Biomaterials 31 (2010) 4032–4047

Contents lists available at ScienceDirect

Biomaterials

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

Extended delivery of hydrophilic drugs from silicone-hydrogel contact lenses containing Vitamin E diffusion barriers

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ARTICLE INFO

Article history:
Received 17 December 2009
Accepted 19 January 2010
Available online 13 February 2010

Keywords:
Silicone contact lens
Vitamin E
Diffusion barriers
Extended release
Ophthalmic drug delivery

ABSTRACT

This paper proposes an approach for increasing drug release durations from contact lenses and other biomedical devices by *in situ* creation of transport barriers of Vitamin E that force drug molecules to diffuse through long tortuous path. Results show that the increase in release duration is quadratic in Vitamin E loading, which is consistent with proposed mathematical models. Loadings of 10 and 40% Vitamin E increase release time of timolol by a factor of about 5 and 400, respectively for NIGHT&DAY™ lens. Similar results have been obtained for other hydrophilic drugs including fluconazole and dexamethasone 21-disodium phosphate (DXP). Vitamin E loading in the NIGHT&DAY™ lens leads to slight increase in lens sizes (6.5% increase for 30% loading), a slight reduction in oxygen diffusion (about 40% reduction for 75% loading), and a more significant reduction in the ion permeability (50% reduction for 10% loading). Additionally, Vitamin E loading has a beneficial effect of blocking UV radiation which will reduce the corneal damage due to UV light.

1. Introduction

Controlled delivery vehicles are especially important for ophthalmic applications because topical delivery via eye drops, which accounts for about 90% of all ophthalmic formulations, is extremely inefficient [1]. Drugs instilled as eye drops have a short residence time of about 2 min in the tear film leading to a low bioavailability of less than 5%. The systemic uptake of the remaining 95% can lead to undesirable side effects [2] and reduced efficacy of therapeutic systems [3], and low compliance due to a high frequency of administration. To address the deficiencies of eye drops, a number of researchers have explored drug delivery via soft contact lenses, which are effective devices for drug delivery 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 [4–6]. Most prior studies focused on soaking hydrophilic lenses in commercial drug solution followed by insertion into the eye [7–12]. While these systems are more effective than eye drops, these cannot provide extended release of drugs due a short duration of drug release. To increase drug release durations, Chauhan and coworkers have proposed the development of nanoparticle laden gels that can load substantial amount of drug in the gel, which can be released at a controlled rate from the nanoparticles [13–16]. Also, a number of researchers have focused on developing biomimetic and 'imprinted' contact lenses [17–21]. 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 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. Karlgard et al. recently measured the uptake and release of a number of ophthalmic drugs by commercially available HEMA based and extended-wear silicone contact lenses *in vitro* studies [22]. The release studies showed that the commercial extended-wear lenses release the drugs in a short period of time and are thus unsuitable for extended drug delivery. The aim of this paper is to develop a new approach for extending the release duration of currently used commercial contact lenses without compromising any other important property.

The release of a molecule from a contact lens is controlled by diffusion within the lens material. For one dimensional diffusion-controlled process, the duration of release can be approximately calculated by l^2/D, where l is the path length that a compound needs to traverse and D is the molecular diffusivity, which is fixed for a given commercial lens. For a typical contact lens, l is the thickness of the lens, which varies in the radial direction but is on average approximately 80–100 μm for a typical lens. The period of time over which a drug is released from a contact lens can be increased by either increasing l or by decreasing D. In most diffusion-controlled systems, augmentation of diffusivity has been

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doi:10.1016/j.biomaterials.2010.01.113

Table 1
List of silicone hydrogel extended wear commercial contact lens (dipoter -6.50) explored in this study ($n = 6$).

Commercial name[a] (manufacturer)	Material[a]	Dry weight measured [mg]	Water content, *Q* measured (listed[a]) [%]	*EW* measured [%]	Diameter [mm]	
					Wet measured (listed[a])	Dry measured
ACUVUE® ADVANCE™ (Johnson&Johnson Vision Care, Inc., Jacksonville, FL)	Galyfilcon A	19.7 ± 0.3	46.2 ± 0.7(47)	86.1 ± 2.3	14.40 ± 0.31(14.0)	11.46 ± 0.34
ACUVUE® OASYS™(Johnson&Johnson Vision Care, Inc., Jacksonville, FL)	Senofilcon A	21.7 ± 0.1	36.9 ± 0.9(38)	58.4 ± 1.5	14.12 ± 0.26(14.0)	12.18 ± 0.29
NIGHT&DAY™ (Ciba Vision Corp., Duluth, GA)	Lotrafilcon A	22.2 ± 0.3	23.6 ± 0.3(24)	27.3 ± 0.6	13.92 ± 0.07(13.8)	12.85 ± 0.15
O_2OPTIX™ (Ciba Vision Corp., Duluth, GA)	Lotrafilcon B	25.9 ± 0.2	31.5 ± 1.3(33)	46.0 ± 2.7	14.43 ± 0.23(14.2)	12.78 ± 0.12
PureVision™ (Bausch&Lomb, Inc., Rochester, NY)	Balafilcon A	21.0 ± 0.2	35.0 ± 0.7(36)	3.9 ± 1.7	14.18 ± 0.15(14.0)	12.49 ± 0.17

[a] Referred from product packages.

performed by changing the bulk material to one of a different diffusivity. However, because of the strict requirements of a contact lens where many material properties cannot be compromised, there are practical limits to the selection of the bulk material. Furthermore, an effective strategy to modifying the diffusion process must be applicable to a wide range of bioactive agents with a similar bulk material. The concept proposed here is directed towards controlling the diffusion of a bioactive agent in a contact lens matrix by the creation of diffusion barriers within the lens, such that an included bioactive agent is forced to take a long tortuous path to diffuse from the lens, resulting in extended release. The concept of using transport barriers has been explored extensively for designing membranes that retard gas transport [23–26], but this concept has not been applied to retard drug transport from a biomedical device. The diffusion barrier can be any solid or liquid material that is impermeable to the relatively drugs and that can be dispersed within the lens material in a manner that keeps the lens transparent. A number of ophthalmic drugs are charged at physiological pH and so hydrophobic molecules will likely form effective barriers. It is also important to ensure that the barrier material is biocompatible so that diffusion of the compound forming the barrier into the tear film does not cause toxicity.

Vitamin E, which is a hydrophobic liquid, is a powerful antioxidant and has been shown in some animal studies that the topical application of Vitamin E inhibits a number of eye diseases including keratocyte apoptosis after surgery, ethanol–induced apoptosis in the corneal epithelium, etc. [27,28]. Also, there have been a number of *in vivo* studies suggesting Vitamin E retard cataract development [29–33]. Due to the potential benefits of delivering Vitamin E to the eye, there have been several attempts to develop ophthalmic solutions containing Vitamin E [34,35]. Considering the physical properties such as hydrophobicity and low aqueous solubility and its biocompatibility and potential therapeutic benefits, we focus on using it as the diffusion barrier. Three different ophthalmic drugs were explored in this study: timolol (beta blocker used for treating glaucoma), dexamethasone 21-disodium phosphate

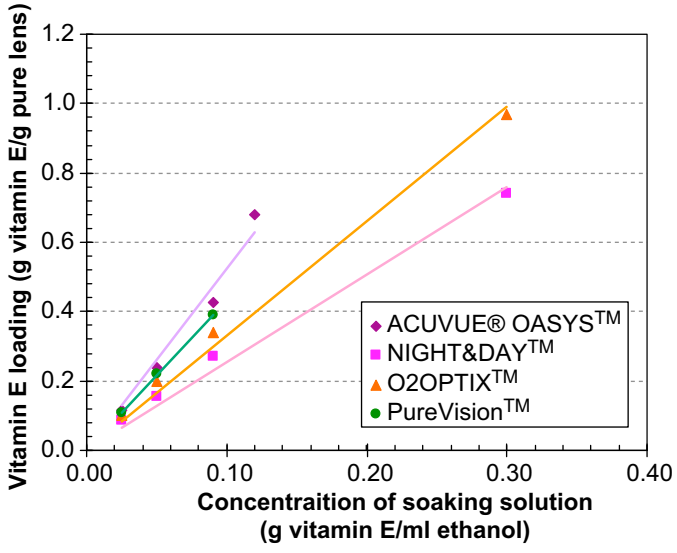

Fig. 1. Correlation of Vitamin E loading and concentration of soaking solution for different lenses. The lines are the best fit straight line to data. The slope and R^2 of the line are 5.26, 0.9692 (ACUVUE® OASYS™), 2.53, 0.9860 (NIGHT&DAY™), 3.30, 0.9918 (O_2OPTIX™), 4.35, 0.9997 (PureVision™), respectively.

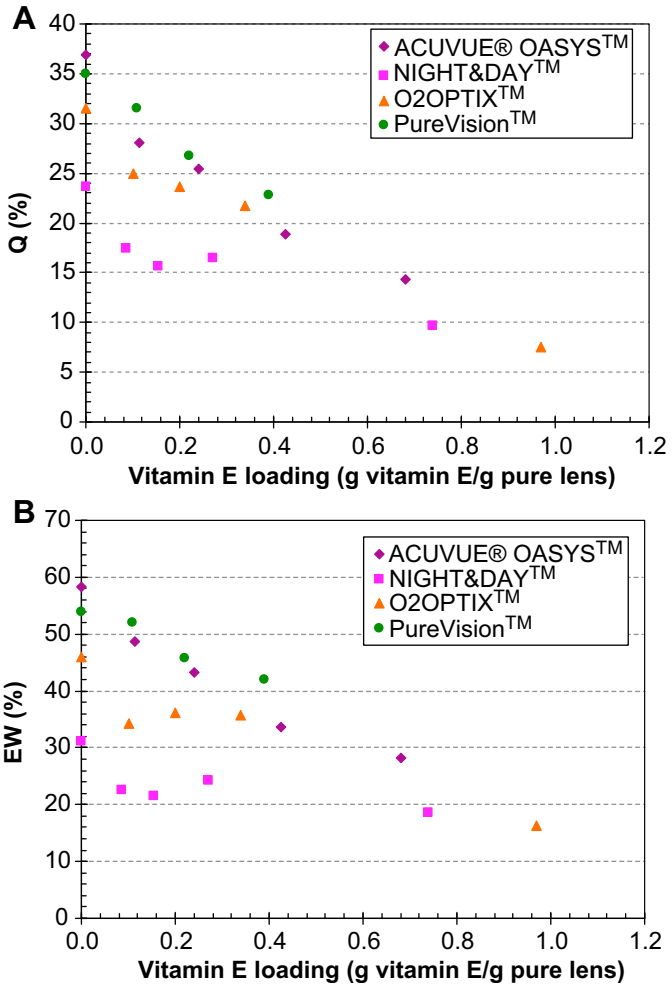

Fig. 2. Plot of A) water content (Q) B) EW of Vitamin E loaded lenses versus Vitamin E loading.

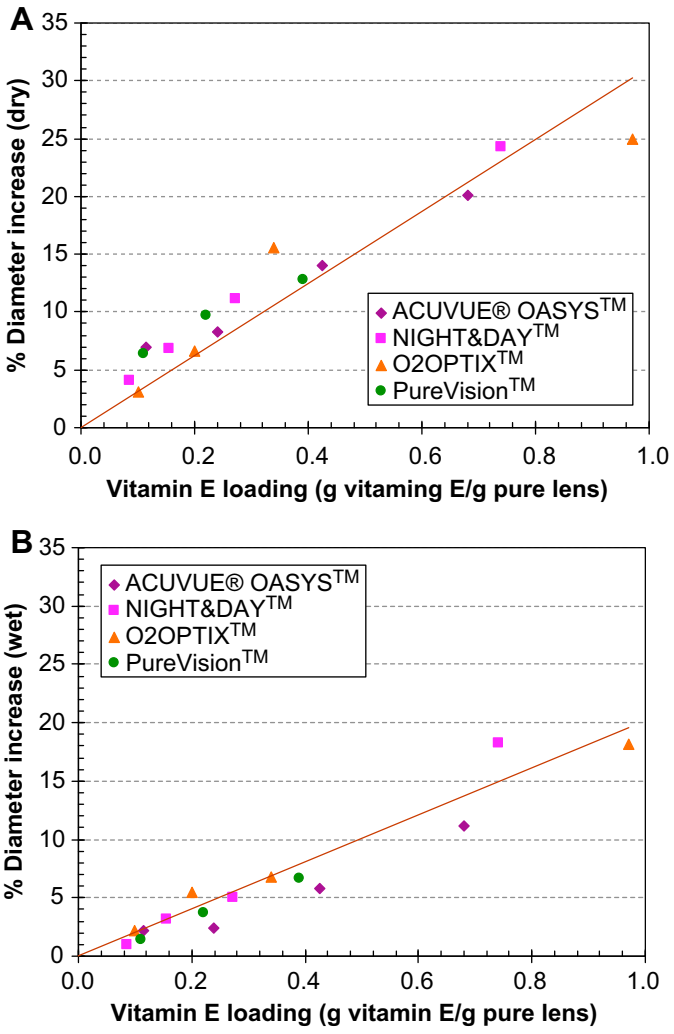

Fig. 3. Percent increase in diameter of A) dry lenses B) wet lenses before and after loading Vitamin E. Lines are best fit straight lines passing zero to the data.

