EXTENDED RELEASE OF MACROMOLECULAR COMFORT AGENTS FROM SILICONE HYDROGEL CONTACT LENSES

by

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ABSTRACT

Contact lens induced dry eye (CLIDE) affects approximately 80% of contact lens wearers. Extrapolating to the world wide population of 300 million contact lens wearers, there are approximately 200 million wearers who express dissatisfaction with their current lenses. The design of contact lenses have evolved to promote high oxygen diffusion (Dk) to promote comfort and ocular health. Since the advent of silicone hydrogel lenses in the market in the later 1990's, silicone hydrogel lenses have dominated the lens market in recent years, making up 60% of all lens fittings in the United States in 2009. Several brands are approved for 30 day continuous, extended wear, making these lenses very popular with consumers. However, most lens wearers still express dissatisfaction with their lenses due to CLIDE-related symptoms. Controlled drug delivery methods applied to soft contact lenses deliver have been shown to deliver macromolecular comfort agents to the eye. Yet controlled drug delivery from silicone hydrogels has yet to be shown in silicone hydrogel contact lenses. This represents a large technology gap. To fill this unmet need, we have designed novel contact lenses (based on Lotrafilcon B silicone hydrogels), which are capable of controlled delivery of 120 KDa hydroxypropyl methylcellulose (HPMC) through application of biomimetic molecular imprinting. This is the first instance controlled and tailorable release of ocular therapeutics from a silicone hydrogel lens. By adjusting the ratio of acrylic acid (M) to HPMC (T) in 100 μm thick lenses, the rate of HPMC delivery can be tailored to deliver

1,000 μg HPMC for up to 60 days. By adding divinyl functional monomers (xLer) to the Lotrafilcon B mixture, significant control was granted over swelling, optical clarity and modulus.

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Beyond all, I want to thank my parents for their support and encouragement. The successful conclusion of this project is a measure as much of their success as it is of mine. Everything I have, everything I have accomplished including the completion of this work is due to their support. Any and all subsequent rewards derived from this work are dedicated to them and everything I am is because of them. Last of all, I would like to thank my sister and brother-in-law for their interest in this project and their moral support. They both deserve my special thanks and gratitude.

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CHAPTER 1

INTRODUCTION

There are approximately 35 million contact lens wearers in the United States and each year, the number of lens wearers increases. However, ~80% of lens wearers report end of day dryness and discomfort associated with lens wear. Of this number, 30% report severe discomfort derived from dry eye. This condition is referred to as contact lens induced dry eye (CLIDE). Other conditions, such as Sjogren syndrome, keratoconjunctivitis sicca, and seasonal allergies cause significant discomfort to non-lens wearers from ocular dryness. These conditions are generally treated topically through ocular eye drop formulations delivered to the anterior segment of the eye. The natural tear flow causes 90+% of applied drug to be lost to systemic drainage within 5-10 mins of application. Thus to be effective, eye drops must be instilled several times a day. Patient compliance is highly variable and carrying the eye drop formulation containers is cumbersome. The application of eye drops is inefficient, as a large volume of the instilled drop can be lost to spillage from the eye upon instillation and systemic drainage, and the eye can be exposed to long periods without drug.

In the past, such contact lens related issues have been managed by a combination of factors, such as reducing the wear time of the lenses, formulating contact lenses from high water content materials, replacing a worn lens with a new lens or prescribing wearers with a new brand of lenses or some topical treatment. However, drug delivery

from hydrogel contact lenses can be designed to treat any of a wide variety of conditions and engineered to release comfort agents to alleviate the discomfort of dry eye.

Controlled drug delivery from soft contact lenses is among the most exciting developments in ophthalmology. Clinical studies of drug loaded lenses have consistently shown increased drug bioavailability, dug residence time, and drug concentration within the tear fluid when compared to eye drops. However, therapeutic soft contact lenses (TSCLs) have not yet become a mainstream method of ocular therapy. It has only been recently that controlled release mechanisms have been applied to soft contact lens formulations. Since then, controlled release from hydrophilic contact lenses materials has been repeatedly demonstrated with small molecule therapeutics (anti-microbial, anti-glaucoma, anti-histamine). The only commercial product that releases a therapeutic to promote comfort is a hydrophilic lens and releases for approximately a day.

Silicone hydrogel lenses have recently become available for extended, continuous wear and, as such, are ideal platforms for drug release. Thirty day wear lenses can be loaded with drug, placed on the eye and continuously release clinically relevant amounts of drug to the eye, even during sleep. Few published accounts of silicone hydrogel TSCLs have been observed due to the complicated nature of the material. To date, the few published accounts have been diffusion controlled drug soaked lenses. To date, no tailorable controlled release of any therapeutic has been demonstrated in the literature for silicone hydrogel lenses. Given that 60% of the fittings in the United States in 2009 were in silicone hydrogel lenses, there is high interest in developing effective drug delivery from silicone hydrogels of both comfort agents and ocular medication.

Of the demonstrated methods of controlling drug release, molecular imprinting is the most versatile and effective method of tailoring drug release to any desired rate. Molecular imprinting exploits the natural tendency of drug molecules to form non-covalent interactions with monomers in the pre-polymer formulation. The non-covalent interactions (i.e. hydrogen bonding and ionic interactions) and form thermodynamically stable complexes between the monomer to complexes with the template drug. When polymerization occurs, macromolecular memory sites are permanently formed in the network. When the template is removed, the memory sites remain and interact with drugs as they diffuse through the hydrogel. These interactions cause changes in the path length of the drug molecule, which is undergoing random Brownian motion according to a concentration gradient. This increases the residence time of the drug in the lens slowing release of the drug reservoir. Biomimetic imprinting can, in turn, promote higher efficiency in both reloading and control over the rate of release. By selecting comonomers that resemble natural amino acids that bind therapeutics and selecting both high and low affinity binding monomers, greater control can be exercised over the binding and release rate.

In this work, we have developed a therapeutic silicone hydrogel contact lens capable of sustained release of 120 KDa hydroxypropyl methylcellulose (HPMC), an ocular comfort agent. By creating macromolecular memory sites, we demonstrated tailorable release rates to achieve 50+ days release in an infinite sink model (350 μm thickness) and 30+ days (~100 μm thickness) in a microfluidic device that mimics the flow rate of the eye. HPMC is a common macromolecular comfort agent in over-the-counter (OTC) eye drop formulations and can be used at various molecular weights.

HPMC (a polysaccharide composed of substituted glucose) resides on the anterior surface of the eye and retains water. During the blinking action, the water absorbed in the coils of the HPMC is forced out, replenishing the aqueous layer of the tear film. Additional comfort is derived from the increase in viscosity of the tear film due to the presence of the HPMC. As a result, the force on the anterior surface due to the blinking action is reduced, lowering the shear stress and thus the irritation to the eye.

This project was funded by CIBA Vision, Inc., one of the leading international manufacturers of soft contact lenses. They provided the material, Lotrafilcon B (LFB), which is the material for several brands of lenses. During the course of the project, alterations were made to the formulation resulting in a novel formulation and lens capable of sustained release via molecular imprinting. Various comfort agents were explored for use, and several techniques to control the release rate were considered before it was found that the molecularly imprinted lenses provided the greatest control over HPMC mass release. Lens release was performed in traditional in vitro conditions (infinite sink) and with the use of a microfluidic flow device developed by our lab. By comparing release through the traditional in vitro data and with the microfluidic device, the lens release rate was optimized by adjusting crosslinker concentration (xLer/T), monomer to template ratio (M/T ratio) and HPMC reservoir concentration.

Chapter 2 outlines the specific aims and goals of this project. **Chapter 3** describes the development and commercial success of silicone hydrogel contact lenses. However, lens wear and other disorders can lead to the condition known as dry eye as described in **Chapter 4**, which demonstrates the need to produce a combination device capable of alleviating dry eye symptoms. **Chapter 5** reviews the progress of

ophthalmology and ocular drug delivery and the development of soft contact lenses. The variety of drugs and methods of release in the field are reviewed in **Chapter 6**. Other work undertaken by our lab has shown that comfort agents can be delivered via contact lenses and controlled through biomimetic molecular imprinting. This work and the principle of biomimetic imprinting is reviewed in **Chapter 7**. The commercial production process and composition of silicone hydrogels is discussed in **Chapter 8** and compared with the laboratory production process undertaken in the course of this research. **Chapter 9** describes the materials and methods used in the project. The first step in the experimental work of this project was to match the LFB formulation to the re-wetting agent and method of controlled delivery best able to produce a therapeutic soft contact lens capable of delivering a therapeutic concentration of agent for 30 days. The experiments and results of this inquiry are overviewed in **Chapter 10**, while **Chapter 11** discusses the creation of HPMC-imprinted, silicone hydrogel contact lenses. Conclusions of the project are overviewed and summarized in **Chapter 12**. **Appendix A** includes a review of all acronyms and abbreviations used in the text, defines the monomers used in commercial lens materials discussed in the text and, finally, outlines the most common uses and wear times of traditional hydrophilic contact lenses. **Appendix B** lists the major lens brands and manufacturers for selected years between 1990 and 2010. **Appendix C** provides the experimental modulus values for lenses formulated in the course of the report. **Appendix D** displays the calibration curves used to determine HPMC concentration in the HPLC. **Appendix E** details experiments not discussed in the main document and involves the use and description of surfactants to disperse macromolecular re-wetting agents into the LFB lens. **Appendix F** validates that 250 mL of DI water is a

perfect sink environment for HPMC release. **Appendix G** describes the release of a lower molecular weight HPMC from silicone hydrogel lenses. **Appendix H** describes the formulations used in the experimental work.

