

Extended Release of Ciprofloxacin from Commercial Silicone-Hydrogel and  
Conventional-Hydrogel Contact Lenses containing Vitamin E Diffusion Barriers

by

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## **Author's Declaration**

This thesis consists of material all of which I authored or co-authored: see Statement of Contributions included in the thesis. This is a true copy of the thesis, including any required final revisions, as accepted by my examiners.

I understand that my thesis may be made electronically available to the public.

## **Statement of Contributions**

I would like to acknowledge the names of my co-authors who contributed to this thesis:

- Dr. Lyndon Jones, PhD
- Dr. Chau-Minh Phan, PhD

## **Abstract**

### **Purpose:**

Contact Lenses (CLs) are ophthalmic devices globally used by more than 140 million people to correct vision problems. To overcome the drawbacks of eye drops, drug-delivering CLs have been given much attention because they increase the bioavailability of ocular drugs, resulting in increasing efficacy and reducing potential side effects. These systems typically have a burst and rapid release. To address these concerns, this study aims to develop a contact lens-based ocular drug delivery system using vitamin E as a diffusion barrier to extend the release duration of ciprofloxacin.

### **Methods:**

The purpose of the first experiment in the thesis (Chapter 3) was to develop and evaluate drug delivery contact lenses: Four commercial silicone hydrogel lenses (senofilcon A, lotrafilcon B, comfilcon A, and samfilcon A) and one conventional hydrogel lens (etafilcon A) were soaked for 24 hours in various concentrations of vitamin E dissolved in ethanol (0.0125 - 0.2 g/mL). The amount of vitamin E loaded was calculated by measuring the dry lens weight before and after vitamin E loading. The lenses were loaded with ciprofloxacin for 24 hours. The amount of ciprofloxacin loaded was determined using an extraction protocol. The drug release was evaluated in phosphate-buffered saline solution in an amber glass vial, at 37°C with shaking. The amount of ciprofloxacin released was measured using a UV-VIS spectrophotometer at 270 nm.

The second experimental chapter (Chapter 4) aimed to evaluate the effect of ciprofloxacin loading duration on the uptake and release profiles of senofilcon A. This

was done by applying the same method described in Chapter 3, except ciprofloxacin loading durations for senofilcon A were 24 hours and 7 days.

### **Results:**

The data showed that there was a decrease in ciprofloxacin loading with increasing amounts of vitamin E loaded into the silicone hydrogel lenses. For each lens type, there was an optimal amount of vitamin E loaded that extended the release duration of the drug from 1 hour (without vitamin E) to as long as 16 hours. Senofilcon A with 0.025 g/mL vitamin E loaded exhibited the longest-sustained release for all lens types, achieving 16 hours of release. In contrast, vitamin E loaded into etafilcon A had no effect on the amount of drug loaded or the release duration.

The data obtained in Chapter 4 showed no significant difference in the uptake and release profiles among the different loading durations (24 hours and 7 days), except in lenses with 0.025 and 0.05 g/mL vitamin E concentrations, which absorbed and released more drugs in the 7-day loading duration experiment. In addition, senofilcon A longest release duration (16 hours) achieved in chapter 3 did not further increase in chapter 4 after increasing the drug loading duration to 7 days.

### **Conclusion:**

Vitamin E can be used as a diffusion barrier with commercial silicone hydrogel lenses to provide sustained release of ciprofloxacin. The results suggest that vitamin E may form blockages in channels within a silicone hydrogel lens material, thereby forcing a longer path for drugs to diffuse into and out of the lens material. There is an optimal

amount of vitamin E that needs to be loaded to extend the release duration, and this is lens material dependent. Additionally, increasing the drug loading duration to 7 days was not enough to increase the drug-loaded amount, and subsequently the release duration specifically for senofilcon A loaded with 0.2 g/ml vitamin E concentration.

**Keywords:**

Vitamin E, Ciprofloxacin, Ophthalmic drug delivery, Contact lenses, Extended release.

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## **Dedication**

This thesis is dedicated to my parents, my wife, my children, and Irene whose encouragement and devoted support have been invaluable throughout this journey.

## Table of contents

|                                                                                 |      |
|---------------------------------------------------------------------------------|------|
| Author's Declaration .....                                                      | ii   |
| Statement of Contributions.....                                                 | iii  |
| Abstract .....                                                                  | iv   |
| Acknowledgments .....                                                           | vii  |
| Dedication .....                                                                | viii |
| List of Figures .....                                                           | xii  |
| List of Tables .....                                                            | xiii |
| List of Abbreviations .....                                                     | xiv  |
| List of Symbols.....                                                            | xv   |
| 1 Introduction .....                                                            | 1    |
| 1.1 Bacterial Keratitis.....                                                    | 1    |
| 1.1.1 Definition.....                                                           | 1    |
| 1.1.2 Clinical Description.....                                                 | 1    |
| 1.1.3 Epidemiology.....                                                         | 2    |
| 1.1.4 Outcomes.....                                                             | 3    |
| 1.1.5 Risk Factors.....                                                         | 3    |
| 1.1.6 Treatment.....                                                            | 5    |
| 1.1.7 Other Management Strategies.....                                          | 6    |
| 1.2 Contact Lenses.....                                                         | 7    |
| 1.2.1 History and Inventions of Contact Lenses .....                            | 7    |
| 1.2.2 Contact Lens Materials.....                                               | 8    |
| 1.2.3 Silicone Hydrogel Contact Lenses.....                                     | 11   |
| 1.2.4 Contact Lens Care Systems.....                                            | 13   |
| 1.2.5 Demographics of Contact Lens Wear.....                                    | 13   |
| 1.2.6 Contact Lens as an Ophthalmic Device.....                                 | 15   |
| 1.3 Ocular Drug Delivery via Conventional Eye Drops .....                       | 16   |
| 1.4 Disadvantages of Conventional Eye Drops .....                               | 16   |
| 1.5 Advantages of Drug Delivery Contact Lenses over Conventional Eye Drops..... | 17   |

|       |                                                                                                                                                           |    |
|-------|-----------------------------------------------------------------------------------------------------------------------------------------------------------|----|
| 1.6   | Challenges of Ophthalmic Drug Delivery Silicone Hydrogel and Conventional Hydrogel Contact Lenses.....                                                    | 19 |
| 1.7   | New Approaches for Extended Duration Drug Delivery Contact Lens.....                                                                                      | 20 |
| 1.8   | Vitamin E as a Safe and Effective Diffusion Barrier in Contact Lens Materials.....                                                                        | 24 |
| 1.9   | Ciprofloxacin: A hydrophobic Ocular Antibiotic.....                                                                                                       | 26 |
| 1.10  | Criteria for Success.....                                                                                                                                 | 28 |
| 2     | Thesis Rationale .....                                                                                                                                    | 29 |
| 2.1   | Thesis Objectives.....                                                                                                                                    | 30 |
| 3     | Extended Release of Ciprofloxacin from Commercial Silicone-Hydrogel and Conventional-Hydrogel Contact Lenses containing Vitamin E Diffusion Barriers..... | 31 |
| 3.1   | Introduction .....                                                                                                                                        | 32 |
| 3.2   | Objective.....                                                                                                                                            | 34 |
| 3.3   | Materials and Methods .....                                                                                                                               | 34 |
| 3.3.1 | Materials.....                                                                                                                                            | 34 |
| 3.3.2 | Vitamin E Loading into Contact Lenses.....                                                                                                                | 35 |
| 3.3.3 | Ciprofloxacin Loading into Contact Lenses.....                                                                                                            | 36 |
| 3.3.4 | Measuring the Uptake of Ciprofloxacin into Contact Lenses.....                                                                                            | 37 |
| 3.3.5 | Ciprofloxacin Release from Contact Lenses.....                                                                                                            | 38 |
| 3.3.6 | Statistical Analysis.....                                                                                                                                 | 38 |
| 3.4   | Results .....                                                                                                                                             | 39 |
| 3.4.1 | Vitamin E Loading into Contact Lenses.....                                                                                                                | 39 |
| 3.4.2 | Ciprofloxacin Loading into Contact Lenses.....                                                                                                            | 40 |
| 3.4.3 | Ciprofloxacin Release from Contact Lenses.....                                                                                                            | 42 |
| 3.5   | Discussion .....                                                                                                                                          | 45 |
| 3.6   | Conclusion .....                                                                                                                                          | 50 |
| 4     | Other experiments: Long-term Evaluation of Vitamin E Uptake and Release on Senofilcon A.....                                                              | 51 |
| 4.1   | Introduction.....                                                                                                                                         | 51 |
| 4.2   | Aim.....                                                                                                                                                  | 52 |
| 4.3   | Hypothesis.....                                                                                                                                           | 52 |

|       |                                                             |    |
|-------|-------------------------------------------------------------|----|
| 4.4   | Materials and Methods .....                                 | 52 |
| 4.5   | Results and Discussions.....                                | 53 |
| 4.5.1 | Ciprofloxacin Loading into Senofilcon A Contact Lenses..... | 53 |
| 4.5.2 | Ciprofloxacin Release from Senofilcon A Contact Lenses..... | 54 |
| 4.6   | Conclusion .....                                            | 57 |
| 5     | General Discussion and Conclusions.....                     | 59 |
| 5.1   | Experimental Summary and Discussion.....                    | 59 |
| 5.1.1 | Chapter 3.....                                              | 59 |
| 5.1.2 | Chapter 4.....                                              | 64 |
| 5.2   | Future Work and Limitations .....                           | 66 |
| 5.3   | Conclusion .....                                            | 69 |
|       | References .....                                            | 70 |

## List of Figures

|                   |                                                                                                                                                                                                                                                                                                                 |    |
|-------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----|
| <b>Figure 1.1</b> | Scheme showing the eye structure and the positioning of a contact lens within the tear film.....                                                                                                                                                                                                                | 18 |
| <b>Figure 1.2</b> | Chemical structure of vitamin E used in this study.....                                                                                                                                                                                                                                                         | 25 |
| <b>Figure 1.3</b> | Chemical structure of ciprofloxacin. ....                                                                                                                                                                                                                                                                       | 26 |
| <b>Figure 2.1</b> | Ciprofloxacin and vitamin E loading and releasing process in soft contact lens.....                                                                                                                                                                                                                             | 29 |
| <b>Figure 3.1</b> | Vitamin E loading amounts in different concentrations of vitamin E solutions (0.0125-0.2 g/mL) for various commercially available contact lenses.....                                                                                                                                                           | 39 |
| <b>Figure 3.2</b> | Ciprofloxacin loading in various types of (A) Silicone hydrogel contact lenses and (B) Conventional hydrogel contact lenses for 24 hours in different concentrations of vitamin E (0 - 0.2 g/mL) .....                                                                                                          | 40 |
| <b>Figure 3.3</b> | Ciprofloxacin cumulative release ( $\mu\text{g}$ ) versus vitamin E loaded amount (mg) for A) senofilcon A, B) lotrafilcon B, C) samfilcon A, D) comfilcon A, E) etafilcon.....                                                                                                                                 | 43 |
| <b>Figure 3.4</b> | Percentage release of ciprofloxacin over 24 hours for A) senofilcon A, B) lotrafilcon B, C) samfilcon A, D) comfilcon A, E) etafilcon A. $\blacktriangle$ (0 g/mL), $\blacksquare$ (0.0125 g/mL), $\circ$ (0.025 g/mL), $\blacklozenge$ (0.05 g/mL), $\blacktriangledown$ (0.1 g/mL), $\bullet$ (0.2 g/mL)..... | 44 |
| <b>Figure 3.5</b> | Schematic of a non-loaded and vitamin E-loaded silicone hydrogel lens matrix showing drug release kinetics.....                                                                                                                                                                                                 | 49 |
| <b>Figure 4.1</b> | Percentage release of ciprofloxacin over 24 hours for the best-sustained release of various lens types.....                                                                                                                                                                                                     | 51 |
| <b>Figure 4.2</b> | Ciprofloxacin loading in senofilcon A contact lenses for 24 hours and 7 days in different concentrations of vitamin E solution.....                                                                                                                                                                             | 53 |
| <b>Figure 4.3</b> | Ciprofloxacin cumulative release ( $\mu\text{g}$ ) as a function of time. Ciprofloxacin loading durations: (A) 24 hours and (B) 7 days.....                                                                                                                                                                     | 55 |
| <b>Figure 4.4</b> | Senofilcon A ciprofloxacin released (%) as a function of time. Ciprofloxacin loading durations: (A) 24 hours and (B) 7 days.....                                                                                                                                                                                | 56 |
| <b>Figure 5.1</b> | Schematic of a non-loaded and vitamin E-loaded silicone hydrogel lens matrix showing drug uptake concept.....                                                                                                                                                                                                   | 63 |

## List of Tables

|                  |                                                                                                                                                                                                                                     |    |
|------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----|
| <b>Table 3.1</b> | List of commercial contact lenses used in this study.....                                                                                                                                                                           | 35 |
| <b>Table 3.2</b> | Ciprofloxacin (Cipro) loaded amount ( $\mu\text{g}/\text{lens}$ ) and vitamin E (Vit E) loaded amount ( $\text{mg}/\text{lens}$ ) for each contact lens soaked in various concentrations of vitamin E for 24 hours.....             | 41 |
| <b>Table 3.3</b> | Ciprofloxacin (Cipro) cumulative release amount ( $\mu\text{g}/\text{lens}$ ) and vitamin E (Vit E) loaded amount ( $\text{mg}/\text{lens}$ ) for each contact lens soaked in various concentrations of vitamin E for 24 hours..... | 42 |

## **List of Abbreviations**

|               |                                                                |
|---------------|----------------------------------------------------------------|
| <b>ANOVA</b>  | Analysis of Variance                                           |
| <b>BCS</b>    | Biopharmaceutics Classification System                         |
| <b>Cipro</b>  | Ciprofloxacin                                                  |
| <b>CL</b>     | Contact Lens                                                   |
| <b>Dk</b>     | Oxygen Permeability                                            |
| <b>DNA</b>    | Deoxyribonucleic Acid                                          |
| <b>HCL</b>    | Hydrochloric Acid                                              |
| <b>HIV</b>    | Human Immunodeficiency Virus                                   |
| <b>MIC</b>    | Minimum Inhibitory Concentration                               |
| <b>MIC90</b>  | Minimum Inhibitory Concentration for 90% of Bacterial Isolates |
| <b>Mk</b>     | Microbial Keratitis                                            |
| <b>PBS</b>    | Phosphate Buffered Saline                                      |
| <b>pHEMA</b>  | Poly(2-hydroxyethyl methacrylate)                              |
| <b>PMMA</b>   | Polymethylmethacrylate                                         |
| <b>PoLTF</b>  | Post-lens tear film                                            |
| <b>PrLTF</b>  | Pre-lens tear film                                             |
| <b>SCL</b>    | Soft Contact Lens                                              |
| <b>TRIS</b>   | 3-[tris(trimethylsilyloxy)silyl]-propyl methacrylate           |
| <b>UK</b>     | United Kingdom                                                 |
| <b>US</b>     | United States                                                  |
| <b>UV</b>     | Ultraviolet                                                    |
| <b>UV-VIS</b> | Ultraviolet-Visible Spectroscopy                               |
| <b>Vit E</b>  | Vitamin E                                                      |
| <b>WHO</b>    | World Health Organization                                      |

## List of Symbols

|     |                            |
|-----|----------------------------|
| °C  | Degrees Celsius            |
| g   | Gram                       |
| µg  | Microgram                  |
| µL  | Microliter                 |
| mg  | Milligram                  |
| mL  | Milliliter                 |
| nm  | Nanometer                  |
| n   | Number                     |
| pH  | Potential of Hydrogen      |
| pKa | Acid Dissociation Constant |
| %   | Percentage                 |
| t   | Time                       |
| w/v | Weight/Volume              |

# **1 Introduction**

## **1.1 Bacterial Keratitis**

### **1.1.1 Definition**

Microbial keratitis (MK) is a corneal disease caused by microorganisms including fungi, bacteria, prions, or viruses. This term is recommended over suppurative, ulcerative, or infectious keratitis, which is imprecise.<sup>1</sup> A major focus of my thesis relates to the treatment of bacterial keratitis. This disease can be difficult to differentially diagnose from other forms of MK as there are no agreed diagnostic criteria due to the lack of a reliable criterion for diagnosis.<sup>1</sup> This makes it difficult to differentiate between true pathogens and contaminants, or negative cultures, leading to underestimation of disease prevalence and overestimation of diagnostic value.<sup>2</sup> In 20%-70% of cases of corneal disease corresponding to a believed diagnosis of bacterial keratitis (where investigations such as corneal cultures are negative), the precise cause remains unknown, complicating clinical management.<sup>3</sup>

### **1.1.2 Clinical Description**

Bacterial keratitis commonly presents with painful epithelial defects associated with signs of ulceration and inflammation in the corneal stroma. The infected eye frequently appears red due to diffuse conjunctivitis, sometimes concurrent with episcleritis, and in severe cases, scleritis.<sup>4</sup> Moreover, there may be localized corneal melt (corneal opacity with thinning), associated with fibrinous exudate, anterior uveitis, or a hypopyon. While corneal melt can evolve into a descemetocoele, endophthalmitis is unusual. In certain

cases, especially among older patients, ocular loss due to MK is conceivable.<sup>5</sup> Residual effects typically involve corneal scars with thinning and vascularization, or adherent leukomas, leading to vision impairment from irregular astigmatism and opacity.

