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EVALUATION OF THE THERAPEUTIC EFFECTIVENESS AND SUSTAINED RELEASE CAPACITY OF LEVOFLOXACIN LOADED SILICONE HYDROGEL CONTACT LENSES

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ABSTRACT

Eye infections are mostly managed by multiple instillations of antimicrobial eye drops throughout the duration of treatment. This study compares the effectiveness of a sustained release levofloxacin eluting hydrogel contact lens with conventional eye drop in the treatment and management of ocular surface infections. Two silicone hydrogel contact lenses (Senofilcon A and Narafilcon A) were modified by incorporating levofloxacin by soaking method. Vitamin E (α-tocopherol) was incorporated as diffusion barrier using ethanolic vitamin E solvent. The modified lenses were characterized for loading, transmissibility, and release kinetics. The efficacy of the select hydrogel was compared with levofloxacin eye drop against *Staphylococcus aureus* and *Pseudomonas aeruginosa* using modified Kirk Bauer disk diffusion method. The senofilcon A levofloxacin loaded lens released approximately 80% of the drug in 45 mins while just about 30% of the drug was released at the same time by narafilcon A lens. The transmissibility of both lenses after modification were above 90% and drug release was shown to be by Higuchi model and Fickian diffusion in both levofloxacin lenses and vitamin E loaded lenses. Narafilcon A modified lenses with and without diffusion barrier showed comparative antimicrobial effectiveness with 5% levofloxacin eye drop against *Pseudomonas aeruginosa* and *Staphylococcus aureus.* Levofloxacin release from 10% vitamin E loaded lens showed sustained release without any burst effect. Levofloxacin narafilcon A eluting contact lens can be employed as a suitable sustained release alternative to multiple instillations of eye drops in the treatment and management of anterior ocular bacterial infections.

KEYWORDS: **Sustained release; ocular infections; Hydrogel lens; vitamin e; *Pseudomonas aeruginosa*; *Staphylococcus aureus*.**

INTRODUCTION

Eye infections are common in the developing world accounting for a major cause of visual impairment besides cataract and refractive errors. A good prognosis requires timely intervention and multiple instillations of eye drops throughout the treatment duration. Unfortunately, most patients either present to the clinic after days of self-medication and/or are not adherent to their dosage regimen. Corneal blindness has been attributed to poor patient adherence to medications for chronic eye infections such as bacterial keratitis which require half-hourly to hourly topical drug administration for the first two days with frequency of administration changed subsequently depending on response to treatment.

It has been reported that up to 80% of administered drops drain into the systemic circulation from the conjunctival sac through the lacrimal duct, through the nasopharyngeal mucosa

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into the systemic circulation [1]. These medicinal compounds usually do not undergo first-pass metabolism because they bypass the liver unlike orally administered drugs. Consequently, there is a high probability of adverse effects due to systemic drainage of these medications. Also, low conjunctival sac volume which is approximately 7 – 8 µL (maximum volume of 30 µL when distended) and difficulty in correctly aiming the drop into the conjunctival sac causes much of the medication to run down the cheek resulting in wastage and variation in dosage [2,3].

Microbial keratitis is a major cause of visual impairment in the world [4] and in the developing world, it is estimated that 1.5 to 2 million or more people are diagnosed with keratitis annually [5]. It can be caused by bacteria, viruses, fungi, however bacterial keratitis is the most common form of microbial keratitis [4]. Infection by these organisms usually occur when the epithelium is compromised [6,7]. The main causative agents of bacterial keratitis are *Staphylococcus aureus*, *Streptococcus pneumonia, Staphylococcus epidermidis* and *Pseudomonas aeruginosa* [8] with *P. aeruginosa* being the most prevalent [7]. Treatment initially was with fortified antibiotics – a cephalosporin and an aminoglycoside to cover the gram-positive and gram-negative organisms respectively but recently, fluoroquinolones are the mainstay of empirical treatment [6,9]. The use of fortified antibiotics though effective had some challenges that led to the change to fluoroquinolones. Treatment required half-hourly to hourly administration of the two antibiotics, a beta-lactam and aminoglycoside which exposed the cornea to increased toxicity [10,11]. Reflex tearing due to increased tonicity of the antibiotics will cause dilution of the dose and special mixing of each of the medications by a pharmacist will increase cost and the likelihood of contamination. Consequently, the use of a single antibiotic with broad-spectrum activity against most organisms is clearly preferred [12].