CHAPTER 2

OBJECTIVES

There are approximately 35 million contact lens wearers in the United States. Discomfort in lens wear and increased interest in extended continuous wear lenses has created a demand for continuous 30 day wear lenses capable of releasing re-wetting agent for 30 days. The project proceeded in three parts which were as follows: (1) the identification of a long chain, macromolecular comfort agent capable of being loaded in therapeutically significant amounts into CIBA Vision's Lotrafilcon B formulation, and (2) the identification of a method of controlled release to tailor release rates. The resulting formulation would be molded into a lens that would be better tolerated by the ocular environment through the controlled release of a comfort molecule. Release from contact lenses continuously release comfort molecules thereby maintaining the minimum effective concentration of drug on the surface of the eye to provide comfort. Finally, (3) the variables in the lens formulation would be altered, and the resulting lenses optimized to demonstrate control over the release rate with a maximum of loaded therapeutic as well produce lenses with adequate optical clarity and mechanical properties.

The project's specific aims included: (1) the selection of the most appropriate re-wetting agent by comparing the solubility and relative loading of three macromolecular re-wetting agents into the LFB formulation, (2) the use of controlled release mechanisms

to increase loading of the three re-wetting agents and to produce optically clear lenses with acceptable qualitative mechanical properties at a center thickness of 350 μm (swollen), (3) the selection of the most promising combination of re-wetting agent and controlled release method (i.e. HPMC and molecular imprinting) and synthesizing lenses while quantifying factors such as loading, optical clarity, and swelling as well as duration of release, (4) the selection of functional monomers, in accordance with the principle of biomimetic imprinting, formulated into the LFB-HPMC lenses and study of the effect on clarity, swelling, and release duration, (5) to control clarity and swelling, a variety of crosslinking monomer were introduced to the LFB formulation at various concentrations and the optimum crosslinking monomer selected by the most dramatic increase of optical clarity and decrease in swelling, (6) the duration of release was examined in the altered LFB formulation and the appropriate variables (i.e. crosslinker (xLer) to template concentration and monomer (M) to template (T)) adjusted to produce an extended release, and (7) lenses were molded to a thickness of 100 μm swollen and the differences in optical clarity, swelling, and release duration observed, and the M/T and xLer/T ratios re-adjusted to produce an optically clear lens capable of extended release. The best performing lens were then (8) be placed in a novel microfluidic device designed to mimic the physiological flow rate of the eye to more accurately estimate the in vivo release rate of the eye. Finally, (10) mechanical and tensile studies were performed to determine the modulus.

CHAPTER 3

CURRENT TRENDS IN COMMERCIAL CONTACT LENSES

To demonstrate the recent trends in the marketplace and highlight the directions drug delivery from lenses must follow to meet manufacturer and consumer demands, a review of the commercial market is provided. The major divisions of contact lenses wear are daily disposable, disposable or planned replacement (daily wear), and extended, continuous-wear soft contact lenses. Within the soft contact lens division, there are hydrogel and silicone hydrogel lenses, and both these categories can be subdivided further into specialty divisions including cosmetic, therapeutic, aphakic, toric, etc. In a separate category, gas permeable (GP) lenses (both rigid and flexible) maintain a presence in the contact lens market but can be considered specialty lenses, along with hard polymethyl methacrylate (PMMA) and glass contact lenses which are available upon special order but their contribution to the market is negligible at best [**3.1**].

3.1. Silicone Hydrogel Contact Lenses.

In the past two decades, the number of lenses in the United States has steadily increased as the number of lens wearers has increased [**3.2**]. **Figure 3.1** demonstrates increasing number of commercial lens brands available within the US and thereby the growth of silicone hydrogel lenses. The figure was created from data gathered from references [**3.3-3.13**]. Within each of the three major divisions, some brands are represented more than once as they are approved for multiple wear times. Since 1990, at

least 60% of the lens brands produced have been based from hydrophilic hydrogels, but in recent years, the number of brands available based on silicone contact lenses has grown exponentially. In 1990, 70% (120) of all contact lens brands were based on hydrophilic polymer and increased to 82% (360) of the brands by 2010 (**Figure 3.2**) [**3.3, 3.13**]. Silicone hydrogels lenses first debuted on the market in 1999 with 1 brand and increased to 26 brands (6% of US brands) by 2010 [**3.13**]. Considering the large growth of the silicone hydrogel products and that ~5% of the available brands make up 60% of all the fittings in the US in 2009 [**3.14**], it is reasonable to expect that the brands should increase drastically in the next few years. The delay in growth of silicone hydrogel lenses can be partially attributed to FDA approval of new lens materials. Most silicone hydrogel contact lenses tend to share similar ratios of TRIS, DMA and a proprietary PDMS-based macromer [**3.15**]. However, each new macromer used in lenses for sale in the US must be approved by the FDA.

Silicone hydrogels lenses make up ~5% of the brands in the 2009 contact lens markets but were used in 60% of all US lens fittings in 2009, representing a disproportionate preference by prescribing ophthalmologist and consumers towards silicone hydrogels contact lenses [**3.14**]. Each year, more lens wearers switch from traditional hydrogel lenses to silicone hydrogels due to comfort in spite of the higher cost of silicone lenses [**3.15**]. Only in the past 5 years have most silicone hydrogels become available, and they have still managed to dominate the market. Sales, fittings, and number of GP lenses available to the consumers has changed little over the past two decades and are typically worn only by patients who cannot wear soft contacts lenses. These patients include cornea transplant patients who cannot wear soft contact lenses due to friction

between the stitches, and the hydrogel material or by any patient requiring high levels of oxygen permeability from the lens.

For this reason, it can be expected that extended release of ocular therapeutics from silicone hydrogels will be a dominant trend in ocular drug delivery for coming years. Several articles describing diffusion controlled release have already been published, and more work is forthcoming using more sophisticated methods, such as the methods in this thesis.

3.2. Tables and Figures.

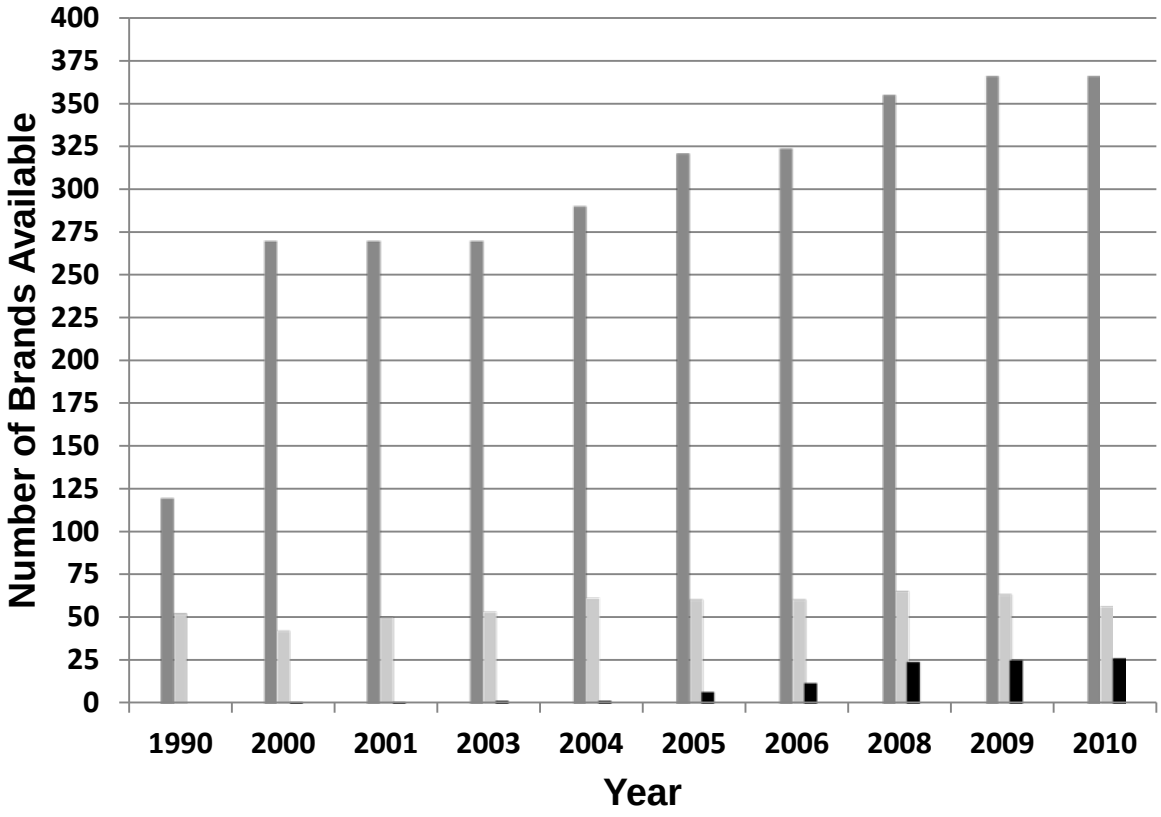


Figure 3.1. Number of Lenses Available in the US Lens Market Based on Material.