### **1.1.3 Epidemiology**

Currently, an evaluation of the global burden of blindness caused by bacterial keratitis is inaccurate. Identifying its prevalence presents a challenge, as data on non-trachomatous opacification of the cornea, the 6<sup>th</sup> leading cause of worldwide blindness, cannot certainly imply bacterial keratitis prevalence.<sup>6</sup> Additionally, data from low and middle-income countries are remarkably deficient. The documented occurrence ratio of MK shows regional variation: South India documents 113 cases per 100,000 population/year,<sup>7-9</sup> and Nepal documents 799 cases per 100,000 population/year.<sup>10</sup> The distribution of the pathogens (bacteria, fungus, parasite) also differs geographically, with fungal keratitis especially common in equatorial regions and low and middle-income countries.<sup>11</sup> The prevalence of MK in China is estimated to be 192 per 100,000 population, assuming fungal keratitis at 7, bacterial keratitis at 75, and viral keratitis at 110 per 100,000 population.<sup>12</sup> Remarkably, occurrence rates of MK in high-income countries have significantly reduced since 1995, with estimates spanning from 4.5 to 37.7 occurrences per 100,000 population in the UK, US, Taiwan, and Australia,<sup>13</sup> following a substantial rise in occurrences during the 1970s accompanied by the widespread use of contact lenses worn on an overnight basis.<sup>14</sup>

#### 1.1.4 Outcomes

The outcome following bacterial keratitis commonly correlates with the particular microorganism involved.<sup>15</sup> Virulent organisms, including *Pseudomonas aeruginosa*, *Streptococcus pneumoniae*, or *Neisseria meningitidis* may trigger rapid development to stromal lysis and total corneal abscess, subsequently leading to corneal perforation. Conversely, infections caused by low virulent Coagulase-Negative *Staphylococci* species can exhibit slow progression or even self-limitation. Visual loss resulting from infection is determined by its corneal location, with bigger central ulcers attributed to larger visual impairment, although secondary visual impairment can stem from secondary glaucoma or cataracts.<sup>16</sup> The prognosis of MK is poorer in low-income nations compared to their high-income counterparts. This variation arises from delayed primary treatment, limited healthcare access, a higher occurrence of fungal infections, and premature empirical application of topical corticosteroids.<sup>17-20</sup> Visual impairment after MK results in lower quality of life<sup>21, 22</sup> and an economic burden resulting from indirect and direct expenses.<sup>23-25</sup>

#### 1.1.5 Risk Factors

Bacteria are commonly part of the natural ocular surface flora, even though it is uncertain if there is a distinct microbiome specifically for the cornea. While there may be some exceptions, such as *Corynebacterium diphtheriae*, *Listeria* species, and *Haemophilus influenzae*,<sup>26</sup> and potentially *Neisseria* species with pilus-mediated cell attachment,<sup>27</sup> bacteria typically associated with keratitis, like *Staphylococcus aureus* and *Pseudomonas aeruginosa*, commonly do not adhere to or penetrate a healthy

corneal epithelium.<sup>28</sup> Most corneal infections are caused by bacterial invasion due to identifiable events that compromise the epithelial barrier. Risk factors include chronic ocular surface diseases, corneal trauma with vegetative matter, and contact lens wear, especially overnight wear.<sup>8, 10, 13, 14, 29-33</sup> Contact lens type and wear regimen are the major risk factors for infection in high-income countries, with the supposed MK occurrence varying between 24 to 130 per 100,000 population/year.<sup>13, 31, 34, 35</sup> *Pseudomonas aeruginosa*, an environmentally widespread gram-negative bacterium, commonly causes bacterial keratitis associated with contact lens wear.<sup>36-39</sup> Contamination of the contact lens care system might result in the formation of a protective biofilm, inhibiting effective disinfection,<sup>28, 40, 41</sup> and insufficient contact with the lens solution might also enable selection of the resistant strains of *Pseudomonas aeruginosa*,<sup>28, 42</sup> leading to an increase in bacterial transfer to the eye.

Additionally, diseases of the ocular surface are predisposing factors for the progression of bacterial keratitis. The majority of the isolates (60-80%) from these conditions are endogenous bacteria, including Coagulase-negative *Staphylococci*, *Streptococcus* species, *Staphylococcus aureus*, and *Corynebacterium* species.<sup>43-45</sup> This colonization could be caused by *Staphylococcus aureus* from adjacent sites like the periocular skin, lid margins, and anterior nares, *Streptococcus pneumoniae* from the obstruction of the nasolacrimal duct, or *Staphylococcus aureus* from the giant fornix syndrome.<sup>4, 30, 46</sup>

Colonization and recurrent infections are more frequent in severe cases of the ocular surface such as Sjogren's syndrome, rheumatoid arthritis, ectodermal dysplasia, atopic keratoconjunctivitis, and Stevens-Johnson syndrome. However, there is no

molecular evidence verifying that the bacterial strains colonizing these contiguous areas are identical to strains isolated from corneal ulcers.<sup>4</sup>

Immunodeficiency may heighten the vulnerability to microbial infection, increasing the incidence of ulcerative keratitis (essentially viral) among HIV-positive individuals compared to those who are healthy.<sup>32</sup> Moreover, the risk of infection is elevated in individuals with diabetes, potentially due to alterations in the microbiota or neurotrophic corneal changes.<sup>30, 47, 48</sup>

### **1.1.6 Treatment**

The management of bacterial keratitis depends on topical antimicrobial treatment, which is limited to a few licensed options. Hence, various antimicrobials such as ceftazidime, cefuroxime, meropenem, teicoplanin, and vancomycin are off-label treatments for bacterial keratitis.<sup>49</sup> In 2020, 41% of topical antimicrobial prescriptions in the United Kingdom were for products not specifically licensed for MK treatment.<sup>4</sup>

Treatment involves eradicating the risk of infection, eliminating or disabling the infectious agent, reducing tissue damage, and supporting healing. Antimicrobial therapy courses should be as concise as possible to increase patient compliance and lower the risks of antimicrobial resistance, treatment costs, and toxicity.<sup>50</sup>

Among the first antibiotics used as a topical ophthalmic treatment were sulfonamides, significantly decreasing the risk of visual impairment after traumatic corneal ulceration.<sup>51</sup> Penicillin followed and then in the 1960s, it was substituted by cephalosporins due to the resistance of *Staphylococcus aureus*. In the 1970s,

gentamicin was used due to a rise in infection cases caused by *Pseudomonas aeruginosa*, which was associated with the increased use of contact lenses.<sup>14, 52</sup> Dual therapy was then introduced to widen treatment coverage, using an enhanced cephalosporin against Gram-positive bacteria plus an enhanced aminoglycoside against Gram-negative bacteria. However, evidence supporting the need for an enhanced concentration (1.4%) of gentamicin is weak, and enhanced aminoglycosides can cause conjunctival necrosis, toxicity of the ocular surface, and reduced healing of the corneal epithelium.<sup>53</sup>

Ofloxacin and ciprofloxacin (2<sup>nd</sup> generation fluoroquinolones) were the first fluoroquinolone antibiotics to be approved as monotherapy, exhibiting strong and moderate efficacy against Gram-negative and Gram-positive bacteria, respectively. Generally, Gram-positive bacteria are among the most commonly identified microbial agents in ocular infections worldwide.<sup>54</sup> Unlike gentamicin, they also show good penetration into bacterial cells. Moxifloxacin, gatifloxacin, and levofloxacin (3<sup>rd</sup> and 4<sup>th</sup> generation fluoroquinolones) were introduced in the 2000s, showing a wider range of susceptibility to Gram-positive bacteria and exhibiting reduced efficacy against *Pseudomonas aeruginosa*.<sup>52, 55, 56</sup> Ciprofloxacin shows a very high efficacy against *Pseudomonas aeruginosa* compared to other topically approved antimicrobials, as determined by minimum inhibitory concentration (MIC) data.<sup>49</sup>

### **1.1.7 Other Management Strategies**

For the treatment of corneal infections, the dose of ciprofloxacin is 3-4 drops instilled at least three times daily.<sup>57</sup> Alternative drug delivery methods have been recommended

to sustain a significant concentration of antimicrobials within the tissue.<sup>58</sup> These methods include nanoparticles,<sup>59</sup> iontophoresis,<sup>60</sup> collagen shields,<sup>61</sup> or drug-delivery contact lenses.<sup>62, 63</sup> Ideally, it would be beneficial to develop a contact lens-based device capable of sustained release of ciprofloxacin over 16 hours (covering a typical working day), to help improve overall clinical treatment efficacy and patient compliance.

## **1.2 Contact Lenses**

### **1.2.1. History and Inventions of Contact Lenses**

The first idea of a contact lens was introduced by the British astronomer Herschel, who proposed the concept of the refractive device by using a lens protected with an animal jelly layer on the cornea. Helmholtz and Javal laid the groundwork for the actual development of contact lenses through the innovation of accurate ophthalmometers in their work.<sup>64</sup> Drs. Fick of Zurich and Kalt utilized glass shells having a radius matching the normal corneal radius, allowing them to publish the premier clinical research on lenses and design the first lenses for keratoconus treatment respectively.<sup>65</sup>

Driven by the effort to correct his severe myopia, Müller published his doctoral thesis in 1889. The principle of contact lens correction for refractive errors that was detailed in his thesis is still in use today. Müller accurately clarified that the lacrimal fluid present between the lens and the eye creates forces of attraction and capillary adhesion causing the lens to be held in place, if it resembles the shape of the eye's anterior surface. Müller invented the transitional zone present in the limbal region. He correctly

linked discomfort after extended wear of contact lenses to poor lacrimal circulation and was the first to recognize the optical and metabolic functions of the lacrimal meniscus.<sup>65</sup>

Glass-blown scleral lenses were produced by adding glass corneoscleral shells to Müller's evolving design. These scleral lenses were impractical due to their large size, heaviness, and allowance of only limited tear exchange. To resolve this latter issue and enhance tear flow, Josef Dallos in Budapest incorporated fenestrations into the corneoscleral lenses. In addition, he pioneered the technique of manufacturing corneoscleral lenses from an eye mold.<sup>64</sup>

In 1948, Kevin Tuohy, using polymethylmethacrylate (PMMA), was the first to develop the rigid corneal contact lens, which sat on the cornea only, and was smaller than the corneal diameter. However, this lens caused discomfort and had a significant amount of edge standoff due to its moncurve design. George Butterfield's patented design resolved these issues. To ensure stability and allow proper tear flow, Butterfield incorporated peripheral curves on the lens's posterior surface so the base curve could better match the corneal central curvature.<sup>66</sup>

### **1.2.2 Contact Lens Materials**

The fitting of contact lenses was acknowledged as an essential part of the optometry profession by the American Optometric Association in 1945. Textbooks on contact lens fitting started to appear in both optometry and ophthalmology.<sup>64</sup>

Contact lens fitting and utilization were completely revolutionized by the innovation of hydrogel, soft, water-containing lenses. By 1961, Professor Otto Wichterle had

secured a patent for the spin-casting method used to manufacture hydrogel contact lenses.<sup>64</sup> In 1965, the National Patent Development Corporation in the United States acquired Wichterle's patents, and the breakthrough came, although it had limited success when initially marketed in Europe. Subsequently, Bausch & Lomb purchased Wichterle's patents and scaled up production significantly in 1970. Bausch & Lomb introduced the N series of soft lenses in 1972, heralding the widespread popularity of soft contact lenses.<sup>64</sup>

The development of hard contact lenses continued alongside the introduction of soft lenses, particularly since astigmatism could not be corrected by hydrogel contact lenses. It became apparent that hypoxia caused the corneal edema seen clinically with the wear of PMMA lenses. This spurred the search for a material that could offer a higher oxygen permeability.<sup>64</sup> In 1971, Norman Gaylord used a silicone methacrylate polymer to develop a rigid lens with higher oxygen permeability than PMMA. Subsequently, various fluorosilicone monomers were incorporated into rigid lenses to significantly increase its oxygen permeability, which could also correct corneal irregularities and various refractive errors, including reasonably high degrees of corneal astigmatism.<sup>67</sup>

Interestingly, silicone elastomer materials were among the initial gas-permeable materials subjected to experimentation. However, the hydrophobic nature of this very “rubbery”, flexible material and its tendency to become stuck to the surface of the eye made this material lack commercial appeal. Although encountering these difficulties, researchers like Robert Mandell and Irving Fatt emphasize the requirement for enhanced oxygen permeability in both soft and rigid lenses.<sup>64</sup> A substantial milestone

was reached with the publication of a groundbreaking article by Holden and Mertz in 1984, which charged the industry with the crucial task of bringing safer contact lenses to the market, with no edema results being seen post their wear.<sup>68</sup>

At that time, there was an increase in interest in designing overnight or extended-wear contact lenses. Initially introduced to correct aphakia in 1981, they soon gained popularity among a significant percentage of soft contact lens users for cosmetic purposes.<sup>64</sup>

In a brief span, there was a rise in the number of patients diagnosed with MK. While some cases were associated with lens case contamination or inadequate patient hygiene, the principal issue persisted: hypoxia resulting in epithelial breakdown and microbial adherence. Infections persisted despite the arrival of disposable soft lenses, that largely alleviated cleaning and storage issues in the early 1990s.<sup>64</sup>

In response to the challenge suggested by Mertz and Holden's research, silicone was added to the fundamental hydrogel matrix, accompanied by surface modification to enhance comfort and wettability. These led to a surge in using daily- and extended-wear lenses.<sup>64</sup> Furthermore, improvements in design and oxygen permeability, such as multifocal contact lenses for presbyopia and toric contact lenses for astigmatism correction, have driven soft contact lenses to become the predominant mode of contact lens correction.<sup>64</sup>

### 1.2.3 Silicone Hydrogel Contact Lenses

In 1984, Holden and Mertz stated that hydrogel polymers that depended only on their water phase for oxygen transport were inadequate to prevent corneal edema from overnight wear.<sup>68</sup> This swelling effect was also associated with increased limbal hyperemia, acidosis, endothelial responses, and epithelial microcysts.<sup>69</sup> Consequently, silicone hydrogel materials were developed, with the silicone component being the primary and efficient carrier of oxygen through the lens. Hence, these drawbacks of conventional hydrogels were reduced with the introduction of silicone hydrogels.<sup>70</sup>

Silicone hydrogels' first generation was developed by merging macromers with TRIS (silicone monomer).<sup>71</sup> In May 1997, lotrafilcon A (Alcon) gained approval for daily wear and in October 2001 for overnight wear. This surface-treated fluoro-silicone-containing hydrogel had a 24% water content. It also featured co-continuous water and gel phases.<sup>72</sup>

Balafilcon A contact lenses (Bausch + Lomb) received U.S. approval in February 1999. These lenses were copolymers including N-vinyl pyrrolidone, silicone cross-linker, silicone vinyl carbamate, and vinyl alanine as wetting polymer. They had a water content of 36% and a 113.3 Dk value. Further, balafilcon A received approval for overnight wear for up to seven days in November 2001. These advancements marked a renaissance in overnight wear, fulfilling the oxygen transmissibility criteria determined by Holden and Mertz.<sup>72</sup>

The origin of the silicone hydrogel's second generation started with galyfilcon A (Johnson & Johnson), featuring an increased hydrophilic silicone polymer patented by Tanaka et al. It had a 47% water content and a 60 Dk value. The incorporation of polyvinyl pyrrolidinone offered wettability without the necessity for surface treatment.<sup>72</sup>

Silicone hydrogel's third generation contained mainly silicone macromers. As an example, comfilcon A (CooperVision) boasted an increased water content at 48% and a 128 Dk value. These properties (increased water content and higher Dk values) exemplify the progress from elastofilcon - the initial silicone-based material - characterized by a mere 0.2% water content and a 360 Dk value.<sup>72</sup>

Delfilcon A (Alcon), a newer biphasic material, was developed as a daily disposable contact lens, featuring a core of silicone hydrogel with 33% water content and an attached water gradient at the surface that averages 80% water, increasing to approximately 100% at the surface.<sup>73</sup> The material has a 140 Dk value. Recently, this water gradient concept has been expanded to a reusable material (lehfilcon A, Dk= 123) by incorporating a 2-methacrylphosphoryl choline group.<sup>72</sup> This advancement increased compatibility with care systems for daily wear use of contact lenses and provides resistance to lipid and bacterial lipid adhesion. This material is developed to create a structure and a biomimetic surface that closely imitates the ocular surface.<sup>74-</sup>

77

Silicone hydrogels have now provided adequate oxygen to sustain long term health of the cornea, but studies continue to address issues such as lens compatibility with care systems, infection, and other lens-related concerns. Providing beneficial counsel and ensuring regular check-in with patients are essential for maintaining problem-free

long-term wear of contact lenses.<sup>72</sup> Currently, there are 21 silicone hydrogel contact lenses and 15 different silicone hydrogel materials available on the market, excluding the recently released lehtfilcon.<sup>78</sup>

#### **1.2.4 Contact Lens Care Systems**

Care systems, vital for the clinical success of lenses, have developed significantly along with advancements in lens materials. Initially, these systems counted on homemade saline and early heating units, which later transformed into the first hydrogen peroxide and chemical systems. Early chemical systems that contained disinfectants like thimerosal, benzalkonium chloride, and chlorhexidine caused chemical keratitis. Recognizing these difficulties, newer, safer disinfectants were produced.<sup>79</sup> Modern one-bottle systems now use disinfectants such as POLYQUAD or polyhexamethylene biguanide combined with cleaning agents and surfactants and are assembled with disposable cases.<sup>80</sup>

#### **1.2.5 Demographics of Contact Lens Wear**

Of the 150 million individuals who wear contact lenses globally, 45 million live in the United States.<sup>81, 82</sup> Data from the annual Contact Lens Fitting Survey showed that the majority of contact lens wearers were females, with the average age for fittings ranging between 18 and 50 years across all surveyed countries (38% new fits). Interestingly Taiwan and Korea have the highest fits to females (> 80%).<sup>83</sup>

The proportion of rigid lens fittings has remained relatively stable worldwide at 10% for multiple years. Netherlands leads in rigid lens usage, with a significant 47% (45% non-orthokeratology and 2% orthokeratology designs).<sup>83</sup> Additionally, scleral lenses account for 22% of the prescribed rigid lenses, and high Dk corneal lenses represent 52% of fits, the largest fraction among all rigid lens categories.<sup>83</sup>

Daily disposable soft contact lenses make up 45% of fittings worldwide, with silicone hydrogel contact lenses comprising over 73 % of soft daily-wear fittings. However, daily reusable soft contact lens fits have decreased to 40% across all surveyed countries, with a notable 72% fits in Uruguay.<sup>83</sup>

