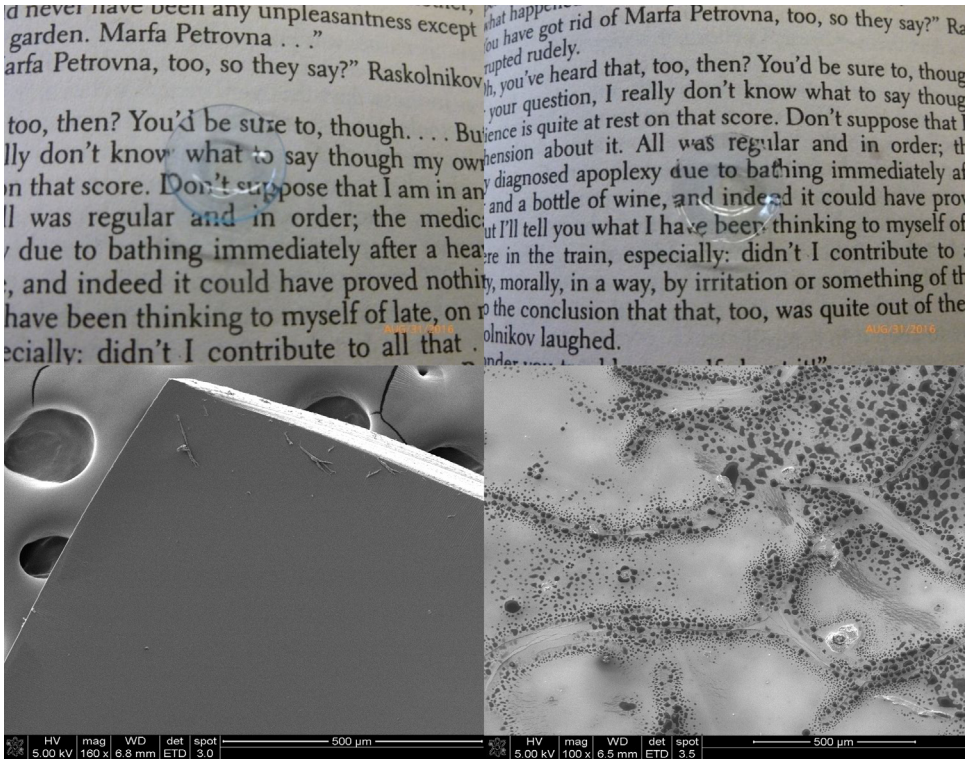

Fig. 7. Photographs of ACUVUE® TruEye™ (top left) and ACUVUE® TruEye™ 20% Vitamin E loading (top right) and SEM Images of control (bottom left) and 20% Vitamin E loading (bottom right). SEM images taken with a FEI Nova NanoSEM 430.

single phase pHEMA materials (Peng et al., 2010). As shown in Peng et al. (2010), the path length for drug molecules diffusing across the lens scales as h(1 + α(φ − φ*)), where h is the half thickness of the lens, α is a measure of aspect ratio which is unique to each lens, φ is the volume fraction of vitamin E in the dry gel, φ* is the solubility limit of vitamin E and (φ- φ*) is the fraction that is present as Vitamin E barriers. Using the time scale for diffusion of l^2/D, where l is path length and D is the diffusion coefficient, and modeling the increase in thickness as $h = h_0(1 + \varphi/3)$, where h_0 is half the thickness of a pure lens, the following relationship can be obtained for the release time τ

$$\tau \sim \frac{h_0^2}{D}\left(1 + \frac{\varphi}{3}\right)^2 (1 + \alpha(\varphi - \varphi^*))^2 \tag{6}$$

The term $(1 + \varphi/3)^2$ does not make a contribution greater than 2 and for the range of vitamin E loadings analyzed, only approaches 1.2. This term can be neglected, and the ratio of τ to τ_0, or the time scale of the