Levofloxacin, a fluoroquinolone antibiotic and the drug of choice in this investigation, acts by inhibiting the DNA gyrase or topoisomerase IV enzymes needed for bacterial chromosome replication [13]. It is a third-generation fluoroquinolone and a broad-spectrum antibiotic used in the empirical treatment of ocular bacterial infections. For bacterial conjunctivitis and keratitis, levofloxacin is administered every 1- 2 h for the first 3 days and subsequently 4 – 5 h daily till the resolution of infection [14] and every 4 h for 14 days for the prevention of postoperative endophthalmitis [15]. The frequency in eye drop administration is required to ensure rapid resolution of the eye infection needed to avoid corneal scaring associated with delayed onset of treatment or poor management.

Various authors have commented on the poor bioavailability of conventional eye drops in the treatment of eye diseases and have investigated novel approaches to prolong release of ophthalmic drugs. Drug eluting contact lenses have shown some promise in this regard. In this study, we compare the suitability of two silicone hydrogel contact lenses (senofilcon A and narafilcon A) in sustaining the release of levofloxacin and the antimicrobial effectiveness of levofloxacin eluting contact lens in relation to the conventional eye drop. A previous study on the use of ofloxacin and vitamin E confirmed the effectiveness of the antibiotic eluting contact lens [16]. Here, levofloxacin, an isomer of ofloxacin with increased solubility is being investigated as the preferred isomer for contact lens incorporation. Its effectiveness in comparison to the eye drop and the effect of vitamin E in prolonging its release were also investigated.

MATERIALS AND METHODS

Materials

Levofloxacin (LVF) was purchased from Macklin Pharmaceuticals PVT LTD, Ghaziabad, NCR Delhi, India. Disodium phosphate was obtained from Molychem, Mumbai, India, Sodium chloride from BDH laboratory, England, Potassium dihydrogen phosphate from LOBA Chemie, Mumbai, India, Potassium Chloride by Emsure, Massachusetts, USA. Freshly distilled water and deionized water was obtained from Department of Pharmaceutics and Pharmaceutical Technology laboratory, University of Lagos, 1M Sodium hydroxide, 98% Ethanol solution from BDH Limited Poole England. Levofloxacin eyedrop (0.5%w/v) was obtained from Aristopharma Ltd, Bangladesh. The silicone hydrogel contact lenses used in this study are listed in Table 1.

Incorporation of α-tocopherol into the hydrogel lens

Vitamin E (VE) was incorporated [17] into the silicone hydrogels by immersing a freshly rinsed and dried hydrogel into a 0.023% ethanol-vitamin E solution for 24 h to get ~10% vitamin E loading and immersed into a 0.047% ethanol-vitamin E solution to get ~20% vitamin E loading. The vitamin E loaded lenses were thoroughly rinsed in distilled water to remove residual alcohol on the lenses. All procedures were carried out in triplicate.

Drug loading into hydrogel lens

Levofloxacin was loaded into the lenses by immersing the freshly rinsed lens into a 2 mL 5mg/mL levofloxacin solution for 2 days or until equilibrium and for 7 days for levofloxacin hydrogel lens and levofloxacin-vitamin E hydrogel lens respectively[17]. This loading process was carried out in triplicates.

Determination of lens clarity

The clarity of the modified lenses was determined by immersing the lens in the release medium in the cuvette and the transparency determined using the UV/Vis spectrophotometer kinetic analysis at a wavelength of 600 nm [16]. A transmittance of 90% and above is considered to be acceptable [18].