(anti inflammatory corticosteroid), and fluconazole (antifungal). These drugs were chosen because they are hydrophilic at the physiological pH, which should have negligible affinity to the desired Vitamin E barriers.

2. Materials and methods

2.1. Materials

Five commercial silicone contact lenses (diopter −6.50) that are used in this study are described in Table 1. Dexamethasone 21-disodium phosphate (DXP, ≥99%), timolol maleate (≥98%), fluconazole (≥98%), 2-hydroxyethyl methacrylate (HEMA, 97%), sodium hydroxide pellets (97+%), ethanol (≥99.5%), and Dulbecco's phosphate buffered saline (PBS) were purchased from Sigma–Aldrich Chemicals (St. Louis, MO) and ethylene glycol dimethacrylate (EGDMA) from Sigma–Aldrich Chemicals (Milwaukee, WI). Sodium chloride (99.9+%) were purchased from Fisher Chemical (Fairlawn, NJ). Darocur® TPO was kindly provided by Ciba Specialty Chemicals (Tarrytown, NY) and Vitamin E (D-alpha tocopherol, Covitol® F1370) was gifted by Cognis Corporation. All chemicals were used as received without further purification if not specifically mentioned.

2.2. Drug loading into pure lenses

The commercial silicone contact lenses were rinsed with deionized (DI) water and then dried in air before further use. The drug timolol maleate was converted to timolol base for further use by increasing the pH of timolol maleate solution, and then separating out the precipitated timolol base. All other drugs were used as supplied. The drug (timolol, DXP, fluconazole) was loaded into the lenses by soaking the lens either in 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. During soaking the lens in either solution, the dynamic concentration in the solution was not monitored since the absorbance of these drugs in this concentration range was beyond the measurement limit of the UV–vis spectrometer. At the end of the loading stage the lens was taken out and excess drug solution was blotted from the surface. The lens was then dried in air overnight, and used for later 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 by simply mixing Vitamin E and ethanol with vortexing for a few seconds followed by moderate magnetic stirring for several minutes. After the loading step, the lens was taken out and excess Vitamin E–ethanol solution on the lens surface was blotted, and the lens was then dried in air overnight.

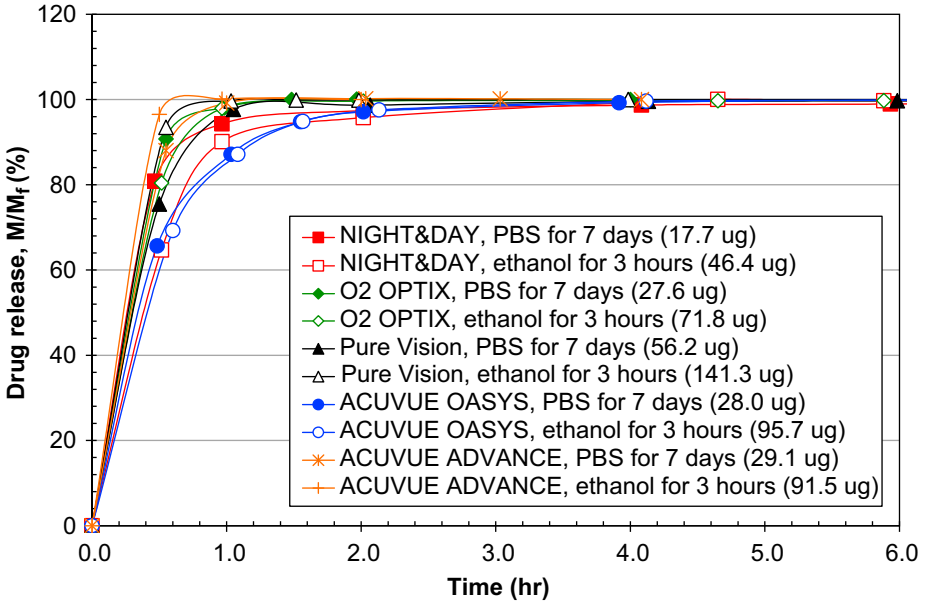

Fig. 4. Effect of timolol loading method on profile of timolol release by commercial contact lenses. Drug release (M) divided by total amount released (M_f) are plotted as a function of time. Timolol was loaded by soaking the lens in 0.8 mg/mL of indicated medium for indicated duration of time. Total amount of drug released for each lens is marked in parenthesis on the legends.

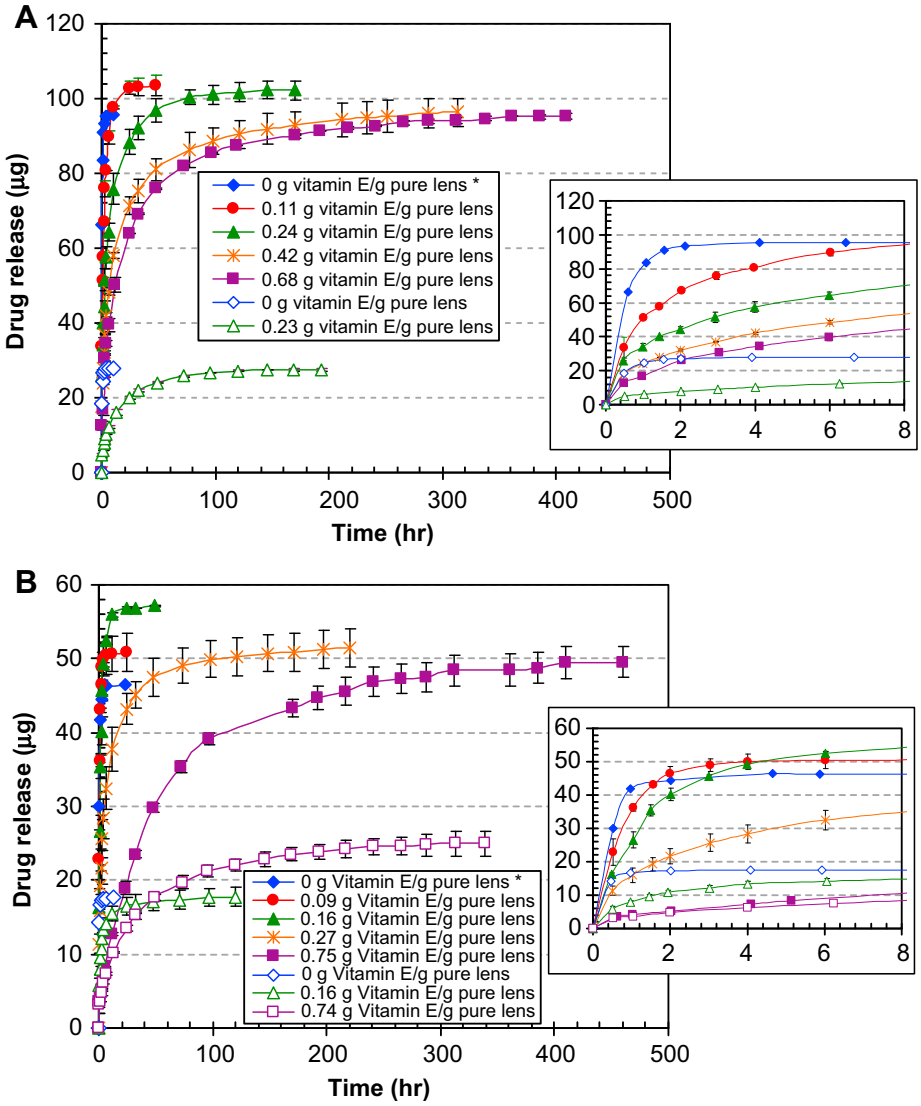

Fig. 5. Profiles of timolol release by Vitamin E loaded contact lenses. Timolol and Vitamin E were loaded together by soaking A) ACUVUE® OASYS™ B) NIGHT&DAY™ C) O_2OPTIX™ D) PureVision™ contact lens in either timolol/Vitamin E–ethanol solution (0.8 mg timolol in 3 mL of Vitamin E–ethanol solution of various concentrations) for 24 h (shown as solid markers), or in timolol–PBS solution (0.8 mg/mL) for 7 days (shown as hollow markers). Vitamin E loadings are indicated. Some of data are presented as mean ± S.D. with $n = 3$.

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 this drug/Vitamin E–ethanol 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.

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 the PBS was analyzed by measuring the absorbance of solution with a UV–vis spectrophotometer (Thermospectronic Genesys 10 UV). The absorbance of solution was measured at wavelength of 241 nm for DXP, 294 nm for timolol, and 210 nm for fluconazole. Control experiments were conducted to ensure that diffusion of Vitamin E from the lenses was negligible and so it did not interfere with the drug detection.

2.6. Ion permeability measurements

Ion permeability of lenses was measured by using a homemade horizontal diffusion cell that consists of a donor and a receiving compartment, which were both fabricated from Plexiglas. The ion permeability of the lens was determined by measuring the rate of transport of ions across the lens. To mount the lens in the diffusion cell, the circular edge of the dried lens was glued to the outer edge of a 1 cm hole cut into a plastic spacer. The spacer along with the lens was then soaked in DI water for longer than 3 h to fully hydrate the lens. The excess water on the spacer was wiped off and the spacer was subsequently placed in between the two compartments of the diffusion cell, and clamped. Latex O-rings were also inserted in between the spacer and each of the compartments to ensure sealing. The latex O-rings were boiled in DI water for 40 min for three times before placing in the diffusion cell to leach out impurities. After assembling the diffusion chamber, the receiving chamber was filled with 30 mL of DI water and the donor chamber was filled with 18 mL of 0.1 M NaCl solution. The ion conductivity of the fluid in the receiving chamber was measured as a function of time with a conductivity meter with temperature sensor (Con 110 series, OAKTON®), and linear regression was applied to the data after reaching pseudo-steady state (after 70 min) to obtain the best fit slopes (S). The rate of conductivity change (S) can be converted to the rate of ion transport, which can then be related to the ion permeability of the lenses by using Fick's law.

