Journal of Controlled Release 148 (2010) 110–116

Contents lists available at ScienceDirect

Journal of Controlled Release

journal homepage: www.elsevier.com/locate/jconrel

Extended release of dexamethasone from silicone-hydrogel contact lenses containing vitamin E

Jinah Kim, Cheng-Chun Peng, Anuj Chauhan *

Department of Chemical Engineering, University of Florida, Gainesville, FL 32611, United States

ARTICLE INFO

Article history:
Received 12 March 2010
Accepted 23 July 2010
Available online 4 August 2010

Keywords:
Dexamethasone
Contact lens
Silicone hydrogel
Vitamin E
Drug delivery
Barriers
Model
Extended release

ABSTRACT

Ophthalmic drug delivery by contact lenses is expected to be more efficient due to continuous extended release of drug and increased residence time in the tear film. However, commercial contact lenses release ophthalmic drugs for a short period of about an hour and are thus not suitable for extended delivery use. Here we explore a novel approach of increasing the release duration of dexamethasone (DX) from commercial contact lenses by loading Vitamin E into the lenses. The Vitamin E was loaded into the lenses by soaking the lenses in Vitamin E–ethanol solution followed by ethanol removal through evaporation. The results show that with about 30% of Vitamin E loading in the contact lens, the DX release time can be increased to 7 to 9 days for ACUVUE® OASYS™, NIGHT&DAY™, and O_2OPTIX™, which is a 9 to 16 fold increase compared to the DX release duration by pure contact lens without Vitamin E loading. The DX delivery by contact lens can be viewed as a one-dimensional transport by a flat thin film, and a mathematical model based on the drug diffusivity difference between Vitamin E and silicone hydrogel was also proposed to explain the DX release time increase by Vitamin E loaded contact lens.

1. Introduction

Ophthalmic drug delivery via soft contact lenses has been widely studied recently due to the high degree of comfort, biocompatibility, and significant increase in drug residence time and bioavailability associated with contact lenses compared to drug delivery via eye drops, which accounts for about 90% of all ophthalmic formulation currently [1–4]. Eye drop treatment is extremely inefficient, since only less than 5% drugs get absorbed, and the remaining drug enters the bloodstream by transnasal and conjunctival absorption, which might lead to serious side effects [5]. Furthermore, application of ophthalmic drugs as drops results in a rapid variation in drug delivery rates to the cornea that limits the efficacy of therapeutic systems, and the requirement of frequent application leads to lower patient compliance [6].

Silicone hydrogel contact lenses can be prescribed for extended wear lasting several weeks due to their high oxygen permeability, and thus these lenses are the most suitable candidates to serve as extended drug delivery vehicles. However, Karlgard et al. measured the *in vitro* delivery of several ophthalmic drugs by commercially available HEMA based and silicone contact lenses [7] and showed that a majority of the drug taken up by the gels was released within a few of hours. To increase drug release durations, Chauhan and coworkers have proposed the development of nanoparticle laden gels that can be loaded with a substantial amount of drug, which can be released at a controlled rate from the nanoparticles [8–11]. Also, a number of researchers have focused on developing biomimetic and 'imprinted' contact lenses [12–17]. The imprinting leads to an increase in the partition coefficients and slower release of drugs. While the approaches listed above are effective at increasing the drug release duration from contact lenses, all studies focused on hydrophilic hydrogel based contact lenses, which are not suitable for extended wear due to limited oxygen permeability. Kim et al. [18] recently developed new silicone-hydrogel materials that showed extended release of timolol and dexamethasone for times ranging from 2 weeks to 3 months from 100 μm thick gels. However, these materials have not been utilized as contact lenses so extensive *in vitro* and *in vivo* testing is needed to demonstrate the suitability of these materials for use as contact lenses.

In a recent study, Peng et al. showed that the release duration of hydrophilic drugs from commercial silicone-hydrogel contact lenses can be significantly increased by incorporating Vitamin E into the lenses [19]. Specifically, about 20% loading of Vitamin E in commercial contact lenses such as NIGHT&DAY™ increases the release duration by a factor of about 40 while reducing ion and oxygen permeability by 90 and 20%, respectively. The reduced values of ion and oxygen permeability are still sufficient to ensure on-eye movement and prevent corneal hypoxia. The Vitamin E loaded lenses exhibit slower release of hydrophilic drugs because Vitamin E is a hydrophobic solute and so hydrophilic molecules need to diffuse around the Vitamin E barriers leading to an effective increase in release times.

The current study focuses on the novel approach of developing extended drug release contact lenses for hydrophobic drugs by

* Corresponding author. Chemical Engineering, University of Florida, Gainesville, FL 32611-6005, United States. Tel.: +1 352 392 2592; fax: +1 352 392 9513.
E-mail address: Chauhan@che.ufl.edu (A. Chauhan).

0168-3659/$ – see front matter © 2010 Elsevier B.V. All rights reserved.
doi:10.1016/j.jconrel.2010.07.119

creating barriers in the lenses which retard drug diffusion without significantly impacting oxygen transport, which is a key requirement for extended wear. We propose that hydrophobic molecules could partition and diffuse through Vitamin E and the high viscosity of Vitamin E will lead to reduced diffusivity. To test this hypothesis, we explore the transport of dexamethasone, a hydrophobic corticosteroid through Vitamin E laden silicone hydrogel contact lenses.

