ORIGINAL PAPER

Nig. J. Pharm. Res. 2019, 15 (1) pp 1-8
ISSN 0189-8434, e-ISSN 2635-3555 **Available online at http://www.nigjpharmres.com**

In vitro Release from Antibiotic-loaded Silicone Hydrogel Contact lenses for the Treatment of ocular bacterial infections

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A – Research concept and design; B – collection and/or assembly of data; C – data analysis and interpretation; D – writing the article; E – critical revision of the article; F – final approval of article.

Abstract

Background: Effective treatment of corneal infections require frequent eye drop instillations, unfortunately, non-compliance is a challenge.
Objectives: In this study, the effectiveness of antibiotic-loaded contact lens as a prolonged release device in the treatment of corneal bacterial infection is investigated.
Materials and Method: Ofloxacin (OFL) and Chloramphenicol sodium succinate (CPL) were loaded onto silicone hydrogel contact lenses (CLs) via soaking method. Drug release, effect on clarity of the lenses at different concentrations and ability to inhibit growth of corneal ulcer causative bacteria were investigated.
Results: Drug release from the lenses was directly proportional to the amount of drug loaded and the lenses at the different loading concentrations showed transmittance of 95 to 97%. The Air Optix® lenses showed higher release of drug compared to Acuvue Oasys® lenses ($p < 0.05$). The difference in drug release was significant at $p < 0.05$. The microbiological study showed zones of inhibition in Mueller Hinton agar seeded with *Pseudomonas aeruginosa* and *Staphylococcus aureus*.
Conclusion: This study shows that contact lenses can be used to control drug delivery to the eye and is a probable alternative ocular delivery technique in the treatment or prevention of corneal infections.
Keywords: Antibiotics; prolonged release; contact lens; corneal infections

INTRODUCTION

Corneal ulcer is a debilitating corneal infection which if not aggressively treated may lead to corneal blindness (Kilic *et al*., 2018; Pinnock *et al*., 2017). The major causes of corneal ulcer are contact lens wear or unhygienic use of contact lenses, eye surgery, corneal trauma, extended use of steroids, Non-Steroidal Anti-Inflammatory Drugs and some systemic diseases such as Diabetes mellitus and Human Immunodeficiency Virus (HIV) (Lakhundi *et al*., 2017; Robertson *et al*., 2017). Corneal ulcer can be caused by acanthamoeba, bacterial, fungal or viral agents (Lakhundi *et al*., 2017; Mascarenhas *et al*., 2014) but bacterial keratitis is responsible for essentially 90% of microbial keratitis (Lakhundi *et al*., 2017; Ruiz Caro *et al*., 2017). Treatment is usually by the monotherapy with flouroquinolones or by fortified therapy using vancomycin or tobramycin when the monotherapy is not effective (Austin *et al*., 2017; Farahani *et al*., 2017). Healing sometimes occurs with scarring leading to loss of vision or impaired vision.

Topical antibiotics are required to be administered as often as every hour for the first 2 days of treatment during the day and even in the night for severe ocular infections (Gokhale, 2008). This poses a challenge of compliance and makes it difficult for complete resolution of the ulcer. Failure to attain complete healing may result in corneal surgery which is expensive and requires donated cornea tissue transplantation.

In this study, the use of contact lens as a drug delivery device in the treatment of corneal diseases will be investigated. The antibiotic-loaded contact lens is expected to increase the residence time of the antibiotic on the cornea, reduce the frequency of administration, loss of drug through tear drainage, blinking and reduce the incidence of systemic toxicity via nasolacrimal drainage compared to topical eye drops (Gudnason *et al*., 2017; Maulvi *et al*., 2017). It will also serve as a bandage which provides a stable environment for healing (Mohammadpour *et al*., 2015).

Fluoroquinolones have been shown by various authors to be a class of drugs that are effective in the treatment of corneal ulcer (Austin *et al*., 2017; Daniell *et al*., 2003; Farahani *et al*., 2017; Gangopadhyay, 2000; Pawar & Majumdar, 2006). Chloramphenicol a broad spectrum antibacterial drug, indicated primarily for the treatment of conjunctivitis (Brayfield, 2017) is rarely used in the United States because of probable adverse drug reactions such as aplastic anaemia and blood dyscrasias associated with its use (Fraunfelder & Fraunfelder, 2013). The use of contact lens as a delivery vehicle for chloramphenicol will eliminate the need for multiple instillations of eye drops and therefore reduce the nasolacrimal drainage into the systemic circulation and thus the possibility of causing adverse effects.