2.7. Oxygen permeability measurements

To measure the oxygen permeability, lenses were mounted in a horizontal diffusion cell by following the same procedure as described in the previous section. To create oxygen gradients in the cell, the donor compartment was filled with 18 mL of DI water that was equilibrated with air, and the receiving chamber was filled with 32 mL of DI water that was degassed by bubbling nitrogen for 10 min. Both compartments were kept well-stirred with minimal boundary layer thicknesses

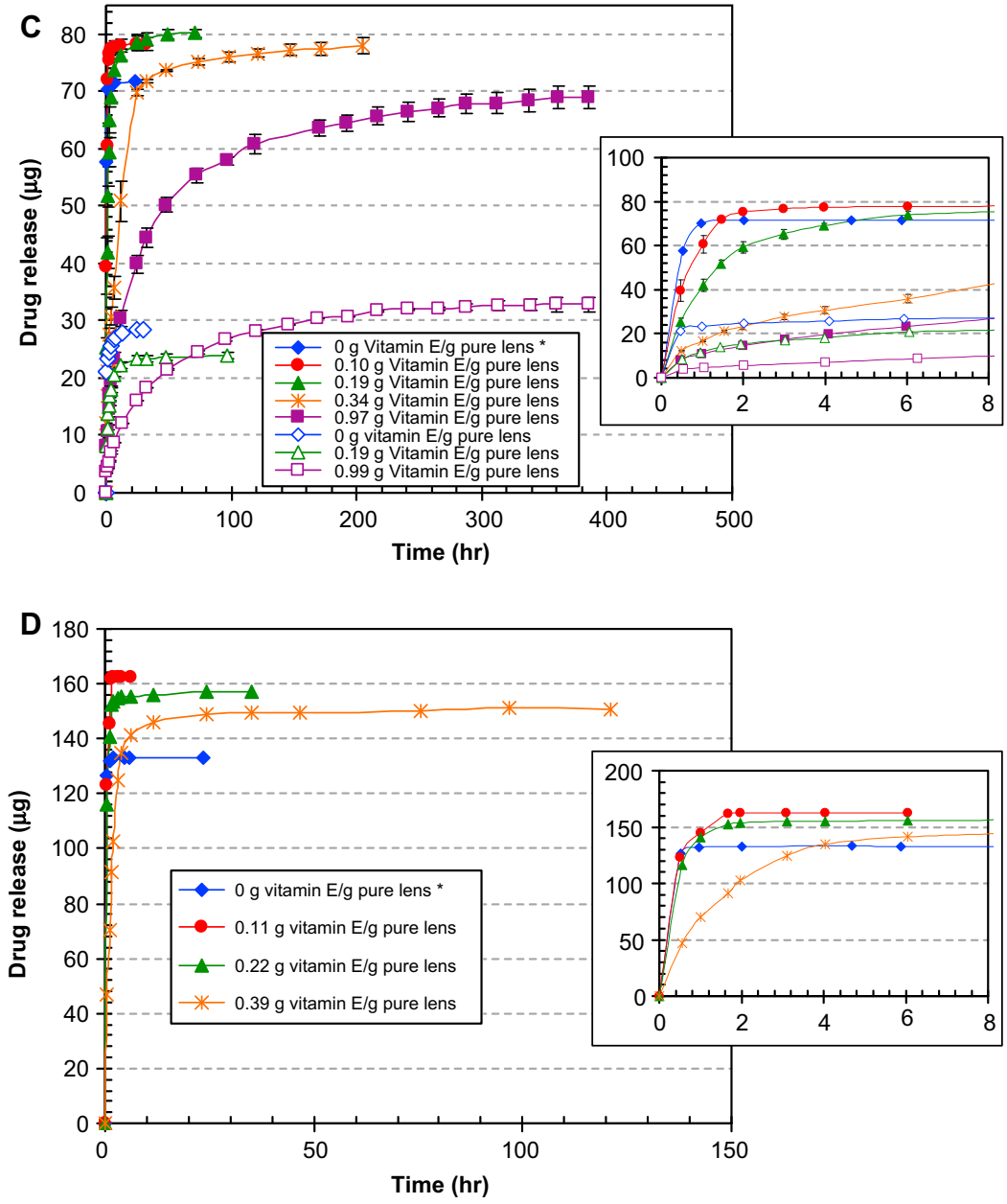

Fig. 5. (*continued*).

adjacent to the lens by stirring at 900 rpm. The dissolved oxygen concentration in the receiving reservoir was measured every 12 s by an oxygen sensor (DO-BTA, Vernier®) for a total duration of 2 h. The measured data was fitted to a mathematical model described later to determine the oxygen permeability of the lens.

2.8. Transmittance measurement of Vitamin E loaded contact lens

The transmittance of Vitamin E laden lenses was measured using UV–vis spectrophotometer (Thermospectronic Genesys 10 UV). The lenses were hydrated by soaking in PBS overnight, then cut into stripes and mounted on the outer surface of a quartz cuvette. The cuvette was placed in the spectrophotometer and the transmittance values were measured at wavelengths ranging from 200 nm to 500 nm.

3. Results and discussion

3.1. Vitamin loadings in the lenses

Vitamin E loadings into each lens for different initial concentration of Vitamin E loading solutions are shown in Fig. 1. Vitamin E loading has a linear dependency on the concentration of Vitamin E loading solutions. In addition, ACUVUE® OASYS™ and NIGHT&-DAY™ have the highest and the lowest affinity for Vitamin E, respectively. The Vitamin E loaded lenses were transparent for all loadings.

3.2. Water content of pure and Vitamin E loaded lenses

Water contents (Q) of lenses are listed on each lens package and were also measured.

$$\text{Water content}(Q) = \frac{W_{eq} - W_l - W_{ve}}{W_{eq}} \times 100 \quad (1)$$

where W_{eq}, W_l, and W_{ve} are mass of hydrated lens at equilibrium, mass of dry pure lens, and mass of Vitamin E loaded in the lens, respectively. Both the listed and measured Q's are shown in Table 1.

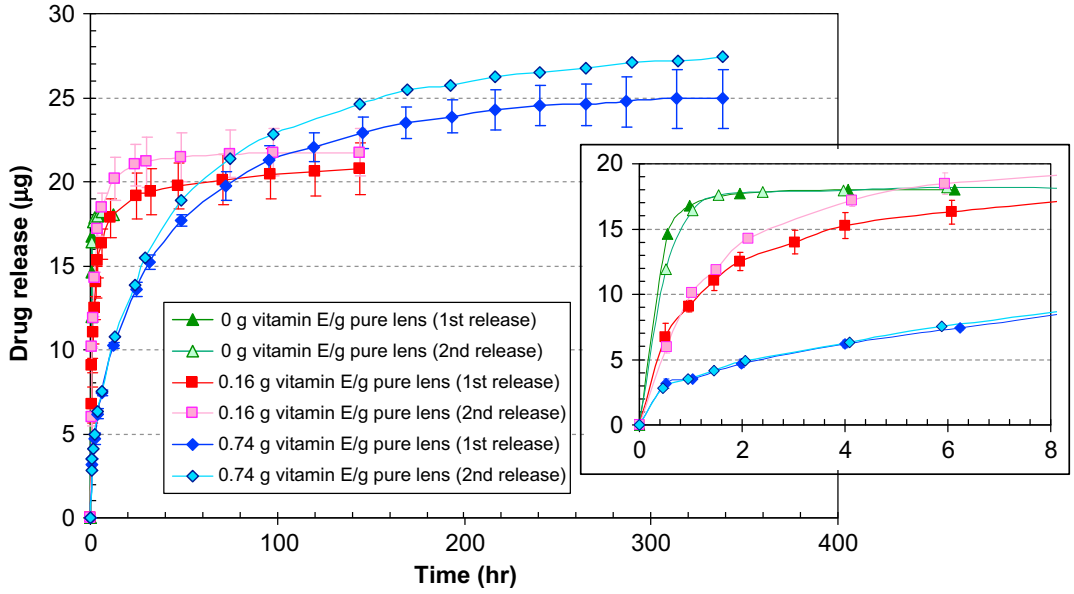

Fig. 6. Profiles of repeated timolol releases by Vitamin E loaded contact lenses. For the second releases timolol was loaded by used soaking Vitamin E loaded lens in timolol–PBS solution (0.8 mg/mL) for 7 days. Vitamin E loadings are indicated. Some of data are presented as mean ± S.D. with $n = 3$.

Additionally, the values of the equilibrium water content (EW) which is defined as mass of water absorbed by unit mass of pure lens, i.e.,

$$\text{Equilibrium water content(EW)} = \frac{W_{eq} - W_l - W_{ve}}{W_l} \times 100 \quad (2)$$

are also listed in Table 1. Results show that ACUVUE® ADVANCE™ has the highest EW (86.0 ± 2.3) and NIGHT&DAY™ has a relatively low EW (31.1 ± 5.5). The effect of Vitamin E loading on Q and EW are clearly seen in Fig. 2. In Fig. 2A, water content of Vitamin E loaded lenses tends to decrease relatively linearly as Vitamin E loading increases. However, W_{eq} of Vitamin E loaded lenses increases as Vitamin E loading, which may be causing the decrease in the Q values. To observe the effect of Vitamin E loading on water amount absorbed in lens polymers, EW was plotted verses Vitamin E loading in Fig. 2B. The EW for Vitamin E loaded lenses is also less than that for the pure lenses for each type of lens but the trends are different. The EW's of ACUVUE® OASYS™ and PureVision™ lenses linearly decrease and the values of EW are 46% and 44% respectively for about 20% Vitamin E loading. The EW's of NIGHT&DAY™ and O_2OPTIX™ lenses decrease by about 10% for Vitamin E loadings of about 10% but there is negligible decrease in EW's with further increase in Vitamin E loadings. The latter behavior for the NIGHT&DAY™ and O_2OPTIX™ lenses suggests that at low loadings, the Vitamin E is solubilized in the lens and so it reduces the water content of the gel because of its hydrophobicity but beyond a critical weight fraction the extra Vitamin E simply phase separates, and thus it has no further effect on the EW. The critical Vitamin E loading which can be solubilized by the NIGHT&DAY™ and O_2OPTIX™ appears to be less than 10%, which is consistent with the values obtained in the later sections based on drug transport data (6.2% for NIGHT&DAY™ and 9.7% for O_2OPTIX™). The continuous linear decrease in EW for ACUVUE® OASYS™ and PureVision™ lenses suggests that these lenses can either solubilize large amounts of Vitamin E or the Vitamin E that phase separates coats the polymer and thus continues to reduce the EW.

3.3. Size change due to Vitamin E loading

The sizes of the contact lenses are expected to increase due to Vitamin E uptake. The diameters of the lenses both with and without Vitamin E were measured both in dry and hydrated states, and the size changes of lenses after loading the Vitamin E are shown in Fig. 3. The % dry and hydrated diameter increase are the increase in the dry and hydrated diameter divided by the dry and hydrated diameter of the lens without Vitamin E, respectively. The solid lines in the figure are the best fit straight lines. Fig. 3A shows that the dry diameter change of lenses is about 30% of the Vitamin E loading. For example, about 30% Vitamin E loaded lens shows increase of about 10% in diameter in dry state, which suggests that the expansion of lens by Vitamin E loading is isotropic. In Fig. 3B, wet diameter change is much less than dry diameter change, which is expected because Vitamin E does not absorb water. For example, lenses with about 30% Vitamin E loaded lens expand about only 6.5% in diameter. From application perspective, changes in wet diameter should be small to preserve the power of the contact lens, and all the lenses show less than 8% increase in wet diameter for about 40% of Vitamin E, which can likely be tolerated by eyes. There may be further changes to the corrective power due to refractive index changes in the lens. In any case, if there is a significant change in the power of the lens, the listed power for a lens can be modified from the original value.

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

Fig. 4 shows the dynamics of timolol release by each of five contact lenses soaked in 0.8 mg/mL of timolol–PBS solution or timolol–ethanol solution. The soaking duration was either 24 h or 7 days in PBS and 3 h in ethanol, but the release profiles for 24 h in PBS were not drawn in Fig. 4 since they were identical to those for 7 days soaking in PBS. To observe the effect of different loading methods on timolol release dynamics, mass of drug released divided by total drug released is plotted as a function of time. All the lenses release 90% of timolol in less than 1.5 h. In addition, timolol release profiles for different loading methods overlap for