Dexamethasone is a glucocorticoid steroid that relieves eye inflammation and swelling, heat, redness, and pain caused by chemicals, infection, and/or severe allergies. Prolonged systemic administration of steroid can cause serious side effects such as diabetes, hemorrhagic ulcers, skin atrophy, myopathies, osteoporosis and psychosis [20]. In view of the potential for side effects, controlled release of dexamethasone from contact lenses could be clinically useful. Furthermore, there are several other ophthalmic drugs that are hydrophobic and have size similar to dexamethasone, and thus it can be considered as a test drug to explore transport of small, hydrophobic molecules through Vitamin E-laden silicone hydrogel contact lenses. This study will lead to an understanding of the effect of Vitamin E loading on extended drug delivery for hydrophobic drugs, which in turn will allow for rational design for extended release of other drugs from the lenses. Additionally, the results of this study could be applied to design of extended wear devices for several other drug delivery applications.

2. Materials and methods

2.1. Materials

Five commercial silicone contact lenses (diopter-6.50) are used in this study, including ACUVUE® ADVANCE™ and ACUVUE® OASYS™ from Johnson&Johnson Vision Care, Inc. (Jacksonville, FL), NIGHT&DAY™ and O_2OPTIX™ from Ciba Vision Corp. (Duluth, GA) and PureVision™ from Bausch&Lomb, Inc. (Rochester, NY). Dexamethasone (DX, 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 kindly provided by Cognis Corporation. All chemicals were used as supplied without further purification.

2.2. Drug loading into pure lenses

The commercial silicone contact lenses were rinsed with deionized (DI) water and then air-dried before further use. To evaluate the effect of different loading approaches, DX was loaded into the lenses by either soaking the lens in either 2 ml of a drug-PBS solution for 1 or 7 days or in the same volume of a drug–ethanol solution for 3 h. While soaking the lens in either solution, the dynamic concentration in the solution was not monitored. At the end of the loading stage the lens was taken out and excess drug solution was blotted from the surface of the lens. The lens was then air-dried and subsequently used for release experiments.

2.3. Vitamin E loading into pure lenses

Vitamin E was loaded into lenses by soaking the lens in 3 ml of a Vitamin E–ethanol solution for 24 h. Vitamin E–ethanol solutions of various concentrations were prepared as reported in our earlier study [19]. After the loading step, the lens was taken out and excess Vitamin E–ethanol solution on the lens surface was blotted out, and the lens was then air-dried overnight. The Vitamin E loading amount was determined by measuring the weight of dry lens before and after loading Vitamin E into the lens. The linear correlation of Vitamin E loading in the lens to the concentration of Vitamin E loading solutions was also reported in our earlier study [19].

2.4. Drug loading into Vitamin E loaded lenses

The drug was loaded in Vitamin E loaded lenses either by directly adding drug in the Vitamin E–ethanol solution before soaking the pure lens in the solution or by soaking the Vitamin E loaded lens in a drug-PBS solution. For the case of adding drug in a Vitamin E–ethanol solution, the drug was dissolved in 3 ml of a Vitamin E–ethanol solution and then the pure lens was soaked in the drug/Vitamin E–ethanol solution for 24 h. For the case of soaking in drug-PBS solution, the Vitamin E loaded lens was soaked in 2 ml of a drug–PBS solution until equilibrium. While loading DX into lenses, changes in drug concentration of soaking solution were monitored. The total amount of drug loaded into the gel was determined by finding the total amount of drug-loss from the aqueous solution by measuring the absorbance of final solution after soaking at 241 nm for DX with a UV–VIS spectrophotometer (Thermospectronic Genesys 10 UV).

2.5. Drug release experiments

The drug release experiments were carried out by soaking a drug loaded lens in 2 ml of PBS. During the release experiments, the dynamic drug concentration in PBS was analyzed in the same manner as described above for the drug loading experiments. Control experiments were conducted to ensure that diffusion of Vitamin E from the lenses was negligible and thus did not interfere with the drug detection.

2.6. Viscoelastic measurement

The viscoelastic response of pure Vitamin E was measured as a function of frequency with 0.1% strain in a cone and plate rheometer (AR-G2, TA Instruments, New Castle, DE) with 1000 μm gap at 25 °C.

3. Results and discussion

3.1. Transparency of the Vitamin E-laden contact lenses

An image of a Vitamin E loaded contact lens is shown in Fig. 1. As evident from the image, the Vitamin E loaded lenses are transparent irrespective of the Vitamin E loading, but attain a slightly yellowish color at high Vitamin E loadings. Other key properties of Vitamin E loaded lenses such as ion and oxygen permeability are suitable for extended wear applications, as shown previously [19].

3.2. Dynamics of drug transport from contact lenses without Vitamin E

The DX release profiles from five different contact lenses for three different loading methods are shown in Fig. 2. Since DX is a hydrophobic drug and has limited solubility in PBS, DX-PBS solution of 0.08 mg/ml, which is close to the maximum solubility of DX in PBS at room temperature, was used for DX loading into lenses. The concentration of DX-ethanol was the same, i.e., 0.08 mg/ml, as that of DX-PBS solution for comparison, though the solubility of DX in ethanol is about 1 mg/ml. For ACUVUE® ADVANCE™, ACUVUE®

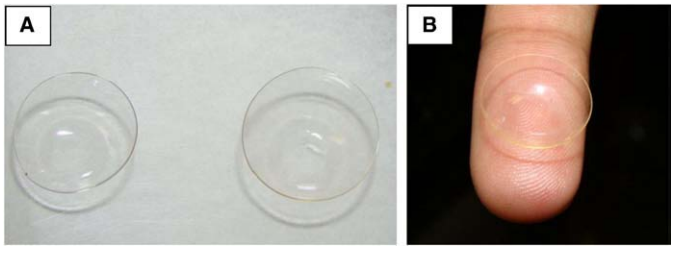

Fig. 1. Images of Commercial NIGHT&DAY™ contact lens (left in panel A) and NIGHT&DAY™ lens with 30%Vitamin E loading (right image in panel A and panel B).

