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Extended drug delivery by contact lenses for glaucoma therapy

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ABSTRACT

We combine laboratory-based timolol release studies and *in vivo* pharmacodynamics studies in beagle dogs to evaluate the efficacy of glaucoma therapy through extended wear contact lenses. Commercial contact lenses cannot provide extended delivery of ophthalmic drugs and so the studies here focused on increasing the release duration of timolol from ACUVUE® TruEye™ contact lenses by incorporating vitamin E diffusion barriers. The efficacy of timolol delivered via extended wear contact lenses was then compared to eye drops in beagle dogs that suffer from spontaneous glaucoma. The lenses were either replaced every 24 h or continuously worn for 4 days, and the pharmacodynamics effect of changes in the intraocular pressure (IOP) of timolol from the ACUVUE® TruEye™ contact lenses can be significantly increased by incorporation of vitamin E. The *in vivo* studies showed that IOP reduction from baseline by pure contact lens on daily basis was comparable with that by eye drops but with only 20% of drug dose, which suggested higher drug bioavailability for contact lenses. In addition, by inclusion of vitamin E into the lenses, the IOP was reduced significantly during the 4-day treatment with continuous wear of lens.

1. Introduction

There are about 38 million contact lens wearers in the United States and approximately 125 million wearers worldwide, and the worldwide contact lens market is estimating at $6.8 billion, while the U.S. market is estimated at $2.6 billion in 2011 [1,2]. The lenses are primarily utilized as devices for vision correction, but cosmetic and therapeutic usage of contact lenses have been explored by many researchers [3–5]. Currently, more than 90% of ophthalmic drugs are delivered through eye drops, which are inefficient due to the rapid tear turnover and drug absorption in the conjunctiva. The drug loss to the systemic circulation leads to drug wastage and potential side effects [6]. Also, the short drug residence time in tears results in a low corneal bioavailability of about 1–5% and rapid clearance, which hence requires frequent instillation of drops with large drug loadings to maintain the drug concentration within the therapeutic window [3,7,8]. The drawbacks of eye drops have driven explorations in design of alternate devices for ophthalmic drug delivery including possibly delivering drugs through contact lenses. Ophthalmic drugs for treating corneal disease can be delivered very effectively through contact lenses because of the placement of the lenses on the cornea separated by a thin fluid layer called post-lens tear film (POLTF). The drug molecules released from the contact lens into POLTF will have a residence time in front of the cornea for at least 30 min, compared to 2 min for eye drops [4]. The increased residence time will lead to increase in drug bioavailability to possibly as large as 50% compared to 1–5% by eye drops [5].

To explore the concept of drug delivery by contact lens, a number of researchers have conducted laboratory-based drug release studies from contact lenses, and these studies show that both conventional and silicone hydrogel contact lenses release ophthalmic drugs in a short period of a few hours [9–11]. Recently several contact lens systems have been developed to increase the drug release duration, including nanoparticle-laden lenses [12–16], biomimetic and imprinted contact lenses [17–22], and contact lens with layered structure [23]. Also, Chauhan and coworkers recently developed a new approach of creating sustained release from silicone hydrogel contact lenses by incorporating biocompatible diffusion barriers through incorporation of vitamin E aggregates, and these vitamin E loaded lenses maintains proper oxygen permeability, ion permeability, and light refractive property to be used as extended wear contact lenses [9,11,24].

A number of research groups focusing on development of therapeutic contact lenses have focused on extended delivery of glaucoma medications from the lenses. Glaucoma affects about 60.5 million people, leaving 8.2 million with bilateral blindness [25]. It is in fact the second largest cause of blindness in the world after cataract [26,27]. Glaucoma leads to elevated intraocular pressure (IOP) in the eye and degeneration of the axons of retinal ganglion cells (RGCs), which leads to loss of vision and potentially to blindness if not treated [28]. Glaucoma is commonly managed by delivering medications that can mitigate the ocular hypertension, that is, sustained elevation of IOP above 21 mmHg in human [29]. Most

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current glaucoma therapies are based on drug delivery via eye drops one or more times daily to control the development of glaucoma [28]. Medications through eye drops are effective to lowering the IOP but only when administered appropriately. However, proper administration of topical medications requires the correct placement of the eye drop onto the surface of the globe, the correct number of administrations per day, and the correct time interval between multiple dosing and multiple medications. The challenge of topical eye drop medication unfortunately leads to poor glaucoma medical adherence [30,31] and studies suggest that fewer than half of the patients are able to maintain consistently lowered IOP with topical ophthalmic eye drops [32,33]. Moreover, the diligence and manual dexterity required for the adherence of topical eye drop medication makes it more challenge for elder people, who have higher incidence of glaucoma [34–36].