The growth of silicone hydrogel lenses has been a significant trend in the commercial lens market. Silicone hydrogels (■) lenses first appeared in the market in 1999, and the number of available brands has grown exponentially. In 2010, 26 various brands were available to consumers, and they are the most popular among lens wearers, though traditional hydrogel (■) lens brands are still available and significantly outnumber both silicone hydrogels and gas permeable (■) lenses. The data was gathered from references [**3.3-3.13**] and sorted based on approved wear times. Since some brands are approved for several lengths of wear time, some brands may be counted twice.

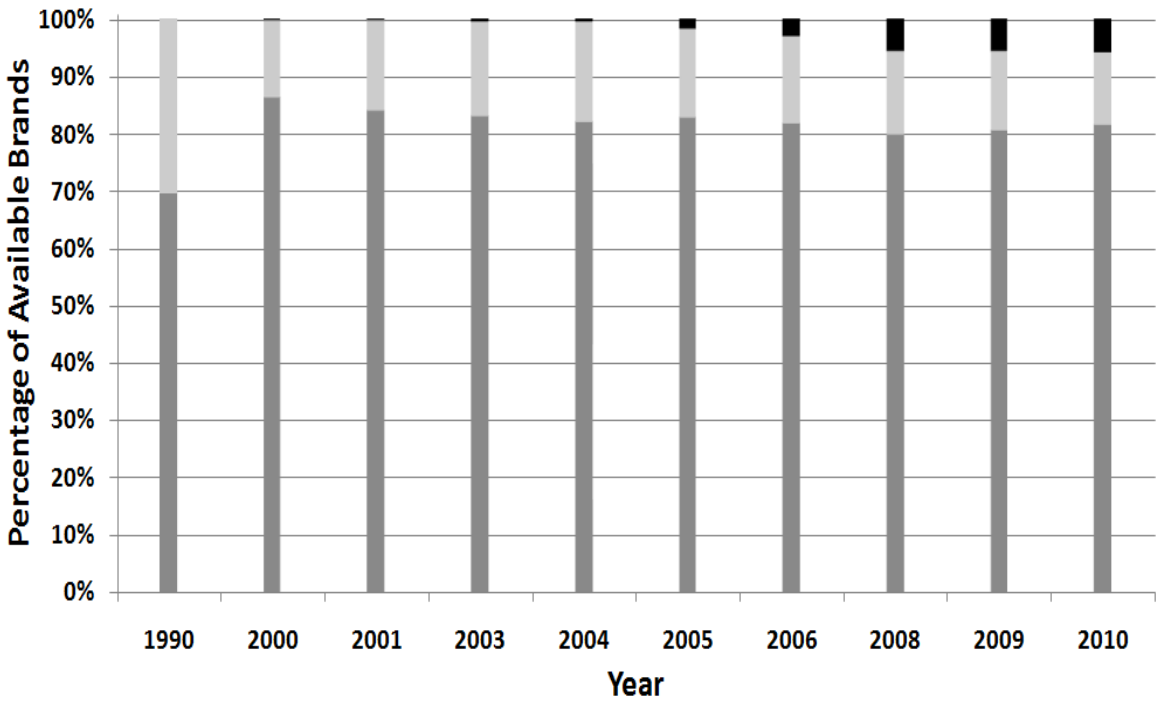


Figure 3.2. Percentage of US Commercial Lens Market Based on Material.

Traditional hydrogel (■) lenses have, for the past two decades, made up at least 60% of the available commercial lens brands. Since the appearance of silicone hydrogel (■) lenses in 1999, the number of available of these lenses has steadily grown and will become a major fraction of the lens market in the future. Gas permeable (■) lenses have maintained about 12% of the market over the past decade. This trend can be expected to continue as GP lenses are typically worn by patients who cannot wear soft contact lenses.

3.3. References.

[3.1] Efron N. Obituary – Rigid Contact Lenses. *Contact Lens and Anterior Eye*. 2010;33:245-252.

[3.2] Nichols J. Contact Lenses 2009 Annual Report. *Contact Lens Spectrum*. 2010;January Issue:1-8.

[3.3] Physicians' Desk Reference for Ophthalmic Medicines. Medical Economics Company, Inc: Thomson Healthcare: Montvale NJ;1990

[3.4] Physicians' Desk Reference for Ophthalmic Medicines. Medical Economics Company, Inc: Thomson Healthcare: Montvale NJ; 2001

[3.5] White P, Scott C. Contact Lenses & Solutions Summary. *Contact Lens Spectrum Supplement*. 2000 July.

[3.6] White P, Scott C. Contact Lenses & Solutions Summary. *Contact Lens Spectrum Supplement*. 2001 July.

[3.7] White P, Scott C. Contact Lenses & Solutions Summary. *Contact Lens Spectrum Supplement*. 2003 August.

[3.8] White P, Scott C. Contact Lenses & Solutions Summary. *Contact Lens Spectrum Supplement*. 2004 July.

[3.9] White P, Scott C. Contact Lenses & Solutions Summary. *Contact Lens Spectrum Supplement*. 2005 July.

[3.10] White P, Scott C. Contact Lenses & Solutions Summary. *Contact Lens Spectrum Supplement*. 2006 July.

[3.11] White P, Scott C. Contact Lenses & Solutions Summary. *Contact Lens Spectrum Supplement*. 2008 July.

[3.12] White P, Scott C. Contact Lenses & Solutions Summary. *Contact Lens Spectrum Supplement*. 2009 July.

[3.13] White P, Scott C. Contact Lenses & Solutions Summary. *Contact Lens Spectrum Supplement*. 2010 July.

[3.14] Morgan P, Efron N, Helland M, Itoi M, Jones D, Noichols J, van der Worp E, Woods C. Global Trends in Prescribing Contact Lenses for Extended Wear. *Contact Lens and Anterior Eye*. 2011;34(1):32-35.

[3.15] Vogt J, Nicolson P. Soft Contact Lens Polymers: An Evolution. *Biomaterials*. 2001;22:3273-3283.

CHAPTER 4

DRY EYE AND RE-WETTING AGENTS

Dry eye syndrome can be typically classified into one of two categories: aqueous tear deficiency or evaporative dry eye. Both divisions relate to the volume and stability of the ocular tear film. Conditions within these groups include glandular disorders and blockage, tear film evaporation due to environment, age, and gender. Contact lens wear and LASIK surgery can also cause dry eye through evaporation and deficiency from scarring, respectively. All these conditions can typically be managed through eye drops and artificial tears, which sequester water and maintain film consistency. Regardless, understanding the structure and composition of the tear film is vital to the understanding and treatment of dry eye.

4.1. Contact Lens Induced Dry Eye Among Contact Lens Population.

Contact lens induced dry eye (CLIDE) is a significant problem with lens wear and is a major cause of consumer dissatisfaction and discontinuation of lens wear [**4.1, 4.2**]. Of the nearly 35 million contact lens wearers in the United States, surveys indicate that up to 80% of wearers endure end of day discomfort due to ocular dryness, while 30% of these wearers suffer from severe discomfort by complete dryness of the tear film [**4.1-4.4**]. Worldwide, there are between 100-300 million lens wearers, and collectively they constitute a significant market. In addition, dry eye syndrome, officially known as keratoconjuctivitis sicca, causes severe discomfort when there is insufficient tear fluid to

keep the anterior surface of the eye wet. This condition affects nearly 50 million people in the US [**4.5**]. As a result, a large potential market exists for contact lenses capable of controlled release of re-wetting agents for both lens wearers and non-wearers.

4.2. The Anatomy and Makeup of the Tear Film.

The tear layer on the anterior surface of the eye is a thin aqueous and lipid film that flows over the epithelial cells of the eye. In healthy normal eyes, the tear film is 4-9 μm thick, and the volume is completely replaced approximately every 1-3 minutes. The tear film be described in three distinct layers: the mucin layer (0.01-0.07 μm thick) that lines the epithelial cells and ensures wettability and protects the eye from bacteria and the shear stress from the blinking action [**4.5-4.9, 4.13**] Flowing along the mucins is an aqueous layer (4-9 μm thick) that allows oxygen transport to the eye along with antimicrobial enzymes [**4.7-4.10, 4.13**]. The final layer (0.1 μm thick) is the interface between the water and the atmosphere which is composed of lipids that retard evaporation of the tear fluid. The integrity and volume of these three layers must be maintained for normal eye function or else discomfort and disease can cause further damage to the ocular surface. **Figure 4.1** represents the normal tear film as it flows over the anterior surface of the eye.