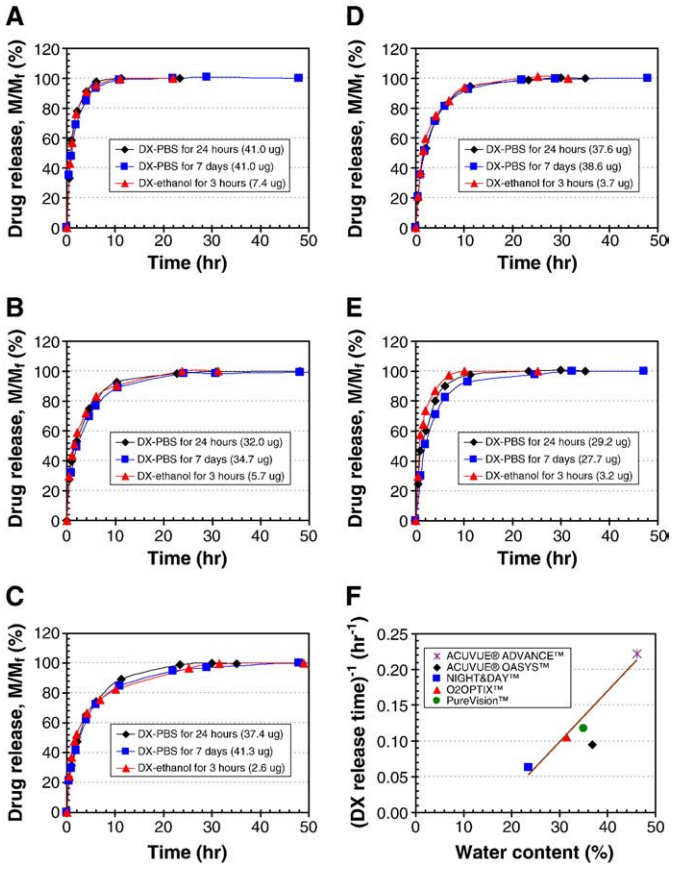

Fig. 2. Effect of DX loading method on profile of DX release by A) ACUVUE® ADVANCE™ B) ACUVUE® OASYS™ C) NIGHT&DAY™ D) O_2OPTIX™ E) PureVision™ contact lenses. F) The plot of (DX release time)$^{-1}$ versus water content of contact lenses. Drug release (M) divided by total amount released (M_f) are plotted as a function of time. DX was loaded by soaking the lens in 0.08 mg/ml of indicated medium for indicated duration of time. Total amount of drug released for each lens is marked in parenthesis on the legends.

OASYS™ and O_2OPTIX™, the DX release profiles of three different loading methods are identical. However, the DX release behaviors by NIGHT&DAY™ and PureVision™ lenses exhibit a slight dependency on loading methods. For these lenses, there is not much difference in the total release amount of DX from the lenses soaked in DX-PBS solution for two different soaking times, but slower DX release is observed from lenses that were soaked for 7 days than that for 24 h. This suggests that equilibrium time for DX loading for these two lenses could be longer than 24 h. Among five lenses, NIGHT&DAY™ lens shows the longest release time (16 h for 90% of total release) followed by ACUVUE® OASYS™ (10.5 h), O_2OPTIX™ (9.5 h), and PureVision™ (8.5 h), and then ACUVUE® ADVANCE™ has the shortest release time (4.5 h) by loading the drug with DX-PBS solution for 7 days. There is a good correlation between the water content of the lenses reported by the manufacturers and the duration of release as shown in Fig. 2F, with increasing water content resulting in shorter release durations. For total release amount of DX, PureVision™ and ACUVUE® OASYS™ lenses release relatively smaller amounts (about 28 μg and 35 μg, respectively) compared to the other three lenses (about 38–41 μg). There is no correlation between amount of drugs released and the water content, which is likely because the hydrophobic drugs are expected to partition in the silicone rich phases, and so the partition coefficients in the gels will be mainly influenced by the silicone composition of the gels. All the lenses soaked in DX-ethanol solution release substantially low amount of DX (2–8 μg). The solubility of DX in ethanol is very high and the partition coefficient of DX between lens and ethanol is very low in the drug loading step, which results in low loading of DX.