The lack of compliance associated with glaucoma therapy through eye drops could potentially be minimized by developing an extended release device in the eyes, such as contact lenses, that can deliver medication for extended periods after a single instillation. Thus, in addition to increasing bioavailability and reducing side effects, use of contact lenses for extended drug delivery could improve patient adherence and thus lead to better patient care and clinical outcomes in glaucoma. Especially, this novel drug delivery method could be beneficial to the younger glaucoma patients who were contact lens wearers prior to the diagnosis of glaucoma, which forced them to discontinue lens wear due to the need to remove lenses prior to drug instillation.

Chauhan and coworkers showed that vitamin E diffusion barriers can lead to extended release in buffered saline of several ophthalmic drugs including timolol, which is a very common glaucoma drug [11]. Additionally, a preliminary *in vivo* study with beagle dogs showed efficacy from the vitamin E loaded lenses replaced daily [37]. However both studies could achieve only about 1 day of drug release duration. Since the *in vivo* study was conducted only for daily wear and replacement, it could not prove the feasibility of extended glaucoma therapy with extended wear contact lenses.

The goals of this study are to further demonstrate that vitamin E incorporation in contact lenses can increase the release duration and that extended delivery of drugs from contact lenses can achieve desired pharmacodynamics effects. To our knowledge this is the first such study focusing on extended delivery of ophthalmic drugs from lenses worn continuously for multiple days. Timolol, a beta-adrenergic receptor antagonist, is used in this study for glaucoma therapy because it has become the 'gold standard' drug for IOP reduction since its approval by FDA in 1979 [38] and also because of the potential of significant cardiac side effects from systemic exposure to timolol [39]. Timolol is widely used for managing glaucoma in both humans and small animals by decreasing production of aqueous humor to reduce the IOP [40,41]. This study utilizes a colony of beagle dogs who are affected by or carriers of a hereditary form of primary open angle glaucoma, the most common form of glaucoma in human beings [42]. Beagle dogs have been used in several prior studies as animal models for glaucoma due to the ease of maintaining the colony, and the predictable onset and long clinical course of glaucoma, which allow various anatomic physiologic, pharmacologic, and pathologic studies [40,43–47]. Another benefit of using beagle dogs in this study is that the cornea shape and size of these dogs are similar to that of human beings, and therefore the commercially available contact lens for human can be used in this study without further modification.

2. Materials and methods

2.1. Materials

ACUVUE® TruEye™ (narafilcon A) silicone hydrogel contact lenses (diopter −3.50) manufactured by Johnson & Johnson Vision Care (Limerick, Ireland) were used in this study. The base curve and diameter of the lens are 6.5 and 14.2 mm, respectively, and the center thickness of lens is 85 μm. Timolol maleate (≥98%), ethanol (≥99.5%), and Dulbecco's phosphate buffered saline (PBS) were purchased from Sigma-Aldrich Chemicals (St. Louis, MO). Vitamin E (D-alpha tocopherol, Covitol® F1370) was gifted by Cognis Corporation. All chemicals were of reagent grade and used without further purification.

2.2. Vitamin E loading into contact lenses

ACUVUE® TruEye™ lenses were rinsed with deionized (DI) water before further use. To load vitamin E into the contact lenses, each rinsed lens was soaked in a 3 ml of 0.02 or 0.05 g/ml vitamin E-ethanol solution for 24 h. After the loading step, the lenses were taken out and subsequently submerged in 30 ml of DI water to extract ethanol. After 3 h the lens was removed into fresh DI water to repeat the extraction process. In these extraction steps, ethanol diffuses out from the lenses into the aqueous phase, while vitamin E is retained due to the negligible solubility of vitamin E in water. The retained vitamin E phase separates into nanosized barriers in the lenses. After the two-step extraction, the lenses were taken out and the excess water on the surface was blotted out. The lenses were then quickly dipped in ethanol for a few seconds to remove the vitamin E deposited on the lens surface. The lenses were then kept in fresh PBS solution before further use. A few lenses were dried and weighted to determine the amount of vitamin E loaded into the lenses for the two different concentrations of vitamin E in the ethanol solution. The dried lenses were discarded after the weight measurements and not used in drug release or in *in vivo* studies due to the concern that rehydration after drying might not lead to complete recovery of the original shape of the lenses.

2.2.1. Drug loading into the contact lenses

The drug timolol was loaded in the lenses by soaking in a 3.5 ml of 1.5 mg/ml timolol maleate-PBS solution till equilibrium was achieved. The duration of soaking was chosen to be 7 days for the control lenses without vitamin E, but was increased to 21 days for the vitamin E loaded lenses to account for the increase in uptake and release times due to the vitamin E barriers. At the end of the loading stage, the lenses were taken out and blotted to remove the excess drug solution from the surface, and subsequently used for the drug release experiments.