Many studies have been carried out to show the feasibility of the use of drug-loaded contact lenses as an alternative to conventional eye drops (Ciolino *et al*., 2016; Filipe *et al*., 2016). Paradiso *et al*, (2016) carried out a study on the uptake and extended release of levofloxacin and chlorhexidine using contact lenses with vitamin E diffusion barriers as a possible treatment for ocular keratitis however, the antimicrobial effectiveness of the lenses was not assessed.

This current study is aimed at determining how much of the antibiotics can be loaded onto silicone hydrogel contact lenses (AIR OPTIX® AQUA and ACUVUE OASYS®) which have a characteristic high oxygen and ion permeability, the effect different commercial lenses have on the release of drugs and the ability of the loaded drugs (ofloxacin and chloramphenicol sodium succinate) to be released and inhibit the primary organisms implicated in ocular bacterial infections – *Pseudomonas aeruginosa* and *Staphylococcus aureus* (Robertson *et al*., 2017).

METHODOLOGY

Materials

Ofloxacin (OFL) pharmaceutical secondary standard, chloramphenicol sodium succinate (CPL) European Pharmacopoeia reference standard, chloramphenicol succinate sodium ≥ 80% (HPLC), phosphate buffer saline (PBS), pH 7.4 *TRU-M were purchased from Sigma Aldrich, USA. Sodium chloride was obtained from Kermel, BDH laboratory, England, Potassium dihydrogen phosphate from JHD, Guang dong Guanghua Sci Tech Co ltd, China, Air Optix Aqua (Lotrafilcon B) were purchased from Novartis and Acuvue Oasys (Senoflicon A) from Johnson & Johnson Vision care, USA. Freshly distilled water was obtained from Department of Pharmaceutics laboratory, University of Lagos and Type A water used was obtained from National Agency for Food, Drug Administration and Control (NAFDAC).

USAN United States Adopted Name, DMA N,N-Dimethylacrylamide; HEMA 2-hydroxyethylmethacrylate; mPDMS monofunctional dimethylsiloxane; EDGMA Ethylene glycol dimethacrylate; PVP polyvinylpyrolidone, *Tris*-(trimethylsiloxy)methacryloxy-propylsilane

Method

Drug loading into Contact lenses (CLs)

The commercial contact lenses were rinsed with deionized (DI) water, dried in air overnight and weighed. OFL was loaded into Senofilcon A CLs by soaking in 0.5 mg/mL and 2.3 mg/mL OFL-PBS solution for 4 and 7 days respectively. OFL was also loaded into Lotrafilcon B CLs by soaking in 2.3 mg/mL OFL-PBS solution for 7 days.

CPL was loaded onto Senofilcon A CLs by soaking in 0.5 mg/mL and 6.36 mg/mL CPL-PBS solution for 4 and 7 days, respectively and in Lotrafilcon CLs by soaking in 6.36 mg/mL CPL-PBS solution for 7 days. The drug loaded lenses were dipped in deionized water to remove excess drug on the surface of the lens. Excess fluid on the lenses was removed by dabbing with absorbent paper.

Drug release was monitored with UV/VIS spectrophotometer (J.P.Selecta, Spain) at 278 nm for CPL and 294 nm for OFL and the absorbance reading continued until the same absorbance value was obtained for 3 consecutive readings.

Table I: Properties of silicone hydrogel lenses used

Lens	Manufacturer	USAN	Monomers	Oxygen permeability (x 10^{-11})	Water content
AIR OPTIX® AQUA	Novartis	Lotrafilcon B	DMA, Siloxane macromer, TRIS	140	33%
ACUVUE OASYS®	Johnson & Johnson	Senofilcon A	DMA, HEMA, mPDMS, Siloxane macromer, EGDMA, PVP	86	38%

USAN, United States Adopted Name, DMA N,N-Dimethylacrylamide; HEMA 2-hydroxyethylmethacrylate; mPDMS monofunctional dimethylsiloxane; EDGMA Ethylene glycol dimethacrylate; PVP polyvinylpyrolidone, *Tris*-(trimethylsiloxy)methacryloxy-propylsilane