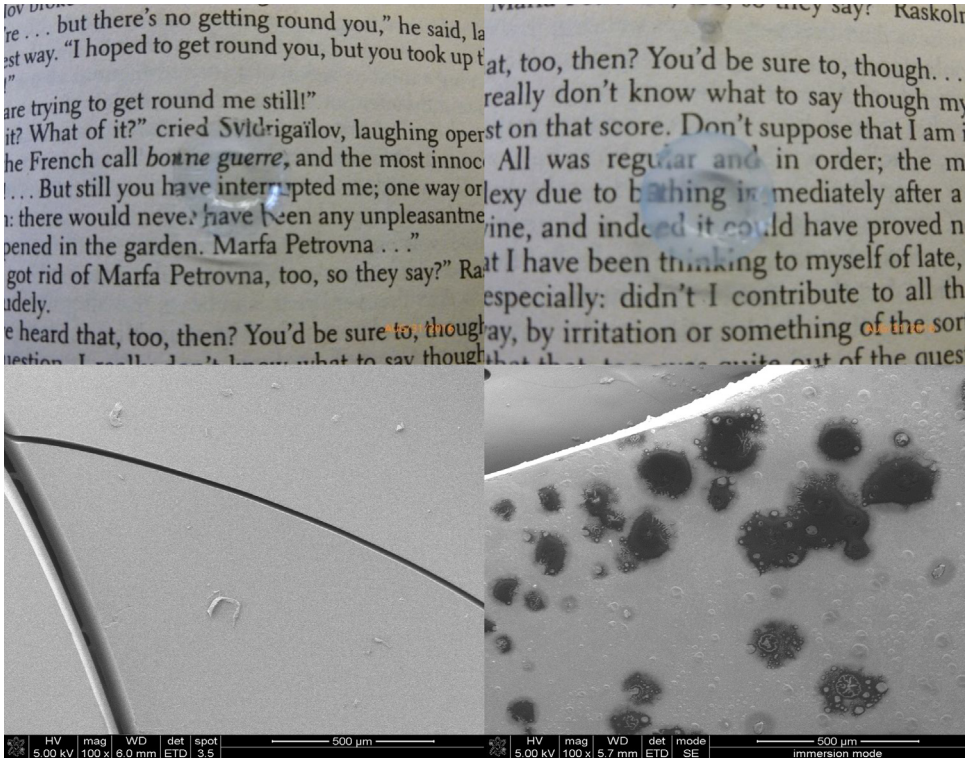

Fig. 8. Photographs of ACUVE® Moist® (left) and ACUVE® Moist® 20% Vitamin E loading (top right) and SEM Images of control (bottom left) and 20% Vitamin E loading (bottom right). SEM images taken with a FEI Nova NanoSEM 430.