2.2.2. Drug release in PBS

The laboratory-based drug release experiments were carried out by soaking the drug-impregnated lenses in 2 ml fresh PBS. The dynamic drug concentration in aqueous solution was determined by measuring the absorbance at 294 nm with a UV–VIS spectrophotometer (Thermospectronic Genesys 10 UV). Since timolol has a high solubility in water, and the volume of aqueous medium is much larger than that of the hydrated contact lens, the aqueous reservoir can be considered as a perfect sink. Thus, the residual drug in the lens is negligible when equilibrium is reached, and the initial drug loading in the lens can be estimated as the total amount of drug release into the aqueous reservoir.

2.2.3. Lens preparation for the in vivo experiments

The *in vivo* experiments were done both with control lenses and lenses loaded with vitamin E. The control lenses were loaded with 60 μg timolol by soaking in a 3.5 ml of 2.5 mg/ml timolol maleate-PBS solution for 7 days, which is sufficiently long for reaching equilibrium partitioning of the drug. The vitamin E loaded lenses, which contain 0.23 g vitamin E per gram of dry lens, were designed to be worn *in vivo* for 4 days and thus were loaded with 200 μg drug by soaking in 3.5 ml of 8.0 mg/ml timolol maleate-PBS solution for 21 days to ensure the equilibrium drug concentration in the lens after loading process. For comparison, another set of control lenses were loaded with 200 μg drug by soaking in 3.5 ml of 8.0 mg/ml timolol maleate-PBS solution for 7 days. All samples were prepared and storage in a clean environment to prevent contamination of the lenses through different loading durations. It

is reiterated that for *in vivo* studies, all lenses were kept in hydrated state during the preparation process to maintain the original shape.

In the remainder of this paper, the notation CL-1 and CL-4 denote control lenses without vitamin E that are loaded with the lower (60 μg) and the higher (200 μg) amounts of drug for 1 and 4-day wear, respectively. Similarly, the notation VE-4 refers to vitamin E loaded lenses loaded with 200 μg timolol for 4-day wear.

2.3. Animal model

Before investigating the effect of these timolol loaded contact lens on glaucomatous dogs, each enrolled study dog (10 adult Beagle dogs with inherited open angle glaucoma) had their IOP estimated via applanation tonometry (Tono-Pen-XL (Mentor O and O, Norwell, MA)) in both eyes (OU) 3 times daily (08:00, 12:00 and 16:00) at the same times of day for 4 days to establish a baseline for each individual animal. A topical anesthetic (proparacaine hydrochloride 0.5%) was applied to each eye prior to the measurement of IOP OU. It is noted that one week of washout was included prior to the baseline measurement, and also prior to all other drug delivery studies. The one week washout was chosen because the half-life of timolol is about 1 hour in the dog and 2.5 to 5.5 hours in human [48–50], and thus one week is sufficiently long for the washout.

All the *in vivo* studies considered here are summarized in Table 1. The study Eye Drop is the control study in which the drug is delivered via eye drops and the IOP reduction is determined. The other three studies focus on delivering timolol via drug impregnated contact lenses. CL-1 and CL-4 are both studies with lenses without vitamin E. The difference between these two studies is that lenses were replaced daily in the CL-1 study, while the lenses were worn continuously for 4 days in the CL-4 study. The lenses in the CL-4 study release drug for less than a day and thus if the *in vivo* release profiles correlate well with the laboratory-established release profiles, the IOP reduction in the CL-4 study should not last during the entire wear time. The lenses in the VE-4 study were loaded with vitamin E to increase the release duration and were worn continuously for 4 days. This study was designed to prove that the duration of the IOP reduction increases with vitamin E loading and that continuous release of drug from contact lenses can achieve desired pharmacodynamics effect. Each of these four studies is detailed below.

Eye drop: The control study with eye drops was conducted with 10 dogs. Each study animal received one drop of timolol maleate 0.5% ophthalmic solution to the right eye (OD) twice a day (08:30 and 16:00) for 4 days. IOP OU was measured immediately after the eye drop administration during the 4 day treatment and the same time in the following day. It is noted that in this study the IOP measurement protocol is different than those for the studies with lenses due to the difference of drug administration schedule.

CL-1: After one week period for drug washout, pure ACUVUE® TruEye™ without vitamin E which was designed to release 60 μg timolol was placed in the right eyes of 8 dogs at 08:30 and IOP OU were measured at time zero and then two times daily (12:00 and 16:00) for 5 days. In these experiments, freshly drug-impregnated contact lenses replaced the previous day's lens on a daily basis every morning so that each contact lens was in the eye for 24 hours. On Day 5, the contact lenses were removed from the eye but IOP OU was continuously measured.

CL-4: Next, pure ACUVUE® TruEye™ without vitamin E which was designed to release 200 μg timolol was placed in the right eyes of 10 dogs at 08:30 in the first day and IOP OU were measured 3 times daily (08:30, 12:00 and 16:00) for 5 days. The lenses were kept in the eye for 4 days and removed at 8:30 on Day 5, followed by continuous measurement of IOP OU three times on Day 5.