The amount of drug loaded into the silicone hydrogel lenses could be determined by the difference between the initial and final concentrations of the loading solution but because of the high aqueous solubility of the drugs (Phan *et al.,* 2018) the difference between the initial and final concentrations of the loading medium is infinitesimal making it difficult to determine accurately. Since the drug loading and release occurs under sink conditions (Hsu *et al*., 2013), and hydrophilic drug rarely adsorbs into the lens (Gonzalez-Chomon *et al.*, 2013), it is assumed that most of the drug loaded into the lens is released in to the aqueous medium (Phan *et al.*, 2018). Hence, the partition coefficient was calculated with the formula below

$$K = \frac{V_{rel}C_{rel}}{V_{lens}C_{load}}$$

Where V_{rel}Volume of release in medium, C_{rel} is the concentration of the drug in the release medium, V_{lens} is the volume of the hydrated lens and C_{load} is the concentration of the loading medium.

Drug release from CLs loaded with drugs

The drug release studies were carried out by soaking the drug loaded CLs in 3.5mLof PBS except for the 6.36 mg/mL loaded CPL lenses which were soaked in 20 mL PBS for Senofilcon A lenses and 25 mL PBS for Lotrafilcon B lenses. This is due to the high release resulting from the high solubility of chloramphenicol sodium succinate (50 mg/mL). Below this volume, the concentration of CPL released from the lenses loaded with 6.36 mg/mL CPL solution will be beyond the measurement limit of the UV-VIS spectrophotometer. The dynamic drug concentration in the PBS (release medium) was analyzed by measuring the absorbance of the release medium at wavelength 278 nm for CPL and 294 nm for OFL hourly until the same absorbance was obtained after three consecutive readings. Control study was carried out by soaking a lens without drug in PBS and absorbance measured at the same wavelengths with UV-VIS spectrophotometer. Drug release experiment was carried out between 22 – 24 ^{o}C. The tests were done in triplicate for each of the drugs at different soaking concentrations and in different lenses.

Clarity of drug loaded contact lens

The clarity of the drug-loaded lenses was characterized by measuring their transmittance. The transmittance was determined using kinetics analysis of UV-VIS spectrophotometer (J.P. Selecta, Spain) at a wavelength of 600 nm (ElShaer *et al*., 2016). The tests were carried out in triplicates.

Microbiological Study

Pseudomonas aeruginosa and *Staphylococcus aureus* were cultured and isolated using cetrimide agar and mannitol salt agar, respectively. The 0.5% McFarland standard was prepared using 1% Barium Chloride and 1% Sulphuric acid. Test suspensions of 1 x 10^6 colony forming units per ml (CFU/mL) of each of the organisms were prepared in saline solution and the optical density compared to the McFarland standard until the turbidity of the test suspensions matched the standard. The accuracy of the 0.5% McFarland standard prepared was confirmed by running the standard through a UV/VIS spectrophotometer at a wavelength of 625 nm. An absorbance range of 0.08 to 0.13 is acceptable (Hudzicki, 2009).

OFL loaded and CPL loaded CLs were placed in Mueller Hinton (MH) agar inoculated with *P. aeruginosa* and *S. aureus*. A lens without any drug was also placed on bacteria seeded MH agar to serve as negative control. Ofloxacin disks containing 5 µg/ml drug and 30 µg/ml chloramphenicol disks were used as positive controls. All procedures were carried out under laminar flow to prevent contamination.

The culture media containing drug-loaded lenses and antibiotic disks were incubated at 37^{o}C for 24 hrs. After incubation, the 90 mm petri dish was inverted

over a black background in a well illuminated room and the diameter of the zone of inhibition was read to the nearest whole number in millimeters.

STATISTICAL ANALYSIS

Drug loading and drug release studies were conducted in triplicates and the values expressed as mean ±SD. Statistical data analysis were carried out using Microsoft Excel Office software. Significant differences ($p \leq 0.05$) of mean values were determined by Tukey Kramer test.

RESULTS

Drug Release from Senofilcon and Lotrafilcon lenses in PBS

Chloramphenicol Loaded Contact Lenses

The amount of CPL released by the CPL-loaded Senofilcon and CPL-loaded Lotrafilcon are shown in the Figure 1.