While daily-wear lenses are deemed the safest option for contact lens wear, they represent just 12% of new fittings in Colombia. In contrast, over 60% of all soft contact lens fittings in Australia, Canada, Denmark, Japan, and the United Kingdom consist of daily-wear lenses.<sup>83</sup>

The utilization of soft extended-wear contact lenses differs greatly among countries, ranging from 0% in about a third of the surveyed countries to 19% in Bulgaria. In countries with significant lens wearers, over 90% of extended-wear patients opt for silicone hydrogel contact lenses, with the Netherlands having the lowest percentage with only 33% using this material type.<sup>83</sup>

When serious issues arise for a contact lens wearer, they are extensively reported and investigated. Multiple factors come into effect, including nonadherence with the cleaning routines, inadequate disinfection of lenses, and breaks in the protective epithelial layer. In addition, geographical variations in *Acanthamoeba* or fungal presence in the environment, and variations in materials and lens-wearing habits, also

contribute. Ladage and Cavanagh have enhanced our perception of the root causes by indicating that microbial attachment to desquamated epithelial cells is diminished with high oxygen-permeable material, irrespective of wearing regimen.<sup>64</sup>

While the optimal contact lens remains elusive, it is apparent that a wide majority of the 150 million people who wear them experience comfortable, clear vision with minimal complications, avoiding the trouble of glasses or the possible hazards associated with refractive surgery.<sup>64</sup>

### **1.2.6 Contact Lens as an Ophthalmic Device**

Contact lenses are ophthalmic devices globally used by millions of people to correct vision problems such as hyperopia, myopia, and astigmatism.<sup>82</sup> They have an immense market worldwide; by 2024, it will likely reach more than 19 billion dollars annually in the US alone.<sup>82</sup> Besides being successful refractive error correction devices, contact lenses are therapeutically used for corneal irregularities, myopia control, and post-refractive surgery rehabilitation.<sup>82,84</sup> Contact lenses are also being studied to control presbyopia by changing their shape<sup>84</sup> and have been used to change eye color, as wearable biosensors, and for use as drug delivery systems.<sup>82</sup> The use of the contact lens for ophthalmic drug delivery was first reported in 1965.<sup>85</sup> Since then hundreds of studies have been conducted looking at the potential for the contact lens to be an efficient drug delivery device.<sup>86</sup>

### **1.3 Ocular Drug Delivery via Conventional Eye Drops**

Topical administration of ocular drugs via eye drops is an easy and noninvasive method, making it the preferred delivery application for most ophthalmic diseases.<sup>87</sup> In addition to being patient-friendly, eye drops are cost-effective and are used in the vast majority of cases that require topical ocular treatment.<sup>88</sup> Topical ophthalmic drops are commonly used to treat glaucoma, dry eye syndrome, conjunctivitis, and fungal, viral, or bacterial infections.<sup>89</sup>

### **1.4 Disadvantages of Conventional Eye Drops**

Although eye drops are the predominant approach to ophthalmic drug delivery, they have limited efficacy due to their diminished bioavailability, resulting from low precorneal volume, reflex blinking, and nasolacrimal drainage from the eye.<sup>87</sup> These anatomical and physiological conditions in the eye lead to a drug residence time of only a few minutes, hence the bioavailability of < 5% of the eye drops administered.<sup>90, 91</sup> The systemic absorption of the remaining 95% results in reduced efficacy, undesired side effects, and increased dosage frequency, leading to low patient compliance.<sup>91</sup> In addition, eye drops may offer a low degree of accurate dosing, due to many factors, including consistency of delivering the same drop size from the bottle to the eye, the accuracy of the drop instillation by the patient onto the ocular surface, and adequate handling of the drug solution bottle.<sup>84</sup> In addition, the incorporation of preservatives into most multidrop bottles can lead to ocular surface toxicity, dry eye complaints, and changes to the ocular surface tissue when chronically used over many years.<sup>92</sup>

### **1.5. Advantages of Drug Delivery Contact Lenses over Conventional Eye Drops**

To overcome the drawbacks of eyedrops, many novel ocular formulations and measures have been developed, such as nanoparticles, punctal plugs, mucoadhesive polymers, implants, and drug-delivering contact lenses.<sup>93</sup> Delivering ocular drugs via contact lenses has been heavily investigated, with the aim of making them an effective vehicle for treating a wide variety of ophthalmic diseases.<sup>84, 90, 94-97</sup> When the lens is applied to the eye, the tear film is separated into 2 layers (Figure 1.1): a layer covering the anterior surface of the contact lens called the pre-lens tear film (PrLTF), and a second layer lies between the contact lens posterior surface and the corneal surface of the eye called the post-lens tear film (PoLTF). This division of the tear film benefits drug-delivering contact lenses because the PoLTF is extremely thin and has a reasonably small turnover rate.<sup>98</sup> When the drug-delivering contact lens releases its drug into the post-lens tear film, the low tear flow rate helps sustain a higher concentration of the drug behind the contact lens. This, along with the increased residence time, can result in potentially higher bioavailability and greater ocular penetration of the drug leading to increased efficacy.<sup>90, 99, 100</sup> Additional advantages may include reduced frequency of drug administration, diminished systemic absorption resulting in reduced potential side effects, and a more sustained drug release profile.<sup>90,</sup>

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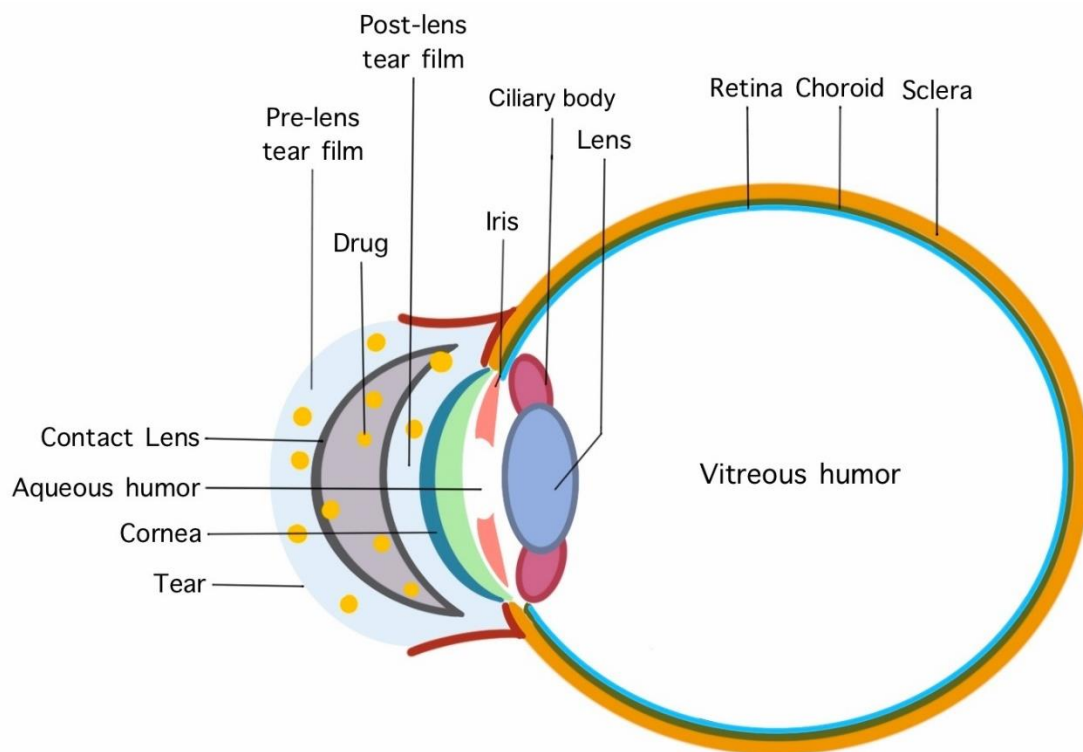


**Figure 1.1.** Scheme showing the eye structure and the positioning of a contact lens within the tear film.

In addition, if a drug-delivering contact lens system can maintain sustained release for several days, patients can wear or have the lens applied to receive their drug continuously for a set duration. When an efficient drug daily dosage is loaded into the drug-delivering lens, the contact lens vision correction role may increase patient compliance by reducing the frequent administration of the drug, especially among regular lens wearers, since inserting lenses is already integrated into their daily routine.<sup>84</sup> Furthermore, contact lenses are biocompatible, preservative-free (terminally sterilized), and release drugs in a more controlled manner than eye drops.<sup>84,91</sup>

## 1.6 Challenges of Ophthalmic Drug Delivery Silicone Hydrogel and Conventional Hydrogel Contact Lenses

Ocular drugs can be loaded into contact lenses by several methods, including simply dipping or soaking the lens in the drug of interest,<sup>101</sup> molecular imprinting,<sup>102</sup> colloidal nanoparticles,<sup>103</sup> supercritical fluid technology,<sup>104</sup> surface modifications,<sup>105</sup> or incorporating the drug in the formulation of the lens during fabrication.<sup>106</sup> The latter method is less preferable as it does not protect the integrity of the incorporated drug. Using this approach, the incorporated drugs might be degraded, modified, or their final concentration may change from that which is expected.<sup>84</sup> The relatively simple “soaking” method is the technique commonly used to load ophthalmic drugs into a contact lens material.<sup>106</sup>

Soft contact lenses have many internal aqueous channels, which can accommodate the uptake (and subsequent release) of ocular drugs by molecular diffusion, resulting from the concentration difference between the lens and drug-soaking solution.<sup>106</sup> The ability of the contact lens material to uptake and release ocular drugs depends on various parameters, including its thickness, water content, charge, hydrophobicity, and the drug soaking duration to load the drug into the lens.<sup>106</sup> Furthermore, the drug's solubility, molecular weight, and affinity play an important role in its uptake and release profile.<sup>106</sup> Choosing a contact lens/drug combination is another crucial factor in having adequate uptake and release profiles, as using a hydrophilic drug to be loaded into a hydrophilic hydrogel contact lens material can optimize the uptake profile, and choosing a drug with high affinity to a contact lens material can extend the drug release profile and vice versa.<sup>84</sup> The soaking method has been used for many ophthalmic drugs,

including timolol,<sup>107</sup> fluoroquinolones,<sup>96</sup> aminoglycosides,<sup>108</sup> dexamethasone,<sup>94</sup> and pirfenidone.<sup>109</sup>

## **1.7 New Approaches for Extended Duration Drug Delivery Contact Lens**

While using contact lenses as drug delivery devices is more effective than inserting eye drops,<sup>87</sup> these systems typically have a burst and rapid release of the drug that is unsuitable for treating most ocular diseases, as the release prevents therapeutically relevant dosing for an extended period of time.<sup>91,96</sup> Thus, these challenges must be overcome to make the contact lens an effective ocular drug delivery concept. By comparing Poly(2-hydroxyethyl methacrylate) pHEMA with silicone hydrogel, Karlgard et al. showed that pHEMA-based materials released higher amounts of drugs than silicone hydrogel materials, and both contact lenses released drugs within a few hours.<sup>110</sup> This trend has been shown in other studies.<sup>111, 112</sup> Hence, to achieve a sustained release of a drug, further modifications must be applied to both conventional and silicone hydrogel contact lenses. Many approaches have been investigated to reduce this initial burst release and extend the drug release duration of the contact lens material containing the drug of interest.<sup>91, 94, 96, 113</sup>

Some methods used to extend drug release from contact lenses include:

### **a) Nanoparticles**

Nanoparticles have been efficiently utilized as an ocular drug carrier due to their significant size.<sup>114, 115</sup> These nanoparticles can be fabricated from a mix of synthetic and/or natural polymers, exhibiting a broad range of characteristics that can be

adequately optimized to achieve drug delivery purposes such as increasing residence time, enhancing drug loading, and sustaining drug release.<sup>115</sup>

Nanoparticles are generally categorized as molecules ranging in size from 1 to 1000 nm.<sup>115, 116</sup> They encompass liposomes, micelles, as well as polymeric and metallic nanoparticles.<sup>116-121</sup> When selecting nanoparticles, it is critical to choose those that are safe and biocompatible, without compromising crucial contact lens properties (oxygen permeability, water content, and optical transmittance).<sup>122-126</sup>

Nanoparticle-laden contact lenses often release drugs in a sustained manner because the incorporated drugs must diffuse through multiple barriers before being released into the tear film.<sup>106, 127-130</sup>

#### b) Microemulsions

These are homogeneous, isotropic, and stable solutions composed of a surfactant, a non-polar compound, and a polar substance.<sup>131</sup> A microemulsion can be characterized as a bicontinuous phase, a mixture of water in oil, or a mixture of oil in water. Their capacity to dissolve hydrophilic and hydrophobic components simultaneously can offer substantial advantages in drug delivery.<sup>84</sup>

Oil-in-water microemulsions are most commonly utilized with contact lenses.<sup>132-136</sup> In this format, the hydrophobic drugs are slowly released into the continuous water phase because they are entrapped within the oil phase due to the barrier effect of the surfactants. Hence, the drug release rate could be adjusted by altering the surfactant's concentration<sup>136</sup> or characteristics, including ionicity<sup>135</sup> and chain length.<sup>132</sup> However, a

major drawback is that the critical characteristics of a contact lens can be affected by the incorporation of microemulsions, including optical transparency and wettability.<sup>84</sup>

In addition, contact lenses with microemulsions are proposed to enhance the delivery of the drug by improving its loading and increasing its release duration. However, the surfactants released from these lenses must be cautiously assessed, because high surfactant concentrations may result in ocular toxicity.<sup>137, 138</sup>

#### c) Molecular Imprinting

Molecular imprinting is a polymerization technique that is used to form functional group- and/or shape-specific regions within a polymer at the molecular level.<sup>139</sup> The functional monomers utilized in this process are commonly small molecules selected for their significant ability to interact non-covalently with the target molecules, using forces such as ionic interactions or hydrogen bonds.<sup>84</sup>

From the drug delivery viewpoint, the strong attraction to the template molecule generated throughout the process of molecular imprinting is proposed to extend the drug release from a material.<sup>139</sup> A vitro study shows that the biomimetic molecular imprinted lens significantly extends the release duration of ketotifen when compared to non-imprinted lenses.<sup>140</sup>

#### d) Ion Interactions

Numerous ocular drugs carry ionic charges or can be prepared to do so, providing an opportunity to interact electrostatically with the charged surface lens material. Such electrostatic interactions between the drug and a contact lens have shown a significant increase in drug loading and attainment of sustained drug release.<sup>141-144</sup> Multiple

contact lens materials currently on the market possess ionic charges. In addition, several studies have shown that the commercially available lenses that are electrostatically charged (such as ocufilcon B, etafilcon A, and balafilcon A) can increase the absorption and release of drugs with complementary charges.<sup>142</sup> Furthermore, several other studies have fabricated ionic materials to investigate their adequacy in absorbing and releasing ocular drugs.<sup>102, 145, 146</sup>

#### e) Cyclodextrins

Cyclodextrins are cyclic oligosaccharides found naturally and utilized in various pharmaceutical applications.<sup>147</sup> They exhibit an extended drug release by forming supramolecular complexes with small-molecule drugs. Furthermore, cyclodextrins can capture low water-soluble molecules, providing enhanced loading within the drug-release matrix. They are categorized by structural unit numbers, with the most frequent being  $\gamma$ -cyclodextrins,  $\beta$ -cyclodextrins, or  $\alpha$ -cyclodextrins.<sup>84</sup> In vitro release experiments showed that hydrogels with  $\beta$ -cyclodextrins exhibited a slower release of puerarin compared to hydrogels without  $\beta$ -cyclodextrins. In addition, the amount of cyclodextrins loaded correlated with the duration of drug release.<sup>147</sup>

#### f) Drug-polymer films

Drug delivery contact lenses can exhibit sustained drug release by incorporating a thin film containing both drug and polymer.<sup>148</sup> This drug-polymer film is enclosed inside the border of a conventional contact lens so that the polymer acts as a diffusion barrier, consequently slowing the drug release. Restricting the film to the periphery of the lens maintains optical clarity at the center of the lens while loading it with a therapeutic dose of the drug.<sup>149</sup> Optimizing the drug release rate is achievable by varying parameters

such as drug-polymer ratio, drug concentration, polymer concentration, and polymer characteristics such as molecular weight.<sup>148</sup>

g) Vitamin E barrier

Vitamin E is hypothesized to form a diffusion barrier within the contact lens matrix. This barrier is believed to extend drug release duration by impeding the diffusion of the drug out of the lens.<sup>94</sup> Several studies have shown that vitamin E-loaded contact lenses have greater bioavailability than eyedrops.<sup>109</sup> Exploration of this drug delivery technology has been chosen as the focus of this thesis and will be detailed in the next sections.