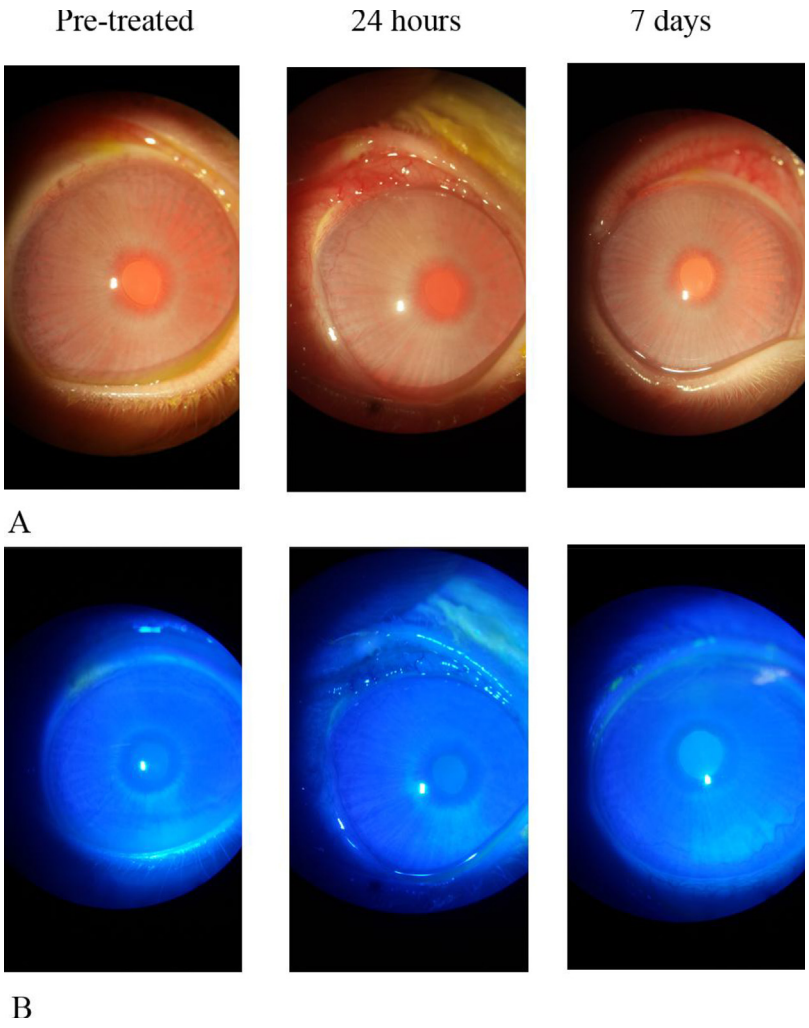

Fig. 9. Daily use of cysteamine loaded contact lenses did not incite adverse response to anterior chamber or corneal surface in rabbit eye.
Slit-lamp images of anterior chamber at different time points shows absence of inflammatory response, corneal or lens opacity (A) Corneal surface integrity was maintained, flourescein dye test was negative at all time points (B).

vitamin E loaded lens to the pure lens, can be modeled as

$$\frac{\tau}{\tau_0} \sim (1-\alpha\varphi^*)^2 + 2\varphi(\alpha-\alpha^2\varphi^*) + \alpha^2\varphi^2 \quad (7)$$

The values for α and φ* can then be determined using a least squares quadratic fit to the data for the dependency of the relative increase in release durations on the vitamin E loading. The in vitro release data shown in Figs. 1 and 2 was used to determine the relative increase in

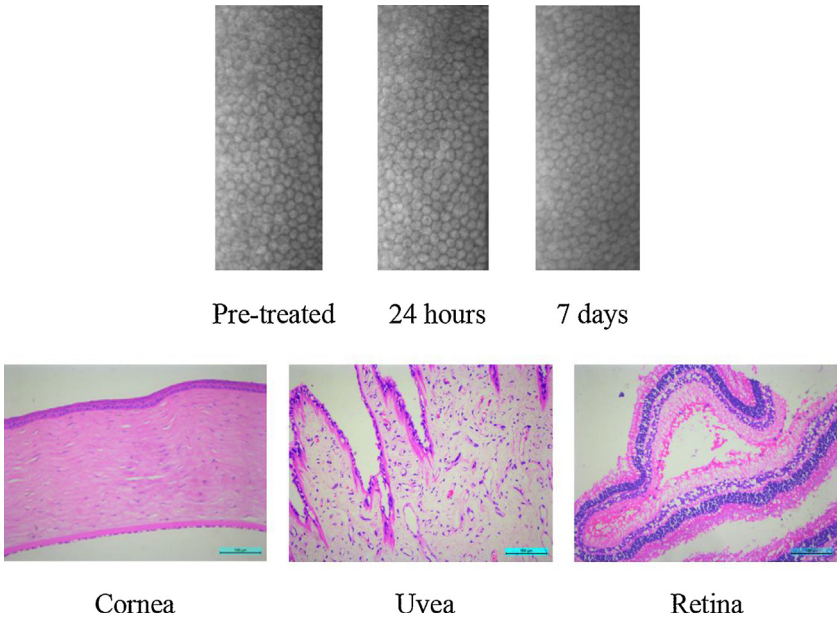

Fig. 10. Cysteamine loaded contact lens used daily for a week does not adversely influence corneal endothelial cells and ocular tissues. Specular microscopy shows normal morphology of endothelial cells at different time points which was comparable to pre-treated eyes. Sections of cornea, uvea and retina stained with H&E stain retain normal histological features.

the release duration for various vitamin E loadings. The obtained values are plotted in Fig. 5 and fitted to Eq. (7) to obtain the best fit values for α and φ* for each lens. The results show a good fit between the model and the results supporting the hypothesis regarding the barrier effect of vitamin E. The high values of α suggest that the barriers have high aspect ratio, which likely means that the barriers are forming due to the bi-continuous microstructure of the silicone hydrogels. The results seen in and Fig. 5 also show that the ACUVUE® TruEye™ has a longer release duration compared to ACUVUE®OASYS®, but the impact of vitamin E incorporation is more significant for the OASYS® lenses. The model predicts that ACUVUE®OASYS® will have longer release duration compared to TruEye™ for vitamin loadings greater than 40%.