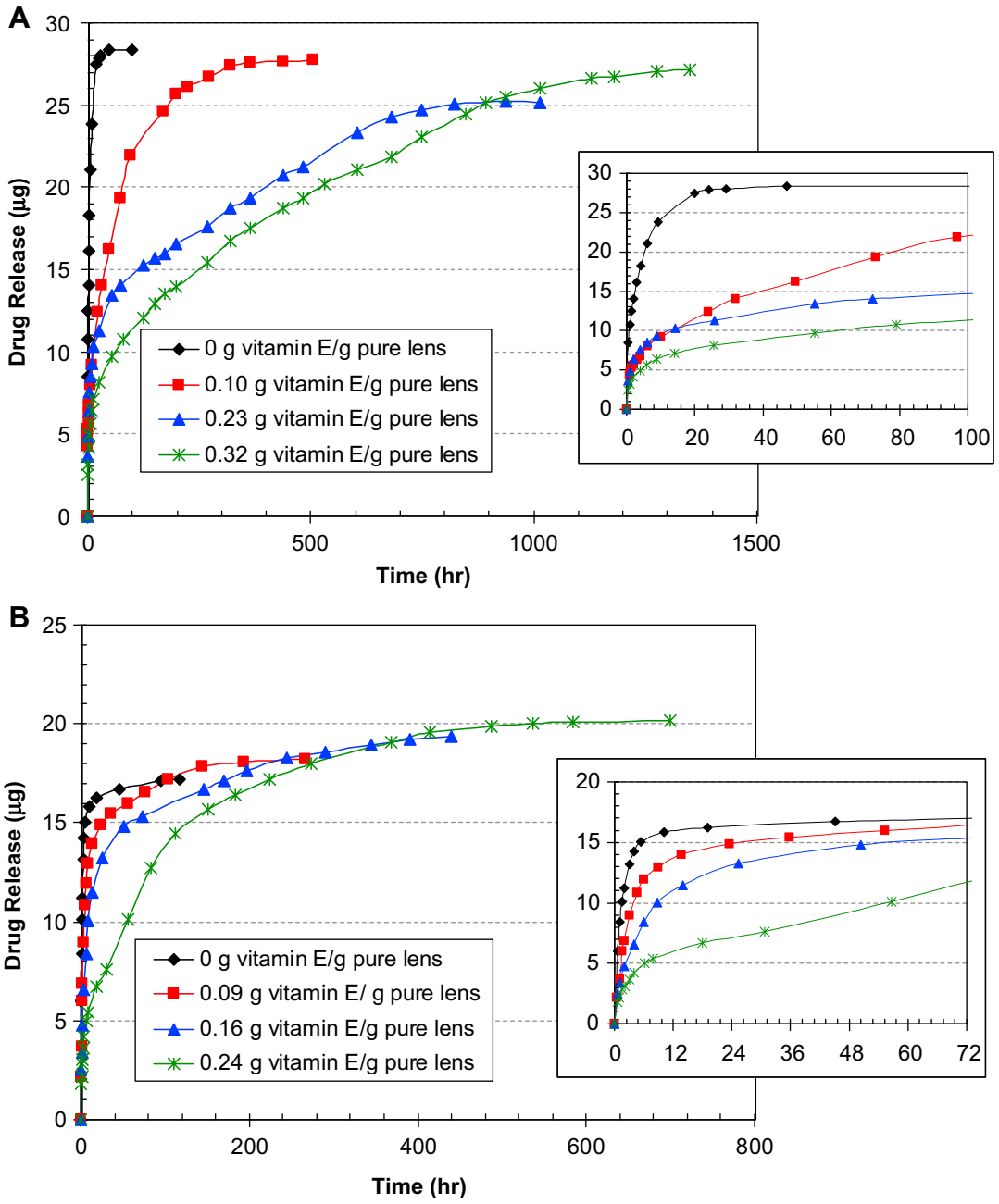

Fig. 7. Profiles of DXP release by Vitamin E loaded contact lenses A) ACUVUE® OASYS™ B) NIGHT&DAY™ C) O_2OPTIX™ D) PureVision™. Vitamin E was loaded first by soaking pure contact lens in Vitamin E–ethanol solution and the lens was dried. And then DXP was loaded by soaking Vitamin E loaded lens in DXP–PBS solution (0.7 mg/mL). Vitamin E loadings are indicated.

each lens except for PureVision™ lens which shows a slightly faster release from the lens soaked in timolol–ethanol solution than that soaked in PBS medium. ACUVUE® OASYS™ lens releases 90% of timolol relatively slowly for 1.2 h compared to the other lenses. ACUVUE® ADVANCE™ lens exhibits rapid timolol release lasting less than 0.5 h and the other three lenses show comparable release durations. It is observed that the release durations of timolol are not correlated to the water content of the lenses. The total amount of drug released is the highest by PureVision™ (about 57 μg), lowest by NIGHT&DAY™ (about 22 μg), and those of the other lenses are similar ranging 26–30 μg based on PBS medium soaking method. The amounts of timolol uptake and release are also uncorrelated to the water content, likely due to differences in the hydrophilic components of the lenses, which lead to differences in drug binding to the hydrophilic component rich phases in the lenses. It is interesting that all the lenses soaked in ethanol solution for 3 h release substantially high total amount of timolol; about 2.5–3 times more than those soaked in PBS solution. For example, ACUVUE® OASYS™ lens soaked in PBS solution for 7 days releases 28 μg of timolol, but that soaked in ethanol solution for 3 h release about 95.7 μg. The increased uptake of timolol from ethanol soaking is likely due to the fact that timolol does not ionize in ethanol and so it preferentially binds to the polymer. In PBS, the drug is almost entirely ionized, which leads to a very large solubility in water, and consequently to small binding to the gel.

The drug release from control lenses, i.e., without Vitamin E, were also conducted with the other two drugs (DXP and fluconazole) but these are not presented here because the major

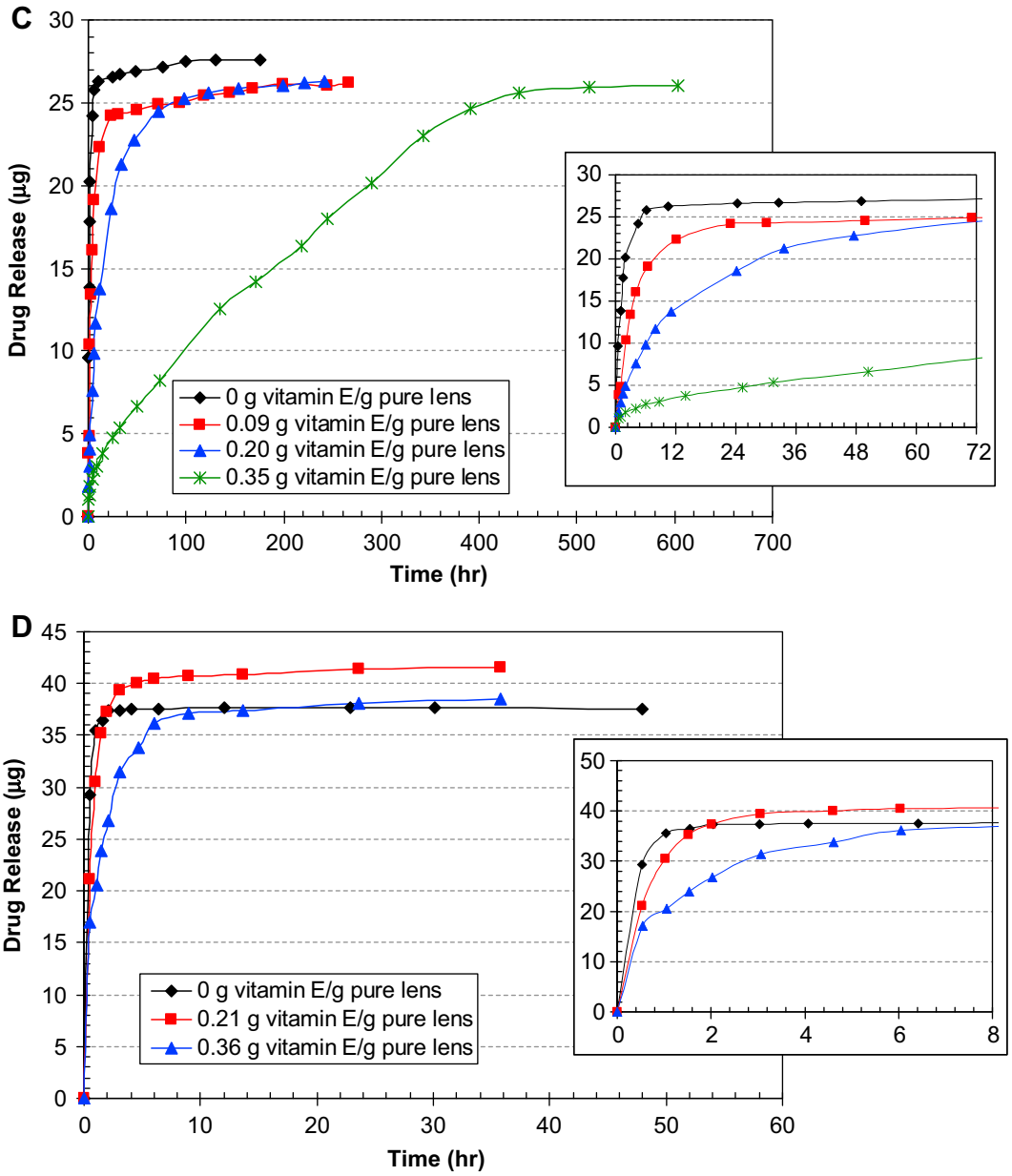

Fig. 7. (*continued*).

conclusions are the same as those mentioned above in the context of timolol. The % release profiles were independent of the method of loading and the total release durations were all about 1–10 h. These control data are presented in later sections while comparing the results with the release from the Vitamin E loaded lenses.

3.5. Dynamics of drug transport from Vitamin E loaded lenses

3.5.1. Timolol–Vitamin E loaded lenses

Fig. 5 shows timolol release dynamics by Vitamin E loaded lenses for different loadings of Vitamin E. Timolol and Vitamin E were loaded into lenses simultaneously by soaking the lens in 0.8 mg/mL of timolol–Vitamin E–ethanol solution for 24 h. For pure lenses (no Vitamin E loading), timolol was loaded by soaking in timolol–ethanol solution of 0.8 mg/mL for 3 h. It is clearly seen in the figure that the rate of timolol release by all the lenses except PureVision™ decreases as Vitamin E loading increases, while the total drug release amount does not change significantly. Specifically, NIGHT&DAY™ shows 9.8-fold release time for 16% Vitamin E loading corresponding to release time of about 5.5 h, 76-fold for 27% corresponding to 43 h release, and 341-fold for 74% corresponding to 192 h release. The total amount of timolol released by NIGHT&DAY™ is lowest at about 50 μg. The drug transport data for PureVision™ lenses suggests that the Vitamin E simply dissolves in the matrix leading to negligible barrier effect. However the drug transport data for ACUVUE® OASYS™ lenses shows a significant barrier effect, which in combination with the EW data suggests that the barrier effect in these lenses likely arises due to Vitamin E that coats polymer fibers rather than forming larger aggregates, which appears to be the mechanism for NIGHT&DAY™ and O_2OPTIX™ lenses.

To explore the effect of the loading method, timolol was also loaded into Vitamin E containing lenses by soaking the lenses in timolol–PBS solution for 7 days. Timolol release profiles of the

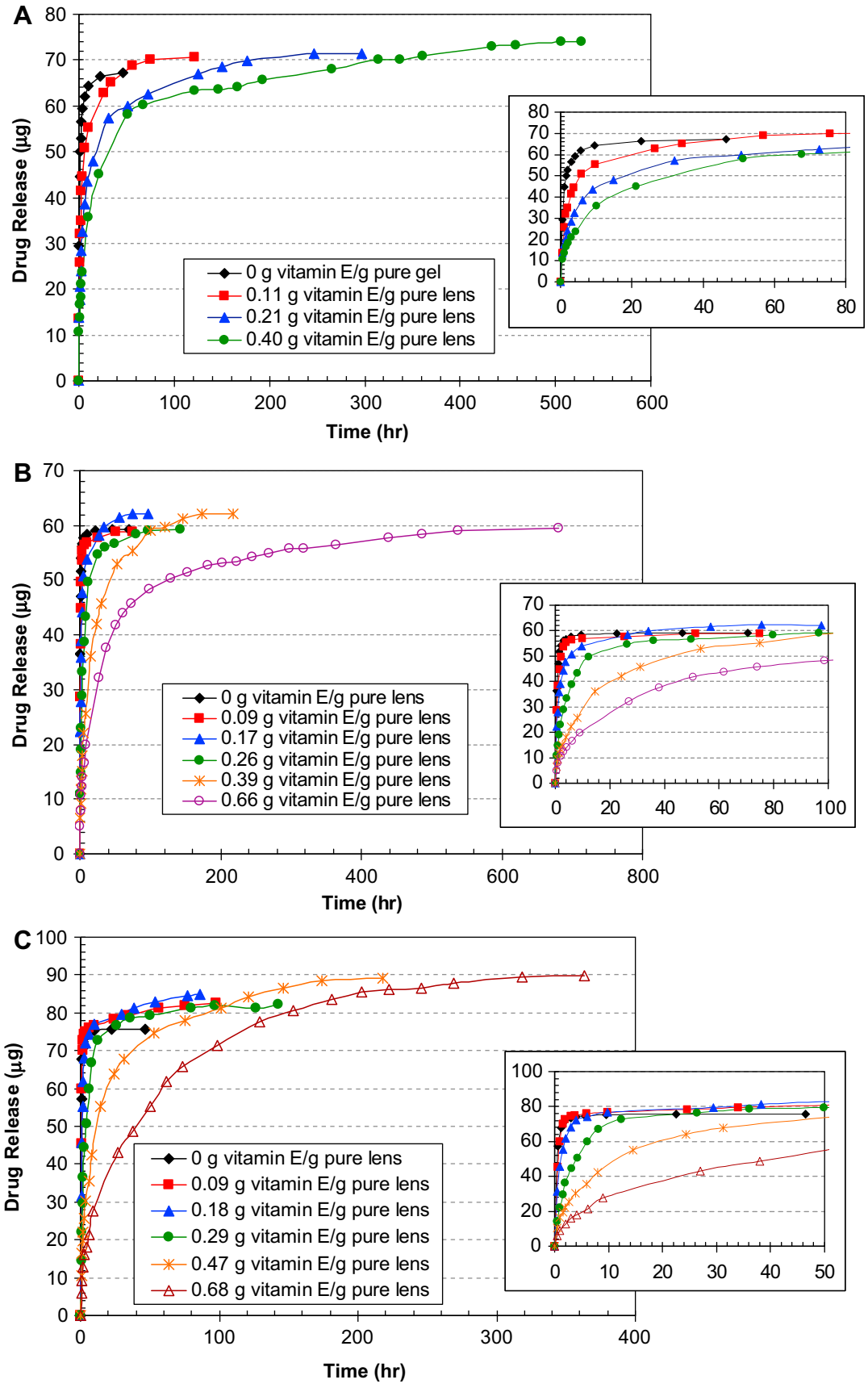

Fig. 8. Profiles of fluconazole release by Vitamin E loaded contact lenses A) ACUVUE® OASYS™ B) NIGHT&DAY™ C) O_2OPTIX™. Vitamin E was loaded first by soaking pure contact lens in Vitamin E–ethanol solution and the lens was dried. And then fluconazole was loaded by soaking Vitamin E loaded lens in fluconazole–PBS solution (0.7 mg/mL). Vitamin E loadings are indicated.