## **1.8 Vitamin E as a Safe and Effective Diffusion Barrier in Contact Lens Materials**

One proven method to slow the release of drugs from contact lens materials uses vitamin E, a biocompatible, lipophilic, and hydrophobic molecule with low aqueous solubility (Figure 1.2).<sup>91, 94, 150-152</sup> The drug release from contact lenses is driven by diffusion within the contact lens matrix.<sup>91</sup> The drug release duration can be increased by either decreasing the drug diffusivity through the lens material or by increasing the path length that a drug needs to cross for it to be released from the contact lens.<sup>91</sup> Vitamin E is a viable candidate, acting as a diffusion barrier due to its biocompatibility, with no reported toxicity to the eye.<sup>91</sup> Moreover, its hydrophobicity enables it to interact with the silicone components of silicone hydrogels to form potential diffusion barriers. Chauhan and coworkers proposed that the hydrophobic drug might segregate and diffuse through vitamin E, which will result in reduced diffusivity due to the high vitamin

E viscosity.<sup>94</sup> The incorporation of vitamin E into commercially available silicone hydrogel contact lenses (senofilcon A, lotrafilcon B, and comfilcon A) significantly extended the drug release profile.<sup>96</sup> Sekar et al. found that vitamin E-loaded silicone hydrogel contact lenses extend bimatoprost (an anti-glaucoma drug) release duration by 10-40 fold (>10 days) without impacting the contact lens properties.<sup>152</sup> This approach of using vitamin E has been used to extend the release duration of a variety of topical ophthalmic drugs, including levofloxacin,<sup>153</sup> dexamethasone,<sup>94</sup> timolol,<sup>95</sup> lidocaine,<sup>151</sup> brimonidine,<sup>154</sup> and ciprofloxacin.<sup>96</sup>

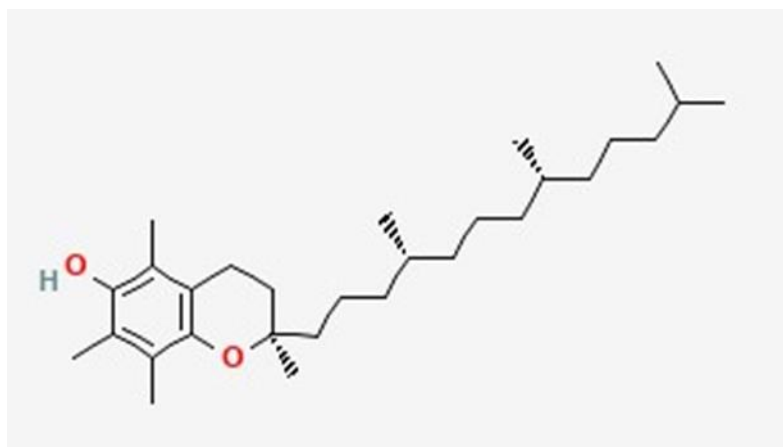


**Figure 1.2.** Chemical structure of vitamin E used in this study.<sup>155</sup>

In addition to its safety profile, vitamin E also has many therapeutic benefits. It inhibits various ocular diseases, including ethanol-induced apoptosis and keratocyte apoptosis, and delays the progression of age-related macular degeneration.<sup>91, 106</sup> Moreover, vitamin E has UV-blocking and powerful antioxidant properties and has been shown to slow the development of cataracts.<sup>91, 106</sup>

## 1.9 Ciprofloxacin: A Hydrophobic Ocular Antibiotic

Fluoroquinolones are one of the most widely used antibiotics in human therapy.<sup>156</sup> The fluoroquinolones inhibit different kinds of enzymes, such as DNA gyrase, DNA topoisomerase IV, and type II topoisomerase.<sup>156</sup> Fluoroquinolones are commonly described as having four 'generations'. While the drugs included in the first generation were not fluorinated, the second generation drugs were fluorinated, expanding their antimicrobial activity to gram-positive bacteria and providing optimal activity against gram-negative bacteria.<sup>156</sup> The third-generation drugs have better antimicrobial activity against gram-positive bacteria than the second-generation drugs.<sup>156</sup> The most recent fourth-generation drugs have antimicrobial activity against anaerobic bacteria in addition to gram-negative and gram-positive bacteria.<sup>156</sup> Ciprofloxacin (Figure 1.3), which belongs to the second-generation fluoroquinolones, is an antibiotic that is widely used to treat bacterial infections including conjunctivitis, corneal ulceration, skin infections, bone and joint infections, and urinary tract infections.<sup>156</sup>

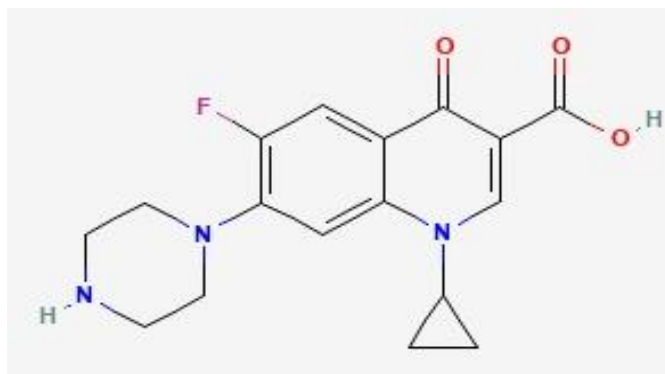


**Figure 1.3.** Chemical structure of ciprofloxacin.<sup>157</sup>

Ciprofloxacin is widely used for the treatment of ocular infections due to its broad spectrum of activity and its excellent penetration into biological fluids and tissues.<sup>158</sup> It

is on the “List of Essential Medicines” of the World Health Organization (WHO).<sup>156</sup> It is also one of the BCS drugs (Class II/IV), which currently make up about 90% of molecules under development and about 40% of the marketed drugs. Ciprofloxacin belongs to BCS Class IV.<sup>159</sup>

Ciprofloxacin 0.3% is available for use for ocular treatment as an ophthalmic drop or ointment.<sup>160</sup> Ciprofloxacin has an extremely short half-life and is rapidly eliminated when administered via conventional eye drops.<sup>161</sup> For acute corneal infection, ciprofloxacin must be instilled onto the ocular surface 1-2 drops every 15 to 30 minutes, and for severe conditions, it must be instilled at least 6 times per day.<sup>161</sup>

The Minimum Inhibitory Concentration for 90% (MIC90) of isolates is a crucial measure for antimicrobial susceptibility testing.<sup>162</sup> MIC90 reflects the antimicrobial concentration at which 90% of the tested bacterial isolates would be inhibited.<sup>162</sup> Based on previous ophthalmic bacterial studies, the MIC90 for ciprofloxacin against common, susceptible, and resistant ophthalmic pathogens ranges between 0.25 and 32 µg/mL, depending on the bacterial species.<sup>163</sup>

Ciprofloxacin has many side effects, ranging from mild (dizziness, headache, pruritis, nausea, diarrhea, abdominal discomfort, and vomiting) to severe (tendinitis, nerve damage, depression, and seizures).<sup>164</sup> To reduce these potential side effects and ensure better patient compliance, the drug would ideally be delivered via controlled and extended release from a contact lens carrier. Furthermore, ciprofloxacin can be considered a model ophthalmic drug to evaluate the upload and release of hydrophobic molecules from non-loaded and vitamin E-loaded conventional and silicone hydrogel contact lenses. Bajgrowicz and coworkers showed that ciprofloxacin released rapidly

(15 minutes – 2 hours) from both conventional and silicone hydrogel contact lenses.<sup>62</sup>

Also, Hui et al. showed that ciprofloxacin-HCL was released immediately (10 minutes) from commercial conventional and silicone hydrogel contact lenses.<sup>142</sup>

### **1.10 Criteria for Success**

To enhance overall clinical treatment efficacy and patient compliance, it would be ideal to develop a contact lens-based device with the following features:

- a. Maintain transparency and comfort throughout the treatment period.
- b. Sustain ciprofloxacin release over 16 hours (covering a typical working day).
- c. Achieve cumulative ciprofloxacin release that meets the MIC90 concentration for both susceptible and resistant bacterial strains (0.25 and 32 µg/mL).
- d. Allow for easy loading of ciprofloxacin (within 24 hours) to ensure commercial viability.

## 2 Thesis Rationale

A contact lens-based drug delivery device has many potential benefits over eye drops, including higher bioavailability and improved patient compliance. However, studies have shown that commercially available contact lenses loaded with a wide variety of topical ophthalmic drugs exhibit a rapid burst and release of a drug, requiring a new approach to control its release. One method that has shown promise with silicone hydrogel materials is through using vitamin E as a diffusion barrier.<sup>94, 165</sup> To date, this has been used to reduce the burst release and increase the release duration of several drugs, from both conventional and silicone hydrogel contact lenses. However, the use of such a concept has not been investigated to control the release of ciprofloxacin from these lenses. Further, there are no known studies of the effect of vitamin E on the uptake of ciprofloxacin into conventional or silicone hydrogel contact lenses. Therefore, this research aims to develop a contact lens-based drug delivery system that incorporates vitamin E to obtain sustained release of ciprofloxacin.

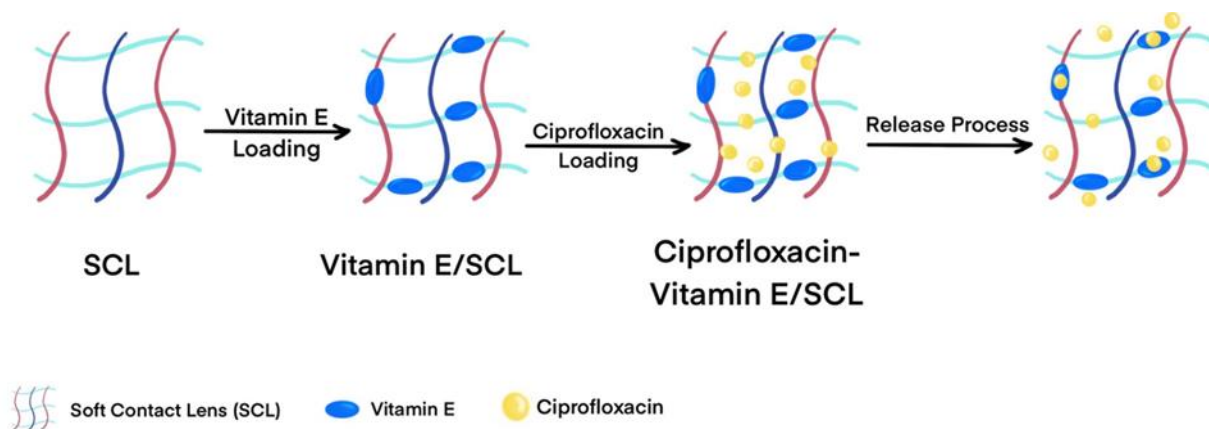


**Figure 2.1.** Ciprofloxacin and vitamin E loading and releasing process in soft contact lens.

## **2.1 Thesis Objectives**

- Evaluate the uptake and release kinetics of a hydrophobic ocular antibiotic (ciprofloxacin) from non-loaded and vitamin E-loaded drug-delivering conventional and silicone hydrogel contact lenses.
- Evaluate the effect of ciprofloxacin's loading duration on the loading and release profiles of contact lenses that exhibit the longest release duration.
- Assess the cumulative release of ciprofloxacin from contact lenses that have best-sustained release profiles, ensuring they reach the MIC90 concentration for both susceptible and resistant bacterial isolates.

### **3 Extended Release of Ciprofloxacin from Commercial Silicone-Hydrogel and Conventional-Hydrogel Contact Lenses containing Vitamin E Diffusion**

#### **Barriers**

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### 3.1. Introduction

Topical administration of ocular drugs via eye drops is the most common method to treat most ocular diseases, including glaucoma, conjunctivitis, dry eye syndrome, and infections.<sup>87, 89</sup> Nevertheless, it is important to note that eye drops have limited efficacy due to their low bioavailability (< 5%) resulting from reflex blinking, low precorneal volume, and nasolacrimal drainage from the eye.<sup>87, 90, 91</sup> The remaining 95% is absorbed systemically, resulting in low patient compliance and undesired side effects.<sup>91</sup> As a result, there have been several alternative drug-delivery methods that have been explored, including punctal plugs, nanoparticles, mucoadhesive polymers, and drug-delivery contact lenses.<sup>93</sup> The latter has been investigated due to its potential to increase drug residence time on the eye, while also providing sustained release.<sup>87, 90, 91</sup> These benefits would reduce the burden of frequent administration, leading to improved patient compliance.<sup>90</sup>

However, to make an effective contact lens-based drug delivery device, several challenges must be overcome including the burst and rapid release of the drug.<sup>84, 91, 96</sup> Studies have shown that commercial contact lens materials often exhibit a burst release of the incorporated drug within a few hours, which is inadequate for therapeutic use over an extended period of time.<sup>84, 110-112</sup> Hence, commercial lenses must be modified for them to exhibit an appropriate sustained drug release.<sup>142</sup> To this end, researchers have been exploring various methodologies to create a drug-delivery contact lens that reduces burst release and prolongs release duration.<sup>91, 94, 96, 113</sup> Some researchers have proposed the development of imprinted contact lenses, which leads to an extended release of the drug by increasing its distribution.<sup>140, 166-168</sup> Other researchers have focused on developing

nanoparticle-laden gels that can lead to a controlled release of the loaded drug from nanoparticles.<sup>125, 169, 170</sup> All the methods mentioned above, however, may involve complex or multi-step synthesis or modification processes, which would be expensive to manufacture at a large scale. An approach that utilizes a coating on a lens post-manufacturing is more attractive in terms of commercialization.

One promising strategy is the use of lipophilic vitamin E,<sup>94, 153, 165, 171</sup> which is proposed to create hydrophobic barriers to prolong the drug release by decreasing its diffusivity.<sup>94, 97, 172</sup> To prolong the release duration, either the diffusivity of a drug through the lens matrix must be decreased or its path length through the lens must be increased; vitamin E achieves both of these goals.<sup>91</sup> Vitamin E acts as a diffusion barrier by creating a longer diffusion path through the lens hydrogel matrix, thereby increasing the release duration of a drug. The use of vitamin E as a diffusion barrier for contact lenses has been shown to be effective for various drugs.<sup>91, 94, 150-153, 165, 171</sup> Moreover, studies have shown that the high viscosity of vitamin E reduces the diffusivity of the hydrophobic drug in the contact lens, resulting in increased release duration.<sup>94, 151</sup> Previous studies have shown that the release duration of the anti-glaucoma drug Bimatoprost increased to > 10 days by incorporating vitamin E into silicone hydrogel contact lenses.<sup>152</sup> Other studies have demonstrated extended release with vitamin E-loaded contact lenses for other topical ocular drugs, including dexamethasone,<sup>94</sup> timolol,<sup>95</sup> lidocaine,<sup>151</sup> levofloxacin,<sup>153</sup> and brimonidine.<sup>154</sup>

Ciprofloxacin is an important and widely used second-generation fluoroquinolone, employed in treating various bacterial infections including corneal ulceration, conjunctivitis,

urinary tract infections, skin infections, and bone infections.<sup>156</sup> The topical administration of ciprofloxacin experiences rapid elimination when delivered through eye drops.<sup>161</sup> In addition, ciprofloxacin has various side effects.<sup>164</sup> Sustainable and extended release of ciprofloxacin from a drug-delivering contact lens would ideally enhance patient compliance, provide a therapeutically relevant amount of drug for an extended period of time, and reduce its side effects. Previous studies showed that commercially available conventional hydrogel and silicone hydrogel contact lenses released ciprofloxacin within the first 2 hours.<sup>62, 142</sup> Therefore, unmodified commercial contact lenses are unlikely to provide the desired therapeutic release profile for clinical treatment. The aim of this study was to evaluate the uptake and release of ciprofloxacin using commercially available contact lenses loaded with vitamin E.

### **3.2. Objective**

To develop a contact lens-based ocular drug delivery system using vitamin E as a diffusion barrier to extend the release duration of ciprofloxacin.

### **3.3. Materials and Methods**

#### **3.3.1. Materials**

Four commercial silicone hydrogel contact lenses (ACUVUE® OASYS™; AIR OPTIX AQUA®; BIOFINITY®; Bausch + Lomb ULTRA®) and one commercial conventional hydrogel contact lens (ACUVUE® 2) were used in this study. Their properties are described in Table 3.1. Ciprofloxacin hydrochloride monohydrate (≥ 98%),

vitamin E (DL- $\alpha$ -Tocopherol acetate, synthetic  $\geq 96\%$ ), acetic acid, and phosphate-buffered saline (PBS) were purchased from Sigma–Aldrich Chemicals (St. Louis, MO). All chemicals were used as received without further modifications. The contact lenses were obtained in their original packaging. Each contact lens had a prescription of  $-3.00$  dioptries and a base curve between 8.5 and 8.7 mm.

**Table 3.1.** List of commercial contact lenses used in this study.

|                                                | ACUVUE®<br>OASYS™                                                    | AIR OPTIX®<br>AQUA                   | BIOFINITY®                                            | Bausch +<br>Lomb<br>ULTRA®         | ACUVUE® 2            |
|------------------------------------------------|----------------------------------------------------------------------|--------------------------------------|-------------------------------------------------------|------------------------------------|----------------------|
| <b>US adopted name</b>                         | Senofilcon A                                                         | Lotrafilcon B                        | Comfilcon A                                           | Samfilcon A                        | Etafilcon A          |
| <b>Manufacturer</b>                            | Johnson &<br>Johnson                                                 | Alcon                                | CooperVision                                          | Bausch +<br>Lomb                   | Johnson &<br>Johnson |
| <b>Water content (%)</b>                       | 38                                                                   | 33                                   | 48                                                    | 46                                 | 58                   |
| <b>FDA Group</b>                               | V                                                                    | V                                    | V                                                     | V                                  | IV                   |
| <b>Center thickness<br/>(mm)</b>               | 0.07                                                                 | 0.08                                 | 0.08                                                  | 0.07                               | 0.08                 |
| <b>Oxygen permeability (x10<sup>-11</sup>)</b> | 103                                                                  | 110                                  | 128                                                   | 163                                | 22                   |
| <b>Principle monomers</b>                      | mPDMS +<br>DMA + HEMA<br>+ siloxane<br>macromer +<br>TEGDMA +<br>PVP | DMA + TRIS +<br>siloxane<br>macromer | FM0411M +<br>HOB + IBM +<br>M3U + NVP +<br>TAIC + VMA | MA + siloxane<br>macromer +<br>PVP | HEMA + MA            |

DMA – N,N-dimethylacrylamide; HEMA – 2-Hydroxyethyl methacrylate; MA – methacrylic acid; NVP – N-vinyl pyrrolidone; TRIS – tris-(hydroxymethyl) aminomethane; PVP-Polyvinylpyrrolidone; mPDMS-polydimethylsiloxane; TEGDMA-Triethylene glycol dimethacrylate; HOB-4-hydroxybutyl methacrylate; FM0411M-2-ethyl E2-E(2-methylprop-2-enoyl)oxyethylcarbamate; IBM-isobornyl methacrylate; M3U- $\alpha$ - $\omega$ -bis(methacryloyloxyethyl iminocarbonyl ethyloxypropyl)-poly(dimethylsiloxane)-poly(trifluoropropylmethylsiloxane)-poly( $\omega$ -methoxy-poly(ethylene glycol)propylmethylsiloxane); TAIC-1,3,5-triprop-2-enyl-1,3,5-triazine-2,4,6(1H,3H,5H)-trione; VMA-N-vinyl-N-methylacetamide.