VE-4: Finally, after another 1-week period of drug washout, ACUVUE® TruEye™ with 0.23 g vitamin E/g pure lens loading which was designed to release 200 μg timolol was placed in the right eyes of 10 dogs at 08:30 in the first day and IOP OU were measured 3 times daily (08:30, 12:00 and 16:00) for 5 days. The lenses were kept in the eye for 4 days and removed at 8:30 on Day 5, followed by continuous measurement of IOP OU three times on Day 5.

In each of the studies, the eyes were observed for ocular irritancy and the response was quantified according to the McDonald and Shadduck scoring system [51]. All animals in this study were housed and cared for according to the guidelines from the Association for Research in Vision and Ophthalmology (ARVO) and the Institutional Animal Care and Use Committee (IACUC) at University of Florida (UF) prior, during and after the experiments. All *in vivo* experiments procedures were approved by the IACUC at UF and were performed in compliance with the ARVO Statement for the Use of Animal in Ophthalmic and Vision Research. For all the medication methods explored in this study, no significant discomfort, irritation or ocular toxicity was observed.

2.4. Statistics analysis

Each of the measured parameters was compared between each administration method and the untreated controls to determine if there was a difference in the effects among these therapeutic methods. The drug delivery methods comparisons were performed using SPSS programs (Version 16.0 for Window®, Chicago, IL) utilizing one-way ANOVA tests for multi-comparison and Games–Howell tests for Post Hoc test since the sample size are not equal among each set of experiment run. Within each test week, the average measurements for IOP for each day were compared with subsequent measurements to detect significant changes ($P<0.05$) using the Games–Howell tests and ANOVA for repeated measurements.

Table 1
Summary of various drug delivery methods considered in this study. The drug release capacity, release duration and estimate uptake by eye were calculated based on release studies in PBS.

Method	Description	Drug release capacity	Total drug dose over 4-day treatment (μg)
Eye drop	0.5% timolol ophthalmic solution, one drop, twice a day for 4 days.	150 μg/drop	1200
CL-1	Pure ACUVUE® TruEye™, replaced daily for 4 days.	60 μg/lens	240
CL-4	Pure ACUVUE® TruEye™, continuously wear for 4 days.	200 μg/lens	200
VE-4	ACUVUE® TruEye™ with 0.23 g/g vitamin E/pure lens, continuously wear for 4 days.	200 μg/lens	200

3. Results and discussion

3.1. Drug release in PBS

The timolol release profiles in fresh PBS from ACUVUE® TruEye™ lenses with or without vitamin E are shown in Fig. 1. At room temperature, pure ACUVUE® TruEye™ released 80% of loaded timolol to PBS in the first 4 hours, and released the remaining drug in 24 hours. The drug release duration increased as the vitamin E loading inside the contact lens increased. Specifically, the duration to release 80% of the loaded timolol increased from 4 hours for the control lens to 22 and 84 hours, for the lenses with 9% and 23% vitamin E, respectively. The drug loading

in the lenses was not significantly affected by vitamin E incorporation because of the solubility of the drug in vitamin E is negligible, which forces the drug molecules to diffuse around the vitamin E barriers in the lenses leading to the increased release times. The mass of drug loaded into the contact lenses after soaking in 3.5 ml of 1.5 mg/ml drug-PBS solution was determined to be 36.6 ± 3.1 μg. The drug concentration in the loading solution did not decrease measurably due to the large ratio of fluid to lens volume and thus these experiments showed that the ratio of the drug mass loaded in the lens and the drug concentration in the solution was 0.025 ml. Based on this ratio, it was determined that lenses should be soaked in solutions at concentrations of 2.5 and 8 mg/ml to load 60 and 200 μg of drug in lenses for the subsequent in vivo experiments.

To our knowledge, this is the first study on ocular drug delivery by ACUVUE® TruEye™ lenses. The timolol release duration in PBS for the pure ACUVUE® TruEye™ is significantly higher than those from other commercial silicone hydrogel contact lens, including ACUVUE® ADVANCE™ (Galyfilcon A), ACUVUE® OASYS™ (Senofilcon A), NIGHT&DAY™ (Lotrafilcon A), O_2OPTIX™ (Lotrafilcon B) and PureVision™ (Balafilcon A) [11]. About 90% of the loaded timolol in the lens is released in 6.5 h by ACUVUE® TruEye™, while the duration for 90% release is less than 1.5 hours from other silicone hydrogel contact lenses. The partition coefficient for timolol is relatively similar among ACUVUE® TruEye™ and other silicone hydrogel contact lens.

