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Dual drug delivery from vitamin E loaded contact lenses for glaucoma therapy

Kuan-Hui Hsu [a], Blanca E. Carbia [b], Caryn Plummer [b], Anuj Chauhan [a,*]

[a] Department of Chemical Engineering, University of Florida, PO Box 116005, Gainesville, FL 32611-6005, United States
[b] College of Veterinary Medicine, University of Florida, PO Box 100101, Gainesville, FL 32610, United States

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ABSTRACT

Glaucoma patients frequently instill eye drops multiple times each day, which is a cause for reduced compliance. Additionally, eye drops suffer from other limitations including low bioavailability, which can lead to side effects. We propose to develop drug-eluting contact lenses for managing glaucoma with increased bioavailability and improved compliance.

Contact lenses are developed for extended simultaneous release of timolol and dorzolamide, both of which are commonly prescribed hydrophilic drugs. The extended release is achieved by loading lenses with vitamin E barriers. *In vitro* release studies are performed with control and vitamin E loaded lenses for both drugs loaded separately and then together in the same lens. The safety and efficacy of combination therapy by contacts are demonstrated in a Beagle model of glaucoma.

Simultaneous loading of timolol and dorzolamide increases the release duration of both drugs. Also vitamin E incorporation is highly effective in increasing the release durations of both drugs to about 2-days. The lenses loaded with both drugs exhibited superior IOP reduction compared to eye drops with about 6-fold lower drug loading. More importantly, combination therapy by continuous wear of vitamin E loaded contact for 2-days, followed by a new set of contacts for another two days, reduced IOP during the 4 days of wear time and for another 8 days after removal of the contacts.

Vitamin E loading is very effective for providing combination therapy by contact lenses due to the increase in release durations of several drugs. The contact lens based therapy reduces IOP with lower drug dose compared to eye drops and may significantly improve the compliance as the effect of the therapy lasts significantly longer than the wear-duration.

1. Introduction

Glaucoma affects about 60.5 million people, leaving 8.4 million with bilateral blindness [1,2]. The World Health Organization estimates that by 2020 the number of cases for blindness due to glaucoma will increase to 12 million [2]. In the U.S., approximately 120,000 are blind from glaucoma, accounting for 9–12% of all cases of blindness. The financial impact of glaucoma on the US economy is in excess of $1.5 billion annually [3]. Currently, most of the antiglaucoma medications are applied topically through eye drops which are not very efficient. Due to the short residence time of drug and physiological and anatomical barriers in the eye, less than 5% of active ingredients can reach to the target tissue, with the remaining drug reaching other organs through the systemic circulation resulting in unwanted side effects [4,5]. To compensate for the low bioavailability, eye drops are often prescribed with high-frequency dosing regimens which exacerbate the side effects and additionally, reduce patient compliance. The poor patient compliance is a major problem for treating chronic diseases such as glaucoma because patients feel no instant benefit from treatment, which is accompanied by unpleasant side effects [6–8].

Contact lenses have been proposed as a potential candidate for ophthalmic drug delivery for improving bioavailability and patient compliance. The drug released from the contact lenses into the thin tear film in between the lens and the cornea has a residence time of up to 30 min, which leads to an estimated bioavailability as large as 50% [9,10]. The higher bioavailability allows reduction in the mass of drug instilled, thereby reducing the systemic uptake and the associated undesired side effects. Unfortunately, the release durations of most ophthalmic drugs from commercial contact lenses are a few hours, which is a limiting factor in drug delivery via contact lenses [11,12]. Recently, studies have focused on

* Corresponding author. Tel.: +1 352 392 9513.
E-mail addresses: vansin@ufl.edu (K.-H. Hsu), becarbia@ufl.edu (B.E. Carbia), plummerc@ufl.edu (C. Plummer), Chauhan@che.ufl.edu (A. Chauhan).

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developing novel methods for increasing the drug release durations, as summarized in several good reviews [13–16]. Chauhan and coworkers have developed extended drug release contact lens modified by vitamin E diffusion barriers which significantly increase the drug release duration while retaining transparency and other critical lens properties [17,18]. The safety and efficacy of the vitamin E loaded contact lenses were also proven in *in vivo* studies in a Beagle dog model of glaucoma [19,20]. These studies showed that vitamin E loaded contact lenses could be safely worn for extended duration of four days, with a continuous release of timolol resulting in IOP reduction comparable to eye drops, but with a reduced dose of 20% compared to the drops.

Vitamin E loaded lenses are particularly suitable for glaucoma therapy because most patients require multiple medications to control the IOP. As demonstrated by Peng et al. [17], the presence of vitamin E diffusion barriers in the contact lens reduces the drug transport rate by increasing the diffusion path length in the lens matrix, and thus the approach is effective for a large number of drugs [18,21–24]. In this study, we report *in vitro* and *in vivo* studies on the feasibility of simultaneously delivering glaucoma drugs timolol maleate and dorzolamide hydrochloride from vitamin E loaded contact lenses. These drugs were chosen because both of these drugs are commonly prescribed and the mixture of timolol and dorzolamide is also commercially available (Cosopt®). Timolol, a β-adrenergic antagonist and dorzolamide, a carbonic anhydrase inhibitor decrease IOP by inhibiting the production of aqueous humor, but through different mechanisms [25]. Previous studies have confirmed a better efficacy in lowering IOP by combination therapy than monotherapy [26–28] and fixed combination showed comparable clinical effect as concomitant therapy [29–32]. To our knowledge this is the first study proving the efficacy of simultaneous release of glaucoma drugs from contact lenses.