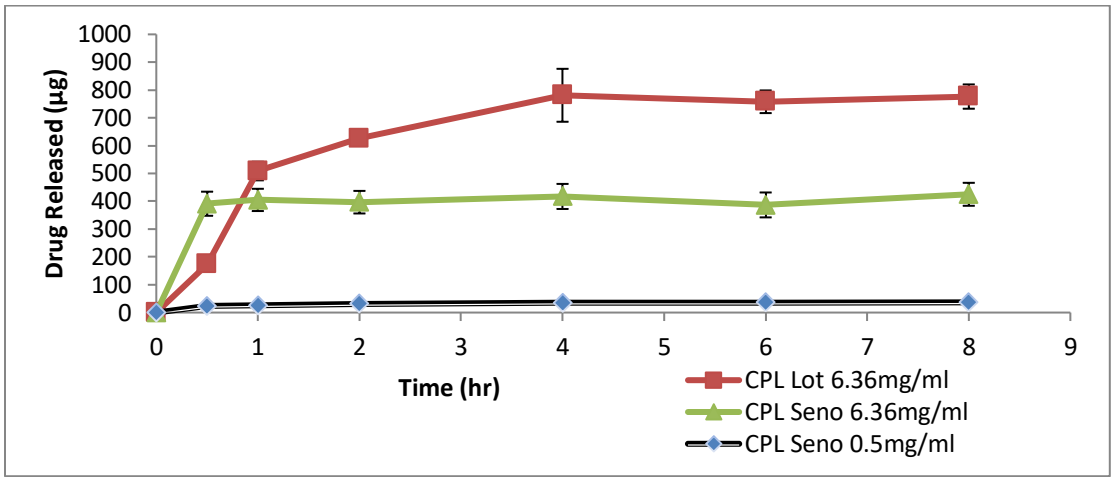

Figure 1: Chloramphenicol succinate release from Senofilcon and Lotrafilcon lenses at different concentrations. Release from lenses were carried out in triplicates and the data obtained recorded in mean ± SD ($p < 0.05$)

Ofloxacin Loaded Contact Lenses

Ofloxacin, release profiles from the different lenses are shown in Figure 2 below.

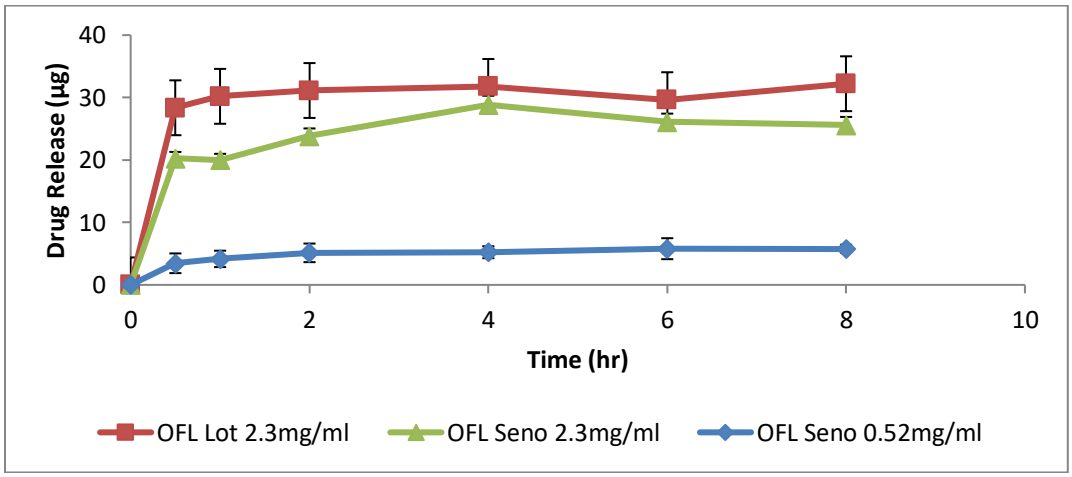

Figure 2: Ofloxacin release from Senofilcon and Lotrafilcon lenses at different drug concentrations. Release was carried out in triplicates and the data obtained recorded in mean ± SD ($p < 0.05$)

Table 2: Partition Coefficient (K) of the drugs in the different lenses (n=3, mean±SD)

Drug	Lotrafilcon B	Senofilcon A
Ofloxacin	0.53 ± 0.38	0.45 ± 0.08
Chloramphenicol Succinate	4.96 ± 0.27	2.72 ± 0.24

Transmittance

Table 3: Percentage transmittance of drug loaded contact lenses

Drug	Percentage transmittance	
	Lotrafilcon B (%)	Senofilcon A (%)
Ofloxacin	96.02 ± 1.38	96.02 ± 0.30
Chloramphenicol	95.20 ± 0.20	95.65 ± 0.46

Microbiological Studies

The result of the antibacterial activity investigated using Kirby Bauer disk diffusion method is as shown in Table 4.

