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Controlled Release of Antibiotics From Vitamin E–Loaded Silicone-Hydrogel Contact Lenses

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ABSTRACT

Symptoms of bacterial and fungal keratitis are typically treated through the frequent application of antibiotic and antifungal eye drops. The high frequency of half hourly or hourly eye drop administration required to treat these indications is tedious and could reduce compliance. Here, we combine *in vitro* experiments with a mathematical model to develop therapeutic soft contact lenses to cure keratitis by extended release of suitable drugs. We specifically focus on increasing the release duration of levofloxacin and chlorhexidine from 1-DAY ACUVUE® TrueEye™ and ACUVUE OASYS® contact lenses by incorporating vitamin E diffusion barriers. Results show that 20% of vitamin E loading in the contact lens increases the release duration of levofloxacin to 100 h and 50 h from 1-DAY ACUVUE® TrueEye™ and ACUVUE OASYS®, respectively, which is a 3- and 6-fold increase, respectively, for the 2 lenses. For chlorhexidine, the increase is 2.5- and 10-fold, for the TrueEye™ and OASYS®, respectively, to 130 h and 170 h. The mass of drug loaded in the lenses can be controlled to achieve a daily release comparable to the commonly prescribed eye drop therapy. The vitamin E–loaded lenses retain all critical properties for *in vivo* use.

Introduction

Ocular keratitis is a common corneal condition that causes pain and light sensitivity and can lead to blindness.[1,2] Almost 50% of ocular keratitis cases are associated with infections, with bacterial infections accounting for about 80% of the total cases.[3] Millions of people all over the world are affected by bacterial keratitis with bigger impact in the Southeast Asian countries.[4] The infections are largely due to gram-positive *Staphylococcus aureus*, *Staphylococcus epidermidis*, and *Streptococcus* and *Bacillus* spp., and some gram-negative bacteria such as *Pseudomonas aeruginosa*, *Serratia marcescens*, *Moraxella lacunata*, *Microbacterium liquefaciens*, and *Haemophilus influenza*.[5] Among those microorganisms, *S aureus* and *P aeruginosa* are the principal isolates in microbial keratitis.[2,6,7] The therapy in >90% of the cases of bacterial keratitis consists in frequent eye instillation of eye drops.[8] The broad spectrum fluoroquinolone antibiotic levofloxacin (LVF) (e.g., QUIXIN®, concentration 5 mg/mL) is frequently the drug of choice for infections caused by *S aureus* and *P aeuriginosa*.[9,10] The frequency of drop application depends on the severity of the infection. A typical therapy requires application of 1-2 drops every 2 h on the first 2 days of treatment, followed by 1-2 drops every 4 h for the next 7 days.[11] Less common, but still very dangerous, are the fungal keratitis, which could lead to the perforation of the cornea and evisceration or enucleation of the eye.[12] Chlorhexidine (CHX) is an inexpensive antimicrobial agent effective against fungal keratitis. Again, in this case, the therapy involves frequent instillation of drops for a prolonged time. Typically, the patient will instill one drop half hourly for the first 3 h, then 1 hourly for 2 days, 2 hourly for 5 days, and 3 hourly for 2 weeks—a total of 3 weeks treatment.[13] This intense eye drops therapy may lead to the risk of side effects due to overdose and systemic toxicity (hepatotoxicity, nephrotoxicity, and neurotoxicity).[14-16] The high frequency of the eye drop administration likely interferes with the patient daily activities and reduces compliance, which is critical for treating infections. Moreover, the delivery of drugs by eye drops is inefficient and, in some instances, might lead to side effects.[17] Only about 2%-5% of the

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drug delivered via eye drops reaches the cornea where the infection is located,[8] and the remaining drug reaches systemic circulation through the conjunctival or the nasal path. To address the disadvantages of eye drops therapy, researchers have explored medicated soft contact lenses (SCLs). Although misuse of contact lenses such as lack of hygiene and/or sleeping with the lenses is considered the major risk factor of keratitis,[18] SCLs may also be used as ophthalmic bandages to protect the ulcerous cornea from external agents and from rubbing due to blinking.[19-25] Furthermore, drug-loaded SCLs may have a continuous therapeutic effect if providing a sustained drug release. When a drug-loaded contact lens is placed on the eye, the drug diffuses through the lens matrix and enters the post lens tear film, where drug molecules have a longer residence time compared to the case of topical application as drops.[26-28] Several research groups have shown that SCLs can increase drug ocular bioavailability and reduce drug loss by blinking and the unproductive systemic absorption.[29-33] Because keratitis therapy requires a few days of drug delivery, a contact lens designed for such therapy should exhibit extended release for at least a few days. It is well known that commercial contact lenses release drugs for only a few hours[31,34-37] and so various researchers have proposed novel approaches to increase the release durations. Chauhan et al. have proposed creation of diffusion barriers to increase the release duration of several ophthalmic drugs.[30,32,38-42] Previous studies have shown that vitamin E is not released from the contact lenses due to the negligible solubility in water or phosphate-buffered saline (PBS) making it a viable candidate as diffusion barrier.[41] Vitamin E has no irritant effect on the eye, and its benefits, for example, over cataracts and keratocyte apoptosis after surgery, were shown in previous research studies on animals.[43-46] Additionally, it has been demonstrated that vitamin E has a positive effect after topical application, due to strong antioxidant properties.[47] Considering the benefits of vitamin E incorporation, we focused on this approach for extended delivery of LVF and CHX. Although LVF and CHX are common ophthalmic drugs, there are very few prior studies focusing on transport of these drugs in contacts. A previous publication by Saramago et al.[31] reported release of LVF and CHX release from various hydrogels including a silicone hydrogel, but commercial lenses were not considered and release profiles were not satisfactory. To our knowledge, only one previous study performed by Danion et al.[48] focused on the extended delivery of LVF from commercial SCLs, whereas no study was done on the delivery of CHX. In that study,[48] the commercial contact lenses (hioxifilcon B), loaded with an LVF solution of 5 mg/mL and coated with a liposome layer, yielded a sustained drug release for 48 h.