The longer release duration from the pure ACUVUE® TruEye™ is insufficient for extended release and thus vitamin E was loaded in the lenses to increase the release duration. The timolol release duration from the ACUVUE® TruEye™ loaded with vitamin E is also significantly larger compared to other silicone hydrogel contact lenses with similar vitamin E loadings. For example, with about 23% of vitamin E loading inside the lens, 80% of the loaded timolol is released in 84 and 25 h by ACUVUE® TruEye™ and ACUVUE® OASYS, respectively [11]. It is noted that ACUVUE® TruEye™ is prescribed only as a daily wear lens even though its Dk/t of 118 for oxygen transmission is sufficient for avoiding hypoxia in overnight wear [52,53]. The sufficient oxygen permeability of ACUVUE® TruEye™ was also evident in our *in vivo* studies as there were no signs of infiltrations or cornea damage from hypoxia.

To understand the mechanism of timolol release from ACUVUE® TryEye™, it is instructive to compare the release profiles with a one-dimensional diffusion controlled model which yields the following equation for % Release at short times [9,11,54],

$$\frac{M_t}{M_\infty}(\%) = \frac{2}{\sqrt{\pi}}\sqrt{\frac{Dt}{h^2}} \times 100 \quad (1)$$

where M_t is the accumulated mass of drug released at time t, M_∞ the accumulated mass of drug release as time approaches infinity and for perfect sink condition $M_\infty = M_0$ (initial drug loading). The above equation predicts that the plot of % Release with square root of time should be linear at short times. Fig. 2 plots % timolol release by vitamin E loaded ACUVUE® TruEye™ as a function of square root of time. The lines in the figure are the best fit straight line to short-time release data (less than 70% of drug release). The fits are all good with R^2 values larger than 0.96, showing that the drug transport in these lenses is diffusion-controlled. By assuming an average thickness of 80 μm, the timolol diffusivity can be determined to be 4.5×10^{-11}, 1.1×10^{-11} and 4.0×10^{-12} m^2/s for lenses with 0%, 9% and 23% vitamin E loading, respectively. Finally, it is noted that here these experiments were conducted at room temperature (~23 °C) instead of at normal temperature of preocular tear film (~35 °C). While the drug release should depends on temperature, based on Stokes-Einstein equation [55], the ratio of diffusivity between room temperature and physiologic temperature can be estimated as (296 K)/(308 K) = 0.96. Thus, it is reasonable to use these laboratory-established drug release results for the design of subsequent *in vivo* experiments.

3.2. In vivo studies

3.2.1. Baseline IOP measurements

The daily variations in the baseline IOP are shown in Fig. 3. For both IOP OD and OS, there are no significant day-to-day differences ($p = 0.893$ for OD and 0.498 for OS), which is as expected. Thus, the baseline IOP is averaged for all days to yield 31.34 ± 0.94 and 29.56 ± 0.87 mmHg for OD and OS, respectively. It is noted that the difference between the baselines of OD and OS (1.78 ± 1.28 mmHg) is not significant ($p = 0.348$).

3.2.2. Timolol treatment in beagle models

The mean ± SEM changes in IOP for each of the tested timolol delivery methods are summarized in Fig. 4 and discussed below.

Eye drop: For timolol delivery by eye drops twice a day, the IOP measured in treated eye had no significant in day to day variation ($p = 0.936$). The IOP in the treated eye decreased from baseline by 4.53 ± 2.29, 6.15 ± 2.30, 5.15 ± 2.08 and 3.65 ± 2.23 mmHg for each day during the drug administration from Day 1 to Day 4, respectively. However, these daily difference were not significant

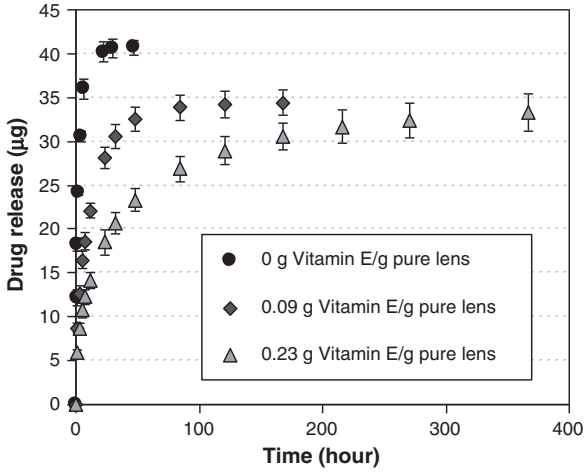

Fig. 1. Timolol release in PBS by ACUVUE® TruEye™ with various vitamin E loadings. Drug was loaded by soaking the lens in a 3.5 ml of 1.5 mg/ml timolol maleate/PBS solution. Data are shown as mean ± S.D with n = 3.

