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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® TrueEye™(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,

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