Many researchers have proposed vitamin E–loaded contact lenses for delivery of ophthalmic drugs,[30,32,38-42] but this study has many new aspects not explored previously. First, in addition to designing the lenses for extended delivery of antibiotics, we are interested in understanding how the properties of the control lenses impact the relative benefits in drug transport achieved by vitamin E loading. To achieve our goal, we compare 2 different types of contact lenses and 2 different types of drugs, both with and without vitamin E. By comparing the release from various scenarios, we can gauge the relationship between lens properties and the effect of vitamin E. We also show that the release durations from the control lenses chosen in this study are significantly longer than some of the ones reported in literature from other drug-loaded SCLs.[34-37]

Finally, another useful contribution of this work is the characterization of the vitamin E–loaded lenses focusing on the properties that are critical to the performance of contact lenses. This aspect is important because there is the risk that, with the efforts to improve the drug release properties of a contact lens, other properties may be compromised. Besides assessing the drug release profiles, the vitamin E–loaded contact lenses were characterized for ion permeability, transmittance, and wettability. These are important properties of the lenses that have to be controlled. In particular, ion permeability was described in the seminal patent[49] as an essential feature to maintain lens motion during wear. Recently, Cerretani et al.[50] proposed a biophysical mechanism consistent with the claimed need for the critical ion permeability. Because vitamin E incorporation will reduce the ion permeability due to the diffusion barrier effect, it is critical to ensure that the level of permeability is still adequate for *in vivo* applications. Similarly, it is important to ensure that incorporation of the hydrophobic vitamin E does not reduce the wettability of the lenses.

A novel aspect of this study is the combination of the *in vitro* experiments with a mathematical model to achieve optimal design in terms of the loading of both drug and vitamin E, such that extended release is achieved while ensuring *in vivo* concentrations within the therapeutic window.

Materials and Methods

Materials

Two brands of commercial silicone contact lenses were used in this study: ACUVUE® OASYS® (Johnson & Johnson Vision Care, Inc., Jacksonville, FL), diopter-6.5, senofilcon A, 38% H_2O, and 1-DAY ACUVUE® TrueEye (Johnson & Johnson Vision Care, Inc.), diopter-8, narafilcon A, 46% H_2O. LVF (≥98%), vitamin E ((±)-α-tocopherol, ≥96%), and ethanol (≥99.5%) were purchased from Sigma-Aldrich Chemicals (St. Louis, MO). CHX diacetate hydrate (≥98%), PBS, and sodium chloride (≥99.9%) were obtained, respectively, from Acros Organics (Gent, Belgium), Corning (Manassas, VA), and Fisher Chemical (Failawn, NJ). All chemicals were used as received. Distilled and Milli-Q deionized water (DI) was used for all preparations.

Vitamin E Loading Into Lenses

Lenses with a range of vitamin E loadings (5-20 wt/wt fraction) were prepared by soaking in solutions with various concentrations of vitamin E (20-41 mg vitamin E/mL solution), according to the procedure previously described.[39-42] This range of vitamin E fractions was chosen because it was demonstrated that for vitamin E fractions higher than 20%, the ion permeability and the oxygen permeability were negatively affected.[39] Briefly, vitamin E was dissolved in ethanol by vortexing for a few seconds followed by magnetic stirring for a few minutes. Previously air-dried contact lenses were soaked in 3 mL of the solution for 3 h at room temperature to load the vitamin E. After the 3 h of loading, lenses were withdrawn from the ethanol solutions, gently blotted, and dried overnight in air. All the samples were dried in the same conditions, namely at 20 ± 1°C and for 14 h. The dried lenses were weighted and mass of vitamin E–loaded in the lenses was determined by subtracting the dry weight of the lenses. Air-dried lenses might still contain residual water, which potentially accounts for some inaccuracy on the determination of vitamin E loading.

To verify any eventual change of the hydrogel structure caused by soaking into ethanol, the contact lenses, equilibrium water content was measured before and after the 3 h of ethanol exposure, as:

$$\mathrm{EWC} = \frac{W_\infty - W_0}{W_\infty} \times 100 \quad (1)$$