3.3. Dynamics of drug transport from Vitamin E loaded lenses

The dynamics of DX uptake and release by Vitamin E loaded lenses for four different Vitamin E loadings are shown in Fig. 3. The insets in the figure show the magnified views of the plots for drug release during the initial hours. In these experiments, Vitamin E was loaded in the lens first then air-dried, and then DX was loaded by soaking the lens in the DX-PBS solutions. The method of loading by direct addition of DX in Vitamin E–ethanol was not used since DX loading through PBS medium was much more efficient as shown earlier. In the figure, all the lenses exhibit increase in loading or release time as Vitamin E loading increases. With similar Vitamin E loadings in the lenses, DX loading time is longest for ACUVUE® OASYS™, followed by NIGHT&DAY™, O_2OPTIX™, and shortest for PureVision™. For DX loading, the effect of Vitamin E loading is similar for NIGHT&DAY™ and O_2OPTIX™ with about 2-fold loading time increase for about 10% Vitamin E loading, and about 10-fold for about 30% loading. However, the effect of about 10% Vitamin E loading for PureVision™ lens on loading duration is negligible and even of about 40% loading shows only 6-fold increase. These behaviors are similar for DX release time increase, even though the changes in release duration are slightly less than in loading duration. For example, NIGHT&DAY™ lenses with 27% Vitamin E loading shows 6.5-fold increase in release duration compared to 9-fold increase in loading duration with the same Vitamin E loading. The difference between the measured DX delivery time of uptake and release is likely caused by the accumulation error of drug loss during the measurement process. The release experiment is conducted in a lower drug concentration range than the uptake experiment, and therefore contains larger relative error. The comparison for the DX uptake and release delivery to an estimated model in perfect condition will be discussed later.

It is noted that the effect of Vitamin E on uptake or release duration increase for hydrophilic drugs in our previous study is much larger than that for DX with comparable Vitamin E loading [19]. For example, by comparing the hydrophilic drug release and DX uptake experiment results, NIGHT&DAY™ with 27% Vitamin E loading has 76 times increase in timolol delivery time while it has only 8.8 times increase in DX even though actual delivery time is longer for DX (142 h) than for timolol (43 h). O_2OPTIX™ with 34% Vitamin E loading also shows larger increase with 34.3 fold for timolol while 15.5 fold for DX. Furthermore, while there is no significant difference in drug delivery time for DX and dexamethasone 21-disodium phosphate (DXP) by pure lens (For example, 10.5 h and 14 h by ACUVUE® OASYS™ , respectively), the Vitamin E loaded lenses deliver DXP for longer duration compared to DX. With about 27% Vitamin E loading, NIGHT&DAY™ shows 40-fold increase in release time for DXP which is about 12 days, and only 8.8-fold delivery time (4.5 days) for DX. These results also support the theory for Vitamin E aggregates inside lens serving as diffusion barriers. Since timolol and DXP are hydrophilic ionic drugs, it cannot diffuse through the highly hydrophobic Vitamin E particles while the hydrophobic DX can partition and diffuse through Vitamin E. The reduction in release rates for hydrophilic drugs is thus likely due to presence of Vitamin E particles that act as diffusion barriers which create an extended tortuous diffusion path. For DX, while it can diffuse through the Vitamin E barrier, the diffusivity may be reduced because of increased viscosity and/or altered adsorption to the polymer, and this reduction in diffusivity of DX through the Vitamin E barrier could lead to the reduction in drug uptake and release rates. This will be discussed further in the section on model development.

To understand the mechanism of transport of hydrophobic drugs through the Vitamin E laden lenses, it is instructive to determine the partition coefficient of the drugs both in the pure gel without Vitamin E and in the lenses with various Vitamin E loadings. These data can then be used to obtain the partition coefficient of the drug in the Vitamin E aggregates later.