In vitro release of levofloxacin from modified lenses

The drug release experiment from the levofloxacin (LVF), levofloxacin-vitamin E 10% (LVF10) and levofloxacin-vitamin E 20% (LVF20) modified lenses was done at λ_{max} 288 nm in 3 mL of simulated tear fluid (STF) in perfect sink condition using the UV/Vis spectrophotometer at pre-determined time intervals [17]. Levofloxacin release was fitted to zero order, first order and Higuchi diffusion models to determine the best fitting kinetic model with the highest correlation coefficient.

Antibacterial susceptibility study of modified lenses

The therapeutic efficacy of the modified lenses compared to levofloxacin eye drop was investigated against gram-negative *Pseudomonas aeruginosa* and gram-positive *Staphylococcus aureus.* These organisms are known to be majorly implicated in corneal infections. The disk diffusion agar method as modified by Ubani-Ukoma et al. [16] for contact lens study was used to investigate the efficacy of the lenses and conventional eye drop against the organisms.

Pseudomonas aeruginosa and *Staphylococcus aureus* were each sub-cultured in cetrimide agar and mannitol salt agar respectively and isolated. Test suspensions of concentration corresponding to 1 x 10^{-6} CFU/mL was obtained by comparing to 0.5% Mcfarland standard. A small volume of 1 mL from each of the calibrated suspensions was poured into sterile petri dishes and MH agar of 25 mL. The petri dishes were left to solidify. The modified lenses – LVF, LVFE10 and LVFE20, were each placed on the prepared petri dishes while the eye drop was instilled into a hole made by a sterile cork borer of 10 mm diameter in the solidified agar. The levofloxacin eyedrop solution (undiluted and 5% diluted) was left to diffuse in the agar for a few hours before incubation.

Statistical Analysis

Drug loading and release studies were conducted in triplicates and the values expressed as mean ± SD. Statistical data analysis was carried out using Microsoft Excel Office software. MS Excel Student T-test was used to compare the release between groups. Significance value was set at $p \leq 0.05$.

RESULTS

Clarity of Drug loaded lenses

The transmissibility of the modified lenses was not compromised (Figure 1) as the lenses retained > 90% visibility confirmed by UV/Vis kinetic analysis of the lenses at 600 nm.

Levofloxacin releases kinetics

Release from Narafilcon A and Senofilcon A lenses

Figure 2 shows comparative release of levofloxacin from two different silicone hydrogel contact lenses (SHCLs) narafilcon A and senofilcon A lenses. Drug release from the senofilcon A was faster compared to that from narafilcon A lens.

Levofloxacin release from Narafilcon A modified lenses

Levofloxacin release results as determined using UV/Vis spectrophotometer over specified time intervals are as shown below. Figure 3 shows drug release from LVF, LVFE10 and LVFE20 narafilcon A contact lenses.

Drug Release Kinetics

Table 2 shows the R^2 values from different release kinetics models and Diffusion constant (n) for Korsemeyer Peppas model.

Antimicrobial Sensitivity Study

The efficacy of the levofloxacin eluting lenses compared to conventional eye drops is shown in Figure 4 and the zones of inhibition are as shown in Table 3. The 5% diluted eye drops (LVF 0.25 mg/ml) and undiluted eye drop (LVF 5 mg/ml) zones of inhibition show the effect ocular barriers have on the instilled eye drops.

Table 1: Properties of Silicone Hydrogel Contact Lenses (SHCLs) used

Lens	USAN	Manufacturer	Constituent Monomers	Oxygen permeability	Power
Acuvue Oasys®	Senofilcon A	Johnson & Johnson Vision Care, USA	mPDSM, DMA, HEMA, Siloxane macromer, EGDMA, PVP	38	+0.50 D
Acuvue TruEye®	Narafilcon A	Johnson & Johnson Vision Care, USA	mPDSM, DMA, HEMA, Siloxane macromer, EGDMA, PVP	46	-0.50 D

*USAN – United States adopted name; DW – Daily wear; EW – Extended wear; HEMA, Hydroxyethyl methacrylate; DMA, N,N-dimethacrylate; EGDMA, Ethylene glycol dimethacrylate; PVP, polyvinyl pyrolidone; mPDMS, monofunctional polydimethylsiloxane.