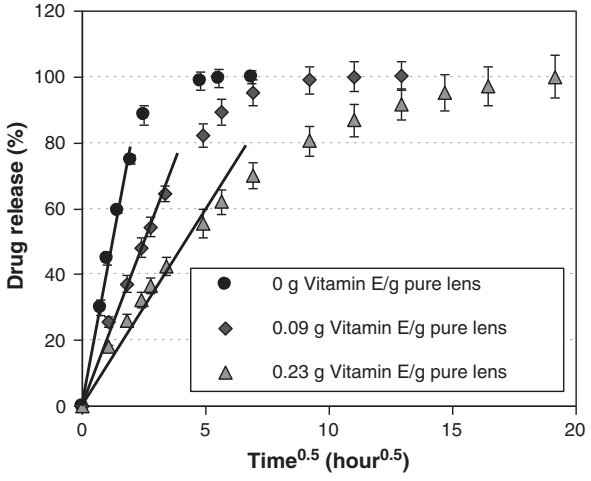

Fig. 2. Timolol release (%) by vitamin E loaded ACUVUE® TruEye™ versus square root of time. The lines are the best fit straight lines. The fitted slope and R^2 are 40.11 and 0.989, 19.79 and 0.991, 11.89 and 0.960 for lenses with 0%, 9% and 23% of vitamin E loading, respectively. Data are presented as mean ± S.D. with n = 3.

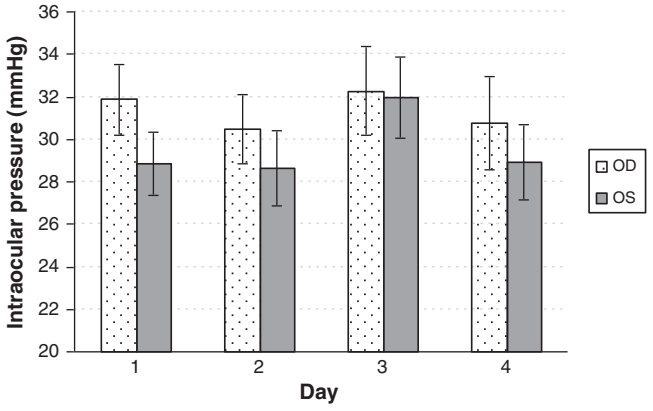

Fig. 3. Baseline measurement of intraocular pressure at right (OD) and left eye (OS) of 10 beagle dogs. Data are presented as mean ± SEM.

($p = 0.388$, 0.123, 0.170, and 0.585, respectively). The IOP in the treated eye was insignificantly lower than the baseline by 3.99 ± 2.91 ($p = 0.744$) on the fifth day even though drug was delivered only for the first four days. No significant difference was detected among IOP reading of each day from baseline in the untreated eye ($p = 0.962$).

CL-1: When timolol was delivered by drug loaded ACUVUE® TruEye™ replaced daily, the daily IOP in the treated eye was significantly decreased from baseline by 6.09 ± 2.00 ($p = 0.045$), 9.21 ± 1.72($p < 0.001$),7.46 ± 1.93 ($p = 0.005$)and 6.01 ± 1.92 mmHg ($p = 0.037$) from Day 1 to Day 4, respectively. The IOP OD was lower than the baseline on Day 5 as well (6.51 ± 1.97 mmHg, $p = 0.024$) even though drug was not delivered beyond Day 4. There was no significant day-to-day difference in IOP OD ($p = 0.630$). For untreated eye, there was no significant difference among the IOP on any day and the baseline ($p = 0.422$).

CL-4: The mean ± SEM change in IOP caused by extended-wear of timolol loaded contact lenses is also summarized in Fig. 4. When pure ACUVUE® TruEye™ with 200 μg timolol were placed on the eye, the IOP of the treated eye was significantly decreased from the baseline by 6.09 ± 2.00 mmHg in the first day ($p = 0.043$), but the IOP difference from baseline became insignificant after Day 2 in the treated eye. During Day 3 and beyond, the IOP in treated eye was significantly higher than that in Day 1 (5.79 ± 2.37 mmHg, $p = 0.017$) and comparable to the baseline. For the untreated eye, the IOP did not significantly differ from the baseline ($p = 0.206$) or among each day ($p = 0.188$).

VE-4: Finally, for drug delivery by vitamin E loaded ACUVUE® TruEye™ lens, the IOP in the treated eye decreased from baseline by 4.01 ± 1.62 ($p = 0.140$), 4.34 ± 2.34 ($p = 0.447$), 6.34 ± 2.53 ($p = 0.158$) and 8.62 ± 2.44 ($p = 0.019$) mmHg from Day 1 to Day 4, respectively. No significant day-to-day difference in IOP OD was observed from Day 1 to Day 5 ($p = 0.519$). Also, no significant difference of IOP in the untreated eye was detected from baseline (0.612) or among each day (0.765).