Table 4: Average zones of inhibition after 24hrs of incubation

	Zone of inhibition in mm	
Disk	*Pseudomonas aeruginosa*	*Staphylococcus aureus*
CPL Loaded Lens	22.1 ± 2.8	44.2 ± 1.7
CPL Disk* 1 (30 µg)	19.6 ± 0.9	22.0 ± 2.8
CPL Disk* 2 (30 µg)	20.2 ± 0.4	20.0 ± 1.2
OFL Loaded Lens	32.9 ± 2.7	32.4 ± 1.2
OFL Disk*1 (5 µg)	18.4 ± 1.1	25.2 ± 1.9
OFL Disk* 2 (5 µg)	18.2 ± 0.8	22.6 ± 1.3
Pure Lens	0.0	0.0

*standard antibiotic disks

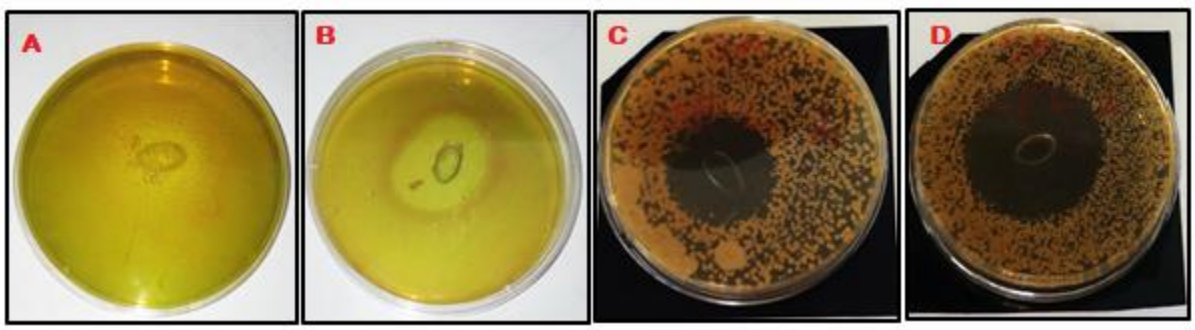

Figure 3: Chloramphenicol (A) and Ofloxacin (B) loaded lenses on *P.aeruginosa* cultures, Ofloxacin (C) and Chloramphenicol (D) loaded lenses on *S.aureus* cultures

Drug Uptake and release from Contact lenses

Drug release from both OFL and CPL-loaded lenses show a higher release from Lotrafilcon lenses compared to Senofilcon lenses (Figures 1 and 2). This could be explained by the different monomer compositions of the lenses (Table 1).

The drug uptake and release from lenses is influenced by different factors such as the monomer composition of the CL, the partition coefficient (K) of the drug in the lens and the charge on the hydrogel (Guidi *et al*., 2014; Phan *et al*., 2018; Xu *et al*., 2018). Hydrophilic monomers such as NVP, DMA and HEMA while increasing the water content and oxygen permeability of the hydrogel also increases drug loading in to the lens. Silicone monomers such as TRIS, PDMS and TPVC also enhance oxygen permeability and prolong drug release from the lenses (Xu *et al*., 2018). The ratios of the monomers in the commercial lenses are not known, hence, the extent of effect of each of the monomers on the release and loading properties of the drugs cannot be ascertained. Since Lotrafilcon lens was able to release more of the drugs compared to the Senofilcon lens, this suggests that the constituent monomers of the Lotrafilcon lens and the combination ratio can be used to produce lenses with increased release. This informed the use of the antibiotic-loaded Lotrafilcon lens for the microbiological study shown in Figure 3.

Some studies have been carried out to determine the effect of each of the constituent monomers on the release and uptake of specific drugs (Guidi *et al*., 2014; Xu *et al*., 2018). Studies with commercial lenses and formulated lenses increase the scientists' knowledge of the ideal composition of monomers for a particular drug. Consequently, the hydrogel composition can be optimized for maximum drug uptake and release.