### 3.3.2. Vitamin E Loading into Contact Lenses

The contact lenses were removed from their original packaging solution, soaked in PBS for 30 minutes, removed and gently wiped using lens paper (VWR, Radnor, PA). The vitamin E solution was formulated by mixing vitamin E and ethanol with moderate stirring for a few minutes. The lenses were loaded in 3 mL of vitamin E loading solution

at various concentrations of vitamin E (0 g/mL, 0.0125 g/mL, 0.025 g/mL, 0.05 g/mL, 0.1 g/mL, and 0.2 g/mL) for 24 hours, which was found to be sufficient for equilibrium to be established between the lens and the solution.<sup>173</sup> After the loading step, the lenses were removed from the vitamin E soaking solution and briefly dipped in ethanol to remove any loosely bound vitamin E on the lens surface. The lenses were then incubated in PBS for 24 hours which was determined to be adequate to remove remaining ethanol and to prepare the lenses for the drug-loading step.

A set of non-loaded contact lenses and other sets of each concentration of vitamin E-loaded contact lenses (n=3) were dried in air overnight at room temperature and weighed, using an analytical scale (QUINTIX124-1S, Sartorius®, QC, Quebec), to determine the gain in weight due to vitamin E loading. The amount of vitamin E loaded in each lens was calculated by measuring the dry lens weight before and after vitamin E loading into the contact lens (Equation 1). The lenses used in the weighing experiment were only used to obtain the vitamin E loading amount.

**Equation 1:**

**Amount of vitamin E** = weight of vitamin E-loaded dry lens – weight of pure dry lens.

### **3.3.3. Ciprofloxacin Loading into Contact Lenses**

A solution containing 3 mg/mL of ciprofloxacin was made by dissolving ciprofloxacin in acetic acid (pH 4.8). Ciprofloxacin is insoluble in solution at physiological pH 7.4.<sup>159</sup> Acetic acid was used in lieu of PBS because it buffers in this region (acetic acid pKa = 4.76).<sup>174</sup> Ciprofloxacin was loaded into lenses by soaking each lens for 24 hours in 3 mL of the ciprofloxacin solution. After the loading stage, the lens was removed

and dipped for 1 second in an acetic acid solution to remove any loosely bound ciprofloxacin on the contact lens surface. Finally, a KimWipe (Kimtech Science™, Mississauga, ON) was used to remove any surplus solution from the lens surface.

#### **3.3.4. Measuring the Uptake of Ciprofloxacin into Contact Lenses**

The total amount of ciprofloxacin loaded into the contact lens was determined using an extraction protocol.<sup>175</sup> Each contact lens was incubated in 3 mL of (1:1) methanol/acetic acid solution with shaking at room temperature for 24 hours. A sample of 300 µL was removed from the extraction solution to measure its absorbances on a UV–VIS spectrophotometer at 280 nm ( $\lambda_{\text{max}}$  of ciprofloxacin in methanol/acetic acid solution). The total amount of ciprofloxacin extracted from each lens was calculated from a standard calibration curve which was constructed as follows:

##### **Preparation of working standard**

1. Nine test tubes were marked serially from 1-9 and kept in a test tube holder.
2. Test tube #1 had 10 mL of acetic acid. No ciprofloxacin/acetic acid solution was added to this tube.
3. Test tube #2 had 0.5 mL ciprofloxacin/acetic acid solution and was added to 9.5 mL acetic acid.
4. The dilution process was conducted for the rest of the test tubes.

##### **Determination of absorbances**

1. The UV-VIS spectrophotometer was turned on and the calibration process was completed.

2. A 96-well plate was loaded with 300  $\mu$ L of solution of each tube solution and inserted separately in the machine.
3. Absorbances of all the solutions were recorded
4. The concentration on the x-axis and absorbance on the y-axis were plotted using Microsoft Excel on the computer and a standard curve was formed.
5. From the standard curve, the straight-line equation and regression ( $R^2$ ) value were found.

### **3.3.5. Ciprofloxacin Release from Contact Lenses**

The release of ciprofloxacin was conducted in 3 mL of PBS in an amber glass vial at 37°C with shaking.<sup>94, 151, 176</sup> At  $t = 0.5, 1, 2, 4, 6, 8, 12, 16,$  and 24 hours, 300  $\mu$ L sample was removed, and the amount of ciprofloxacin released at each time point was measured. The removed sample volume was replaced by fresh 300  $\mu$ L of PBS to maintain the sink condition.

### **3.3.6. Statistical Analysis:**

GraphPad Prism 5 software, Version 8.0.1 (GraphPad, La Jolla, CA, USA) was used to plot the graphs and to perform all the statistical analysis. Data were expressed as mean $\pm$ standard deviation ( $n = 3$ ). A repeated measures Analysis of Variance (ANOVA) was performed to determine differences across various time points within the same lens type and to measure the uptake of vitamin E and the amount of ciprofloxacin loaded. An ANOVA was performed to determine differences between lens types. A  $p$ -value  $< 0.05$  was considered statistically significant.

### 3.4. Results

#### 3.4.1. Vitamin E Loading into Contact Lenses

The amount of vitamin E loaded into each contact lens material for different concentrations of vitamin E soaking solutions is shown in Figure 3.1.

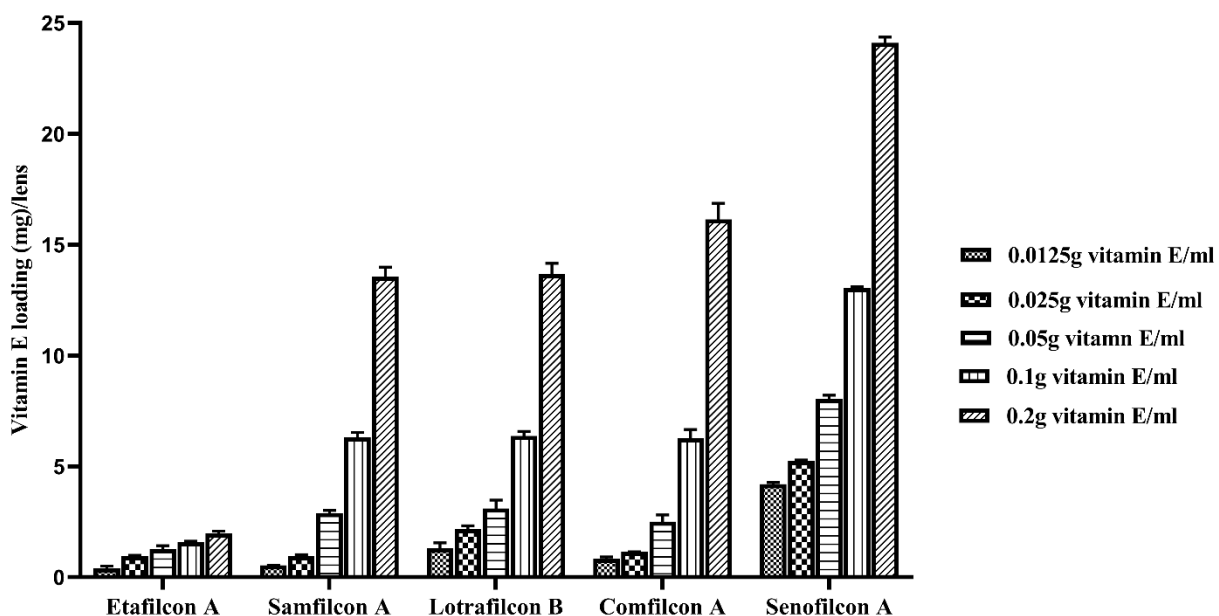


**Figure 3.1.** Vitamin E loading amounts in different concentrations of vitamin E solutions (0.0125 -0.2 g/mL) for various commercially available contact lenses.

The results show that the loaded amount of vitamin E increases as the concentration of vitamin E in the loading solution increases for all lens types. The amount of vitamin E loaded into the lens is expected to increase with the concentration of vitamin E in the loading solution until the lens reaches its maximum capacity. This maximum capacity varies depending on the type of lens. In addition, senofilcon A (silicone hydrogel) and etafilcon A (conventional hydrogel) have the highest and the lowest amounts of vitamin E loaded, respectively. Figure 3.1 also shows that the amount of vitamin E loaded in the hydrogel lens is extremely low due to its hydrophilic properties. For example, only

2.0±0.1 mg of vitamin E is loaded into etafilcon A with a 0.2 g/mL vitamin E loading solution, whereas 24.1±0.3 mg of vitamin E is loaded into senofilcon A when exposed to the same vitamin E loading solution.

### 3.4.2. Ciprofloxacin Loading into Contact Lenses

The amounts of ciprofloxacin loaded into each contact lens material in different concentrations of vitamin E are shown in Figures 3.2A and 3.2B.

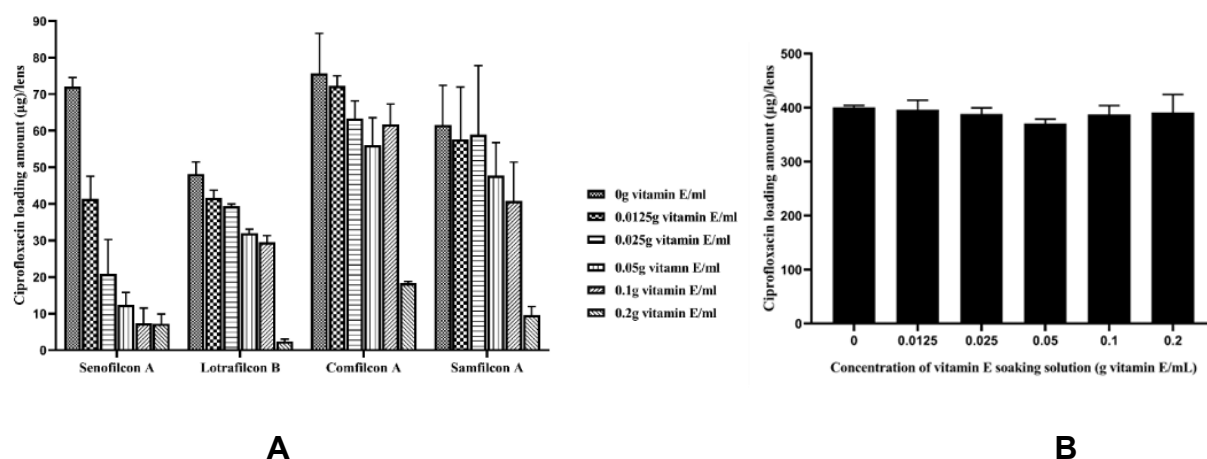


**Figure 3.2.** Ciprofloxacin loading in various types of **(A)** Silicone hydrogel contact lenses and **(B)** Conventional hydrogel contact lenses for 24 hours in different concentrations of vitamin E (0 - 0.2 g/mL)

The amounts of ciprofloxacin loaded into the lens are inversely related to the concentrations of vitamin E loading solutions in silicone hydrogels (Figure 3.2A). Among the silicone hydrogel materials, lenses without vitamin E have the highest loaded amount of ciprofloxacin compared to all the other conditions ( $P < 0.05$ ). Furthermore, as the concentration of vitamin E in the loading solution increases, the amount of ciprofloxacin loaded in the silicone hydrogel lens decreases. In contrast (Figure 3.2B), the loaded

amount of ciprofloxacin was not significantly altered by the incorporation of vitamin E for etafilcon A ( $P > 0.05$ ). In addition, Figure 3.2A shows that comfilcon A has the highest capacity for ciprofloxacin binding, at all vitamin E concentrations, compared with all other silicone hydrogel lenses ( $P < 0.05$ ).

Table 3.2 shows that the highest loaded amount of ciprofloxacin is achieved in the hydrogel lens material at all vitamin E concentrations, in comparison to the silicone hydrogel lenses ( $P < 0.05$ ). Moreover, there is an inverse relationship between the amount of vitamin E loaded versus the amount of ciprofloxacin loaded in silicone hydrogels but not in conventional hydrogels.

**Table 3.2.** Ciprofloxacin (Cipro) loaded amount ( $\mu\text{g}/\text{lens}$ ) and vitamin E (Vit E) loaded amount ( $\text{mg}/\text{lens}$ ) for each contact lens soaked in various concentrations of vitamin E for 24 hours. (Bold numbers: highest amount loaded for each lens type).

| Vit E loading solution (g/mL) | Etafilcon A                   |                                     | Comfilcon A                    |                                     | Samfilcon A                    |                                     | Senofilcon A                   |                                     | Lotrafilcon B                  |                                     |
|-------------------------------|-------------------------------|-------------------------------------|--------------------------------|-------------------------------------|--------------------------------|-------------------------------------|--------------------------------|-------------------------------------|--------------------------------|-------------------------------------|
|                               | Vit E (mg/lens)               | Cipro ( $\mu\text{g}/\text{lens}$ ) | Vit E (mg/lens)                | Cipro ( $\mu\text{g}/\text{lens}$ ) | Vit E (mg/lens)                | Cipro ( $\mu\text{g}/\text{lens}$ ) | Vit E (mg/lens)                | Cipro ( $\mu\text{g}/\text{lens}$ ) | Vit E (mg/lens)                | Cipro ( $\mu\text{g}/\text{lens}$ ) |
| 0                             | 0                             | <b>400.1<math>\pm</math>4.0</b>     | 0                              | <b>75.7<math>\pm</math>11.0</b>     | 0                              | <b>61.6<math>\pm</math>10.9</b>     | 0                              | <b>72.1<math>\pm</math>2.5</b>      | 0                              | <b>48.2<math>\pm</math>3.3</b>      |
| 0.0125                        | 0.4 $\pm$ 0.1                 | 396.0 $\pm$ 18.0                    | 0.8 $\pm$ 0.1                  | 72.3 $\pm$ 2.7                      | 0.5 $\pm$ 0.1                  | 57.6 $\pm$ 14.4                     | 4.2 $\pm$ 0.1                  | 41.4 $\pm$ 6.2                      | 1.3 $\pm$ 0.3                  | 41.7 $\pm$ 2.1                      |
| 0.025                         | 0.9 $\pm$ 0.1                 | 388.1 $\pm$ 11.5                    | 1.1 $\pm$ 0.1                  | 63.4 $\pm$ 4.8                      | 0.9 $\pm$ 0.1                  | 58.9 $\pm$ 18.9                     | 5.2 $\pm$ 0.1                  | 20.9 $\pm$ 9.5                      | 2.2 $\pm$ 0.2                  | 39.4 $\pm$ 0.6                      |
| 0.05                          | 1.3 $\pm$ 0.2                 | 370.4 $\pm$ 8.2                     | 2.5 $\pm$ 0.3                  | 56.1 $\pm$ 7.5                      | 2.9 $\pm$ 0.1                  | 47.7 $\pm$ 9.0                      | 8.0 $\pm$ 0.2                  | 12.4 $\pm$ 3.4                      | 3.1 $\pm$ 0.4                  | 32.0 $\pm$ 1.1                      |
| 0.1                           | 1.6 $\pm$ 0.1                 | 387.3 $\pm$ 16.6                    | 6.3 $\pm$ 0.4                  | 61.8 $\pm$ 5.5                      | 6.3 $\pm$ 0.2                  | 40.8 $\pm$ 10.7                     | 13.0 $\pm$ 1                   | 7.3 $\pm$ 4.2                       | 6.4 $\pm$ 0.2                  | 29.6 $\pm$ 1.8                      |
| 0.2                           | <b>2.0<math>\pm</math>0.1</b> | 391.0 $\pm$ 33.5                    | <b>16.1<math>\pm</math>0.7</b> | 18.3 $\pm$ 0.5                      | <b>13.6<math>\pm</math>0.4</b> | 9.6 $\pm$ 2.3                       | <b>24.1<math>\pm</math>0.3</b> | 7.31 $\pm$ 2.7                      | <b>13.7<math>\pm</math>0.5</b> | 2.4 $\pm$ 0.6                       |

### 3.4.4. Ciprofloxacin Release from Contact Lenses

The cumulative release of ciprofloxacin and vitamin E loaded amount for each contact lens at different concentrations of vitamin E is listed in Table 3.3

**Table 3.3** Ciprofloxacin (Cipro) cumulative release amount ( $\mu\text{g}/\text{lens}$ ) and vitamin E (Vit E) loaded amount ( $\text{mg}/\text{lens}$ ) for each contact lens soaked in various concentrations of vitamin E for 24 hours. (Bold numbers: highest amount released for each lens type).