Normally, about 10 μL of water lines the anterior surface of the eye with an additional reservoir of 7-9 μL stored behind the lower lid. When blinking occurs, the reservoir is spread out across the ocular surface and partially replenishes the layer. In addition, the blinking action provides a pumping action that helps clear the stagnant fluid. Dry eye sufferers have a reduced volume of this aqueous layer, which results in discomfort and diminished vision, which occurs when there is insufficient water to keep

the refractive index of the lens and cornea constant. When the sclera, cornea, and lens dry out, cracking and scratching of the tissue occurs, leading to severe pain.

Drainage of the tear fluid occurs by several competing methods, including evaporation, spillage from the ocular cavity in the form of tears, or the removal of fluid through the puncta and openings of the lacrimal duct. The last accounts for 90% of the drainage, removing tears at an average rate of 25-50 μL over 90 seconds [**4.5-4.9**]. The balance is made up mostly through evaporation. If the eye is held open, the time for the fluid layer to break up or become a discontinuous phase is 15-50 seconds in healthy eyes. This effect is accelerated for dry eye sufferers resulting in a break up time of less than 10 seconds.

In addition to providing comfort, the tear fluid aids in the transport of oxygen to the eye. This is an important factor in both ocular health and comfort and contact lens design. The ocular lens is completely dependent upon this transport of oxygen as there is no vasculature in the cornea. The rate of oxygen diffusion is approximated to be 7.8 μL/ cm^2 per hour [**4.11**]. This becomes an important factor in lens design. When the contact lens is placed on the surface of the eye, a polymeric shield is placed between the eye and atmosphere forming a powerful transport barrier to oxygen. Lens materials must be designed to overcome this barrier.

Lens wear has been shown to induce dry eye and discomfort especially at the end of the day [**4.1-4.4**]. This is due to disruption of the tear film due to the presence of the lens, which promotes tear evaporation and protein adhesion to the contact lens. This effect is magnified by high water content lens. The lens induces dry eye by absorbing tear fluid, promoting evaporation from the front of the lens, and disrupting the tear flow

profile. High water comfort lenses, however, have been required traditionally for increasing oxygen and protein transport. Lenses were designed to optimize oxygen transport by sacrificing resistances to contact lens induced dry eye.

4.3. Re-Wetting Agents.

Several wetting agents are used in artificial tears and re-wetting drops including polyvinyl alcohol (PVA), polysaccharides such as hyaluronic acid (HA), carboxymethyl cellulose (CMC), methyl cellulose (MC), and hydroxypropyl methylcellulose (HPMC), and polyvinyl pyrrolidone (PVP). Other drops use lipids to replenish the lipid layer and discourage tear evaporation or viscosity enhancers to reduce the shearing stress on the anterior surface and slow drainage. **Figure 4.2** shows the chemical structure of common re-wetting agents.

4.4. Description of HPMC.

Though this work began with several possible comfort agents, hydroxypropyl methylcellulose (HPMC) quickly became the re-wetting agent of highest interest. HPMC is a non-polar, linear polysaccharide which is commonly used in re-wetting drops. In addition, HPMC is widely used as a thickener and emulsifier in food additives as well as an excipient and scaffold in drug delivery. HPMC is composed of beta-linked D-glucose units, though the ratio of substituents of the repeating D-glucose units can vary highly depending on the source and molecular weight of HPMC (**Table 4.1**). There are a maximum of three possible substitution sites in each repeating glucose unit typically varying between methyl or isopropyl alcohol groups or a proton (**Figure 4.1**). The ratios of these groups vary among HPMC chains depending on molecular weight and source of

origin. The chain molecular weight can be purchased at varying weights between 10 and 200 KDa.

Since HPMC is hygroscopic, it retains water, which makes it ideal for re-wetting agents. In addition, HPMC displays solubility in a wide variety of solvents unlike other re-wetting agents covered in this work. Given the highly complex biphasic nature of the silicone hydrogel contact lens, it is necessary that the selected comfort agent be soluble in both hydrophilic and hydrophobic sections of the lens material to produce optically clear lenses and have the most control over drug release. HPMC displays solubility in both ethanol and water, though increased solubility can be granted by adding hydrophilic monomers to the formulation. For these reasons and since it is a common re-wetting agent, we selected it as the primary re-wetting agent in this project.

4.5. Tables and Figures.

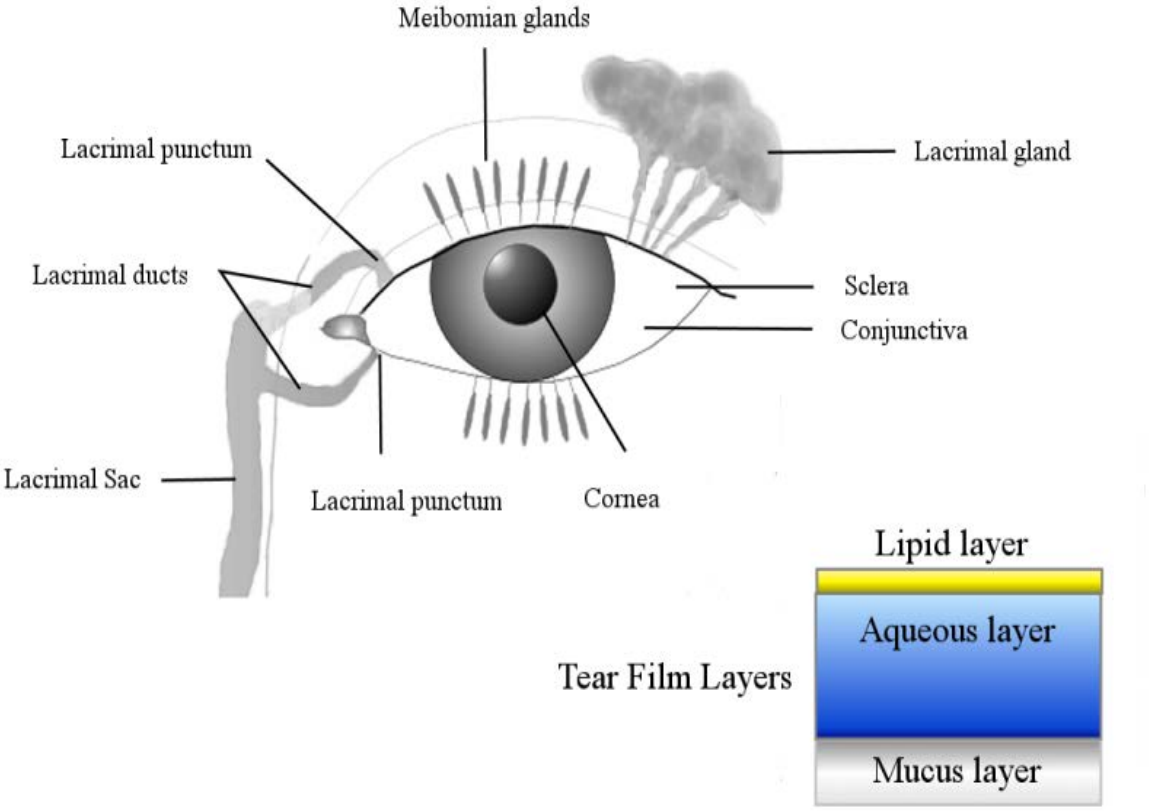


Figure 4.1. Layers of the Tear Fluid on the Anterior Eye.

Tear fluid typically flows downward from the lacrimal gland, across the anterior surface of the eye and drains through the lacrimal ducts. The tear film is typically 5-10 μm thick; the lipid and mucus layer are 0.1 μm thick and 0.01-0.07 μm thick, respectively. An aqueous layer makes up the balance. The lipid layer reduces tear film evaporation while the mucin layer ensures that the endothelial cells are wettable and protects the cornea from bacteria. Eye drops and comfort agents act in the aqueous layer, replenishing the tear fluid during the blinking action by releasing sequestered water. Figure 4.1 is reproduced with permission from **[4.5].**