In our studies, the daily IOP in treated eye was reduced by each of the approach for delivering timolol. The reduction in IOP was maintained for five days by drug delivered through eye drops, CL-1 and VE-4 even though the drug was not delivered beyond Day 4. This suggests that the effect of timolol on IOP is maintained for a day even after cessation of drug delivery, possibly due to accumulation and

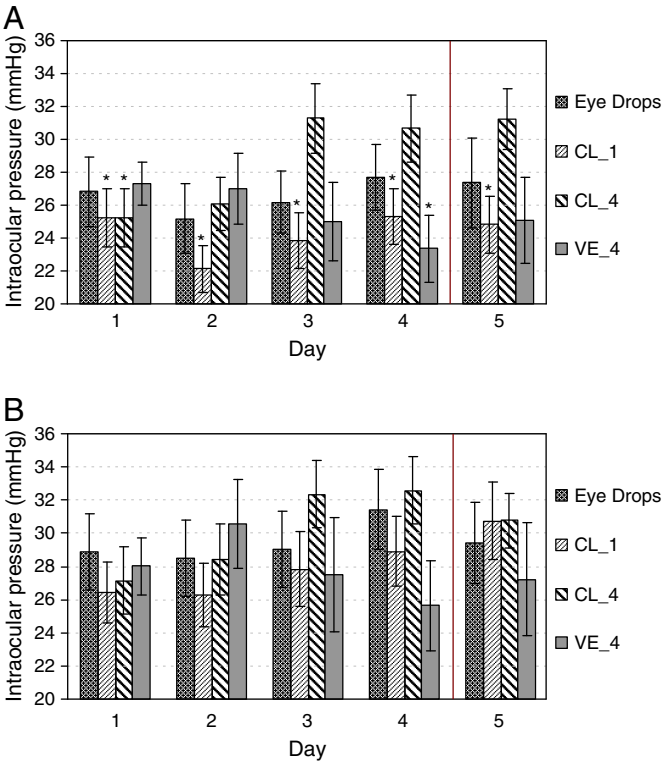

Fig. 4. Intraocular pressure measurement of a) OD (treated eye) and b) OS (untreated eye) with various timolol medication methods. All methods were conducted for 4-day duration while the measurement continued in the subsequent day after last drug administration. Data are presented as mean ± SEM, and * indicated significant difference from baseline ($p < 0.05$).

eventual release of drug in ocular tissue. For the case of drug delivered by CL-4, the IOP in the treated eye was significantly lower than the baseline on the first day, but it increased to the baseline after 2 days. This is consistent with the observation from laboratory-based drug release experiments which showed that pure ACUVUE® TruEye™ lens releases 90% of the loaded timolol in 6.5 hours. The agreement between the release duration in PBS and the duration of the *in vivo* IOP reduction suggests that there is a good correlation between the laboratory-based drug release studies in perfect sink and the *in vivo* release in the eye. It should be noted that the drug transport into the cornea and the conjunctiva along with the tear turn over combine together to create the perfect sink conditions.

3.2.3. Comparison of IOP reduction from various drug delivery approaches

To evaluate the efficacy of each timolol delivery approach, all the measurements for IOP were averaged over the measured duration and compared with each other, and the results were summarized in Table 2. For the IOP in the treated eye, when timolol was delivered by eye drop or pure ACUVUE® TruEye™ replaced daily, the IOP were significantly decreased from baseline by 4.87 ± 1.37 ($p = 0.004$) and 7.19 ± 1.25 mmHg ($p < 0.001$), respectively. For extended-wear contact lenses, the IOP OD decreased from baseline by pure ACUVUE® TruEye™ lenses without vitamin E but the reduction was not significant during the 4-day treatment (2.99 ± 1.34 mmHg, $p = 0.174$). The ACUVUE® TruEye™ lenses with vitamin E loading lowered the IOP in the treated eye from baseline by 5.09 ± 1.32 mmHg ($p = 0.001$) for 4 days. In addition, there was no significant difference in IOP OD among eye drop, CL-1 and VE-4 ($p = 0.170$) in the 4 days. Finally, there was no significant difference of IOP in untreated eye among all the treatment methods ($p = 0.314$).

The CL-1 drug delivery approach, i.e., daily replacement of the drug loaded ACUVUE® TruEye lens™ lowered IOP comparable to

Table 2
Comparison of IOP among different treatment methods during 4-day treatment regimen. Data are presented as mean ± SEM, and * indicated significant difference from baseline ($p<0.05$).

Method	IOP OD (mmHg)	IOP OS (mmHg)
Baseline	31.34 ± 0.94	29.56 ± 0.87
Eye drop	*26.74 ± 0.99	29.47 ± 1.15
CL-1	*24.15 ± 0.82	27.35 ± 1.01
CL-4	28.35 ± 0.96	30.18 ± 1.04
VE-4	*26.25 ± 0.93	28.03 ± 1.22

the eye drop therapy, proving the potential of using contact lenses for managing glaucoma. This is consistent with the results from some earlier study for medicated contact lenses for glaucoma therapy demonstrated in small human trials. The human trials by Schultz et al. [56] involved three glaucoma patients who wore contact lenses prior to glaucoma detection but then stopped using lenses due to the difficulty in administering glaucoma drugs while wearing lenses. These patients were provided lenses that they were originally using, except that the lenses were loaded with their prescribed glaucoma drug (timolol maleate or brimonidine tartrate) by soaking the lenses in the drug solution. The patients were subjected to a three-week washout period, after which they were instructed to wear the drug infused lenses for 30 minutes each day in the morning for two weeks. The results showed that use of the lenses on daily basis maintained IOP at levels equivalent to those obtained with previous eye drop treatment, and no sign of ocular toxicity was observed.