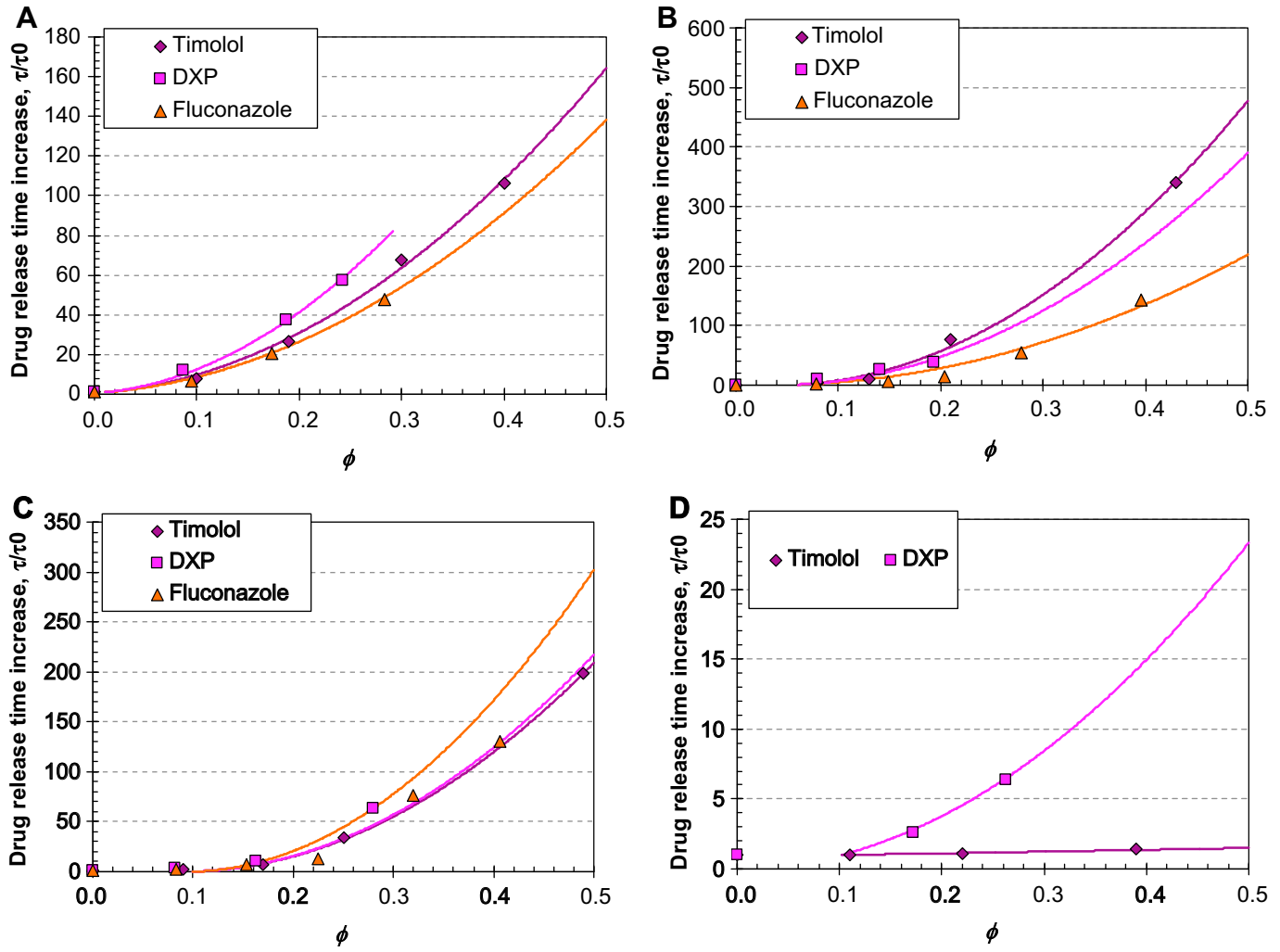

Fig. 9. Drug release duration increase by Vitamin E loaded contact lenses. A) ACUVUE® OASYS™ B) NIGHT&DAY™ C) O_2OPTIX™ D)) PureVision™. The lines are best fit 2nd order polynomial curves to data of each lens. Drug release time is the duration in release of 90% of total drug released.

NIGHT&DAY™, ACUVUE® OASYS™ and O_2OPTIX™ lenses for sequential loading of Vitamin E and timolol are also shown in Fig. 5. It can be clearly seen that this method also increases timolol release duration compared to the control lenses without Vitamin E. Additionally, there is an increase in the total amount of drug released for the higher Vitamin E loading (74% for NIGHT&DAY™, and 97% for O_2OPTIX™). Therefore, loading timolol and Vitamin E at the same time through ethanol medium is much more efficient way for preparation of timolol–Vitamin E loaded lenses. For O_2OPTIX™, with same amount of Vitamin E loading, the release profiles from the lenses where timolol and Vitamin E were loaded sequentially are almost the same as for the case where timolol and Vitamin E were loaded simultaneously. However, for ACUVUE® OASYS™ and NIGHT&DAY™ even though the release durations from different loading methods are similar to each other, the release profiles are slightly different. The difference is likely to be resulted from the non-homogeneous distribution of timolol inside the lens. Timolol loaded by drug–PBS solution goes into the gel matrix by diffusion for longer time, leading to a well distribution in the lens. On the other hand, timolol uptake in drug–ethanol solution might result in high drug concentration in the center region of lens after ethanol evaporation.

The morphology of the Vitamin E laden lens could potentially change over time, which could impact the drug transport. To investigate this issue, NIGHT&DAY™ lenses with various Vitamin E loadings that were utilized in the drug release experiments were soaked in 2 mL PBS solution after the release experiment were over. The lenses were subsequently stored for 6 months and then further soaked in 250 mL DI water with moderate stirring for 48 h to remove the residual timolol prior to be used in second release experiment. The cleaned Vitamin E lenses were dried and weighed to ensure that the Vitamin E loading was kept the same as the initial loading. The dry weight of the lens was within 1% difference of that measured immediately after the initial Vitamin E loading, which proves that Vitamin E does not diffuse out into PBS during the storage. The lenses were then soaked in 0.8 mg/mL timolol–PBS solution for 7 days to load the drug. After the drug loading, the drug release profiles were measured in 2 mL PBS (Fig. 6). The release

Table 2
Model parameters obtained by fitting experimental data to the model.

Contact lenses	ϕ^*	α		
		Timolol	Fluconazole	DXP
ACUVUE® OASYS™	0.0117	24.2	22.0	28.8
NIGHT&DAY™	0.0621	47.6	31.5	42.8
O_2OPTIX™	0.0973	35.2	35.9	42.1
PureVision™‘	0.1019	1.06	–	10.95

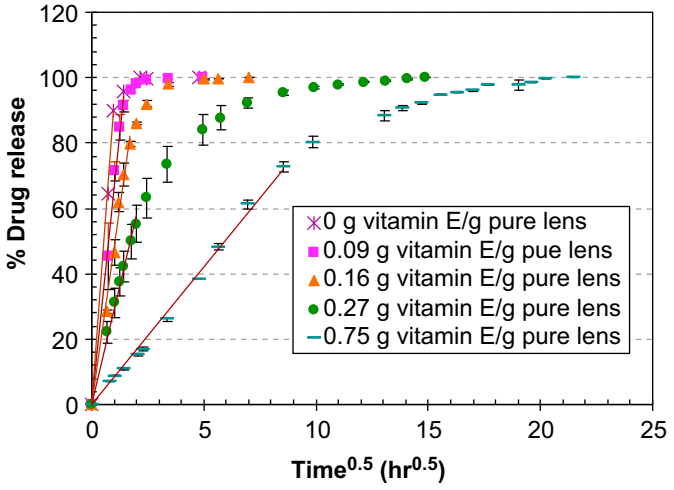

Fig. 10. Plot of % timolol release by Vitamin E loaded NIGHT&DAY™ versus square root of time. The lines are the best fit straight for short-time data. All R^2's are larger than 0.98. Some of data are presented as mean ± S.D. with $n = 3$.

profiles in this case were almost identical to the first release profiles; this proves that the morphology of the Vitamin E laden lenses is stable even when soaked in PBS for 6 months, and thus the drug release behavior of these lenses will not degrade during packaging and shelf storage. The morphology of the Vitamin E laden lenses does not change during PBS soaking likely because of the negligible solubility of Vitamin E in PBS.

3.5.2. DXP–Vitamin E loaded lenses

DXP release profiles for various Vitamin E loaded commercial lenses are shown in Fig. 7. The dry Vitamin E loaded lenses were soaked in 0.7 mg/mL DXP–PBS solution for sufficient time to reach equilibrium. In all experiments of DXP–Vitamin E loaded lenses explored here, the uptake periods were longer than the release equilibrium time, suggesting that equilibrium was achieved during loading. Fig. 7 indicates that, similar to the release rates for timolol, the DXP release rates from all lenses decrease as the Vitamin E loading increases, while the total drug release amount is relatively independent of the Vitamin E loading. With similar Vitamin E loading, ACUVUE® OASYS™ has the longest drug release time, followed by NIGHT&DAY™ and O_2OPTIX™, while PureVision™

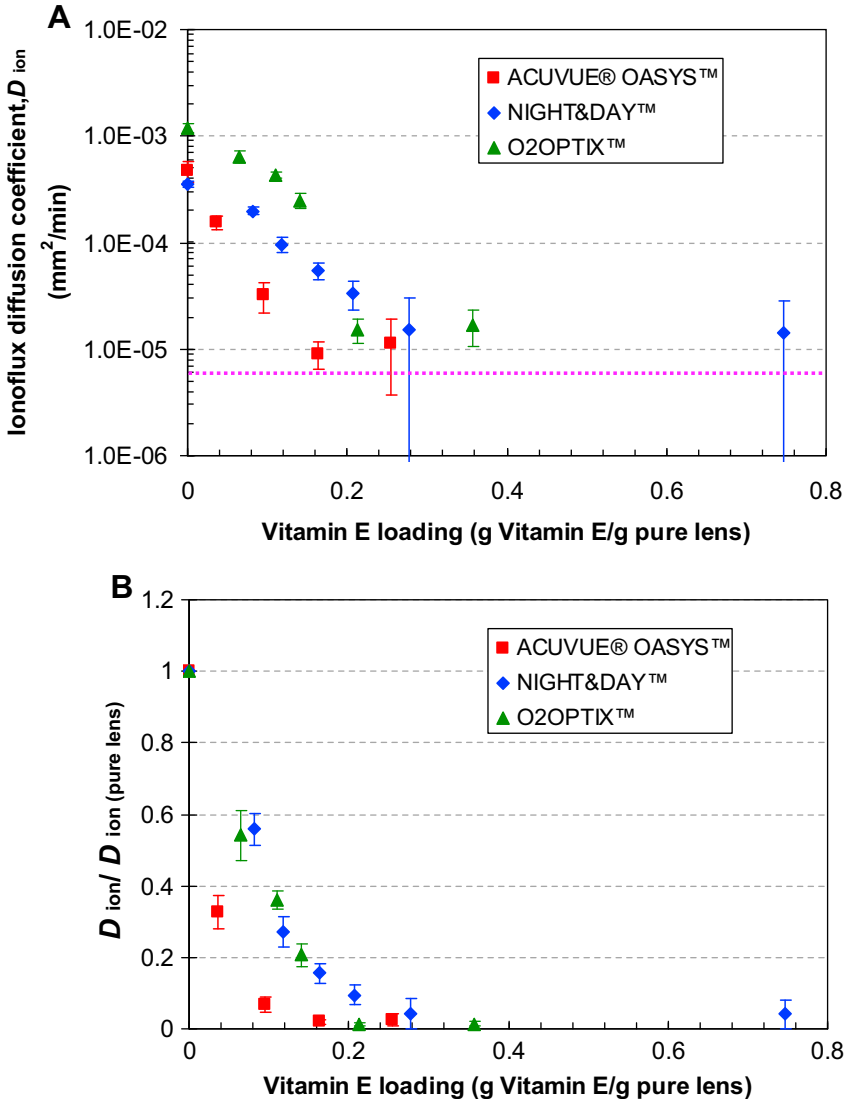

Fig. 11. Effect of Vitamin E loading on ion permeability of lenses. The error bars denote 95% confidence intervals. The solid dash line in A) indicates the minimum requirement for sufficient on-eye movement [37].