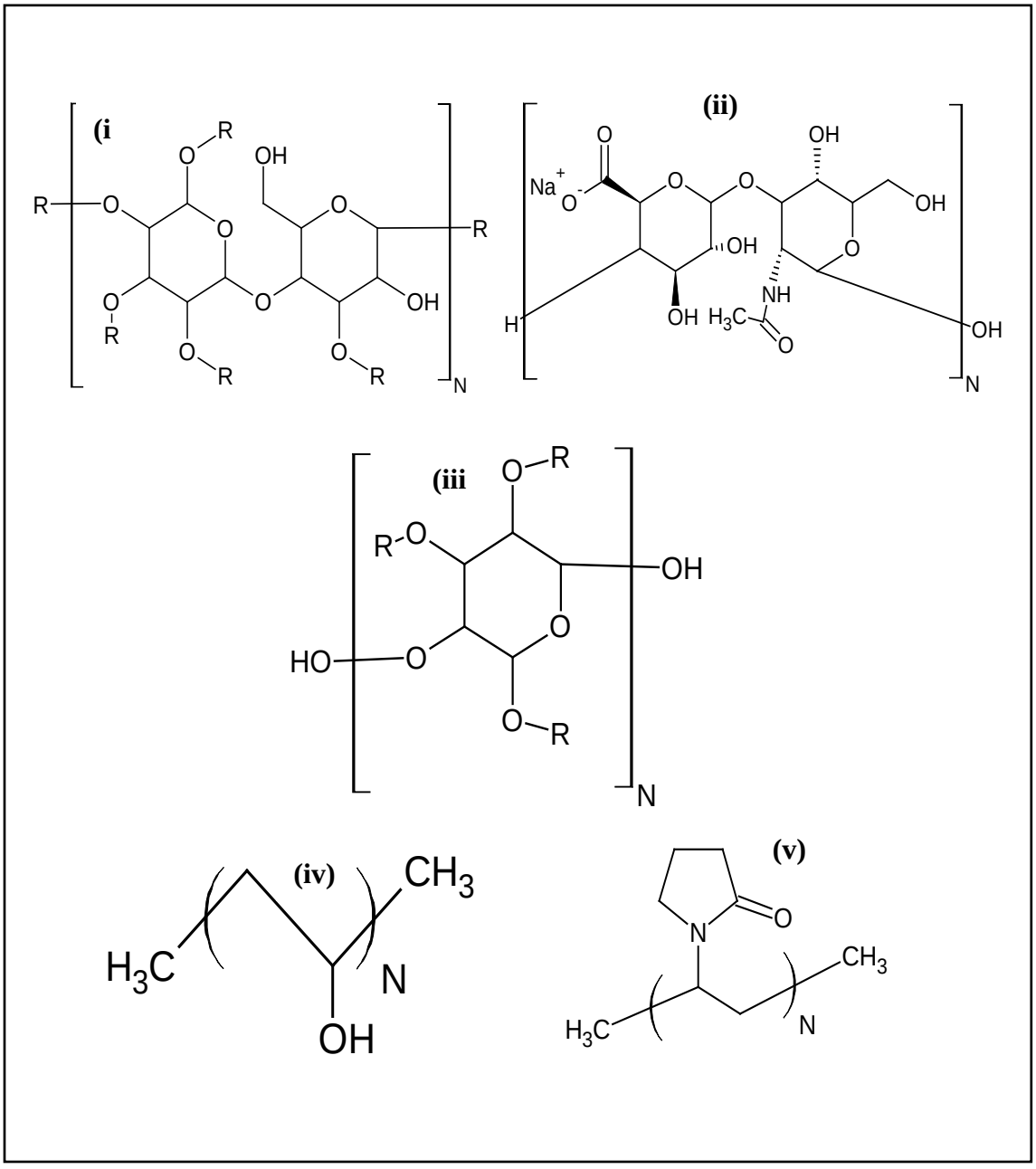


Figure 4.2. Common Re-Wetting Agents in Over-The-Counter Eye Drop Formulations.

Structures represented here are common re-wetting agents in contact lens solutions and eye drop formulations. The macromolecules represented are (i) hydroxypropyl methylcellulose, (ii) hyaluronic acid, (iii) carboxymethyl cellulose, (iv) polyvinyl alcohol

and (v) polyvinyl pyrrilidone. R can vary among HPMC molecular weights and is described in **Table 4.1**.

Table 4.1. Substituents of HPMC Repeating Units as a Function of Molecular Weight

HPMC MW	per Macromolecule Chain				
	# Units	# OH's	# *O*-CH_3	# *O*-IPA	# *O*-H
10 KDa	30	134	55	13	121
90 KDa	282	1261	334	80	1181
120 KDa	376	1682	539	106	1596

4.6. References.

[4.1] Chalmers R, Begley C. Dryness Symptoms Among an Unselected Clinical Population with and without Contact Lens Wear. *Contact Lens and Anterior Eye*. 2006;29(1):25-30.

[4.2] Pritchard N, Fonn D, Brazeau D. Discontinuation of Contact Lens Wear: A Survey. *International Contact Lens Clinic*. 1992;26:157-162.

[4.3] Doughty M, Fonn D, Richter D, Simpson T, Caffry B, Gordon K. A Patient Questionnaire Approach to Estimating the Prevalence of Dry Eye Symptoms in Patients Presenting to Optometric Practices Across Canada. *Optometry and Visual Sciences*. 1997;74:624-631.

[4.4] Begley C, Chalmers R, Mitchell G, Nichols K, Caffery B, Simpson T, DuToit R, Portello J, Davis L. Characterization of Ocular Surface Symptoms from Optometric Practices in North America. *Cornea*. 2001;20:610-618.

[4.5] Ali M. Therapeutic Contact Lenses for Comfort Molecules, Master's Thesis. Auburn University Thesis; 2007.

[4.6] Holly F, Lemp M. Tear Physiology and Dry Eyes. *Survey of Ophthalmology*. 1977;22(2):69-87.

[4.7] Urtti A. Challenges and Obstacle of Ocular Pharmacokinetics and Drug Delivery. *Advanced Drug Delivery Reviews*. 2006;58:1131-1135.

[4.8] del Amo EM, Urtti A. Current and Future Ophthalmic Drug Delivery Systems A Shift to the Posterior Segment. *Drug Discovery Today*. 2008;13(3/4):135-143.

[4.9] Nichols B, Chiappino M, Dawson C. Demonstration of the Mucous Layer of the Tear Film by Electron Microscopy. *Investigative Ophthalmology and Visual Science*. 1985;26(4):464-473.

[4.10] Whikehart D. Water and Ocular Fluids. Biochemistry of the Eye, 2nd Ed. Philadelpha: Buttersworth-Heinemann. 1-14.

[4.11] Brennan N. Corneal Oxygenation During Contact Lens Wear: Comparison of Diffusion and EOP-based Flux Models. *Clinical and Experimental Optometry*. 2005;88(2):103-108.

[4.12] Pritchard N, Fonn D, Brazeau D. Discontinuation of Contact Lens Wear: A Survey. *International Contact Lens Clinical*. 1999;26:157-162.

[4.13] Ali M, Byrne M. Challenges and Solutions in Topical Ocular Drug-Delivery Systems. *Expert Reviews of Clinical Pharmacology*. 2008;1(1):145-161.

CHAPTER 5

OCULAR DRUG DELIVERY AND NATURAL BARRIERS OF THE EYE

Humans are sight oriented beings. Vision is how we experience the world around us, and we use this sense above all the others. For this reason, ophthalmology (the study of the anatomy and physiology of sight and the eye) has existed since the early days of human civilization. For much of recorded history, problems with vision were attributed to the actions of various deities, spirits, fairies or witchcraft. For this reason, the foundations of ophthalmology are based in a curious blending of mysticism and pharmacology that alternated between absurd, ineffectual, and sophisticated treatments. Treatments quickly evolved from dances, mysticism, and ritual to include ointments, washes, and bandages designed to deliver therapeutics as long ago as the Ancient Egyptian civilization. It has been estimated from extant documents that at least 75% of all treatments were formulated into ointments and washes [**5.1**]. Today, more than 90% of all ocular prescriptions are manufactured into drops and ointments [**5.2**].

5.1. Historical Progression and the Natural Barriers of the Eye.

It has only been recently that the greatest breakthroughs in ocular physiology and unparalleled understanding of ocular barriers, both external and internal, have occurred. To create more effective and sophisticated delivery methods, a clear understanding of these barriers needed to be developed. However, proper knowledge of these barriers has been the limiting factor in ophthalmology. To understand the current development of

ocular pharmacy and mechanisms of delivery, a brief review of ancient practices and formulations as well as the progression of knowledge of the ocular system is provided.

5.1.1. Egyptian Ophthalmology. Ancient Egyptians of all classes had high regard for ophthalmologists and often sought treatment for ocular disorders. Physicians and priest alike would prescribe treatments for conditions ranging from inflammation and redness to blindness. Common ingredients would include blood, brains, urine, fat and milk obtained from cattle, pigs, cats, humans, reptiles, geese and donkeys. However, the two almost universal base ingredients included water and honey. Honey, in particular, was considered a panacea for most conditions in Egyptian civilization [**5.3**].

One prescription for resistance to witchcraft called for the patient to apply a paste derived from boiling the body of a large beetle directly to the eye while the head and wings were mixed with snake fat and drunk by the patient [**5.1**]. Prayers and animal sacrifices to deities were recommended in addition to application of a poultice or wash. In Ancient Egypt, almost all diseases, including ocular disorders, were attributed to an imbalance of the *metu* system. The *metu* system (possibly an early theory for the circulatory system) was believed to be a system of ducts that supplied fluids to all areas of the bodies [**5.3**]. Any imbalances could be resolved from wearing an ointment formulated from mixing one half of a human brain with honey overnight, while the other half would be dried, pulverized and used as an ointment or wash the following morning or through the liberal dosage of honey and a convenient laxative.