2. Materials and methods

2.1. Materials

Timolol maleate (⩾98%) and (±)-α-Tocopherol (synthesized vitamin E, ⩾96%) were purchased from Sigma–Aldrich Chemicals (St. Louis, MO, USA). Dorzolamide hydrochloride was purchased from Taizhou Crene Biotechnology Co., Ltd. (Taizhou, Zhejiang, China). Ethanol (200 proof) was purchased from Decon Laboratories Inc. (King of Prussia, PA, USA). Dulbecco's phosphate buffered saline (PBS) was purchased from Mediatech, Inc. (Manassas, VA, USA). All chemicals were used as received without further treatment. The contact lenses used in this study are senofilcon A (ACUVUE® OASYS™, Vistakon, Fl, USA) with diopter −3.50, based curve 8.4 mm and diameter 14.0 mm of which detailed composition is proprietary information. No further modification was done to the lenses for *in vivo* studies due to the similarity in cornea size and shape between the Beagle dogs and human.

2.2. Preparation of vitamin E loaded contact lenses

Higher vitamin E loading concentration results in quadratic increase in drug release duration, but also impairs critical contact lens properties such as oxygen and ion permeability. As shown in the previous study [17], senofilcon A loaded with a vitamin E concentration of 20% (weight of loaded vitamin E in the lens/weight of dried lens) retains all critical properties as an extended wearable contact lens. The 20% vitamin E loaded lens is transparent in appearance with only 3% increment in lens diameter which is likely to have minimum interference with the ability of the lenses to be worn successfully and to correct refractive error.

Commercial contact lenses were removed from the blister packs, rinsed with deionized (DI) water several times and then soaked in 3 ml of 40 mg/ml vitamin E-ethanol solution for 24 h. The contact lenses swelled significantly in ethanol solution which facilitates the vitamin E to diffuse into the lens matrix. Ethanol has been extensively used in contact lens manufacturing for triggering esterification of carboxyl-containing polymer [33], detaching the lens from the mold [34], extracting unreacted components in the gel [35] or coating phosphorylcholine for colored-contact lens [36] and should have negligible impact on lens' optical properties. After reaching equilibrium, the lenses were gently blotted with Kimwipes and then soaked in 350 ml of DI water to extract ethanol for an hour. The same extraction step was repeated twice until the ethanol concentration in the DI water bath was under the detection limit of UV–Vis spectrophotometry. During the extraction process, vitamin E was mostly retained in the lens because of the very poor solubility in water. The extraction of ethanol led to oversaturation of vitamin E in the lens that caused phase separation into the diffusion barriers. After extraction steps, the lens was dipped in pure ethanol for few seconds and submerged in DI water for another 1 min to wash off the vitamin E aggregates depositing on the lens surface. The vitamin E loaded lenses were then kept in 5 ml of fresh PBS solution for later use. Three contact lenses were dried in air before and after loading step to confirm the amount of vitamin E loaded into the lenses by measuring the difference in dried weights. After the dry weight measurements, these lenses were discarded and not used in the following experiments.

2.3. Determination of releasing profiles by in vitro experiments

2.3.1. Measurement of individual drug releasing profiles

Drug loaded contact lenses were prepared by soaking the lens into 3.5 ml of 0.8 mg/ml timolol maleate-PBS solution or 3.5 ml of 0.75 mg/ml dorzolamide hydrochloride solution. The control contact lenses were soaked in drug solution for 24 h and increased to 4 days for vitamin E modified ones. Next, the lenses were removed and gently blotted to remove residual drug solution on the surface. The *in vitro* drug release experiment was carried out under sink condition by soaking the drug loaded lens into 2 ml of fresh PBS and it can be assumed 100% drug release after reaching equilibrium. The concentration of drug released to PBS was measured at predetermined time points by using UV–Vis spectrophotometry (Thermospectronic Genesys 10 UV, Rochester, NY, USA) in the range of 228–315 nm.

2.3.2. Measurement of simultaneous drug releasing profiles

To load with two different drugs, the control lenses were soaked in 3.5 ml of PBS containing timolol and dorzolamide at concentrations of 2.8 mg/ml and 2.5 mg/ml, respectively; while the vitamin E modified lenses were soaked in 3.5 ml of PBS containing timolol and dorzolamide at concentrations of 12.75 mg/ml and 20 mg/ml, respectively. The time of soaking in the solution was 24 h and 4 days for control and vitamin E modified contact lenses, respectively. Next, the lens was taken out from the solution, gently blotted and the drug release experiments were carried out by soaking the lens in 2 ml of fresh PBS and measured the drug concentration in PBS periodically. The measured UV spectrum was a linear combination from the two individual drugs, namely timolol and dorzolamide. The individual drug concentration can be determined by applying the least square fit method as described in Ref. [37]. Briefly, the measured UV spectrum can be expressed as:

$$Abs_\lambda = \alpha \times Timolol_\lambda + \beta \times Dorzolamide_\lambda \quad (1)$$