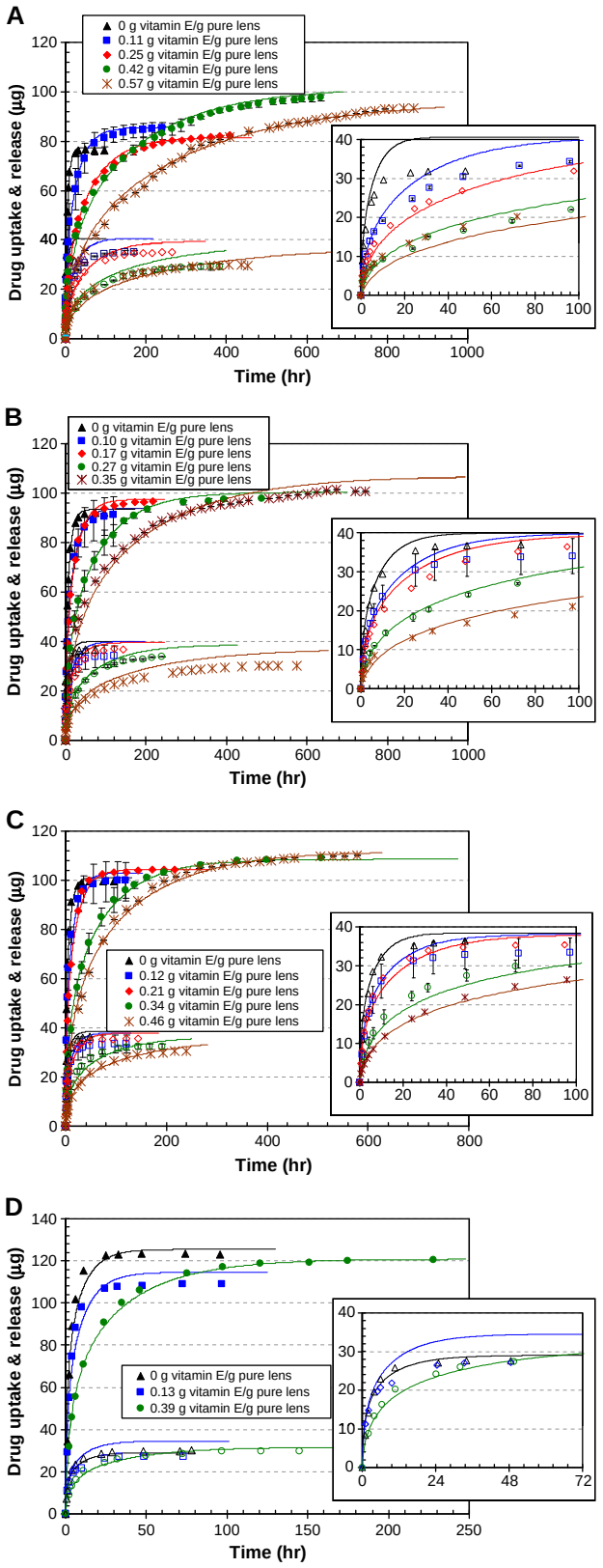

Fig. 3. Profiles of experimental and model fitted DX uptake and release by Vitamin E loaded contact lenses A) ACUVUE® OASYS™ B) NIGHT&DAY™ C) O_2OPTIX™ D) PureVision™. Experiment results are presented by solid and hollow markers for uptake and release, respectively, and model fitted results are presented in solid line. Vitamin E was loaded first by soaking pure contact lens in Vitamin E-ethanol solution and the lens was dried. And then DX was loaded by soaking the Vitamin E loaded lens in DX-PBS solution (0.08 mg/ml). The data with error bars are presented as mean ± S.D. with n = 3. Vitamin E loadings are indicated.

For loading experiment, the partition coefficient of drug in the Vitamin E loaded lens (K) was defined as

$$K = \frac{C_{l,f}}{C_{w,f}} = \frac{V_w\left(C_{w,i} - C_{w,f}\right)}{V_l C_{w,f}} \tag{1}$$

where V_w and V_l are the volumes of the drug-PBS solution and the dry lens (either with or without Vitamin E loading), respectively, and $C_{l,f}$, $C_{w,i}$ and $C_{w,f}$ are the equilibrium concentrations of the drug in the lens phase, and the initial and equilibrium concentrations in the aqueous phase, respectively, in the loading experiment. Partition coefficient of drug in the pure lens (K_{pl}) can be also written as

$$K_{pl} = \frac{C_{pl,f}}{C_{w,f}} = \frac{V_w\left(C_{w,i} - C_{w,f}\right)}{V_{pl} C_{w,f}} \tag{2}$$

where V_{pl} and $C_{pl,f}$ are the volume of the dry pure lens and the equilibrium concentration of the drug in the pure lens phase, respectively. The mass balance of drug in the vial yields

$$M_i = C_{pl,f}V_{pl} + C_{ve,f}V_{ve} + C_{w,f}V_w = K_{pl}C_{w,f}V_{pl} + K_{ve}C_{w,f}V_{ve} + C_{w,f}V_w \tag{3}$$

where Mi is total mass of drug in the vial and $C_{ve,f}$ is the equilibrium concentration of the drug in the Vitamin E aggregates. V_{ve} is the volume of Vitamin E aggregates in the lens and is calculated by $V_l(\phi - \phi^*)$, where ϕ is the volume ratio of Vitamin E in the dry lens and ϕ^* is the Vitamin E loading the could either existing in the form that bounds to the polymer gel or as particles but in regions of the gel that do not contribute to drug transport, which we have obtained previously [19]. Partition coefficient of drug in Vitamin E phase (K_{ve}) can be obtained as

$$K_{ve} = \frac{C_{ve,f}}{C_{w,f}} = \frac{M_i / C_{w,f} - K_{pl}V_{pl} - V_w}{V_l(\phi - \phi^*)} \tag{4}$$

The values of K and K_{ve} are listed in Table 1. K and K_{ve} are comparable for DX, which is due to the hydrophobic nature of the drug and Vitamin E. These partition coefficient values will be utilized in the model presented below.

Table 1
Partition coefficient (K) of DX in lenses soaked in DX-PBS solution.

Contact lenses	Vitamin E loading [g Vitamin E/g pure lens]	K for loading	K_{ve} for loading	K for release	K_{ve} for release
ACUVUE® OASYS™	0	77.4	–	105.7	–
	0.11	89.7	211.6	116.9	234.4
	0.24	76.7	80.3	96.2	61.5
	0.42	94.9	154.3	149.6	294.7
	0.7	80.2	89.0	120.4	152.4
NIGHT&DAY™	0	119.2	–	137.7	–
	0.1	120.3	–	137.8	–
	0.17	111.7	112.2	126.5	98.6
	0.28	106.7	82.1	137.7	250.6
	0.35	110.4	109.5	162.8	299.6
O_2OPTIX™	0	131.3	–	146.3	–
	0.12	131	–	143.9	–
	0.21	120.7	140.9	134.5	153.9
	0.34	119.4	154.0	141.8	205.4
	0.46	115.9	113.8	149.1	214.5
PureVision™	0	290.7	–	326.5	–
	0.13	159.6	–	241.7	–
	0.39	181.3	–	203.8	–