The partition coefficient of cysteamine is less than one in both lenses, with a slightly higher value of 0.74 for 1-DAY ACUVUE® TruEye™ compared to 0.53 for the ACUVUE®OASYS®. The silicone fraction in the ACUVUEOASYS® is likely higher than that in 1-DAY ACUVUE® TruEye™ as evidenced by the water content for ACUVUE®OASYS® of 38% compared to 46% for 1-DAY ACUVUE® TruEye™. Since cysteamine is hydrophilic, a lower partition coefficient for ACUVUE® OASYS® is expected. The release duration of cysteamine is about 3-fold longer in the ACUVUE® TruEye™ lenses compared to ACUVUEOASYS®, but the relative increase in release duration due to vitamin E incorporation is much higher for the OASYS®. The effect of vitamin E is stronger in the ACUVUE® OASYS® lenses because the solubilized fraction φ* is lower and the aspect ratio is α higher. Similar results were obtained earlier with other hydrophilic drugs (Paradiso et al., 2014). The increase in release duration of the drugs due to incorporation of vitamin E will depend on the structure of the barriers, which is likely different across various types of contact lenses due to differences in the microstructure of the lenses. Since, barrier effect is absent in the

single phase hydrophilic gels, we speculate that the barriers form at the interface of the silicone and hydrophilic phases in the lenses. The mass of drug loaded and released from contact lenses decreased with vitamin E incorporation likely due to the decreased hydrophilicity of the lens from the fraction of vitamin E that was solubilized in the lens. The water content and oxygen permeability (about 100 (cm^2/s) (mL of O_2/mL) (mm Hg)) for both lenses differ less than 30%, while the diffusivity of the hydrophilic drugs differ by about 3-fold (Peng et al., 2010). This suggests that the hydrophilic channels in the TruEye™ lens may be more tortuous.

4.1.1. Validation of perfect sink model

The in vitro releases of cysteamine-loaded lenses were assumed to be perfect sink. While this assumption could be justified with the accuracy of fits to the measured release data—for example, correlation between the measured data of 20% vitamin E TruEye® and the perfect sink model gives an R^2 of 0.9958—the accuracy of the calculated diffusivities can be determined by increasing the volume of the release medium and determining if there is an effect on the amount of drug released or the release duration. A release in a volume of 20 mL of unmodified ACUVUE® TruEye™ was comparable to the release time in 4 mL of PBS. Fig. 11 shows that both releases can be modeled by the same perfect sink model. The lens also released 724.4 ± 30.3 μg (n = 5) of cysteamine, which is comparable to the 712.4 ± 28.6 μg released in 4 mL of solution. This 1% increase in release negligible and supports the assumption of perfect sink of cysteamine.