As unusual or ineffective the pharmacology seems, a sophisticated system of diagnosis was developed which from surviving descriptions of symptoms can be considered equivalent to many modern day ocular diseases, which testifies to the acuity

of the Ancient Egyptians. Ocular afflictions and their corresponding treatments can be seen in **Table 5.1**. It is interesting to note that the idea of topical delivery through a combination device was developed even in ancient times. Linens soaked in therapeutics would be pressed directly against the eye in a clear analog to bandage contact lenses [**5.76**].

5.1.2. Chinese Ophthalmology. Chinese physicians were as sophisticated at diagnosing conditions but similarly ineffective in treatment as Egyptian ophthalmologist. Chinese philosophy, however, focused more on flow of energy and pressure in the body, though physiology played a more important role in the treatment of diseases than in Egyptian ophthalmology. For example, vision and the eye were believed to function in conjunction with the liver while the pupil was thought to relate to kidney function. The oldest existing Asian text discussing ophthalmic practices is the *Tzu-Wu Ching* (The Importance of Needling) dating back to 250 BC, which attempted to correlate ocular disease and functions to acupuncture and pressure points in the body [**5.1**]**.** Individual descriptions of 81 specific ocular diseases were found in the *Yin Hai Ching Wai* or the "Exhaustive and Comprehensive Survey of the Silver Sea" [**5.1**]**.** The silver sea is an old Buddhist term for the eye. These diseases were described as separate and distinct conditions, though many of them are now classified as progressions of the same disorder. A prescribed formulation believed to alleviate staphyloma (an abnormal growth of an inner tissue of the eye through weak points in the outer tissues) was composed of a young boy's urine cooked over a fire, mixed with zinc carbonate to produce zinc collyrium and administered topically. Delivery of comfort formulations was already a recognized treatment where eye redness and inflammation would be treated by drops produced by

boiling sage, caraway seeds, red dahlia roots, aster flowers, cicada skins, licorice and several other plants [**5.3**].

5.1.3. Greek and Roman Ophthalmology. The true roots of ocular anatomy began with the Greeks dating back to approximately the 3rd or 4th century, BC. Hippocrates (460-370 BC) laid the groundwork in developing ocular anatomy and treatment by theorizing on the structure of the eye and wrote several treatises on the subject of anatomy and health [**5.4**]. Before his work, physicians were convinced that the eye was a simple device composed of two layers, the sclera and the cornea, which are the most visible and accessible of areas of the eye. Inside the eye, a uniform and clear fluid was recognized to be enclosed. The fluid was of great importance as it was thought to be the mechanism of vision. Fluid near the cornea would capture the image and circulate to the back of the eye where a tube would allow passage of the fluid to the brain, and there the fluid would communicate the information to the brain. Hippocrates attempted to correlate occurrence of inflammation to geographical location and season and recommended that ocular diseases were best treated by bloodletting, application of wine as both an eye wash and through ingestion, bathing, purging and laxatives. In fact, such recommendations remained common practice for almost 2,000 years [**5.1**]. In his book, Hirschberg notes that he was taught these procedures as a medical student [**5.1**]. Hippocrates' other texts prescribe washes and ointments derived from saffron, myrrh, copper oxide and lead. Diet was thought to be essential to vision and inflammation was treated through a strict diet of only a little bread and water. Lentils, fruits, sweets and vegetables were deemed to be harmful to sight [**5.3**].

It was not until Aristotle (384-322 BC), however, that a theory of ocular structure based on dissection emerged [**5.3**]. It is unknown how Aristotle derived his model but he probably dissected the eye of a small mammal and inadvertently discovered the chiasma and ocular blood vessels. He also placed the optic nerve at the back of the eye, which while not correct, was a more accurate placement than others before him. He misinterpreted his findings, though, as he described the blood vessels as a method for the vitreous humor to circulate from the left and right eye and the optic nerve as the tube for fluid to travel to the brain. He described three layers of membranes as uniform consistency and the humor to be uniform in composition and consistency. No special knowledge was demonstrated relating to the purpose or composition of ocular tissues nor any understanding of the mechanics of the eye [**5.3**].

In the first century, AD, Rufus of Epheus proposed a simplistic, schematic of the eye that was recognizably modern. Rufus was the first to recognize that the eye consisted of two chambers and described the newly discovered conjunctiva as the fourth epithelial layer. Galen of Pergamum (129-199 AD) improved on the design by adding the curvature of the cornea and lens and described the posterior chamber. No major anatomical features changed in this model until the 16th century. Though basic anatomy of the eye had been discovered, the features were not yet understood as barriers to drug delivery and the vital understanding needed for effective treatment had not yet emerged [**5.3**].

The Romans treated ophthalmic conditions through washes and drops. Galen promoted washes for treatment which briefly became the dominant form of delivery. Common ingredients for these washes included opium, red copper, antimony, myrrh, saffron, rose petals and gum. Alternative treatments included diet, laxatives, rest, bathing,

wine, and bloodletting. The most popular wash treated inflammation by mixing egg whites, boxtree wood and milk, taken from a healthy young woman by placing her breast on a whetting stone [**5.1**]. Europe during the Dark Ages and the Renaissance followed similar patterns of treatment by washing and ointments, which would continue into the modern age. Treatments for almost any condition during the Dark Ages included laxatives, purging, starvation, and the ingestion of mercury and bloodletting [**5.1**].

Few of the treatments had actual pharmacokinetic or medicinal value. A lack of understanding of anatomy and physiology resulted in ineffective treatments that caused far worse complications. The few medications capable of treating patients suffered from ineffectual delivery. Egyptians, Greeks and Romans showed indications of realizing that washes and ointments were inferior methods of delivery. Early attempts to create combination devices capable of holding a reservoir of therapeutic and placing them in direct contact of the eye used cloth bandages and linens which were soaked in therapeutic solutions. The linen served to delay the release of therapeutic and extend the residence on the eye and could be compared to an early analog for therapeutic lenses [**5.3**].

5.1.4. Historical Anatomy and Physiology. Much attention will be focused on the anatomy of the eye, both external and internal features, as they relate directly to the driving forces in delivery research. Even in ancient times, it was considered a breach of medical ethics to dissect a healthy person's eyes. Typical investigations into anatomical features were based on animal dissections of human cadavers or small mammals, which resulted to ocular models of questionable accuracy to the living human eye. Due to religious and moral tenements, dissection of human remains was condemned and often forbidden, with possible exceptions made for prisoners of war or slaves. Only in recent

times has human dissection become commonplace though considerable moral and ethical constraints are prevalent. However, studying ocular anatomy on anything but a freshly dead corpse is impractical as the vitreous humor drips out of the back of the eye and leaves the eye deflated while the remaining humor gels. Frederick Ruysch developed methods of preserving the eye after death for prolonged evaluation, and Francois Pourfour du Petit pioneered freezing the eye before dissection to gain a cutaway view of the ocular sphere, developing advanced models of the eye. Many anatomical features such as the retina, rods and cones, tear flow, tissue permeability and the mechanism of pupil dilation remained undiscovered until the late 19th century or later.

Ocular physiology has its roots in the works of Aristotle and Hippocrates. However, most progress did not occur until the latter half of the 19th century. Ancient physicians were much more concerned with therapy and treatment than physiology and pathology though effective treatments suffered due to lacking of such knowledge. Failure to grasp the enormous value of barriers and defenses of the eye resulted in ineffectual treatments such as bloodletting and removal of the “bad” vitreous humor to correct vision.

5.2. Current Ocular Treatment Methods.

For years, any discussion of ocular drug delivery has dogmatically stated that the eye is difficult to reach for effective treatment, yet the eye is one of the most easily accessible organs. The anterior surface of the eye is exposed to the atmosphere and can be reached and examined without any invasive procedure or instrument. However, from a drug delivery perspective, the eye is isolated and difficult to reach organ for traditional methods of delivery. Nature provided the eye with effective defenses that

pharmacologically isolate the ocular environment from the rest of the body while anterior features prevent any foreign material from entering the eye. Any orally or intravenously injected drug is filtered and metabolized by the liver before it reaches the eye, which results in less than 2% of the drug reaching the eye [**5.5, 5.6**]. To deliver effective doses, high amounts of medication must be administered which can lead to toxic side effects, and the loss of 98% of the dosage is very inefficient. The eye is connected to no other organ than the brain, which is also well protected, making alternative routes through other tissues impractical. The capillary system does not spread evenly through the eye and areas of the eye completely lack a circulatory system [**5.7**], while the blood ocular barrier prevents effective delivery through the vascular system [**5.7-5.9**]. Topical delivery from the anterior of the eye remains the most effective method of drug delivery, though numerous barriers lower the efficiency. The driving forces behind the progress in ocular delivery have been to overcome or sidestep the natural defenses of the eye. With recent advances in healthcare, understanding of ocular physiology and development of new drugs, controlled and effective drug delivery to the eye is improving but the overall, the field remains in its infancy.