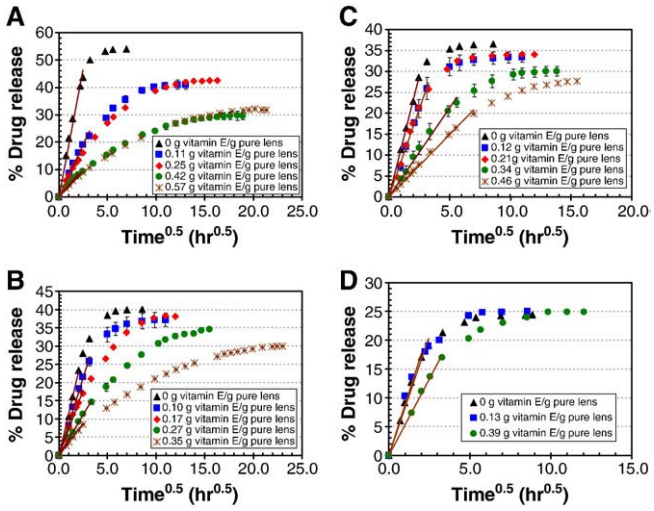

Fig. 4. Plot of % drug release by Vitamin E loaded lenses versus square root of time. The lines are the best fit straight for short time data of DX release by A) ACUVUE® OASYS™, B) NIGHT&DAY™, C) O_2OPTIX™ and D) PureVision™. All R^2's are larger than 0.99. Some of data are presented as mean ± S.D. with n = 3.

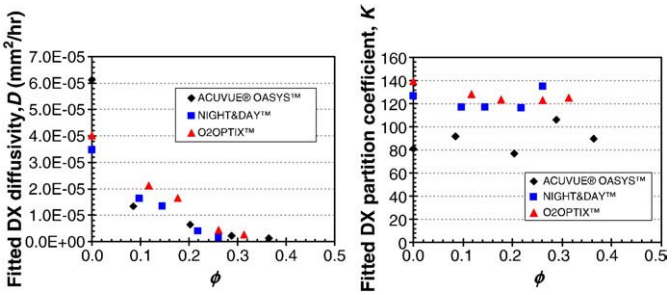

Fig. 5. Fitted DX diffusivity and partition coefficient for contact lenses with different Vitamin E volume fraction (ϕ).

3.4. Diffusivities of drugs in Vitamin E loaded lenses

The thickness of each commercial contact lens varies in the radial direction and depends on the base curve, but the average thickness is about 80–100 μm, which is much smaller compared to the diameter of lens (about 14 mm). Thus, the drug delivery by contact lens can be considered as a one-dimensional diffusion transport. To confirm whether the DX uptake and release by Vitamin E loaded lenses are controlled by one-dimensional diffusion as expected, the drug release profiles can be plotted as percentage of drug release versus square root of time. For diffusion-controlled transport, the percentage of drug release will be linear to the square root of time [19], and the results are shown in Fig. 4. The lines in the figure are the best fit straight line to short time release data. The fits are all good with R^2 values larger than 0.99 showing that the drug transport in these lenses is diffusion controlled.

Below we develop a model based on the one-dimensional diffusion equation to fit the experiment results and obtain the diffusion coefficient of DX in the lenses. Due to the large aspect ratio, we assume that the geometry of contact lens can be modeled as a flat thin film with homogenous thickness 80 μm, which is the typical average thickness of commercial contact lens. The thickness variation in the radial direction can easily be integrated into the model but is not presented here for simplicity. If the drug diffusivity (D) and partition coefficient (K) are independent of the drug concentration, the drug transport to the transverse y-direction can be described as

$$\frac{\partial C_g}{\partial t} = D\frac{\partial^2 C_g}{\partial y^2} \tag{5}$$

where C_g is the drug concentration in the lens gel matrix. The boundary conditions for the drug release experiment are

$$\frac{\partial C_g}{\partial y}(t, y = 0) = 0$$
$$C_g(t, y = h) = KC_w \tag{6}$$

where h is the half-thickness of the gel, which is about 40 μm for pure contact lens without Vitamin E loading. The half-thickness is adjusted with Vitamin E loading amount by isotropic expansion assumption. The first boundary condition assumes symmetry at the center of the gel and the second describes equilibrium of DX concentration between the gel and the aqueous phase. A mass balance on the aqueous reservoir in the beaker yields

$$V_w\frac{dC_w}{dt} = -2DA_g\frac{\partial C_g}{\partial y}\Big|_{y=h} \tag{7}$$

where V_w is the water volume in the beaker and A_g is the cross-sectional area of the lens.

In addition, the initial conditions for the DX delivery are

$$C_g(y, t = 0) = C_{g,i}$$
$$C_w(t = 0) = C_{w,i} \tag{8}$$

For uptake, $C_{g,i}$ is zero and $C_{w,i}$ is the initial concentration of DX solution for loading (0.08 mg/ml). For release, $C_{g,i}$ is the final equilibrium DX concentration in the lens after drug uptake process, and $C_{w,i}$ is zero. The equations were solved by finite difference method with MATLAB®, and the fitted D and K are determined by fitting the model with experimental results by using the function of 'fminsearch' in MATLAB®. The fitting results were shown in Fig. 3. as solid lines. The good fits between the experiment and model results suggest the validity of our proposed model. It is noted that the fits are better for the uptake profiles compared to the release profiles, particularly in the long time period, where the observed DX release amount are less than predicted value. This is very likely caused by the accumulated drug loss during the experiments, which also explains the observation that the experimental partition coefficients for all lenses explored in this study are larger for release than those for uptake. Therefore, the diffusivity values fitted to the uptake data are expected to be more reliable than those from release. Fig. 5 shows the fitted D and K for ACUVUE® OASYS™, NIGHT&DAY™ and O_2OPTIX™ with different Vitamin E loading. For all lenses, while the diffusivity decreases significantly as the amount of Vitamin E in the lens increases, the drug partition coefficient almost remains the same regardless of the Vitamin E loading. The results suggest that while Vitamin E has a similar partition coefficient to the lens gel matrix, the DX diffusivity for Vitamin E is much smaller than that for the lens matrix, likely due to the high viscosity of Vitamin E.