| Vit E loading solution (g/mL) | Etafilcon A     |                                     | Comfilcon A     |                                     | Samfilcon A     |                                     | Senofilcon A    |                                     | Lotrafilcon B   |                                     |
|-------------------------------|-----------------|-------------------------------------|-----------------|-------------------------------------|-----------------|-------------------------------------|-----------------|-------------------------------------|-----------------|-------------------------------------|
|                               | Vit E (mg/lens) | Cipro ( $\mu\text{g}/\text{lens}$ ) | Vit E (mg/lens) | Cipro ( $\mu\text{g}/\text{lens}$ ) | Vit E (mg/lens) | Cipro ( $\mu\text{g}/\text{lens}$ ) | Vit E (mg/lens) | Cipro ( $\mu\text{g}/\text{lens}$ ) | Vit E (mg/lens) | Cipro ( $\mu\text{g}/\text{lens}$ ) |
| 0                             | 0               | <b>398.1<math>\pm</math>33.8</b>    | 0               | 63.6 $\pm$ 9.3                      | 0               | <b>64.6<math>\pm</math>7.5</b>      | 0               | <b>49.1<math>\pm</math>5.5</b>      | 0               | <b>35.6<math>\pm</math>0.4</b>      |
| 0.0125                        | 0.4 $\pm$ 0.1   | 393.3 $\pm$ 38.1                    | 0.8 $\pm$ 0.1   | <b>74.7<math>\pm</math>2.1</b>      | 0.5 $\pm$ 0.1   | 50.2 $\pm$ 6.7                      | 4.2 $\pm$ 0.1   | 38.6 $\pm$ 6.3                      | 1.3 $\pm$ 0.3   | 33.0 $\pm$ 2.1                      |
| 0.025                         | 0.9 $\pm$ 0.1   | 355.7 $\pm$ 3.3                     | 1.1 $\pm$ 0.1   | 65.1 $\pm$ 7.7                      | 0.9 $\pm$ 0.1   | 51.9 $\pm$ 3.7                      | 5.2 $\pm$ 0.1   | 19.8 $\pm$ 3.4                      | 2.2 $\pm$ 0.2   | 30.2 $\pm$ 1.0                      |
| 0.05                          | 1.3 $\pm$ 0.2   | 331.2 $\pm$ 29.6                    | 2.5 $\pm$ 0.3   | 55.8 $\pm$ 6.5                      | 2.9 $\pm$ 0.1   | 47.9 $\pm$ 5.5                      | 8.0 $\pm$ 0.2   | 7.2 $\pm$ 0.9                       | 3.1 $\pm$ 0.4   | 28.5 $\pm$ 4.5                      |
| 0.1                           | 1.6 $\pm$ 0.1   | 363.2 $\pm$ 38.4                    | 6.3 $\pm$ 0.4   | 57.5 $\pm$ 3.7                      | 6.3 $\pm$ 0.2   | 38.2 $\pm$ 8.6                      | 13.0 $\pm$ 1    | 3.4 $\pm$ 2.9                       | 6.4 $\pm$ 0.2   | 23.2 $\pm$ 3.5                      |
| 0.2                           | 2.0 $\pm$ 0.1   | 357.4 $\pm$ 19.9                    | 16.1 $\pm$ 0.7  | 14.8 $\pm$ 1.5                      | 13.6 $\pm$ 0.4  | 5.5 $\pm$ 1.6                       | 24.1 $\pm$ 0.3  | 2.4 $\pm$ 1.1                       | 13.7 $\pm$ 0.5  | 3.7 $\pm$ 0.6                       |

The results in Table 3.3 suggest that ciprofloxacin exhibits its highest total release in control lenses (without any vitamin E) across various types of silicone hydrogel lenses, with the exception of comfilcon A. The results show that as the loading concentration of vitamin E increases, the total release amount significantly decreases in all silicone hydrogel materials. For example, senofilcon A with 0 and 0.2 g/mL vitamin E concentrations released 49.1 $\pm$ 5.5 and 2.4 $\pm$ 1.1  $\mu\text{g}$ , respectively. However, the total

amount of ciprofloxacin released did not significantly change with the incorporation of vitamin E for the hydrogel contact lens material, as shown in Figures 3.3 A-E.

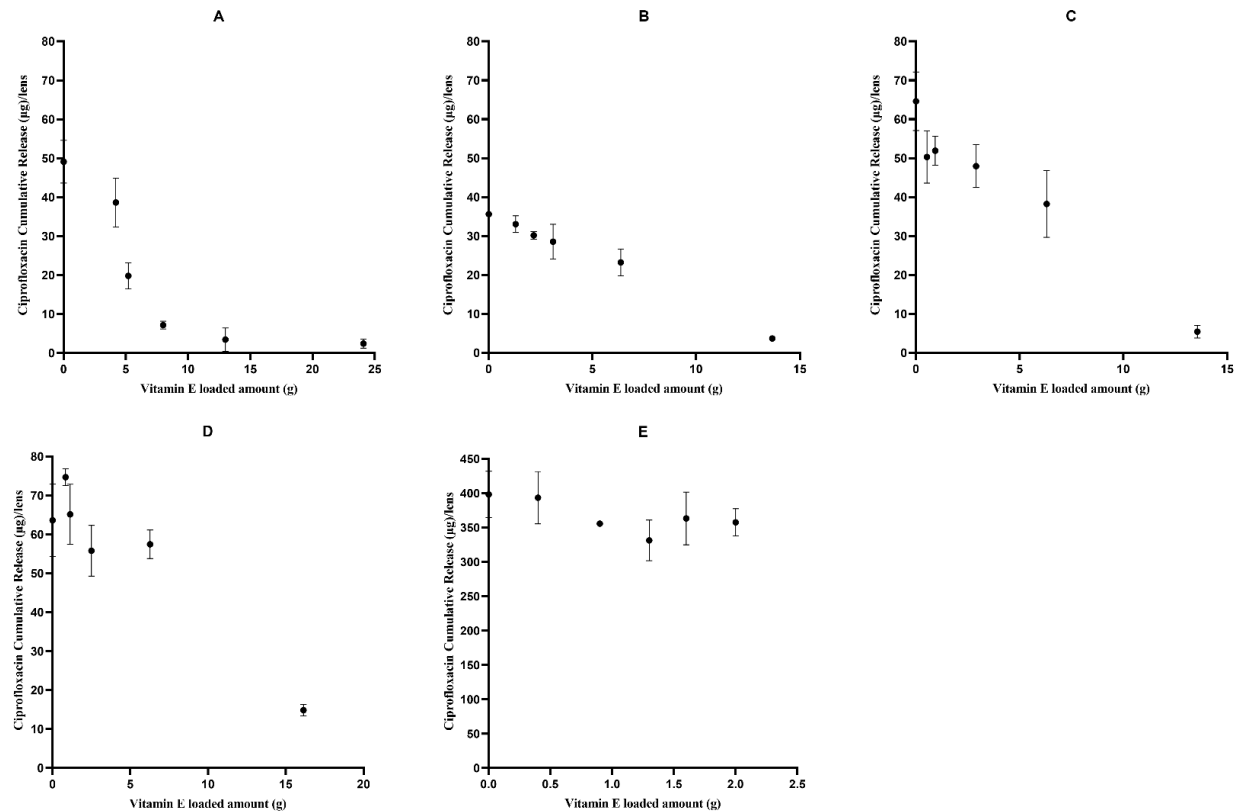


**Figure 3.3.** Ciprofloxacin cumulative release ( $\mu\text{g}$ ) versus vitamin E loaded amount (mg) for **A)** senofilcon A, **B)** lotrafilcon B, **C)** samfilcon A, **D)** comfilcon A, **E)** etafilcon. Note the difference in vertical scale for the hydrogel versus the silicone hydrogel lens materials.

In addition, the highest total release was observed for etafilcon A, a conventional hydrogel, across all concentrations of vitamin E. For silicone hydrogel materials, lenses with higher water contents (comfilcon A and samfilcon A) exhibited higher ciprofloxacin release, whereas those with lower water contents (senofilcon A and lotrafilcon B) exhibited a lower amount of ciprofloxacin release ( $P < 0.05$ ).

Figure 3.3 A-E indicates that lenses without vitamin E exhibit a burst release of ciprofloxacin, but can be tuned to release at a slower rate with the optimal amount of vitamin E loaded. As the loaded amount of vitamin E increases, the ciprofloxacin burst release amount decreases for silicone hydrogel lenses. In contrast, this burst release did not significantly change for etafilcon A.

Figure 3.4 A-E shows the percentage release over time for each contact lens.

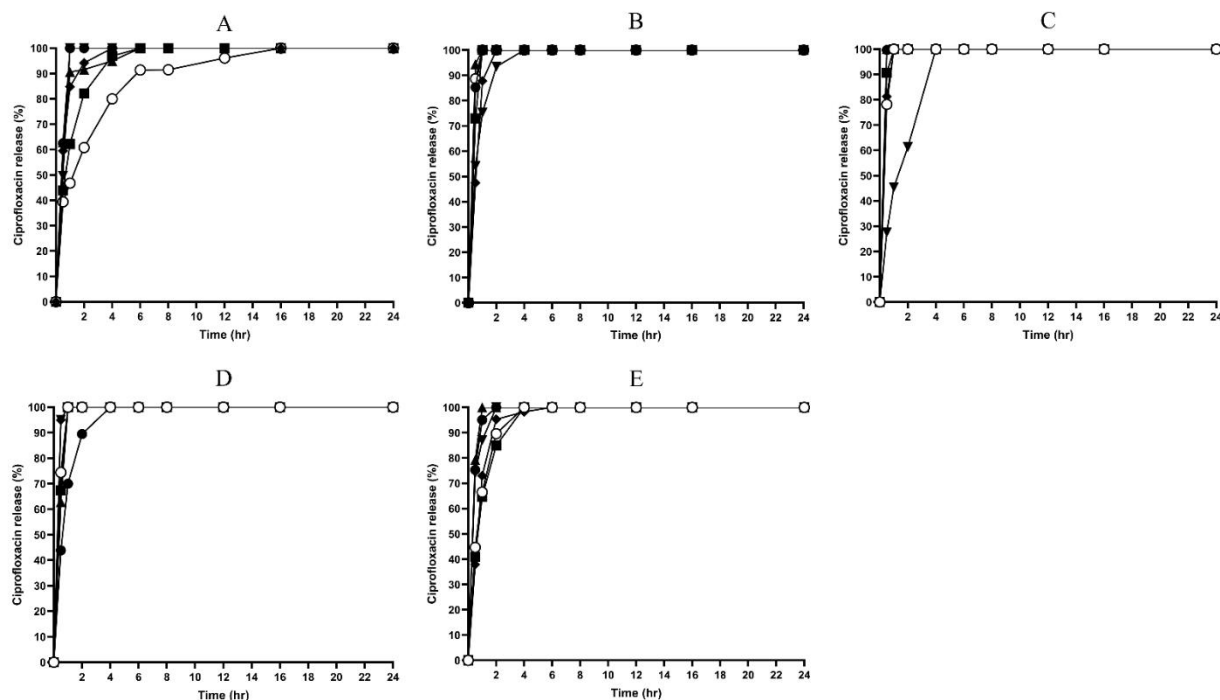


**Figure 3.4.** Percentage release of ciprofloxacin over 24 hours for **A)** senofilcon A, **B)** lotrafilcon B, **C)** samfilcon A, **D)** comfilcon A, **E)** etafilcon A. ▲ (0 g/mL), ■ (0.0125 g/mL), ○ (0.025 g/mL), ◆ (0.05 g/mL), ▼ (0.1 g/mL), ● (0.2 g/mL).

The results obtained in Figure 3.4 show that ciprofloxacin release durations from the silicone hydrogel materials are significantly extended with the incorporation of vitamin E. For example, for an untreated senofilcon A lens (Figure 3.4A), 90% of the released amount is achieved in 1 hour, while it takes approximately 3 and 6 hours for senofilcon

A with 0.0125 and 0.025 g/mL vitamin E concentrations to release the same percentage, respectively.

Among all materials, senofilcon A with 0.025 g/mL vitamin E concentration exhibited the longest release duration of about 16 hours (Figure 3.4A), which is an 8-fold release time in comparison with the control lens. Further, lotrafilcon B and samfilcon A with 0.1, and comfilcon A with 0.2 g/mL vitamin E concentrations show approximately a 4 to 8-fold release time compared to their control lenses, corresponding to a release time of 4 hours. In comparison, the release duration of the hydrogel lens (Figure 3.4E), loaded with various vitamin E concentrations, did not significantly change ( $P > 0.05$ ).

Senofilcon A with 0.025, etafilcon A with 0.05, lotrafilcon B with 0.1, samfilcon A with 0.1, and comfilcon A with 0.2 g/mL vitamin E concentrations have the most sustained release profile for the various combinations. Of these options, senofilcon A with 0.025 g/mL vitamin E loaded had the longest sustained release among all the various options studied.

### **3.5. Discussion**

The results obtained show that four commercially available silicone hydrogel lenses (senofilcon A, lotrafilcon B, comfilcon A, and samfilcon A) and a conventional hydrogel lens (etafilcon A) released ciprofloxacin within the first 2 hours, consistent with observations from prior studies.<sup>62, 96, 142</sup> This rapid release of ciprofloxacin is expected due to the molecular diffusion resulting from the concentration difference between the drug-loaded contact lens and the release solution.<sup>106</sup>

In this study, various concentrations of vitamin E were loaded into silicone and conventional hydrogel commercial contact lenses. Figure 3.1 shows that for both silicone and conventional hydrogels, the amount of vitamin E loaded into the lens increases proportionally with the concentration of vitamin E loading solution. These results align with the outcomes reported in previous studies.<sup>91, 151, 171</sup> Interestingly, the amount of vitamin E loaded in the hydrogel lens material was extremely low compared to those loaded into silicone hydrogel lenses.

Figure 3.2A shows that vitamin E incorporation into silicone hydrogel lenses significantly decreased the uptake of ciprofloxacin ( $P < 0.05$ ). In contrast, the loading amount of ciprofloxacin in the conventional hydrogel (Figure 3.2B), does not significantly change with the incorporation of vitamin E ( $P > 0.05$ ). Thus, vitamin E does not have the same effect in the hydrophilic conventional hydrogel lenses as it does in the relatively hydrophobic silicone hydrogel lenses, likely due to the absence of siloxane components in the conventional lens material. The hydrophobic vitamin E molecule has a higher affinity for the silicone hydrogel material and increases the hydrophobic fraction in the silicone hydrogel lenses compared to conventional hydrogel lenses.<sup>107</sup>

The data obtained in this study show that the total release amount of ciprofloxacin decreases as the loaded amount decreases among the various materials (Tables 3.2 & 3.3). Therefore, the total release amount is correlated to the originally loaded amount.<sup>62,</sup>  
<sup>96</sup> This total release could be modified by simply changing the original loading amount by altering the loading duration and concentration. Hence, conventional and silicone hydrogel lenses could be considered reservoirs that can regulate the release amounts of ciprofloxacin by manipulating the amounts contained within them. In addition, the

hydrogel lens material took up and released more drug than the silicone hydrogel materials for all conditions ( $P < 0.05$ ).

For lenses that do not contain vitamin E, the release of the drug is as expected, a one-step burst release within the first 2 hours. However, ciprofloxacin is released in two steps by incorporating adequate amounts of vitamin E into these lens materials. These results align with previous studies examining drug release from a contact lens.<sup>96, 177</sup> The burst-release step resulted from the dissolution of ciprofloxacin molecules loosely bound to the lens's surface, while the sustained-release step was attributed to the diffusion of ciprofloxacin molecules tightly bound to the vitamin E into the release media.<sup>96</sup>

The results from this current study indicate that the release duration of ciprofloxacin from contact lenses differs among the lens categories. Ciprofloxacin is a hydrophobic drug that exhibits poor diffusion from the siloxane phase to the hydrophilic matrices of the silicone hydrogel lenses, resulting in a longer release duration as opposed to the hydrogel lens material, which comprises only relatively hydrophilic portions. Additionally, in silicone hydrogel lenses, ciprofloxacin's burst release decreases and release duration is increased by vitamin E incorporation. The results obtained suggest that vitamin E may form blockages in channels within a silicone hydrogel lens material, thereby forcing a longer path for drugs to diffuse into and out of the lens material. For each lens type, there was an optimal amount of vitamin E loading that extended the release duration of the drug from 1 hour (without vitamin E) to as long as 16 hours. Senofilcon A with 0.025 g/mL vitamin E concentration exhibited the longest sustained release for all lens types, achieving 16 hours of release. Vitamin E acts as a diffusion barrier in silicone hydrogel lenses, forcing the drug molecule to take a long

tortuous path to diffuse within the lens matrix to the release medium.<sup>91</sup> Furthermore, the high viscosity of vitamin E reduces the diffusivity of the relatively hydrophobic ciprofloxacin molecule, which segregates and diffuses through this hydrophobic vitamin E diffusion barrier.<sup>94</sup>

This study shows a significant correlation between vitamin E loading and ciprofloxacin uptake and release from silicone hydrogel lenses. While it was proposed in previous research that loading vitamin E would slow down drug release by the segregation and diffusion of the hydrophobic drug through the diffusion barrier vitamin E,<sup>94</sup> this current experiment suggests a different concept. It is clear that this correlation is true up to a certain point; however, exceeding this threshold leads to unpredictable outcomes where too much vitamin E loading decreases the total amount of ciprofloxacin loaded and alters the kinetics of ciprofloxacin release. In contrast, little vitamin E loading would not affect the loading and release of ciprofloxacin. Hence, there is an optimal point for each lens type, where an adequate amount of vitamin E incorporation would subsequently result in the loading of an appropriate amount of ciprofloxacin, with an extended release profile.

The results of the ciprofloxacin loading in this study suggest that the hydrophobic molecule vitamin E relatively blocks the uptake of ciprofloxacin by depositing on the hydrophobic sites of silicone hydrogel materials, where the hydrophobic ciprofloxacin typically binds. Additionally, vitamin E reduces the internal pore sizes of the silicone hydrogel lens by aggregating in the hydrophilic channels, thereby obstructing the uptake of ciprofloxacin, as its transport primarily takes place via these channels.<sup>91</sup>

The results of the release experiment in this study suggest that the loading of vitamin E in the silicone hydrogel lens materials results in its deposition and blockage of the preformed hydrophilic channel, thereby forcing ciprofloxacin to navigate an alternative longer path for release (Figure 3.5). In contrast, this mechanism is not exhibited in the hydrogel lens material, which does not form these paths due to the lack of any siloxane portions. Hence, vitamin E does not form any barriers in the conventional hydrogel material studied, resulting in no significant change in the release of ciprofloxacin, compared to the control lenses ( $P > 0.05$ ). This is aligned with previous studies conducted to evaluate various drug releases using hydrogel lens material.<sup>154, 173</sup>

The findings of this study provide a deeper understanding of the manner in which vitamin E loading into commercial contact lens materials impacts the release of topical drugs from conventional and silicone hydrogel lenses.