5.2.1. Circulatory Delivery of Ocular Drugs. Drugs are typically delivered throughout the body by injections or oral ingestion carried by the circulatory system. However, the eye is isolated from the rest of the body and the circulatory system by blood-ocular barriers, which prevents transport of therapeutics from the blood to the eye [**5.10**]. The blood-retina barrier (BRB) separates the eye from the circulatory system and restricts the movement of substances from the blood to the posterior segment of the eye. The BRB is composed of two parts: the endothelial cells of the retinal vessels (inner

barrier) and the retinal pigment epithelium (outer barrier) [**5.11, 5.12**], which forms a strong barrier to hydrophilic substances and limits transport between the vitreous and the blood. Permeability values for small molecules in the RPE are between 0.2 and $18x10^{-6}$ cm/s and can be estimated on the order of 10^{-7} for retinal blood vessels [**5.10**]. Indeed, permeability measurements of the sclera indicate the RPE is a more effective barrier than the sclera at eliminating high molecular weight and hydrophilic entities. The vitreous humor, being 99% water, is an effective barrier to hydrophobic molecules. Without some sort of additional transporter to aid hydrophobic and hydrophilic drugs across their respective barriers, it is very difficult to deliver ocular therapeutics to the posterior of the eye in significant concentrations.

Delivering to the anterior segments via systemic circulation must overcome yet more barriers. This route results in less than 2% of the ingested drug detectable within the vitreous humor. This can be overcome by administrating extremely large doses but toxicity, side effects, and wasted drug prevent this from being a viable alternative. The low permeability of hydrophilic and high molecular weight drugs through the ocular blood barriers make transport through the sclera and anterior of the eye more efficient.

5.2.2. Eye Drops. Eye drops are the dominant form of ocular drug delivery making up greater than 90% of all available formulations [**5.2**]. The market dominance of eye drops is due to the ease of industrial manufacture and application by patients. Eye drops are relatively effective and non-invasive, making them more popular to the average user when compared to ointments. Both ointments and inserts are uncomfortable and hard to apply and more invasive. However, eye drops suffer many drawbacks that drastically limit their usefulness in ocular drug delivery. Eye drops have low bioavailability. Due to

this, drop formulations have to be designed to deliver a maximum dose (usually at or near the toxic level) which is almost immediately washed from the eye. The high dose maximizes the concentration driving force. However, due to the natural flow of tears, 5-15 minutes after the drops are applied, 90+% of the drug is lost to systemic drainage [**5.7**]. Only 1-7% of the drug delivered to the eye by eye drop formulations is typically available to the eye due the flow of the tear film. Poor transport of drugs through the tear film causes most of the drug to be lost and subjects the eye to pulsatile concentration profiles and discontinuous periods of drug activity (**Figure 5.1**) [**5.13**]. After this time, the drug is often below the effective dose, requiring another drop to return the concentration to effective levels. The patient receives, as a result, intermittent doses of high to low levels of drug (**Figure 5.2**) and the effectiveness of the treatment is limited by patient compliance. Additionally during the night, no medication is provided to the eye, resulting in long periods without an effective dosage. Eye drops suffer from other drawbacks, including uneven concentrations, drop size, and phase separation [**5.13**]. Preservatives and stabilizing additives often added to eye drops can be toxic to the eye [**5.7, 5.13, 5.14**] and patient compliance [**5.15**] and ineffectiveness in application remains a serious issue [**5.13, 5.16**].

Typical drop volume from a commercial eye dropper is 25-56 μL with an average of 39 μL [**5.17, 5.18**]. Under ordinary conditions, the eyes contain 7-10 μL of lacrimal fluid. The additional fluid is loss through spillage from the eye and normal drainage. Once the drop is applied, the drainage rate is ~11 μL/ min in humans though the rate increases with increasing drop size [**5.19-5.21**]. By controlling viscosity and drop size, it

is possible to increase bioavailability. Additional factors that affect bioavailability from drops are dropping angle, drug density, drop viscosity, and numbers of drops.

5.2.3. Injections, Ointments, and Inserts. Other technologies including ointments, inserts, injections and gel formulations were developed to overcome drug removal due to tear flow. However, these solutions suffer additional drawbacks preventing them from supplanting eye drops as the dominant form of release. Inserts are placed under the lids or in the cul-de-sac (lower lid) of the eye. However, inserts can be uncomfortable and require a professional to place and remove. Additionally, the insert can fall out of the eye and cannot be replaced by the patient.

5.2.4. Hydrogel Contact Lenses. Hydrogel lenses have shown potential to deliver drugs since 1965, when lenses were soaked in concentrated drug solutions and applied to the eye [**5.22, 5.23**]. Since then, advances in lens technology and delivery methods have shown increased bioavailability and increased residence time of drugs on the surface of the eye as well as potential for continuous and extended release of therapeutics compared to other methods. Recent research has focused on controlling the rate of release from lenses, altering lens materials, medications, and release time, to match current market trends and overcome the many physiological barriers of the eye. The clear benefit of such technology is the increased patient compliance which would merely require patients to wear a lens to receive continuous and effective treatment and replace the lens daily or monthly without any additional care from professionals (**Figure 5.2**). Lower doses mean less drug lost to systemic circulation and lower probability of toxic damage to the eye (**Figure 5.1**). A more detailed analysis of drug delivery via contact lenses is provided in **Chapter 4**.

5.3. Ocular Anatomy as Barriers to Delivery.

Nature has provided the eye with various tissues and structures that effectively hinder topical drug administration. Each tissue has characteristic permeabilities that make effective diffusion by drugs difficult [**5.61**]. The eye can be considered as two separate regions for drug delivery. The anterior and posterior segments are both important targets of ocular drug delivery but are pharmacokinetically isolated from the rest of the body, and different barriers exist for topical drug delivery.

5.3.1. Anterior Barriers of the Eye. The features belonging to the anterior section of the eye are both targets and barriers to drug delivery by affecting transport of drugs. The discussion of anatomy will relate the position of each feature in the eye to the barrier each feature poses to delivery and the progression of delivery technology to overcome the resistance to effective treatment.

As discussed above, the eye and any resulting diseases can be classified into two sections: the anterior and posterior. The anterior segment includes the cornea, iris, ciliary body and the lens [**5.7**]. For convenience, the tear fluid, tear flow and the eyelids will be discussed in conjunction with the anterior segment as topical delivery is affected by these features. The sclera and the cornea make up the outermost anatomical barriers to topical drug delivery and are the parts of the eye most available for general inspection. The cornea is a transparent, dome-shaped structure covering the front of the eye. The human cornea consists of three layers: the corneal epithelium (a major hydrophilic barrier), the stroma (a highly hydrophilic tissue) and the endothelium (a minor lypophilic barrier) which restrict the passage of drug molecules. The cornea is relatively impermeable to solutes with a molecular weight of >1 KDa. Drugs transport through the stroma is

approximately equivalent for all drugs due to a relatively open structure; drugs up to 500 KDa can diffuse through the stroma basically unhindered.

The cornea is a transparent tissue that serves to refract and focus light into the eye [**5.17**]. It is 11.7 mm in diameter and possesses a radius of diameter of 7.8 mm [**24**]. The thickness is 500-700 μm in thickness and thickest in the center [**5.25, 5.26**]. The cornea itself is an effective barrier to drug transport, protecting the eye. Drug permeation is affected by several factors such as lypophilicity [**5.27**], solubility, molecular size and shape [**5.28, 5.30**], charge [**5.31, 5.32**], and ionization [**5.33-5.35**]. A highly hydrophilic drug would find the lypophilic corneal epithelium unsurpassable, while any greatly hydrophobic drug might be able to pass the epithelium only to be stopped by the stroma. Moderately hydrophobic drugs are blocked at the surface of the epithelium while the entire cornea's epithelium blocks mildly hydrophilic drugs [**5.36**]. A drug that could effectively treat the eye interior would have to possess both hydrophilic and hydrophobic components to effectively diffuse through the barriers. Several studies have found strong correlation to permeation and lypophilicity, often described as sigmoidal or parabolic behavior [**5.37-5.39**]. The optimum octanol/buffer distribution coefficient for permeation through the cornea is between 100-1,000 [**5.27, 5.40**]. It is possible for drugs to diffuse across the membranes, however, and overcome the barriers based on simple diffusion. If a drug is present in high enough concentrations or for sufficiently long periods of time, eventually passive diffusion will occur. It should be noted also, that the production of the tear layer is not constant. During sleep when the eyelids are closed, tear flow is dramatically reduced.