3.5. Scaling model for effect of Vitamin E loading on extended DX delivery

The scaling model proposed in our previous work for hydrophilic drugs delivery by Vitamin E loaded silicone hydrogel contact lens is likely not valid for hydrophobic drugs that can partition into the Vitamin E phase. For these hydrophobic drugs the transport occurs partially by diffusion around the Vitamin E aggregates and partially by dissolution and diffusion through these aggregates. Accordingly, the increase in release time is much larger for hydrophilic drugs such as timolol compared to hydrophobic drugs such as DX. The hydrophobic drugs can partition into the Vitamin E aggregates, diffuse through these, and then diffuse into the gel matrix. Thus the transport of

hydrophobic drugs through the Vitamin E-laden gels can be considered as diffusion through regions of the gel matrix and regions of Vitamin E arranged in series. Since the diffusivity of DX is much smaller for Vitamin E than that for the gel matrix, the drug transport time will be determined mainly by the diffusion through the Vitamin E region when the Vitamin E loading amount increases.

For one-dimensional drug diffusion in a pure lens without Vitamin E loading with average thickness h, the drug transport duration τ_0 can be estimated as h^2/D_G, where D_G is the drug diffusivity in the gel matrix. For Vitamin E loaded contact lens, the time it takes for the drug diffuse through the Vitamin E aggregates region can be scaled as $(h(\phi-\phi^*))^2/D_V$, where D_V is drug diffusivity in the Vitamin E aggregates. Thus, the ratio of the transport time increase by Vitamin E loaded lenses (τ/τ_0) is given by the following expression:

$$\frac{\tau}{\tau_0} = \frac{D_G}{D_V}(\phi-\phi^*)^2 + 1 \quad (9)$$

The values of ϕ^* were obtained by fitting the drug transport data for the hydrophilic drugs, which is 0.0117, 0.0621, and 0.0973 for ACUVUE® OASYS™, NIGHT&DAY™ and O_2OPTIX™, respectively [19]. The only unknown parameter D_G/D_V can then be obtained by fitting the experimental data to the above equation. The fitting results for DX uptake duration increase by Vitamin E loaded commercial lenses are shown in Fig. 6. and the fitted D_G/D_V values are 330 for ACUVUE® OASYS™, 395 for NIGHT&DAY™ and 405 for O_2OPTIX™, respectively. The fitted results are satisfied with the assumption in our model that $D_G >> D_V$.

The reduced diffusivity of DX through the Vitamin E barrier is likely due to the high viscosity of Vitamin E. The diffusivity is inversely related to the viscosity and thus the ratio D_G/D_V may be related to the ratio of the viscosity of Vitamin E and water. To test this speculation, the dynamic viscosity of Vitamin E was measured by cone and plate rheometer. The slope of the log-log plot of loss modulus (G″) versus the angular frequency is one, as shown in Fig. 7, suggesting that Vitamin E can be characterized as a Newtonian fluid. The measured viscosity of Vitamin E is 1.918 Pa s, which is about 2100-fold to water at 25 °C (0.89 mPa s). The ratio of diffusivity is about 20% of the viscosity ratio, which is encouraging. The differences between the diffusivity and the viscosity ratios could perhaps be attributed to channeling of drug through specific paths, viz. silicone rich hydrophobic channel, and thus a fraction of the Vitamin E loaded in the gel may not function as a barrier. If one assumes that only about 50% of the precipitated Vitamin E acts as barriers, the ratio of D_G/D_V obtained by fitting the data will increase to 4 times the values reported above bringing it in reasonable agreement with the viscosity ratio.

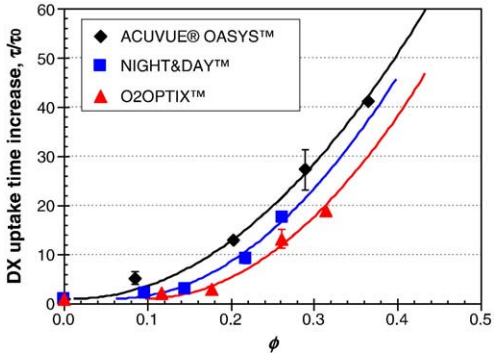

Fig. 6. Effect of Vitamin E volume fraction (ϕ) on increase in drug uptake times. The solid lines are best fits to the data based on Eq. (9).

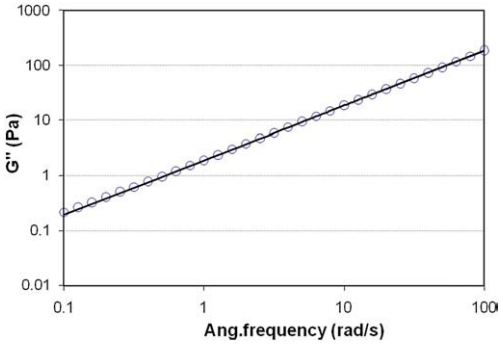

Fig. 7. Dependence of the loss modulus G″ on frequency for pure Vitamin E (as supplied). The slope of the log-log plot of G″ versus the angular frequency is one, suggesting that Vitamin E can be characterized as a Newtonian fluid. The value of Viscosity (η) estimated from the linear fit of G″ to frequency was 1.918 Pa s.