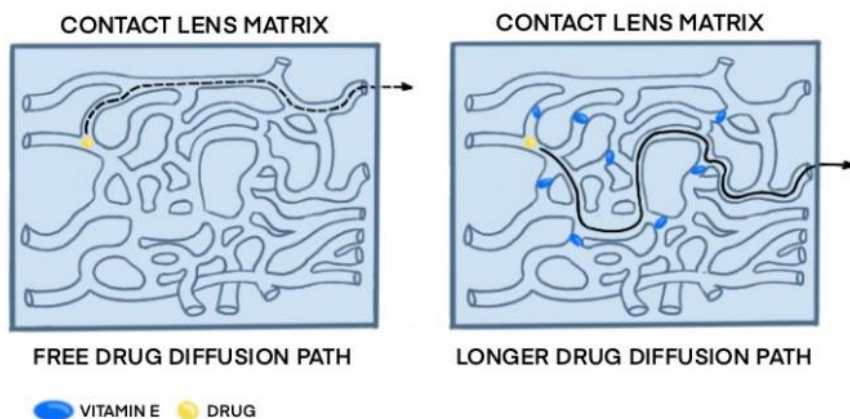


**Figure 3.5.** Schematic of a non-loaded and vitamin E-loaded silicone hydrogel lens matrix showing drug release kinetics.

### 3.6. Conclusion

This *in vitro* study suggests that silicone hydrogel lenses loaded with vitamin E could be an effective device for extended delivery of ciprofloxacin, but *in vivo* studies should be considered in future studies. The technique of *in situ* creation of diffusion barriers in contact lenses that are used in this study, to extend the release of molecules, might be useful in other platforms such as retinal implants, transdermal patches, punctal plugs, and wound healing patches.

## 4 Long-Term Evaluation of Vitamin E Uptake and Release on Senofilcon A.

### 4.1. Introduction

This Chapter is a follow-up to the previous chapter (3).

To evaluate the significant difference in the vitamin E barrier effect for various lens types, the best release profile for each lens and vitamin E combination over 24 hours were plotted in Figure 4.1.

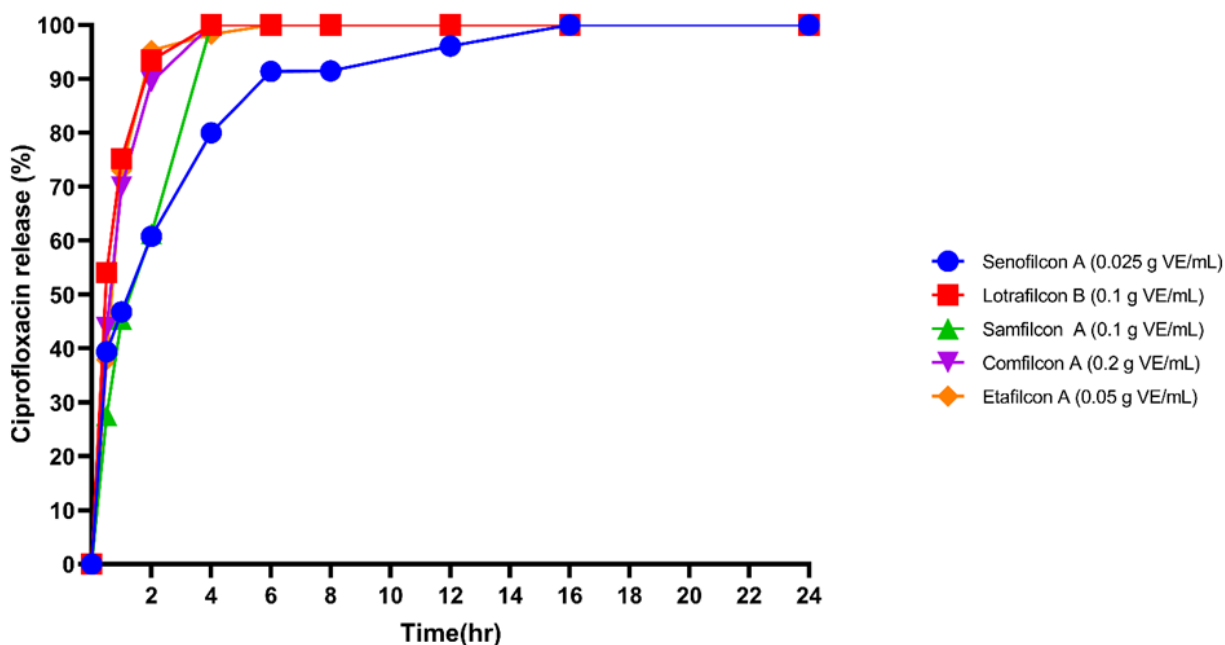


**Figure 4.1.** Percentage release of ciprofloxacin over 24 hours for the best-sustained release of various lens types.

Among the best-sustained release profiles of all conventional and silicone hydrogel contact lenses, senofilcon A exhibits the longest release duration of 16 hours. There is an optimal amount of vitamin E that is loaded for each lens to produce the best-sustained

release profile. This Figure also shows that each lens type has a different release duration than others, even though this represents its best-sustained release. These findings suggest that vitamin E acts differently, even within a silicone hydrogel category. Hence, the loaded amount of vitamin E significantly differs for different lens types to achieve their best-sustained release.

Senofilcon A was used in this chapter's experiments since it had the best-sustained release compared to all other lenses evaluated in the previous experiment, as shown in Figure 4.1.

#### **4.2. Aim**

This experiment aimed to evaluate the effect of ciprofloxacin loading duration on the loading and releasing profiles of senofilcon A.

#### **4.3. Hypothesis**

This experiment hypothesizes that increasing the ciprofloxacin loading duration to 7 days would increase the uptake amount which will lead to an increase in the release amount, and subsequently, the release duration (> 16 hours) for senofilcon A lenses loaded with a high amount of VE (0.2 g/mL).

#### **4.4. Materials and Methods**

The materials and methods used for this Chapter's experiments are the same as those employed in experiments in Chapter 3 (section 3.3). The difference is that only one

type of commercial contact lens (senofilcon A) was evaluated after being soaked in ciprofloxacin solutions for 24 hours and 7 days. In addition, selecting a 7-day loading period would be sufficient to demonstrate varying effects and is more feasible for the commercial market.

## 4.5. Results and Discussions

### 4.5.1 Ciprofloxacin Loading into Senofilcon A Contact Lenses

The amount of ciprofloxacin loaded into each senofilcon A contact lens for 24 hours and 7 days in different concentrations of vitamin E is shown in Figure 4.2.

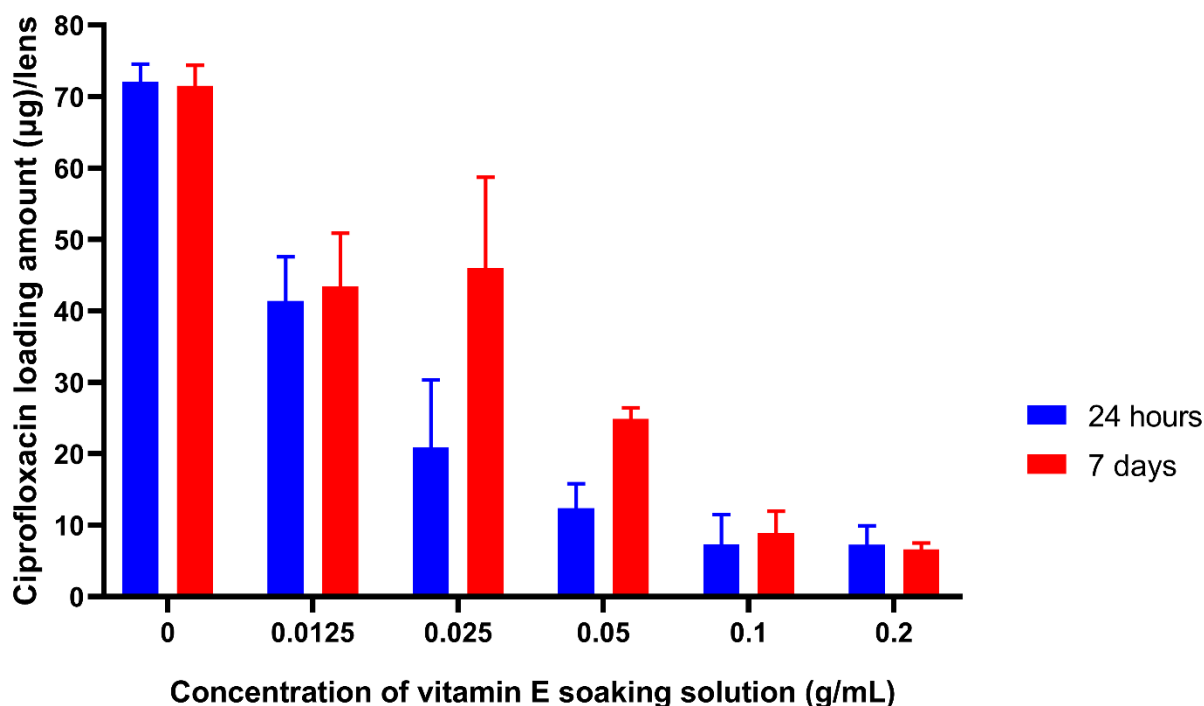


**Figure 4.2.** Ciprofloxacin loading in senofilcon A contact lenses for 24 hours and 7 days in different concentrations of vitamin E solution.

As shown in Figure 4.2, lenses with 0.025 g/mL and 0.05 g/mL vitamin E concentrations have a significant increase in the loaded amount of ciprofloxacin when soaked for 7 days versus 24 hours. Thus, the 24-hour loading duration is not enough for ciprofloxacin to be maximally loaded into these lenses, likely due to the effective diffusion barrier of vitamin E at these specific concentrations. On the other hand, this diffusion barrier of vitamin E is not as effective in the 0.0125 g/mL concentration, resulting in maximum ciprofloxacin loading within 24 hours.

Similarly, contact lenses with 0.1 g/mL and 0.2 g/mL vitamin E concentrations reach their total loaded amount of ciprofloxacin within 24 hours and this is not changed by increasing the loading duration to 7 days. The extremely high amount of vitamin E loadings in contact lenses with 0.1 g/mL and 0.2 g/mL concentrations result in almost a total blockage of the contact lens channels. Specifically, the blockage of almost all the hydrophilic channels results in the loading of only a meager amount of ciprofloxacin in the few remaining unblocked ones within 24 hours.

Hence, ciprofloxacin takes up to 24 hours to reach its maximum loading into contact lenses with 0.0125 g/mL, 0.1 g/mL, and 0.2 g/mL vitamin E concentrations, while this takes up to 7 days in contact lenses with 0.025 g/mL and 0.05 g/mL vitamin E concentrations.

#### **4.5.2. Ciprofloxacin Release from Senofilcon A Contact Lenses**

Ciprofloxacin release profiles for non-loaded and vitamin E-loaded senofilcon A contact lenses for different concentrations of vitamin E are shown in Figures 4.3A and

4.3B. The contact lenses in Figures 4.3A and 4.3B are soaked in ciprofloxacin solution for 24 hours and 7 days, respectively.

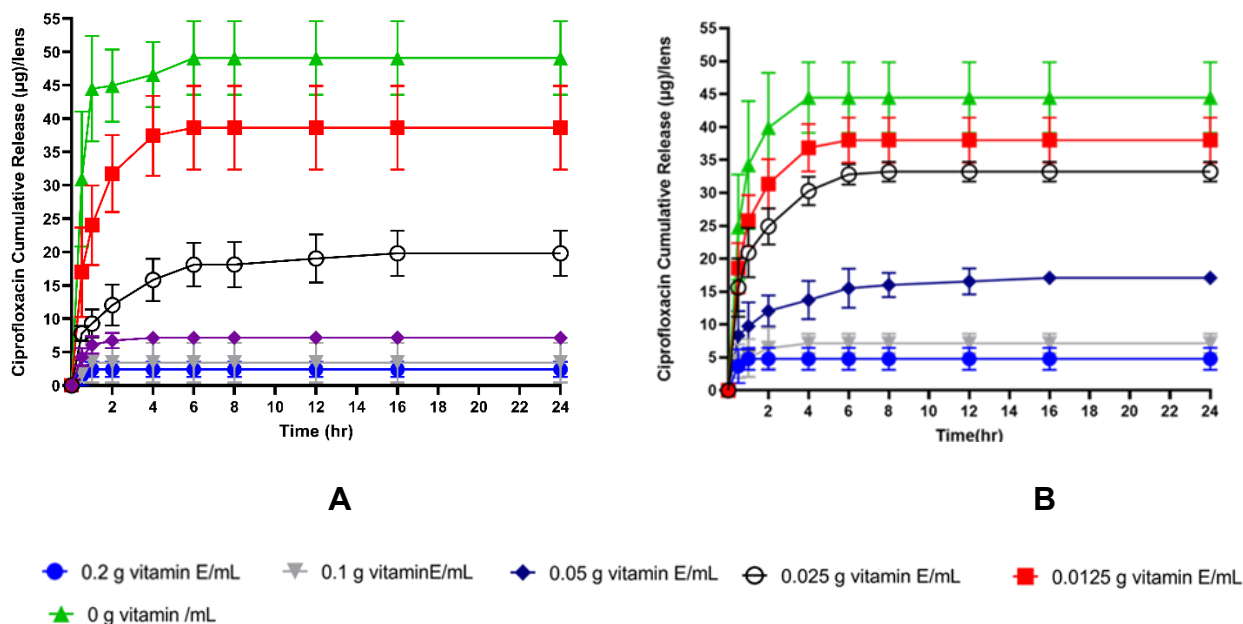


**Figure 4.3.** Ciprofloxacin cumulative release ( $\mu\text{g}$ ) as a function of time. Ciprofloxacin loading durations: **(A)** 24 hours and **(B)** 7 days.

As can be seen in Figures 4.3A and 4.3B, non-loaded and vitamin E-loaded contact lenses exhibit a burst release of ciprofloxacin. In addition, ciprofloxacin release duration increases significantly for contact lenses with 0.025 g/mL and 0.05 g/mL vitamin E concentrations for lenses with 24-hour and 7-day loading durations, respectively. These lenses show approximately an 8-fold release time compared to the control lenses (without vitamin E), corresponding to a release time of 16 hours.

The effect of vitamin E on drug release duration cannot be evaluated in contact lenses with 0.2 g/mL vitamin E concentrations due to the meager amount of ciprofloxacin originally loaded for the 24-hour and 7-day loading durations. Therefore, the diffusion barrier effect of vitamin E is not exhibited in these lenses due to the low amount of ciprofloxacin loaded.

Figure 4.3A shows that lenses with 0.025 g/mL and 0.05 mg/mL vitamin E concentrations released  $19.8 \pm 3.4 \mu\text{g}$  for 16 hours and  $8.0 \pm 2.3 \mu\text{g}$  for 6 hours respectively. On the other hand, Figure 4.3B shows that lenses with 0.025 g/mL and 0.05g/mL vitamin E concentration released  $33.2 \pm 1.51 \mu\text{g}$  for 8 hours and  $17.1 \pm 1.1 \mu\text{g}$  for 16 hours respectively. Therefore, ciprofloxacin cumulative release significantly increased for the 0.025 and 0.05 g/mL lenses that were soaked for a 7-day loading duration.

To observe the effect of different vitamin E concentrations on the release dynamics, the amount of the drug released divided by the total drug released (% released) is plotted as a function of time for each concentration in Figures 4.4A and 4.4B.

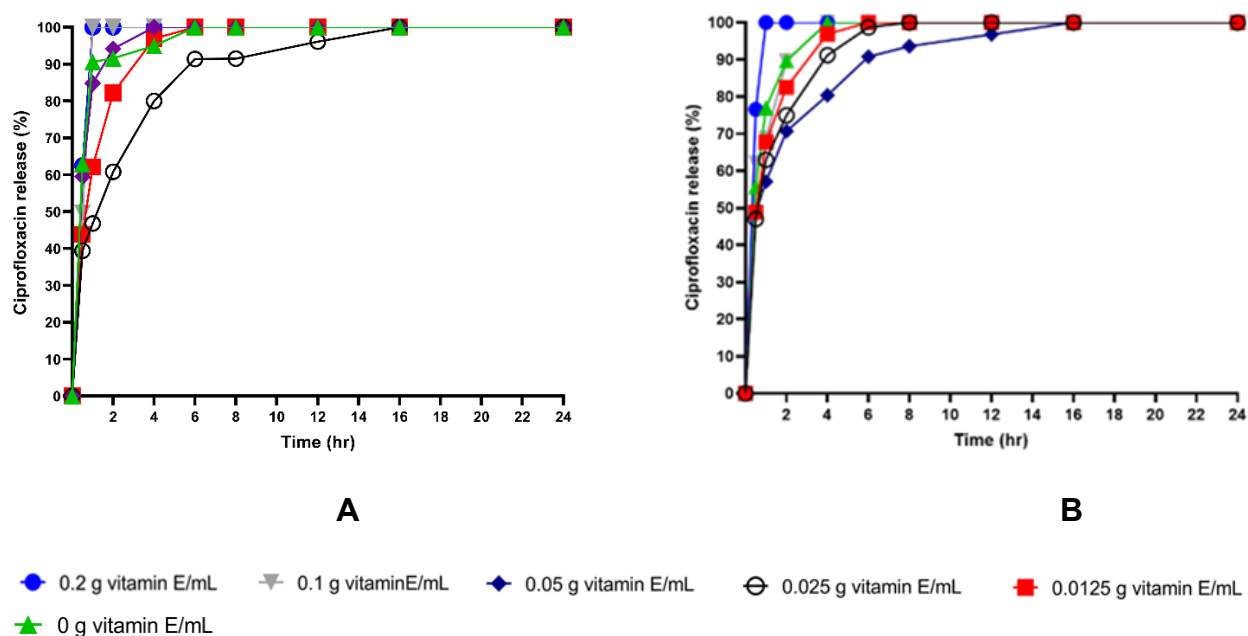


**Figure 4.4.** Senofilcon A ciprofloxacin released (%) as a function of time. Ciprofloxacin loading durations: **(A)** 24 hours and **(B)** 7 days.