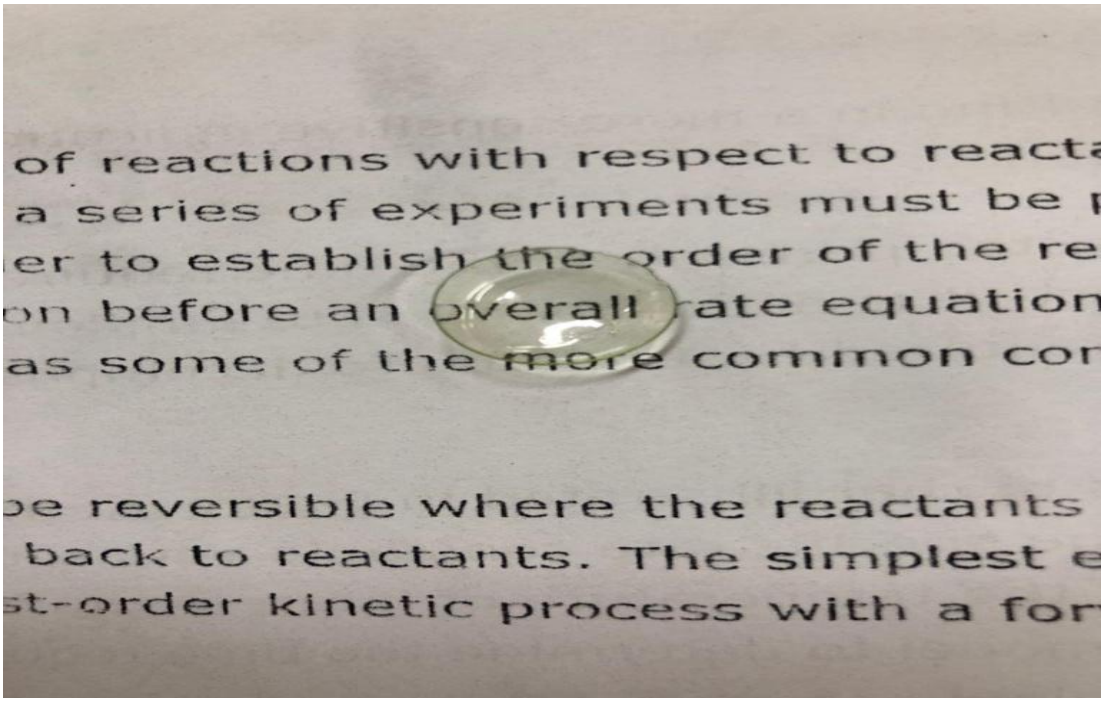

Figure 1: Levofloxacin-eluting contact lens at 20% vitamin E loading on printed paper showing clarity as the words are clearly seen through the modified lens.