4.2. Cysteamine oxidation in contact lens

The drug degraded significantly in both types of lenses with about 15.6 and 30.9% oxidation in 5 h for OASYS® and TruEye™, respectively. The fractional degradation in 5 h decreased significantly with vitamin E incorporation for both types of silicone hydrogel lenses. The decrease was linear in vitamin E loading reaching about 5.3 and 10.4% with 30% vitamin E loading for OASYS® and TruEye™, respectively. By comparing data for TruEye™ (narafilcon A) in this study with that for TruEye (narafilcon B) in Hsu et al., we conclude that the degradation rates are higher in narafilcon A TruEye™ potentially due to the higher oxygen permeability of Narafilcon A. ACUVUE®OASYS® however has higher oxygen permeability but lower degradation rates, which implies that there is a barrier between the oxygen diffusing through the lens and the location of the drug molecules in the lens. In the bi-phasic gel, oxygen most likely diffuses along the silicone-rich channels, while the drug remains mainly in the hydrophilic regions. As discussed earlier, Vitamin E aggregates potentially form at the boundary between these two phases, and thus it creates an extra barrier between oxygen and the drug, slowing down the oxidation, even though the presence of vitamin E barriers does not retard oxygen transport (Peng et al., 2010). ACUVUE® Moist®, a pHEMA contact lens with lower oxygen permeability compared to the silicone hydrogel lenses, yielded 68% degradation after 5 h. This suggests that the environment inside the lens also plays a role in determining the rates of the drug oxidation. We hypothesize that although the overall oxygen permeability of the hydrogel lenses is lower, the entire oxygen transporting through the lens is available for oxidation. The oxygen permeability of silicone hydrogels is higher but the bulk of the oxygen is transported through the silicone phase and is not available for drug oxidation. We also measured the degradation rates in thicker lab-made pHEMA films approximately 160–180 μm in thickness. The degradation in these gels was only about 9.6% after 5 h, which shows that the overall transport barrier to oxygen also impacts oxidation rates. Thus the degradation rates depend on the oxygen transmissibility as well as the microstructure, which in turn creates barriers between the diffusing oxygen and the drug molecules. These mechanisms will likely be very different for oxidation of hydrophobic drugs.

4.3. Modeling in vivo release

As seen in Fig. 6A and B, the cornea permeability has a significant impact on concentration transients in the POLTF. The release rates from the lens are independent of the cornea permeability because the POLTF concentrations are always sufficiently low for sink conditions. The concentration in the POLTF starts at zero and then increases rapidly because the tear volume in the POLTF is very small and the concentrations are low so the mass of drug transported into the cornea is smaller than the flux from the lens. Finally, the concentration reaches a value at which the flux into the cornea exactly balances the flux from the lens into the POLTF. At this point in time, the concentration achieves a maximum, and decreases after that. Finally, after the contact lens has released the entire loaded drug, the concentration in the POLTF becomes zero. The duration of cysteamine release depends on the contact lens type and vitamin E loading, and is relatively independent of the cornea permeability because the rate limiting step is diffusion in the lens. However the concentration and the time needed to reach the peak concentrations strongly depend on the cornea permeability. The low permeability of the cornea results in higher concentration in the POLTF, and it takes longer to achieve that maximum. It is noted that only 50% of the loaded drug is released into the POLTF, with the remaining 50% diffusing into the pre-lens tear film, from where it would likely enter systemic circulation through uptake across the conjunctiva.

The eye drops concentration is limited to 0.55% (~50mM) because higher concentrations caused toxicity in animal studies on a rabbit model (Hsu et al., 2013). As described by Hsu et al, the range of corneal bioavailability in the cornea for eye drops is in the range of 1%–5%, which means that each eye drop of approximately 25 μL will deliver 6.5 μg of cysteamine to the cornea. Assuming 8 doses per day, this gives 50 μg of cysteamine to the cornea per day. Assuming that the toxicity is related to the drug concentration in the tear film, we limit the peak concentration to 3 mg/mL, which is expected to be the peak concentration after instillation of cysteamine eye drops. The concentration transients shown in Fig. 5 can be rescaled so that the maximum is at