It is also noted that in our study the daily replacement of contact lenses (CL-1) achieved the same IOP reduction as eye drops with a drug dosing of only 20% of that in eye drop treatment. This result of comparable efficacy with lower drug dose can also be observed in previous studies focusing on management of glaucoma with hydrophilic Sauflon lenses soaked in pilocarpine by Hillman et al. It was reported that the clinical response to the contact lens soaked in 1% solution was better than that for intensive pilocarpine 4% eye drop therapy [57–59], even though the mass of drug delivered by the eye drop therapy was substantially larger than that loaded in the lenses. Also, Hiratani et al. recently conducted an *in vivo* study in rabbit model to evaluate the usefulness of molecular imprinting technology to obtain therapeutic soft contact lens capable of prolonging the permanence of timolol in the precorneal tear film, compared to conventional contact lenses and eye drops [19]. The results of this study suggested that drug release through contact lens has higher precorneal residence time than that through eye drops. In addition, conventional contact lens with only 17% of the drug dose in eye drops resulted in similar area under the timolol concentration–time curve (AUC) in 3 hours. The *in vivo* results in literature and those reported here support the model predictions of Li and Chauhan regarding higher bioavailability of contact lenses compared to drops [5]. The increased bioavailability reduces the therapeutic dosage of drug loaded in the lens, and more importantly reduces the amount of drug that is lost to the systemic circulation, which has the potential for causing unwanted side effects.

The *in vivo* study was also utilized to estimate the mass of vitamin E that could be released directly in the tears during lens wear. The lenses were from the dogs after the desired wear time and the weight of the dried lenses was compared with the weight of similar dried vitamin E lenses that was not inserted into the eyes. There was no significant difference in the weights which suggests that vitamin E is not released into the tear film. This result is in agreement with previously reported studies in which vitamin E was not released into PBS even during six months of packaging [11]. It is however encouraging that the presence of tear proteins, mucins and other biomolecules does not drive vitamin E diffusion into the tears. It is noted though that some "surfactant-like" drugs (e.g. lidocaine and tetracaine) can facilitate release of vitamin E into PBS, and possibly into the tear film. However, the amount of vitamin E released by the lens even in such cases is small and likely non-toxic, particularly considering the use of vitamin E as a nutritional supplement [60].

Lastly, the aforementioned *in vivo* studies were all conducted with contact lenses that were placed in the eye for a short period of time, or at most replaced daily. While daily replacement of contact lenses has the benefits of increased bioavailability, it will likely not increase patient compliance, which is a major problem in glaucoma therapy. Controlled release of glaucoma drugs from extended wear contact lenses could potentially lead to increased compliance particularly for the glaucoma patients that also require vision correction. Though there is an extensive literature on laboratory-based studies for extended release of ophthalmic drugs through contact lenses in aqueous solutions, there are no studies that prove therapeutic efficacy of extended release from contact lenses. In our studies, we successfully prove that drug and vitamin E impregnated extended-wear contact lenses can be safely worn for an extended period of time while providing therapeutic effects comparable to eye drops. While pure ACUVUE® TruEye™ lens failed to lower IOP from baseline after continuously wear for 2 days, lenses with about 20% of vitamin E loading showed similar efficacy as traditional eye drop treatment that required 2 drops per day for 4 days.

4. Conclusions

This study successfully demonstrates the potential advantages of delivering ophthalmic drugs through contact lenses for the treatment of ocular disease such as glaucoma. Contact lenses used on daily basis achieved same efficacy as eye drops but with only 20% of the drug loading. Incorporation of vitamin E into the lenses can significantly increase the drug release duration from a few hours to several days, and the *in vivo* results shows that IOP can be significantly lowered from baseline by continuously wearing ACUVUE® TruEye™ with 20% vitamin E loading. No sign of discomfort or ocular toxicity was observed for contact lens wear. It is noted that ACUVUE® TruEye™ is currently marketed as daily disposable contact lens by the manufacturer even though it possesses adequate oxygen permeability for overnight wear. Even though the animals in our study did not show any signs of discomfort or corneal damage from hypoxia, further examination is needed to ensure whether the ACUVUE® TruEye™ lenses are suitable for extended wear. Moreover, experiments focused on varying the drug dosing in the lens and direct pharmacokinetics studies should be conducted to further understand the mechanisms and evaluate the benefits of ophthalmic drug delivery by contact lenses.

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