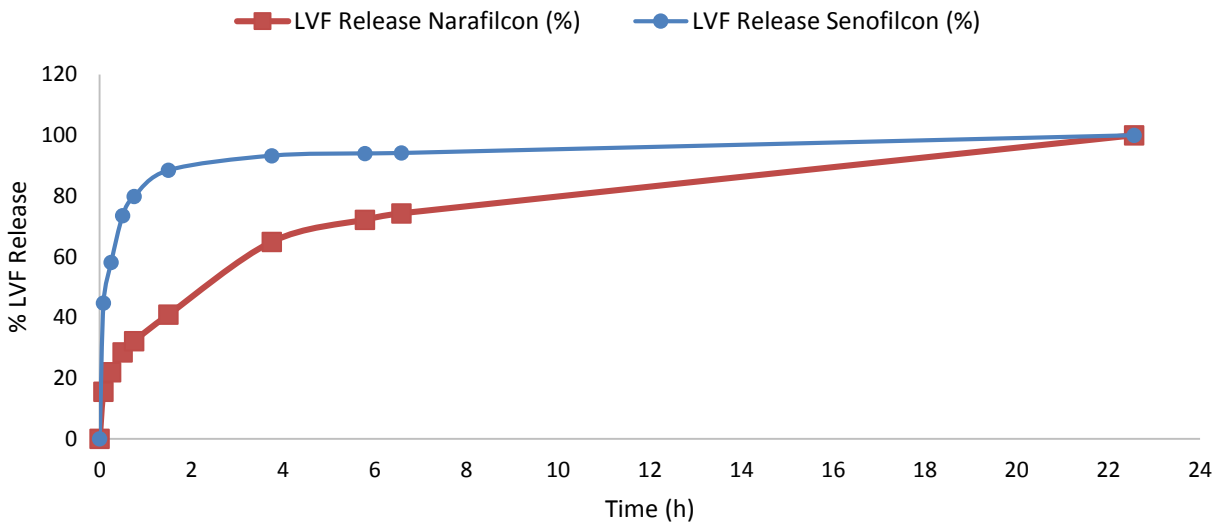

Figure 2: Comparative levofloxacin release from narafiicon A and senofilcon A lenses.

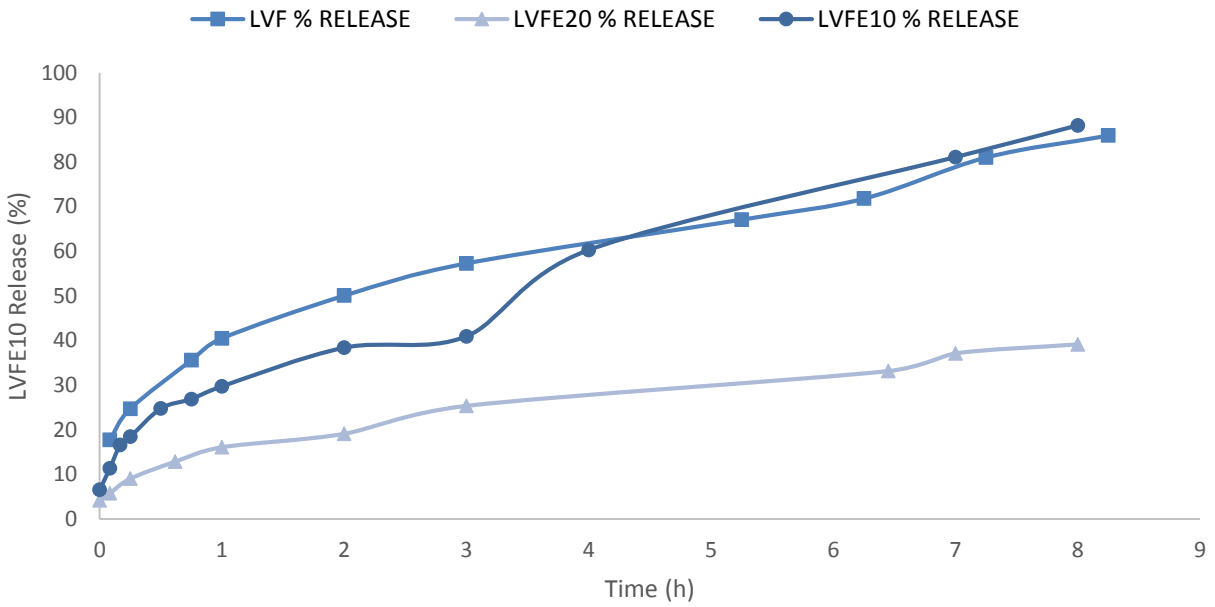

Figure 3: Levofloxacin cumulative percentage release from LVF, LVFE10 and LVFE20 narafilcon A lenses.

Table 2: R^2 values from different release kinetics models and Diffusion constant (n) for Korsemeyer Peppas model.