4. Conclusions

In this paper we show that the drug delivery duration for DX from contact lenses can be significantly increased to more than a week by incorporation of Vitamin E into the contact lenses. The mechanism for the extended release is likely related to the reduced diffusivity of DX through the Vitamin E barriers due to its high viscosity. A mathematical model based on diffusion controlled transport fits the uptake and release profiles from the Vitamin E loaded lenses well showing that the transport is diffusion controlled, and a scaling model fits the dependence of effective diffusivity on the Vitamin E loading.

While in vitro studies are necessary to explore the efficacy of Vitamin E loaded lenses for ophthalmic drug delivery, the results of this study along with those from our prior study [19] strongly suggest that Vitamin E loaded contact lenses could be very useful vehicles for extended drug delivery of both hydrophobic and hydrophilic drugs. Also the novel approach of creating in situ transport barriers through loading of Vitamin E could be useful for extending release durations from other devices.

Acknowledgements

This research was partially supported by the 2009 Seed Opportunity Funds from the University of Florida. The authors thank Dr. Pei-Hsun Wu, Stephen H. Arce and Dr. Yiider Tseng for their assistance in the viscoelastic measurements.

References

[1] N.A. McNamara, K.A. Poise, R.J. Brand, A.D. Graham, J.S. Chan, C.D. McKenney, Tear mixing under a soft contact lens: effects of lens diameter, Am. J. Ophthalmol. 127 (1999) 659–665.
[2] J.L. Creech, A. Chauhan, C.J. Radke, Dispersive mixing in the posterior tear film under a soft contact lens, Ind. Eng. Chem. Res. 40 (2001) 3015–3026.
[3] C.-C. Li, A. Chauhan, Modeling ophthalmic drug delivery by soaked contact lenses, Ind. Eng. Chem. Res. 45 (2006) 3718–3734.
[4] C. Le Bourlais, L. Acar, H. Zia, P.A. Sado, T. Needham, R. Leverage, Ophthalmic drug delivery systems — recent advances, Prog. Retin. Eye Res. 17 (1998) 33–58.
[5] J.C. Lang, Ocular drug delivery conventional ocular formulations, Adv. Drug Deliv. Rev. 16 (1995) 39–43.
[6] P. Segal, Pumps and timed release, FDA Consumer magazine, October 1991.
[7] C.C.S. Karlgard, N.S. Wong, L.W. Jones, C. Moresoli, In vitro uptake and release studies of ocular pharmaceutical agents by silicon-containing and p-HEMA hydrogel contact lens materials, Int. J. Pharm. 257 (2003) 141–151.
[8] D. Gulsen, A. Chauhan, Dispersion of microemulsion drops in HEMA hydrogel: a potential ophthalmic drug delivery vehicle, Int. J. Pharm. 292 (2005) 95–117.
[9] D. Gulsen, C.-C. Li, A. Chauhan, Dispersion of DMPC liposomes in contact lenses for ophthalmic drug delivery, Curr. Eye Res. 30 (2005) 1071–1080.
[10] Y. Kapoor, A. Chauhan, Ophthalmic delivery of Cyclosporine A from Brij-97 microemulsion and surfactant-laden p-HEMA hydrogels, Int. J. Pharm. 361 (2008) 222–229.

[11] Y. Kapoor, A. Chauhan, Drug and surfactant transport in Cyclosporine A and Brij 98 laden p-HEMA hydrogels, J. Colloid Interface Sci. 322 (2008) 624–633.
[12] S. Venkatesh, S.P. Sizemore, M.E. Byrne, Biomimetic hydrogels for enhanced loading and extended release of ocular therapeutics, Biomaterials 28 (28) (2007) 717–724.
[13] S. Venkatesh, J. Saha, S. Pass, M.E. Byrne, Transport and structural analysis of molecular imprinted hydrogels for controlled drug delivery, Eur. J. Pharm. Biopharm. 69 (2008) 852–860.
[14] H. Hiratani, C. Alvarez-Lorenzo, The nature of backbone monomers determines the performance of imprinted soft contact lenses as timolol drug delivery systems, Biomaterials 25 (2004) 1105–1113.
[15] H. Hiratani, Y. Mizutani, C. Alvarez-Lorenzo, Controlling drug release from imprinted hydrogels by modifying the characteristics of the imprinted cavities, Macromol. Biosci. 5 (2005) 728–733.
[16] C. Alvarez-Lorenzo, H. Hiratani, J.L. Gomez-Amoza, R. Martinez-Pacheco, C. Souto, A. Concheiro, Soft contact lenses capable of sustained delivery of timolol, J. Pharm. Sci. 91 (2002) 2182–2192.
[17] H. Hiratani, C. Alvarez-Lorenzo, Timolol uptake and release by imprinted soft contact lenses made of N, N-diethylacrylamide and methacrylic acid, J. Control. Release 83 (2002) 223–230.
[18] J. Kim, A. Conway, A. Chauhan, Extended delivery of ophthalmic drugs by silicone hydrogel contact lenses, Biomaterials 29 (2008) 2259–2269.
[19] C.-C. Peng, J. Kim, A. Chauhan, Extended delivery of hydrophilic drugs from silicone-hydrogel contact lenses containing Vitamin E diffusion barriers, Biomaterials 31 (2010) 4032–4047.
[20] J.C. Melby, Systemic corticosteroid therapy: pharmacology and endocrinology considerations, Ann. Intern. Med. 81 (1974) 505–512.