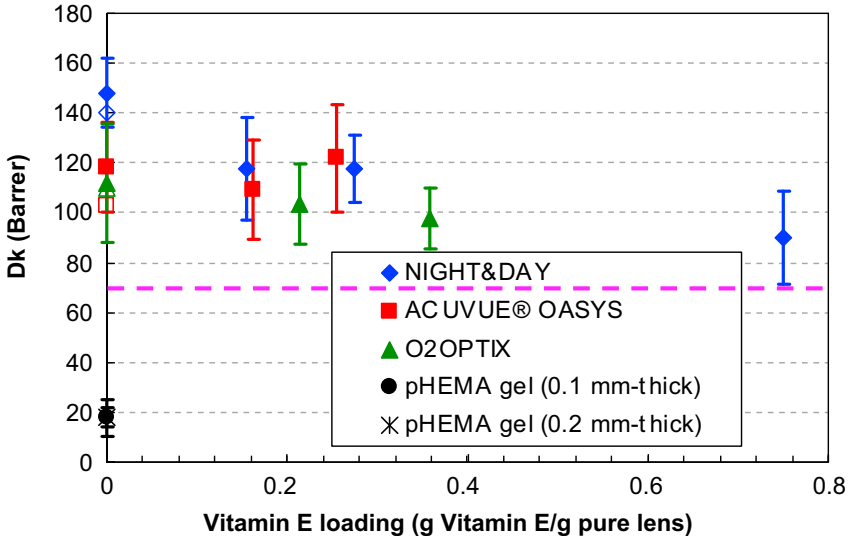

Fig. 12. Effect of Vitamin E loading on oxygen permeability. Data are presented as mean ± S.D. with $n \geq 3$. The reported values from manufacturers are shown in hollow marker. The solid dash line indicates the minimum requirement to avoid deprivation of oxygen to cornea [41].

shows negligible increase. For example, ACUVUE® OASYS™ lens releases about 27 μg of DXP in 7 days for 10% Vitamin E loading and in 3 weeks for 23% Vitamin E loading, while 40 μg of DXP in PureVision™ released in only 8 h even with 36% Vitamin E loaded inside. In addition, even though the drug release duration is much longer, the duration release time increase ratio by Vitamin E loaded lens for DXP is similar to that for timolol with similar Vitamin E loading amount. This suggests that the attenuation in drug release rates is similar for all hydrophilic drugs even though the diffusivities of the drugs in the pure lenses may be vastly different, which will be further discussed later.

3.5.3. Fluconazole–Vitamin E loaded lenses

To further validate the hypothesis that the attenuation in drug release rates is similar for all hydrophilic drugs, we explored transport of an antifungal drug fluconazole in Vitamin E laden lenses. Fig. 8 shows the fluconazole release dynamics from Vitamin E loaded NIGHT&DAY™, ACUVUE® OASYS™ and O_2OPTIX™ lenses. PureVision™ was not tested because of the marginal impact of Vitamin E loading on transport rates of timolol and DXP from this lens.

To load drugs into lenses, the Vitamin E loaded lenses were soaked in 0.7 mg/mL fluconazole–PBS solution for sufficient time to reach equilibrium. The results clearly show a significant reduction in release rates due to Vitamin E loading in the lenses. For example, NIGHT&DAY™ lenses release about 60 μg of fluconazole in 10 h for 17% Vitamin E loading, in 24 h for 26%, 88 h for 39% and 227 h for 66% Vitamin E loading, which is a 6.2, 14, 55 and 142-fold release duration increase, respectively. The total amount of fluconazole released by different lens is similar, with the exception of O_2OPTIX™, which has a slightly higher drug release of about 80 μg. With similar Vitamin E loading, ACUVUE® OASYS™ shows longer fluconazole release period than NIGHT&DAY™ and O_2OPTIX™.

The effect of Vitamin E loading on hydrophilic drug transport is summarized in Fig. 9. The increase in the release times from Vitamin E loaded lenses relative to release times from the control lenses without Vitamin E is relatively similar for the three hydrophilic drugs particularly for ACUVUE® OASYS™ and O_2OPTIX™ lenses. There are some differences from NIGHT&DAY™ lens; fluconazole released by NIGHT&DAY™ lens exhibits a smaller time increase compares to timolol and DXP. The data also clearly shows that for each drug, the release time is quadratic to the Vitamin E loading. These issues are discussed below in the model development section.

3.5.4. Model for hydrophilic drugs

The hydrophilic drugs have a negligible partitioning in Vitamin E. The increase in release times for charged drugs is likely due to the presence of Vitamin E aggregates inside the gel that act as diffusion barriers. These barriers lead to an increase in the length of the path that molecules take to diffuse from inside the gel to the fluid reservoir. The path length of the tortuous path l should scale as $h(1+\alpha(\phi-\phi^*))$, where h is the half thickness of lens, and α depends on the microstructure, including particle size and aspect ratio, of the Vitamin E aggregates distribution in the gel; ϕ is the volume ratio of Vitamin E in the dry gel, and $(\phi-\phi^*)$ is the fraction that is present as the Vitamin E particles. The fraction ϕ^* is assumed to be either existing as bound to the polymer gel or as particles but in regions of the gel that do not contribute to drug transport. For a diffusion-controlled release, the time for release can be scales as l^2/D. The gel thickness increases due to Vitamin E uptake, and by assuming isotropic expansion and small Vitamin E loading, it can be written as $h = h_0(1+\phi/3)$, where h_0 is a half thickness of pure lens. The time of release thus scales as

$$\tau \sim \frac{{h_0}^2}{D}\left(1+\frac{\phi}{3}\right)^2\left(1+\alpha\left(\phi-\phi^*\right)\right)^2 \tag{3}$$

The term $(1+\phi/3)^2$ does not make a significant contribution to increase in release time as for ϕ as large as 1, this term is less than 2. By neglecting this term we get

$$\frac{\tau}{\tau_0} \sim \left(\left(1-\alpha\phi^*\right)^2 + 2\phi\left(\alpha-\alpha^2\phi^*\right)+\alpha^2\phi^2\right) \tag{4}$$

where time τ is the duration in which 90% of release is completed and τ_0 is the corresponding duration for the lens without Vitamin E. It is noted that Equation (4) is only valid for $\phi > \phi^*$. The parameters α and ϕ^* can be obtained by fitting the data shown in Fig. 9 to the above model. The error between the experimental data and model prediction was defined as $\sqrt{\{\sum(\tau/\tau_0)-(\tau/\tau_0)_{ex}\}^2/\sum(\tau/\tau_0)_{ex}}$, where (τ/τ_0) and $(\tau/\tau_0)_{ex}$ are the predicted release time ratio by

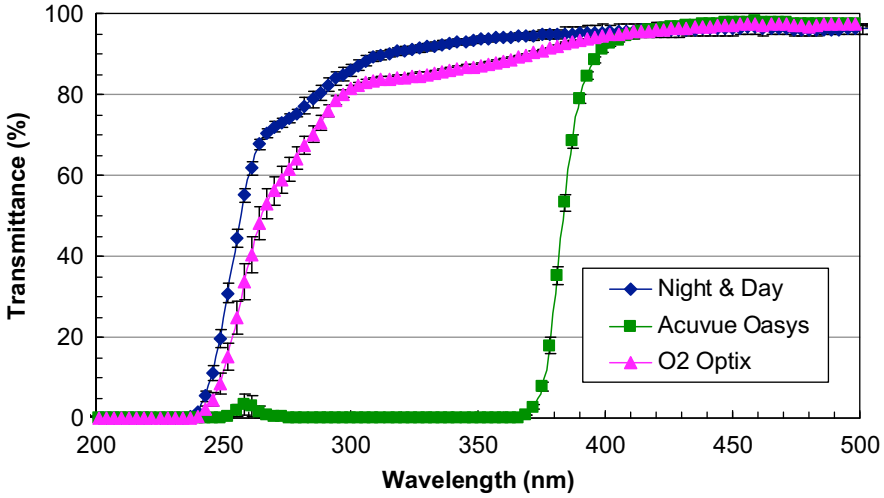

Fig. 13. Transmittance spectrum for commercial contact lenses. All measurements were conducted within 24 h after sample preparation, and data are presented as mean ± S.D. with $n = 3$.

model and the experimental release time ratio, respectively. The parameters α and ϕ^* for timolol, fluconazole and DXP were obtained using the function 'fminsearch' in MATLAB® minimizing the error and are listed in Table 2. For a given lens, the same value of ϕ^* was imposed in all fits since this parameter should be the same for all the drugs as it only depends on the interaction of Vitamin E with the lens matrix. Also the values of α should be similar for all drugs since this is a geometric parameter that only depends on the microstructure of the Vitamin E laden lenses. The good fits between the model and the data with identical ϕ^* and similar α for each drug further substantiate the mechanisms and the model presented above.

3.5.5. Diffusivities of drugs in Vitamin E loaded lenses

Contact lenses have a complex geometry including curvature with variable thicknesses from center to edge depending on power. However, a diameter of a lens (about 14 mm) is much larger than its thickness (about 80–100 μm) and so we can simplify the geometry of lens as thin flat film with variable thickness. Under this assumption, the mass transfer problem for transport in the contact lens can be described by the following equations:

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

where C is the drug concentration in the gel, D is the effective diffusivity and y and t denote the transverse coordinate and time, respectively. The boundary conditions for the drug release experiment are

$$\begin{aligned} &\frac{\partial C}{\partial y}(t, y = 0) = 0 \\ &C(t, y = h(x)) = KC_w \end{aligned} \tag{6}$$

where h is the half thickness of the gel, which depends on the curved lateral coordinate x, C_w is the drug concentration in the release medium. The first boundary condition assumes symmetry at the center of the gel and the second boundary condition assumes equilibrium between the drug concentration in the gel and that in the PBS phase. A mass balance on the PBS in the beaker yields

$$V_w\frac{dC_w}{dt} = -2D\int_0^S P(x)\left|\frac{\partial C}{\partial y}\right|dx \tag{7}$$

where V_w is the PBS volume, $P(x)$ is the perimeter of the lens at the coordinate x, and S is a half of maximum arc length. Finally the initial conditions for the drug release experiments are

$$\begin{aligned} &C(y, t = 0) = C_i \\ &C_w(t = 0) = 0 \end{aligned} \tag{8}$$

The fluid volume is much larger than lens volume and the solubility of timolol, fluconazole and DXP is very high in PBS of this pH 7.4, which satisfies perfect sink condition. Under perfect sink conditions, the set of equations listed above can be solved analytically to give the following solution for the concentration profile in the lens:

$$C = \sum_{n=0}^{\infty}\frac{(-1)^n 4C_i}{(2n+1)\pi}\cos\left(\frac{(2n+1)\pi}{2h(x)}y\right)e^{-\frac{(2n+1)^2\pi^2}{4h(x)^2}Dt} \tag{9}$$

In short-time limit, the concentration profile can also be expressed as

$$C = \frac{2}{\sqrt{\pi}}C_i\int_0^{\frac{h-y}{\sqrt{4Dt}}} e^{-\eta^2}d\eta \tag{10}$$

This result is only valid for times shorter than the $h(x)/\sqrt{4Dt}$. By using Equation (7) and Equation (10), we obtain the following equation:

$$V_w\frac{dC_w}{dt} = 2D\frac{2}{\sqrt{\pi}}\frac{C_i}{\sqrt{4Dt}}\int_0^S P(x)dx = D\frac{2}{\sqrt{\pi}}\frac{C_i}{\sqrt{4Dt}}A_{surface} \tag{11}$$

where $A_{surface}$ is the total surface area of the lens. Equation (11) can be integrated to give,

$$C_w = \frac{2\sqrt{Dt}}{\sqrt{\pi}}C_i\frac{A_{surface}}{V_w} \tag{12}$$

The fractional release $f \equiv V_w C_w / V_{gel} C_i$ can thus be expressed as

$$f = \frac{2\sqrt{Dt}}{\sqrt{\pi}}\frac{A_{surface}}{V_{gel}} = \frac{2}{\sqrt{\pi}}\sqrt{\frac{Dt}{\bar{h}^2}} \tag{13}$$

where $\bar{h}$ is the mean thickness of the gel defined as $\bar{h} \equiv V_{gel}/A_{surface}$. The above equation is only valid for times shorter than $h_{min}/\sqrt{4Dt}$,

where h_{min} is the minimum gel thickness, which typically equals the center thickness for negative power contact lenses.