LENS	Zero Order	First Order	Higuchi	Korsemeyer Peppas (R^2/n)
LVF	0.8975	0.7628	0.9914	0.9965/0.3376
LVFE10	0.9178	0.7057	0.9595	0.9817/0.4085
LVFE20	0.9485	0.7630	0.9935	0.9853/0.3764

Table 3: Average zones of inhibition of levofloxacin loaded lenses after 24 hours of incubation in mm

Disk	*Pseudomonas aeruginosa*	*Staphylococcus aureus*
LVF lens	34.0 ± 1.41	39.0 ± 0.82
LVFE10	28.0 ± 0.07	27.5 ± 0.15
LVF (0.25mg/mL)	28.3 ± 0.58	29.3 ± 0.47
LVF(5mg/mL) Eye drop	46.0 ± 1.29	51.0 ± 3.11

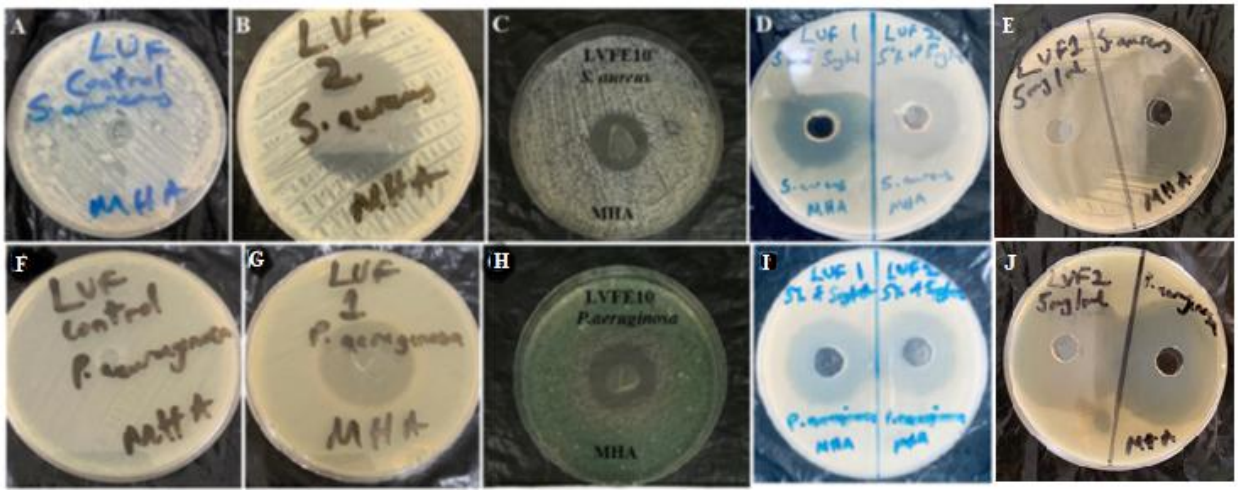

Figure 4: Zone of inhibition in *S. aureus* agar plate A. Contact lens without drug, B. Contact lens loaded with levofloxacin only C. Contact lens with levofloxacin and 10% vitamin E loading, D. 5% diluted levofloxacin eye drop, E. Undiluted levofloxacin eye drop. Zone of inhibition in *P. aeruginosa* agar plate F. Contact lens without drug, G. Contact lens loaded with levofloxacin only H. Contact lens with levofloxacin and 10% vitamin E loading, I. 5% diluted levofloxacin eye drop, J. Undiluted levofloxacin eye drop.

DISCUSSION

Sustained delivery of ocular medications using contact lenses have been widely investigated by various scientists using sophisticated methods of contact lens modification but very few have compared the effectiveness of the modified lenses to existing eye drops.

Two silicone hydrogel lenses with high oxygen permeability which ensures elimination of hypoxia and therefore comfort wear were used. It was shown that narafilcon A exhibited a more gradual levofloxacin release compared to senofilcon A which caused a burst release of about 40% in 5 mins compared to 15% release by narafilcon A in the same time period (Figure 2). In 7 h, senofilcon A lenses released 94% of the drug compared to 74% by narafilcon A lenses. Despite the initial burst release by the lenses, drug release was sustained over a few hours.