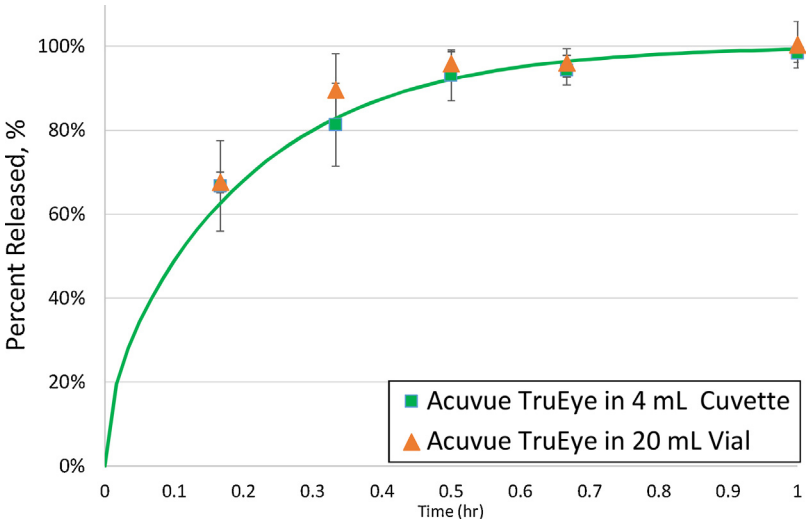

Fig. 11. Comparison of release of Acuvue® TruEye with differing release volumes. 4 mL of PBS saw a release of 712.4 ± 28.6 μg of cysteamine, and 20 mL saw a release of 724.4 ± 30.3 μg.

3 mg/mL by reducing the initial drug loading in the lens by the ratio of the maximum concentration and the desired maximum of 3 mg/mL. The reduced loading will result in less drug delivered to the cornea. The estimated drug delivered to the cornea while limiting the peak concentration to 3 mg/mL is listed in Table for the high and the low end of the cornea permeability values, as well as the permeability estimated from the published data for the mouse model. As seen in Table 4, increase in vitamin E loading increases the mass of drug delivered because the duration of release is longer and so more drug can be loaded while restricting to the limit of 3 mg/mL peak concentration in the POLTF. The predictions in Table 4 show that for vitamin E loadings of 20% or higher, the contact lenses surpass the eye drop regiment of 50 μg/day, with ACUVUE® TruEye™ delivering a higher amount than ACUVUE®OASYS®.

4.4. Safety study

Considering the promising results from in vitro design and modeling, testing safety and efficacy of the drug loaded contact lenses in an animal model would be the ideal next step. Unfortunately the common animal model for cystinosis is a knockout mice that is not suitable for wearing contact lenses. It can be argued though that demonstrating safety is more critical for this case because it is already known that about 50% of the drug released from the contact lenses reaches cornea and that the drug is effective at treating the disease. The safety studies show that cysteamine releasing contact lenses did not elicit any adverse response in the eye over a 7 day period. Cystinosis patients need lifelong therapy thus evaluation of long term usage is warranted.

5. Conclusion

This paper explores mechanisms of drug transport and degradation in vitamin E loaded contact lenses, with a goal of designing a lens for cystinosis therapy, and tests safety of the lenses in a rabbit study. Currently cystinosis therapy requires hourly instillation of eye drops, which is tedious and limits compliance. Also, the degradation of the drug after opening a bottle limits the use to about a week. All of these concerns can be eliminated by designing contact lens for cystinosis therapy. We show that ACUVUE® TruEye™ (Narafilcon A) has the longest release duration amongst all commercial contact lenses explored. The release duration is however not sufficiently long to replace the therapy of 8 eye drops each day. Vitamin E incorporation increases the release duration of both ACUVUE®OASYS® and ACUVUE® TruEye™ but the effect is more pronounced in TruEye likely due to the low solubility of vitamin E in the lens matrix and higher aspect ratio of the barriers. The barriers are not effective in hydrogel lenses, which along with the high aspect ratio in silicone hydrogels suggests that barriers could be forming at the interface of the silicone and hydrogel phases. The presence of vitamin E has an additional beneficial effect of reduction in the oxidation rates, likely due to a transport barrier between the oxygen diffusing through the silicone channels and drug located in the hydrogel phase. Based on this study, it would appear that both ACUVUE®OASYS® and ACUVUE® TruEye™ can be loaded with vitamin E to design a cysteamine eluting contact lenses for effective therapy of cystinosis. The lenses would need to be worn for about 4–5 h each day, which is consistent with the use of a daily disposable lens. Patients that require vision correction in addition to cystinosis therapy could benefit even more by using drug eluting lenses with a power that matches the prescription. Daily use of cysteamine loaded contact lens for did not elicit any adverse response in the eyes in the rabbits over a 7-day use; however, evaluation of long term usage is warranted. These results are promising but pharmacokinetic measurements in animals and efficacy studies in animals and humans are needed to prove the superiority of this approach compared to the current standard of care.

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