Fig. 10 plots % drugs release by Vitamin E loaded NIGHT&DAY™ lenses as a function of square root of time for timolol. 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 0.98 showing that the drug transport in these lenses is diffusion-controlled. The short-time data in the drug release profiles from Vitamin E laden lenses is linear for all drugs and all lenses (data only shown for timolol release from NIGHT&DAY™) proving that the transport is diffusion limited for all cases.

3.6. Ion permeability of Vitamin E loaded lenses

Ion permeability of contact lenses is a critical variable for lens motion on the eye according to Domscheke et al. [36]. The thickness of the lens varies in the radial direction and the exact profiles are not available in literature. To obtain the permeability, each lens was treated as a section of a sphere with radius equal to the known base curve of the lens and 80 μm in thickness. The calculated values of ion permeability are plotted in Fig. 11A as a function of the Vitamin E loading for O_2OPTIX™, NIGHT&DAY™ and ACUVUE® OASYS™ lenses. The results show that the ion permeability of pure O_2OPTIX™ is highest among three lenses and is about 3.4 fold and 2.5 fold that of the pure NIGHT&DAY™ and ACUVUE® OASYS™, respectively. Also it is clearly seen that the ion permeability decreases as Vitamin E loading increases for all the lenses.

The decrease ion permeability for Vitamin E loaded lens can be seen more clearly in Fig. 11B in which the ratio of ion permeability of lens with and without Vitamin E is plotted as a function of the Vitamin E loading. Interestingly, the graphs are almost the same for O_2OPTIX™ and NIGHT&DAY™ and the decrease in ion permeability by Vitamin E is much larger for ACUVUE® OASYS™ for the same Vitamin E loadings compared to the other two lenses. D_{ion} should be larger than 6.0×10^{-6} mm^2/min for sufficient on-eye movement of lens according to Nicolson et al. [37]. Fig. 11 indicates that all Vitamin E loaded lenses in our study have adequate ion permeability to maintain on-eye motion.

3.7. Oxygen permeability of Vitamin E loaded lenses

The oxygen permeability of extended-wear contact lenses must be sufficiently high to avoid deprivation of oxygen to cornea, which could cause adverse responses [38,39]. The lens permeability (Dk) is the product of the diffusivity D and the oxygen partition coefficient k, and it is typically expressed in units of 10^{-11} (cm^2/s)·(mlO_2/(ml mmHg)) or 10^{-11} mlO_2 cm/(s cm^2 mmHg), which is also referred as a barrer or a Fatt. The oxygen permeability is an intrinsic property of a material to transport oxygen through its bulk and is independent of thickness. The oxygen transmissibility, Dk/t, refers to the oxygen transport capacity of a specific contact lens with thickness t, and it generally expressed in units of 10^{-9} cm mlO_2/(s ml mmHg) or 10^{-9} mlO_2/(s cm^2 mmHg). To avoid hypoxia, an extended wearable contact lens must provide at least a minimum oxygen transmissibility (Dk/t) of 87, which cannot be achieved by traditional hydrophilic contact lens [40]. Recently, the suggested minimum value of Dk/t to avoid hypoxia has been proposed to increase to 125 [41]. The reported values of Dk values of various commercial contact lenses are 140 for NIGHT&DAY™, 110 for O_2OPTIX™, 103 for ACUVUE® OASYS™ and 91 for PureVision™. With an approximate average thickness of 80 μm, these commercial silicone-hydrogel contact lenses can provide sufficient oxygen transmissibility to be used for extend wear.

The influence of Vitamin E loading on oxygen transport through the contact lenses was determined by mounting the lenses is a diffusion cell with gradient in the dissolved oxygen concentration across the lens, and then measuring the oxygen concentration in the receiver chamber. Below a model is presented to fit the measured oxygen concentration data to determine the oxygen diffusivity through the lens.

Overall mass balance of dissolved oxygen in the closed diffusion cell is given by

$$V_r C_{r0} + V_d C_{d0} = V_r C_r + V_d C_d \tag{14}$$

where V_r and V_d are the DI water volumes of the receiving and donor compartments, respectively, and C_r and C_d indicate the dissolved oxygen concentrations with initial concentration of C_{r0} and C_{d0} in the receiving and donor chambers, respectively. Since the lens volume is substantially less than the fluid volume, the system reaches a pseudo-steady state very rapidly and thus the oxygen flux through the lens can be expressed as

$$V_r \frac{dC_r}{dt} = Dk\frac{A}{h}(C_d - C_r) \tag{15}$$

where A and h are the surface area and the average thickness of hydrated lens respectively; D is the oxygen diffusion coefficient of the lens material and k is the oxygen partition coefficient between lens and DI water. The above equation implicitly assumes negligible mass transfer resistance in the boundary layers in the receiver and donor compartments. This assumption was verified by showing that the measured oxygen concentration profiles were not sensitive to stirring at stirring speeds of 900 rpm. Equations (14) and (15) can be combined to give:

$$\frac{dC_r}{dt} = Dk\frac{A}{h}\left(\frac{C_{d0}}{V_r} + \frac{C_{r0}}{V_d} - \frac{V_r + V_d}{V_r V_d} C_r\right) \tag{16}$$

The solution to the above equation with the initial condition $C_r(t = 0) = C_{r0}$ is

$$C_r = \frac{V_r V_d}{V_r + V_d}\left(\frac{C_{d0}}{V_r} + \frac{C_{r0}}{V_d}\right)\left[1 - \exp\left(-\frac{V_r + V_d}{V_r V_d} Dk\frac{A}{h}t\right)\right] + C_{r0}\exp\left(-\frac{V_r + V_d}{V_r V_d} Dk\frac{A}{h}t\right) \tag{17}$$

The parameter DkA/h can be obtained by fitting the experiment data to the above equation using the function 'fminsearch' in MATLAB®. The exact value of D through various lenses could not be directly obtained because the detailed shapes of the lenses were not available in literature, but could be calculated by using the approximate surface area of these lenses described in ion permeability section. The validity of this approach was established by measuring oxygen diffusivity through p-HEMA gels prepared of two different thicknesses from the procedures reported in our earlier study [16,17]. The measured value of 14.6 ± 1.3 for the synthesized hydrogel with water content 41.1% was in good agreement with reported value of 12.9 for conventional hydrogel materials of which oxygen permeability is primarily determined by its water content [42].

The effect of Vitamin E loading on Dk of silicone contact lenses is shown in Fig. 12. The calculated Dk values were 148, 118, and 111 for NIGHT&DAY™, ACUVUE® OASYS™ and O_2OPTIX™, respectively, which were also in good agreement with the reported Dk values from the manufacturers and other research groups, providing the accuracy of the measurement methods [43]. The results show Vitamin E loading in NIGHT&DAY™ slightly reduces the oxygen permeability when the Vitamin E amount goes up to about 75%. On the other hand, no significant change was observed for ACUVUE® OASYS™ and O_2OPTIX™ up to about 35% of Vitamin E loading in the

lens. While it is not feasible to quantitatively evaluate the effect of Vitamin E on *Dk* values due to the relatively large standard deviations in the measured values, it is clear that the *Dk* value of these Vitamin E loaded lenses with average thickness 80 μm are still sufficiently high to meet the minimum requirements to avoid hypoxia. The results that Vitamin E loading in the lens has much higher influence on ion transport than on oxygen transport suggests that most Vitamin E aggregates exist in the hydrophilic polymer region in the gel matrix. This is plausible because Vitamin E likely has a much lower solubility in the hydrophilic regions than in the hydrophobic silicone-rich region in the gel matrix. Since ion transport occurs primarily through the hydrophilic channels, the presence of Vitamin E aggregates significant reduces the ion permeability. On the other hand, oxygen transport occurs mainly through the silicone-rich channels, which may not contain Vitamin E aggregates resulting in a minimal attenuation in oxygen permeability.

3.8. Transmittance of Vitamin E loaded lenses

In addition to correcting vision, a contact lens could potentially also prevent or minimize exposure of the corneal tissue to damaging effects of UV light. Currently ACUVUE® is the only brand that claims the benefit of protection against UV radiation [44]. Fig. 13 shows the measured transmittance spectrum for three commercial contact lenses used in our study. NIGHT&DAY™ and O_2OPTIX™ have no significant protection against UVB (280–315 nm) and UVA (315–400 nm), while ACUVUE® OASYS™ completely blocks UVB and UVA radiation. These results match the reported UV transmittance characteristics of silicone-hydrogel contact lenses reported by the manufacturers and other independent research group [44,45].

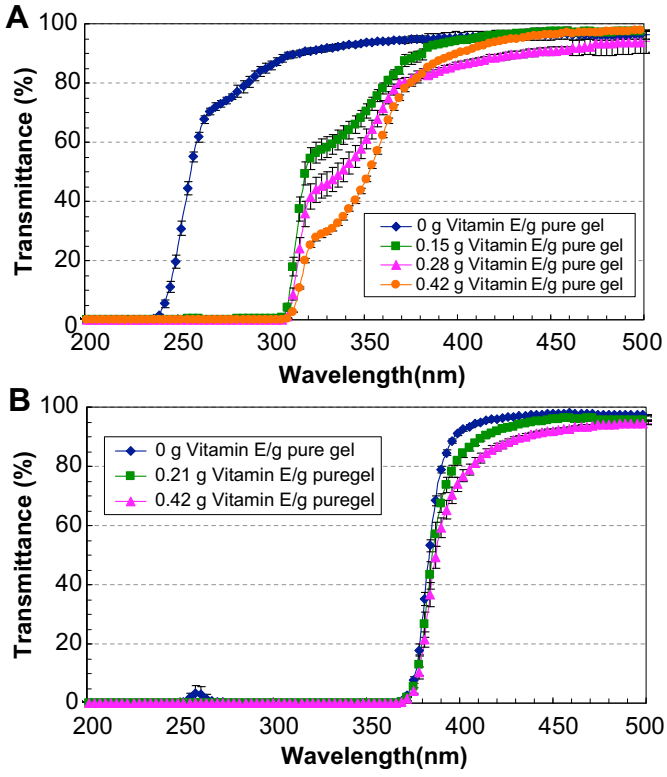

Fig. 14. Transmittance spectrum for A) NIGHT&DAY™ and B) ACUVUE® OASYS™ with different Vitamin E loading. All measurements were conducted within 24 h after sample preparation, and data are presented as mean ± S.D. with $n = 3$.