Further investigation on the effect of incorporating different concentrations of vitamin E into narafilcon A lens showed that 10% vitamin E incorporation is preferred to 20% vitamin E incorporation. This is because at 10% vitamin E concentration, the burst release was reduced while the amount of drug release was not significantly different from the amount of drug released by lens without vitamin E ($p < 0.05$). On the other hand, at 20% vitamin E concentration, the drug release was very slow; just about 40% release after 8 h (Figure 4).

The drug release kinetic study showed that levofloxacin release followed the Higuchi model release and tends towards diffusion as can be shown by the Korsemeyer peppas diffusion constant (n) in Table 2.

The zone of inhibition study of the modified lenses against *P. aeruginosa* and *S. aureus* (Figure 4) compared to the conventional eye drop at 5% dilution showed drug release from the lenses were effective against the causative organisms. The defence mechanisms of the eye which include the blood retinal barrier (BRB), blood aqueous barrier (BAB) continuous tear production, blinking of the eyelid, small volume of the conjunctival sac and the nasolacrimal drainage of administered drugs into the body reduces the bioavailability of the administered drug to 1 to 5% [19–21]. Hence the dilution of the eye drop to 5% to reflect the actual effectiveness after administration. The undiluted eye drop zone of inhibition shown depicts what will be if there were no ocular barrier to administered medications.

Previous studies have shown that the concentration of drug in the contact lenses can be increased by increasing the concentration of the drug in the soaking medium and prolonging the duration of soaking in the medium [17,22]. Other less common and complex methods of increased incorporation of drugs into the lens are by molecular imprinting, layer-by-layer (LBL) incorporation, and supercritical solvent impregnation (SSI) [23–25] .

When the contact lens is placed on the cornea, it divides the tear film into the pre-lens tear film (PLTF) and the post-lens tear film (POLTF) [26,27]. The PLTF is the tear film at the anterior side of the lens while the POLTF is between the posterior side of the lens and the cornea. Drug loaded into the lens can either diffuse out from the lens into the POLTF and into the cornea or through the PLTF to the conjunctiva into the systemic circulation or to the posterior part of the eye via the conjunctiva-scleral route [27].

In vitro drug release studies are usually carried out in release media of about 3 mL volume. The release medium volume is based on the tear fluid flow rate over a 24 hour period which is in the range of 0.5 – 2.2 µL/min and 2.82 ±1.45 µL/min during contact lens wear [28]. This implies that an average of 2 mL or 4 mL of tear fluid in the case of contact lens wear will pass through the eye during a 24 hour period [29]. A perfect sink condition exists when the amount of drug in the release medium is very small compared to the volume of the release medium. Therefore, there will be fast release of the drug from the lens into the release medium. A perfect sink condition also exists in the POLTF because of its thickness (5 µm) and corneal permeability of 10^{-5} to 10^{-7} cm/s [27]. Drug release from the contact lens into the POLTF is longer compared to drug permeation into the cornea. Consequently, the drug volume in the POLTF is low thereby creating a perfect sink.

Incorporation of Vitamin E into contact lenses has shown great promise in the extension of drug release from contact lenses. In addition to its being a simple technique, VE an antioxidant is not released from the lens because of its hydrophobic nature. Studies carried out by previous authors have shown that incorporation of VE into the lenses is safe, does not compromise essential features of the lens as confirmed in our transmissibility study (Figure 2) and is effective in prolonging drug release from the lenses [30–33].

CONCLUSION

Levofloxacin eluting narafilcon A contact lens may be a good alternative to prolonged delivery of medications to the eye for the treatment and/or prevention of ocular infections. Incorporation of vitamin E at 10% concentration reduces the

probability of epithelial toxicity by burst release and ensures the features of the lens is not compromised.

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