As shown in Figure 4.4A, it takes 1 hour for the control lens (without vitamin E) to release 90% of its loaded drug while it takes approximately 1.5 hours, 3 hours, and 6

hours for the contact lenses with 0.05 mg/mL, 0.0125 mg/mL, and 0.025 mg/mL vitamin E concentrations, respectively. Figure 4.3B shows that it takes 2 hours for the control lens (without vitamin E) to release 90% of its loaded drug while it takes approximately 3 hours, 4 hours, and 6 hours for the contact lenses with 0.0125 mg/mL, 0.025 mg/mL, and 0.05 mg/mL vitamin E concentrations, respectively. The effect of vitamin E is not fully exhibited in lenses with 0.2 mg/mL vitamin E concentrations which do not have enough ciprofloxacin loaded initially.

Figure 4.4 shows that the best-sustained releases are attained in contact lenses with 0.025 g/mL and 0.05 g/mL when soaked in ciprofloxacin solution for 24 hours and 7 days, respectively.

The increased cumulative release observed in the 0.025 mg/mL lens after a 7-day loading duration could be advantageous, potentially inhibiting a broader range of common bacterial isolates. However, this benefit comes with a shorter release duration of 8 hours, which may not provide sufficient patient compliance. Despite the extended loading period, none of the lenses soaked in ciprofloxacin for 7 days achieved a release duration exceeding the 16 hours reached in the 24-hour loading experiment.

#### **4.6. Conclusion**

The results reported in this study show that vitamin E loading in senofilcon A (silicone hydrogel contact lens) could significantly increase the release duration of ciprofloxacin (relatively hydrophobic drug). The diffusion barrier effect of vitamin E likely causes the extended release of ciprofloxacin which is exhibited by the macroscopic aggregates of vitamin E particles<sup>91</sup> and by the adsorption of vitamin E on the polymer gel

that could hinder surface diffusion of the drug along the polymer resulting in a reduction in effective diffusion rates.<sup>94</sup> The data obtained in this in vitro study strongly suggest that silicone hydrogel contact lenses loaded with vitamin E could be an effective device for extended delivery of ciprofloxacin into a simple vial, but future in vivo studies must be considered. The technique of in situ creation of diffusion barriers in contact lenses that are used in this study to extend the release of molecules might be useful in other platforms such as retinal implants, transdermal patches, punctal plugs, and wound healing patches.

## **5. General Discussion and Conclusions**

The eye is one of the most vital human body parts, providing essential details about our environment. Corneal diseases such as bacterial keratitis can lead to vision impairment, significantly impacting human lives worldwide. Delivering ocular drugs to the eye has long been a critical challenge in medical science. Conventional techniques for drug delivery using drops are poorly effective at delivering ophthalmic drugs to the eye.<sup>178</sup> As a result, soft contact lenses have acquired increasing interest in ophthalmic drug delivery because of their capacity to improve drug bioavailability in ophthalmic tissues. In addition, vitamin E incorporation into these lenses for extended drug release represents a remarkable advancement in ophthalmic drug delivery systems. This research has shown that incorporating an adequate amount of vitamin E can effectively alter the drug release profile of a silicone hydrogel contact lens to deliver a sustained therapeutic drug dose, which would result in enhanced patient compliance and increased treatment efficacy. These findings suggest that the sustainable delivery of ciprofloxacin from vitamin E-loaded silicone hydrogel contact lenses could be promising for treating ophthalmic infections.

### **5.1. Experimental Summary and Discussion**

#### **5.1.1. Chapter 3**

Chapter 3 of this thesis evaluated the effect of vitamin E as a diffusion barrier to slow the delivery of a topical drug from conventional and silicone hydrogel contact lenses.

The in vitro release experiments showed that vitamin E-loaded silicone hydrogel contact lenses exhibited a significantly prolonged release period compared to the control lenses (without vitamin E). In contrast, this effect was not demonstrated with conventional hydrogel contact lenses (etafilcon A). Furthermore, these contact lenses exhibited a significant difference in the uptake and release amounts of ciprofloxacin. As shown in Tables 3.2 & 3.3, the non-loaded and vitamin E-loaded etafilcon A lenses exhibit the highest uptake and release amounts of ciprofloxacin among all types of contact lenses. Although the lower amount of ciprofloxacin released from silicone hydrogels compared to conventional hydrogels can be considered a drawback, this lower release could be advantageous if sustained at a therapeutic level over an extended period.

The conventional hydrogel (relatively hydrophilic material) absorbed and released more drugs than the silicone hydrogels (relatively hydrophobic material) because the drug can be dissolved more efficiently in the more aqueous component of the conventional hydrogel contact lenses. The significant loading of vitamin E in silicone hydrogels compared to conventional hydrogels, could also contribute to the reduction in the amount of drug uptake and release due to the hydrophobic properties of vitamin E, which increases the hydrophobic portion of silicone hydrogel contact lenses. Moreover, the charge on the surface of the lenses also played an important role in the uptake and release profiles of ciprofloxacin. The negatively charged etafilcon A took up the highest amount of ciprofloxacin due to its positive charge condition in the loading solution (pH = 4.8), and it released the highest amount of ciprofloxacin due to its existence as a neutral molecule in the release solution (pH = 7.4).<sup>142</sup>

The primary drawback of commercially available contact lenses was their rapid release of ciprofloxacin. For treating corneal infections, a drug delivery system should release therapeutically adequate amounts (achieve bacterial MIC90 concentration) of ciprofloxacin in a controlled manner over an extended duration. Ideally, a sustained release of 16 hours (covering a typical working day) would coincide with typical lens wear, and therefore, would be convenient. The release experiment for this study was evaluated in a 3 mL release solution. Hence, the minimum ciprofloxacin release from a lens should be 0.75 µg and 96 µg to achieve the MIC90 concentration for the susceptible and resistant isolates respectively. Therefore, an optimal lens should ideally release an amount of ciprofloxacin within the range of 0.75 µg to 96 µg over a duration of 16 hours. As shown in Table 3.2, all the best-sustained release-conventional and -silicone hydrogel contact lenses (etafilcon A with 0.05 g/mL, senofilcon A with 0.025 g/mL, lotrafilcon B with 0.1 g/mL, comfilcon A with 0.2 g/mL, and samfilcon A with 0.1 g/mL vitamin E concentrations) released adequate amounts of ciprofloxacin that met the MIC90 concentration for the susceptible isolates and only etafilcon A met the MIC90 concentration for the resistant isolates. However, senofilcon A lens with 0.025 g/mL vitamin E concentration had the longest release duration (16 hours) among these lenses. Thus, the 0.025 g/mL senofilcon A lens was the only one that met the MIC90 concentration with an adequate extended-release duration (16 hours), but only for susceptible and common bacterial isolates, not for resistant isolates.

In this in vitro study, vitamin E-loaded senofilcon A was the best possible lens proving that the combination of silicone hydrogel/vitamin E could be a good candidate to be evaluated in future in vivo studies. The best-sustained release of senofilcon A (0.025

g/mL) was achieved by releasing  $19.8 \pm 3.4$   $\mu\text{g}/\text{lens}$  for 16 hours, while the best-sustained release of etafilcon A 0.05 g/mL, lotrafilcon B (0.1 g/mL), comfilcon A (0.2 mg/mL), and samfilcon A (0.1 g/mL) released  $331.2 \pm 29.6$   $\mu\text{g}/\text{lens}$ ,  $23.2 \pm 3.5$   $\mu\text{g}/\text{lens}$ ,  $14.8 \pm 1.5$   $\mu\text{g}/\text{lens}$ , and  $38.2 \pm 8.6$   $\mu\text{g}/\text{lens}$  for 4 hours, respectively.

These results indicate that the release duration of ciprofloxacin from contact lenses differs among the lens categories. Ciprofloxacin is a hydrophobic drug that exhibits poor diffusion from the siloxane phase (hydrophobic) to the hydrophilic matrices of the silicone hydrogel lenses, resulting in a longer release duration as opposed to the hydrophilic conventional hydrogel lenses. Additionally, in silicone hydrogel lenses, ciprofloxacin's burst release decreased and release duration increased by vitamin E incorporation. This suggests that vitamin E may form blockages in channels within a silicone hydrogel lens material, thereby forcing a longer path for drugs to diffuse out of the lens material.

The ciprofloxacin loading experiment in this study suggests that vitamin E (hydrophobic) partially blocks the uptake of ciprofloxacin (hydrophobic) by depositing on its typical binding site, which are the siloxane hydrophobic sites within silicone hydrogel materials (Figure 5.1). Additionally, vitamin E further obstructs the uptake of ciprofloxacin by blocking its primary diffusion path through the hydrophilic channels within the silicone hydrogel materials.<sup>91</sup>

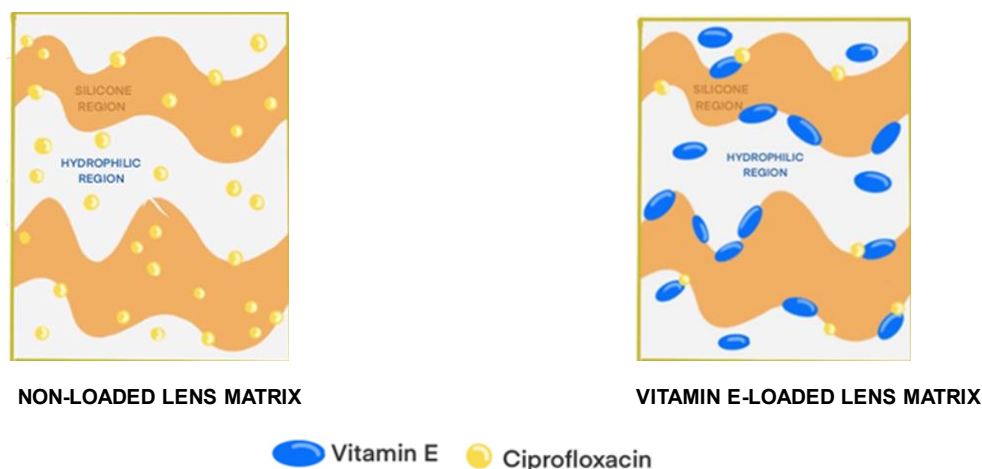


**Figure 5.1.** Schematic of a non-loaded and vitamin E-loaded silicone hydrogel lens matrix showing drug uptake concept.

Chauhan proposed that the high viscosity of vitamin E reduces the diffusivity of the relatively hydrophobic drug, which segregates and diffuses through this hydrophobic vitamin E diffusion barrier, leading to an extended-release duration.<sup>94</sup> While this proposition is true, this current study suggests a more detailed and different concept. This study proposes that the loading of vitamin E in the silicone hydrogel lens materials results in its deposition and blockage of the preformed hydrophilic channel, thereby forcing ciprofloxacin to navigate an alternative longer path for release. Additionally, there is an optimal point for each lens type, where an adequate amount of vitamin E incorporation would subsequently result in the loading of an appropriate amount of ciprofloxacin, with an extended-release profile. Exceeding this threshold leads to unpredictable outcomes where too much vitamin E loading decreases the total amount of ciprofloxacin loaded and alters the kinetics of ciprofloxacin release, whereas little vitamin E loading would not affect the loading and release of ciprofloxacin. In contrast, this is not true for conventional hydrogel lenses due to the lack of siloxane portions. This is aligned with previous studies

conducted to evaluate release of various drugs using hydrogel lens materials.<sup>154, 173</sup> Hence, etafilcon A is not an ideal drug delivery material due to its rapid release, despite absorbing and releasing the highest amount of ciprofloxacin. In addition, etafilcon A demonstrates marked opacification caused by the precipitation of ciprofloxacin at physiological pH, resulting in a significant decrease in comfort and visual properties.<sup>142</sup>

### **5.1.2. Chapter 4**

The main focus of Chapter 4 was to evaluate the effect of ciprofloxacin loading duration on the loading and releasing profiles of senofilcon A. To do this, non-loaded and vitamin E-loaded contact lenses were soaked in ciprofloxacin loading solutions for 24 hours and 7 days. This experiment showed no significant difference in the uptake and release profiles among the different loading durations (24 hours and 7 days), except in lenses with 0.025 and 0.05 g/mL vitamin E concentrations, which absorbed and released more drugs in the 7-day loading duration experiment.

Of all the lenses tested across both loading durations, those with 0.025 mg/mL and 0.05 mg/mL vitamin E concentrations demonstrated the longest release duration (16 hours). Specifically, the lens with 0.025 mg/mL concentration in the 24-hour loading duration exhibited the longest release duration with a lower total amount of ciprofloxacin released. In contrast, the lens with the same vitamin E concentration in the 7-day loading duration released a higher total amount of ciprofloxacin but over a shorter period. Thus, the 0.025 mg/mL lens is generally the most optimal choice for both loading durations.

However, selecting the appropriate loading duration should consider the specific disease being treated and the patient's compliance.

This study demonstrated that only a limited amount of molecules (vitamin E and ciprofloxacin) can be loaded into each contact lens. It was observed that as the amount of vitamin E loaded increases, the amount of ciprofloxacin that can be loaded decreases. In addition, the amount of ciprofloxacin can be increased for certain lenses by increasing the loading duration. Therefore, finding the right balance between these two loaded molecules (vitamin E and ciprofloxacin) is crucial to achieve an optimal amount of ciprofloxacin and a prolonged release duration. Ideally, it would be beneficial for a lens to release an adequate amount of ciprofloxacin for up to 16 hours. However, releasing this adequate amount over a shorter duration, such as 6 or 8 hours, may still be satisfactory depending on the bacterial isolates being treated. Understanding this concept could be valuable for future research, as it may allow for targeting other diseases that require varying amounts of drug release or different release durations. This approach could be particularly beneficial when applied on a case-by-case basis.

By increasing the ciprofloxacin loading duration to 7 days, the proposed goal of this experiment was to increase the uptake amount which will lead to an increase in the release amount, and subsequently, the release duration (> 16 hours) for the lenses loaded with a high amount of vitamin E (0.2 g/mL vitamin E concentration). The latter was not achieved, since the loaded amount of ciprofloxacin did not significantly change for the 0.2 g/mL vitamin E concentration lenses. Hence, the longest release duration (16 hours) exhibited in the 24-hour loading duration lenses did not further increase for the 7-day loading duration lenses.

In conclusion, five commercially available soft contact lenses were evaluated for their uptake and release profiles when coated with vitamin E and soaked in the ophthalmic antibiotic ciprofloxacin. All the control lenses released therapeutically relevant levels of ciprofloxacin into the release solution but did so for an inadequate short duration. However, the incorporation of vitamin E significantly extended the release duration, specifically for senofilcon A. Senofilcon A could be a promising ciprofloxacin delivery device that combines both high oxygen transmissibility and therapeutically extended release profiles. Additionally, the other three silicone hydrogel lens materials tested (comfilcon A, samfilcon A, and lotrafilcon B) had a shorter release duration than senofilcon A. Hence, the loading of vitamin E into suitable drug-delivering silicone hydrogel lenses is greatly promising for innovating ophthalmic drug delivery.

## **5.2. Future Work and Limitations**

The future of drug-delivering contact lenses appears to be promising, but several limitations have been identified in this thesis and should be addressed in future studies. The first significant limitation is that only one hydrogel material (etafilcon A) was evaluated, which is insufficient to make a broad statement about conventional hydrogel materials. The question here is, would other hydrogel materials exhibit the same behavior, or might the trend differ? For example, other conventional hydrogel lenses with lower water content than etafilcon A would absorb and release less of the drug, as the drug does not dissolve as readily in these materials. Additionally, other conventional hydrogel lenses that are charge positive or charge neutral would also absorb less of the drug, since

ciprofloxacin carries a positive charge in the loading solution (pH = 4.8).<sup>142</sup> Hence, to overcome this limitation, other types of conventional hydrogel lenses should be evaluated in future experiments.

Another significant limitation of this study is that only senofilcon A released ciprofloxacin over an extended period, but the amount released was reduced and did not meet the MIC90 concentration (32 µg/mL) for the resistant bacterial isolates. Therefore, to address this limitation, future studies should evaluate other types of silicone hydrogel lenses using microbial assays to confirm the clinical efficacy of the released amount of ciprofloxacin.

Furthermore, future research should evaluate the integration of a wider range of ocular drugs into vitamin E-loaded lenses. This should include drugs with different solubility profiles and molecular weights to understand better the delivery system's versatility and limitations. Continued development and research in this field can result in patient-friendly and highly effective treatments for various ophthalmic conditions, eventually enhancing patient ocular health and quality of life.

While the future holds promise for drug-delivering contact lenses, various challenges persist. Certain ocular conditions are more ubiquitous among elderly patients, yet they could be unsuitable candidates for drug delivery via contact lenses due to dryness and decreased tear volume, which can render soft contact lens wear uncomfortable. In addition, a considerable number of individuals still find wearing contact lenses uncomfortable, and prolonged use is linked to infection risks such as MK. In addition, hurdles including, regulatory obstacles, storage concerns, and high costs

associated with clinical trials pose essential barriers to both clinical implementation and commercialization. Overcoming all these barriers is crucial for progress. To fulfill this, it is necessary to concentrate efforts on conditions that stand to gain the most from the drug-delivery contact lens. Simply showing enhanced efficacy compared to conventional eye drops could not be adequate; enhancing patient compliance is also crucial. While extending the duration of drug release to 16 hours presents scientific interest and would ideally improve compliance, determining the adequate release duration will rely on factors including, the specific disease, regulatory considerations, and patient acceptance.

### **5.3. Conclusion**

The results of the experiments in this study are promising for the incorporation of vitamin E in silicone hydrogel contact lenses resulting in extended drug-delivery systems. Future in vitro and in vivo studies must be conducted to assess the effect of vitamin E on the optical and mechanical properties of the lenses to ensure that the customized contact lenses can be effectively applied to the patient's eye without compromising their comfort or vision.

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