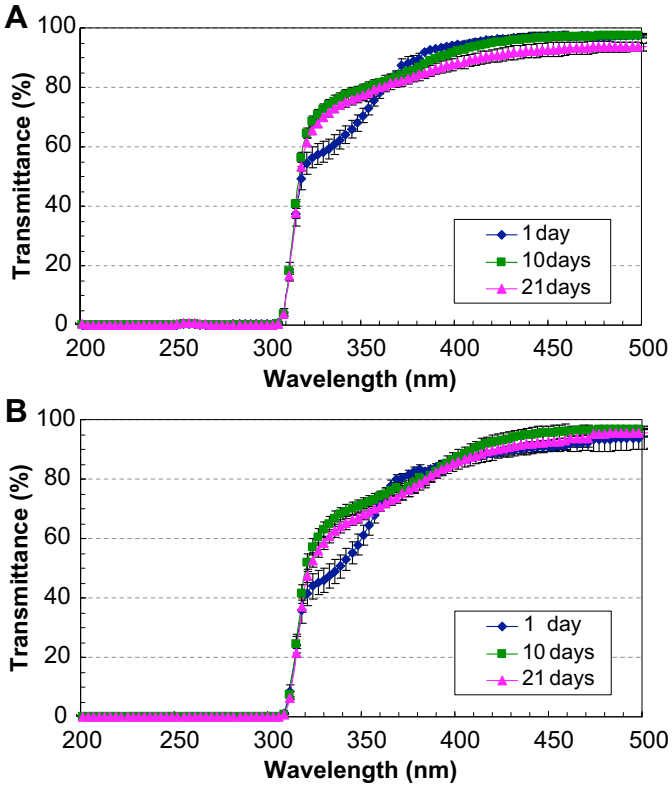

Fig. 15. Transmittance spectrum of NIGHT&DAY™ with Vitamin E loading A) 0.15 g Vitamin E/g pure lens and B) 0.28 g Vitamin E/g pure lens, and data are presented as mean ± S.D. with $n = 3$.

The effect of Vitamin E loading on the transmittance spectrum of NIGHT&DAY™ and ACUVUE® OASYS™ is shown in Fig. 14. The results clearly show that Vitamin E loaded NIGHT&DAY™ lenses completely block UVB radiation and also partially block UVA radiation proportionally to the Vitamin E loading. Since ACUVUE® OASYS™ block UV radiation, Vitamin E loading only marginally increases the UV protection for these lenses. The UV radiation is known to induce photo-oxidation of Vitamin E transforming Vitamin E into various photoproducts [46,47]. To explore the effect of photo-oxidation on protection again UV radiation, the transmittance spectra of lenses was measured as a function of time while exposing the lenses to natural light. While the UVB blocking effect of Vitamin E was retained, the ability to absorb UVA radiation decreased for a few days and then reached equilibrium, as shown in Fig. 15.

4. Conclusions

The results reported here conclusively show that Vitamin E loading in commercial silicone contact lens can substantially increase the release duration of hydrophilic drugs without impacting transparency. There are significant reductions in ion permeability and slight reduction in oxygen permeability, but the reductions are not sufficient to preclude use of the Vitamin E laden commercial lenses for extended wear. The mechanism of increase in duration is due to the barrier effect of Vitamin E. While it is reasonable to assume that the effect is caused by the presence of particles of Vitamin E, it is also possible that Vitamin E does not form macroscopic aggregates and is simply adsorbed on the polymer gel. The surface adsorption could impede surface diffusion of the drug along the polymer leading to a reduction in effective

diffusion rates. Also contrasts between effect of Vitamin E on ion and oxygen transport suggest that the Vitamin E aggregates may only form in the hydrophilic channels of the silicon-hydrogel lenses. Further investigations are needed to obtain the microstructure of the Vitamin E phases in the gels, and relate it to the drug, ion and oxygen transport. In addition, future clinical studies are needed to determine the impact of Vitamin E addition on comfort and lens motion. Also, the release profiles from the Vitamin E laden contact lenses are not zero-order and that may have significant clinician implications. While the results presented have focused on drug contact lenses, the approach of *in situ* creation of transport barriers in silicone-hydrogels could be used in other areas where extended release of solutes is desired, such as puncta plugs, ophtha coils, retinal implants, transdermal patches, wound healing patches, cornea replacement materials, etc.

Acknowledgements

This research was partially supported by 2009 Opportunity Seed Funds from the University of Florida.

Appendix

Figures with essential color discrimination. Figs. 1–15 in this article are difficult to interpret in black and white. The full color images can be found in the on-line version, at doi:10.1016/j.biomaterials.2010.01.113.

References

[1] Bourlais CL, Acar L, Zia H, Sado PA, Needham T, Leverge R. Ophthalmic drug delivery systems. Prog Retin Eye Res 1998;17(1):33–58.
[2] Mitra AK, editor. Ophthalmic drug delivery systems. New York, NY: Marcel Dekker, Inc.; 1993. p. 60.
[3] Segal P. Pumps and timed release. FDA Consumer Magazine; October 1991.
[4] McNamara NA, Polse KA, Brand RJ, Graham AD, Chan JS, McKenney CD. Tear mixing under a soft contact lens: effects of lens diameter. Am J Ophthalmol 1999;127:659–65.
[5] Creech JL, Chauhan A, Radke CJ. Dispersive mixing in the posterior tear film under a soft contact lens. Ind Eng Chem Res 2001;40:3015–26.
[6] Li CC, Chauhan A. Modeling ophthalmic drug delivery by soaked contact lenses. Ind Eng Chem Res 2006;45:3718–34.
[7] Hillman JS. Management of acute glaucoma with pilocarpine-soaked hydrophilic lens. Br J Ophthalmol 1974;58:674–9.
[8] Ruben M, Watkins R. Pilocarpine dispensation for the soft hydrophilic contact lens. Br J Ophthalmol 1975;59:455–8.
[9] Arthur BW, Hay GJ, Wasan SM, Willis WE. Ultrastructural effects of topical timolol on the rabbit cornea – outcome alone and in conjunction with a gas permeable contact-lens. Arch Ophthalmol 1983;101:1607–10.
[10] Wilson MC, Shields MB. A comparison of the clinical variations of the iridocorneal endothelial syndrome. Arch Ophthalmol 1989;107:1465–8.
[11] Schultz CL, Nunez IM, Silor DL, Neil ML. Contact lens containing a leachable absorbed material. US Patent No. 5723131, 1998.
[12] Schultz CL, Mint JM. Drug delivery system for antiglaucomatous medication. US Patent No. 6410045, 2002.
[13] Gulsen D, Chauhan A. Dispersion of microemulsion drops in HEMA hydrogel: a potential ophthalmic drug delivery vehicle. Int J Pharm 2005;292:95–117.
[14] Gulsen D, Li CC, Chauhan A. Dispersion of DMPC liposomes in contact lenses for ophthalmic drug delivery. Curr Eye Res 2005;30(12):1071–80.
[15] Kapoor Y, Chauhan A. Ophthalmic delivery of cyclosporine A from Brij-97 microemulsion and surfactant-laden *p*-HEMA hydrogels. Int J Pharm 2008;361:222–9.
[16] Kapoor Y, Chauhan A. Drug and Surfactant transport in cyclosporine A and Brij 98 laden *p*-HEMA hydrogels. J Colloid Interface Sci 2008;322:624–33.
[17] Venkatesh S, Sizemore SP, Byrne ME. Biomimetic hydrogels for enhanced loading and extended release of ocular therapeutics. Biomaterials 2007;28:717–24.
[18] Hiratani H, Alvarez-Lorenzo C. The nature of backbone monomers determines the performance of imprinted soft contact lenses as timolol drug delivery systems. Biomaterials 2004;25:1105–13.
[19] Hiratani H, Mizutani Y, Alvarez-Lorenzo C. Controlling drug release from imprinted hydrogels by modifying the characteristics of the imprinted cavities. Macromol Biosci 2005;5:728–33.
[20] Alverez-Lorenzo C, Hiratani H, Gomez-Amoza JL, Martinez-Pacheco R, Souto C, Concheiro A. Soft contact lenses capable of sustained delivery of timolol. J Pharm Sci 2002;91:2182–92.
[21] Hiratani H, Alvarez-Lorenzo C. Timolol uptake and release by imprinted soft contact lenses made of *N*, *N*-diethylacrylamide and methacrylic acid. J Control Release 2002;83:223–30.
[22] Karlgard C, Wong NS, Jones L, Moresoli C. In vitro uptake and release studies of ocular pharmaceutical agents by silicon-containing and *p*-HEMA hydrogel contact lens materials. Int J Pharm 2003;257:141–51.
[23] Falla WR, Mulski M, Cussler EL. Estimating diffusion through flake-filled membranes. J Memb Sci 1996;119:129–38.
[24] Lape NK, Nuxoll EE, Cussler EL. Polydisperse flakes in barrier films. J Memb Sci 2004;236:29–37.
[25] Nam S, Lee K. Preparation and characterization of palladium alloy composite membranes with a diffusion barrier for hydrogen separation. Ind Eng Chem Res 2005;44:100–5.
[26] Dameron AA, Davidson SD, Buuton BB, Carcia PF, McLean RS, George SM. Gas diffusion barriers on polymers using multilayers fabricated by Al_2O_3 and rapid SiO_2 atomic layer deposition. J Phys Chem C 2008;112:4573–80.
[27] Yılmaz T, Aydemir O, Özercan IH, Üstündağ B. Effects of vitamin E, pentoxifylline and aprotinin on light-induced retinal injury. Ophthalmologica 2007;221:159–66.
[28] Bilgihan K, Adiguzel U, Sezer C, Akyol G, Hasanreisoglu B. Effects of topical vitamin E on keratocyte apoptosis after traditional photorefractive keratectomy. Ophthalmologica 2001;215:192–6.
[29] Ohta Y. Possibility of clinical application of vitamin E to cataract prevention. J Clin Biochem Nutr 2004;35:35–45.
[30] Nagata M, Kojima M, Sasaki K. Effect of vitamin E eye drops on naphthalene-induced cataract in rats. J Ocul Pharmacol Ther 1999;15(4):345–50.
[31] Kojima M, Shui YB, Murano H, Sasaki K. Inhibition of steroid-induced cataract in rat eyes by administration of vitamin-E ophthalmic solution. Ophthalmic Res 1999;28(Suppl. 2):64–71.
[32] Ohta Y, Yamasaki T, Niwa T, Majima Y, Ishiguro I. Preventive effect of topical vitamin E-containing liposome instillation on the progression of galactose cataract. Comparison between 5-week- and 12-week-old rats fed a 25% galactose diet. Exp Eye Res 1999;68:747–55.
[33] Ohta Y, Yamasaki T, Niwa T, Majima Y. Preventive effect of vitamin E-containing liposome instillation on cataract progression in 12-month-old rats fed a 25% galactose. J Ocul Pharmacol Ther 2000;16:323–35.
[34] Hofmann RE, Bottoni DJ. Glutathione antioxidant eye drops. US Patent No. 5817630, 1998.
[35] Braswell AG, Absher KJ, Duarte A. Liquid eye drop composition. US Patent No. 6194457 B1, 2001.
[36] Domschke A, Lohmann D, Winterton L. On-eye mobility of soft oxygen permeable contact lenses. Proceedings of the ACS Spring National Meeting, San Francisco: PMSE, 1997.
[37] Nicolson P, Baron RC, Chabrecek P, Court J, Domscheke A, Griesser HJ, et al. Extended wear ophthalmic lens. US Patent No. 5760100, 1998.
[38] Schein O, Glynn R, Poggio E, Seddon J, Kenyon K. The relative risk of ulcerative keratitis among users of daily-wear, extended wear soft contact lenses. N Engl J Med 1989;321:773–8.
[39] Poggio E, Glynn R, Schein O, Seddon J, Shannon M, Scardino V, et al. The incidence of ulcerative keratitis among users of daily-wear and extended-wear soft contact lenses. N Engl J Med 1989;321:779–83.
[40] Holden B, Mertz G. Critical oxygen levels to avoid corneal edema for daily and extended wear contact lenses. Invest Ophthalmol Vis Sci 1984;25:1161–7.
[41] Harvitt D, Bonanno J. Re-evaluation of the oxygen diffusion model for predicting minimum contact lens *Dk*/*t* values needed to avoid corneal anoxia. Optom Vis Sci 1999;76:712–9.
[42] Young MD, Benjamin WJ. Calibrated oxygen permeability of 35 conventional hydrogel materials and correlation with water content. Eye Contact Lens 2003;29(2):126–33.
[43] Efron N, Morgan PB, Cameron ID, Brennan NA, Goodwin M. Oxygen permeability and water content of silicone hydrogel contact lens materials. Optom Vis Sci 2007;84(4):328–37.
[44] http://www.acuvue.com/products-acuvue-oasys.htm.
[45] Moore L, Ferreira JT. Ultraviolet (UV) transmittance characteristics of daily disposable and silicone hydrogel contact lenses. Contact Lens & Anterior Eye 2006;29:115–22.
[46] Krol ES, Kramer-Stickland KA, Liebler DC. Photoprotective actions of topically applied vitamin E. Drug Metab Rev 2000;32:413–20.
[47] Kramer-Stickland KA, Krol ES, Liebler DC. UV-B-induced photooxidation of vitamin E in mouse skin. Chem Res Toxicol 1999;12:187–91.