The partition coefficient values in Table 2 gives an idea of the ratio of the drug concentration in the lens and the concentration in the soaking medium. The higher K values for Lotrafilcon lenses show they were able to take up more drugs compared to the Senofilcon lenses with lower values for OFL and CPL lenses; this also explains the higher release from the Lotrafilcon lenses. Furthermore, the partition coefficient of OFL lenses is less than 1 as opposed to the CPL lenses (Table 2). This means that there was a higher uptake of chloramphenicol compared to ofloxacin.

4.2 Therapeutic Release Rate

Assuming a drop volume of 25µl and administration of twelve drops daily in severe infections, 300 µl of chloramphenicol eye drop solution will be administered in a day. About 5% of this volume (i.e. 15 µl) will be bioavailable (ElShaer *et al*., 2016; Paradiso *et al*., 2016; Zhang *et al*., 2014). CPL is administered as a 0.5%w/v solution. Therefore, in 15 µl, approximately 75 µg of CPL will be bioavailable.

Several studies have shown that drug-loaded contact lenses increases the bioavailability of administered drug from 5% to 50% (Carvalho *et al*., 2015; Maulvi *et al*., 2016). The total amount of CPL released from Senofilcon CLs soaked in 0.5 mg/ml is 38 µg (Table 1) and 50% of this is just 19 µg. Compared to expected release of 75 µg from 0.5%w/v chloramphenicol eye drop, the CPL loaded contact lens soaked in 0.5 mg/ml CPL-PBS solution will not be able to meet the therapeutic dose. However, CPL lenses soaked in 6.36 mg/ml CPL-PBS solution released over 400 µg for Senofilcon lenses and over 700 µg for Lotrafilcon lenses within 24 hr. (Figure 1). This amount is much more than the therapeutically effective dose. This implies that the higher the soaking concentration, the greater the release. Therefore, to get the desired release, a suitable concentration should be made.

Ofloxacin Hydrochloride, a fluoroquinolone antibacterial used in the treatment of corneal ulcer and conjunctivitis is topically applied as a 0.3% w/v solution (Brayfield, 2017; Gangopadhyay, 2000) and has the following treatment regimen for bacterial corneal ulcer - Days 1 and 2: Instill 1 to 2 drops every 30 mins while awake

Days 3 -7: 1 to 2 drops every hour while awake; Days 7 -9: 1 to 2 drops every six hours

Assuming a drop volume of 25 µl, a total volume of 600 µl of OFL eye drop solution will be administered in a day; 5% of this volume (i.e. 30 µl) will be bioavailable (ElShaer *et al*., 2016; Paradiso *et al*., 2016). Since OFL is administered as a 0.3%w/v solution, in 30 µl, approximately 90 µg of OFL will be bioavailable. The total drug release from OFL CLs is approximately 25 µg for senofilcon lenses and about 30 µg for Lotrafilcon lenses. To meet the required dosage, OFL lens will need to be replaced daily or drug loaded into the lens will be increased.

Clarity of drug loaded lenses

A transmittance value of 90% and above is considered acceptable to ensure clarity (ElShaer *et al*., 2016). The lenses loaded with drugs each had transmittance value of at least 95% (Table 3). This implies that at the concentration of the soaking media, the clarity of the contact lenses was not compromised.

Microbiological Studies

The antimicrobial assay show that the drug-loaded contact lenses released the loaded antibiotics which were active against the test microorganisms (Figure 3). Chloramphenicol loaded lens in *Pseudomonas*

aeruginosa seeded plate had the lowest zone of inhibition; this implies that *P. aeruginosa* is more susceptible to ofloxacin than chloramphenicol. The lenses without drug showed no zones of inhibition (Table 4). The results obtained show that antibiotic-loaded contact lenses can be used in the management of ocular bacterial infections.

CONCLUSION

In conclusion, ofloxacin and chloramphenicol loaded contact lenses can be used as alternatives to antibiotic eye drops since the amount of drugs released from the lenses are comparable and in some cases higher than the amount of drug released by the eye drops. This will ensure improved compliance as frequent administration would no longer be necessary. Furthermore, it has been shown that the amount of drug uploaded to the lenses can be varied by increasing or reducing the concentration of the soaking media.

Though the lenses showed burst release which needs to be controlled to avoid toxicity, further studies will investigate the effect of vitamin E on the release of the antibiotics from the lenses and their effectiveness in treatment and/or prevention of corneal infections.

FUNDING

This research was funded by the Association of African Universities (AAU) 2016.

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Conflict of Interest: None declared

Received: 21 January, 2019

Accepted: 25 March, 2019