The sclera is the tough, white membrane of the eye. In general, the membrane network is much larger for the sclera than the cornea and, as a result, is much more permeable [**5.41**]. The outermost barriers to delivery are the tear film layer, the transport properties of tear flow, both of which occur on top of the sclera and cornea, and the eyelids. These are the serve pre-dominant physical barriers to drug delivery [**5.42**]. Due to low permeability values, rates of drug transport across the cornea and sclera are slow even in the presence of high concentrations. Long periods of exposure are required before relevant concentrations are absorbed. As such, a high, stable concentration of drug must be present in the tear film for a long period of time. However, tear flow quickly reduces drug concentration. The normal tear volume on the eye is 6-7 μL and normal drainage is around 1.1 μL/ min [**5.43**]. When an eye drop is applied, tear volume increases and drainage increases to 1.5 μL/ min [**5.44, 5.45**]. Under normal tear volume and turnover rate, tear fluid is completely exchanged around 5 min of instillation, and the mean contact time of the drug on the ocular surface is less than 2 min. By lowering drop volume and increasing viscosity, tear drainage rate decreases and bioavailability increases, but still remains far from ideal. This is the problem that prohibits any increases in effectiveness from traditional eye drops.

The first protective mechanism that hinders topical drug delivery is the tear film and lacrimal system which heavily influences bioavailability through drainage, induced lachrymation, drug binding to tear proteins, enzyme metabolization, electrolyte composition and pH/buffer effects [**5.46-5.48**]. The importance of the tear fluid as drainage has already been discussed, but the tear fluid provides other functions such as maintaining comfort lubricating the eyelids and epithelial cells of the cornea and

conjunctiva. It also performs many bactericidal functions and aids in the transport of oxygen and carbon dioxide [**5.46, 5.49, 5.50**]. The proteins, electrolytes, and enzymes have potential to greatly affect the efficiency of any delivery system [**5.51**]. The tear layer is typically 9-10 μm thick and can be thought of as having three layers: one of lipids which can reduce and control tear evaporation [**5.52**], an aqueous layer containing proteins and salts [**5.53**], and a mucous layer which coats the epithelium and improves wettability [**5.54**]. There are several common proteins in the tear fluid, but albumin makes up the majority. Common protein concentrations can be between 6-10 mg/ mL [**5.46**]. Enzymes present in the tear film can include lysozyme (1.5-3 mg/ mL), lactate dehydrogenase, pyruvate kinase, malate dehydrogenase, amylase and esterase [**5.46, 5.55, 5.56**]. Electrolytes in the tear fluid include sodium, potassium, calcium and choride and play an important role in the osmotic pressure of the eye [**5.49, 5.57**]. These electrolytes can interact with ionic drugs and affect residence time [**5.58**] and in some cases affect the mechanism of delivery. Typical pH values reported for tear fluid are 7.4. The excellent review in reference [**5.46**] is recommended to the reader for greater detail.

The obvious progression to ointments and adhesive polymers to resist tear flow through viscosity is unpopular among consumers as they are difficult to apply and blur vision. As such, contact lenses demonstrate the best option to overcome lacrimal fluid drainage. Hydrogel contact lenses are in direct contact with the surface of the eye, increasing the probability a molecule will be absorbed into the eye. Furthermore, the polymer lens protects the reservoir of drug inside the lens from being washed away by the lacrimal system.

The conjunctiva is a vascularized mucous membrane which covers the anterior part of the sclera and lines the inner surface of the eyelids [**5.7, 5.59**]. The conjunctiva is an important source of drug loss in the eye as the permeability of the conjunctiva for most drugs is higher than for the cornea. In addition, the surface area of the vasculature is much larger (16-18 cm^2) than the cornea (1 cm^2) [**5.21**]. Drug uptake is typically an order of magnitude greater for the conjunctiva than the cornea [**5.9, 5.60**]. Once absorbed by the conjunctiva, the drug moves throughout the body by the circulatory system, exposing other organs to the drug. New studies have demonstrated that several transporters (e.g. P-glycoprotein, amino acid, etc) play a critical role in achieving influx and efflux of drugs through the conjunctiva. Control over drug loss to the conjunctiva can be controlled by several pathways including selection of drug that is more likely to be absorbed by the cornea or sclera; the reader is referred to the excellent review of permeability ratios for ocular tissues [**5.61**]. In addition, increasing the residence time on the cornea can contribute to higher selectivity of drugs. Eye drops show no selectivity between tissues. Mucoadhesive polymers and hydrogel lenses increase residence times.

5.3.2. Posterior Barriers of the Eye and the Optic Nerve. The vitreous humor is the liquid portion inside the ocular sphere. The fluid gives the eye its size and shape and is responsible for 2/3 of the mass and volume of the eye. The humor is 99% water with a very small amount of collagen. The collagen gives the humor the viscosity and consistency of a gel. The humor serves as the continuous phase between the front and rear of the eye. Drugs topically delivered to treat the posterior of the eye must pass through the anterior eye into the vitreous humor and through the humor to the back of the eye. Any drug intended to treat posterior eye diseases must be water soluble and must be

present in concentrations sufficient to treat the condition. In this, therapeutic contact lenses may improve upon eye drops as a higher concentration of drug can be absorbed between the anterior sections of the eye and promote higher concentrations of drug in the humor. It must be noted, though, that more common methods of delivery to the posterior occurs through intravitreal injections, which delivers much more mass directly to the humor that can be achieved through contact lenses, but injections are uncomfortable and typically done by professionals and cannot be done by patients. Contact lenses can be placed and removed by patients and are much more comfortable.

After passing through the ocular surface barriers, the drug reaches the aqueous humor, an anterior segment between the cornea and the lens. The aqueous humor is a clear fluid secreted by the iris-cillary body that circulates through the anterior chamber at approximately 1% per minute and drains out via the trebecular meshwork. It supplies nutrients and antioxidants to the cornea and lens without interfering with visual clarity [**7**]. Typically, less than 3% of the instilled drug reaches this point. Drugs delivered via the corneal route can be diluted to the point of inefficacy, even before moving into the posterior segment. Drugs are eliminated from the anterior chamber via aqueous humor turnover, metabolic pathways, blood circulation of the anterior uvea [**5.62, 5.63**], and metabolic enzymes, such as esterases, aldehydes, and keton reductases [**5.64**] located in ocular tissues.

The blood ocular barriers consist of the blood-aqueous barrier, which is located in the anterior part of the eye, and the blood-retinal barrier that is located in the posterior part of the eye. These barriers separate the eye from the rest of the body by using tight junctions and efflux proteins. The blood-aqueous barrier (BAB) is formed by the

epithelial cells of the iris-ciliary body and the blood-retinal barrier (BRB) is composed of two parts: the outer part consists of the retinal pigment epithelium (RPE) and the inner part of the retinal endothelial cells [**5.64**]. In the posterior segment, the tissues support the retina and encase the vitreous humor, a highly viscous fluid. The choroid, a vascularized tissue, is inside the sclera and nourishes the outermost layers of the retina. The retina is inside the choroid and it is constituted of several layers which can be classified into two major groups: the neural retina and the RPE that rest on the Bruch's membrane, the innermost layer of the choroid [**5.7**].

The blood-retinal barrier limits drug distribution from the blood stream to the posterior ocular tissues, and it is a selectively permeable to more lypophilic molecules [**5.60**]. However, it is impermeable to polar or charged compounds in the absence of a transport mechanism [**5.5**]. It shares similar features with blood–brain barrier (BBB). RPE is capable of a number of specialized transport processes. It allows selective exchange of nutrients between the choroid and retina [**5.64**]. The RPE has tight junctions that form a strong barrier to the permeation of hydrophilic drugs from the sclera or systemically delivered drug from the choroid into the neural tissue and the vitreous humor [**5.7**], but in the case of small lypophilic drugs the sclera and RPE have similar permeabilities [**5.65**]. The retinal endothelial cells prevent that drugs coming from the circulatory system from reaching the neural retina. The retinal endothelial cells have intercellular tight junctions limiting the paracellular transport of compounds. The retinal vessel walls have poor permeation of small hydrophilic molecules and proteins, while lypophilic compounds can penetrate more easily [**5.66**].

Drug delivery to the posterior of the eye can follow numerous routes. When using topical administrations, the drugs that are absorbed into the eye through corneal route first enter the aqueous humor and then are distributed to the intraocular tissues, (i.e. iris-ciliary body, vitreous, and choroid-retina), and the drugs that penetrate into the eye via non-corneal routes enter the conjunctiva and sclera, reach the vitreous and must pass across choroid and RPE without entering the aqueous humor [**5.37**]. Consequently, they will generally be diluted or eliminated to a sub-therapeutic dosage.

Drug delivery inserts and injections have been the most common methods of reaching the posterior segment of the eye [**5.7**]. These techniques are efficient in delivering the drug; however, they are invasive and may carry serious complications such as postoperative endophthalmitis, intravitreal hemorrhage, and retinal detachment [**5.7, 5.67**]. Anterior segment complications have been observed in some patients following periocular injections, such as cataract, strabismus and high intraocular pressure [**5.60**]. Additionally, some drugs are delivered through systemic circulation with oral or intravenous injections that reach the ocular posterior segment in minute amounts, and expose the body to a systemic toxicity [**5.68**].

Intravitreal injections can be introduced into the vitreous in solution, in a depot formulation or dispersed in microparticles. Particles with molecular weight between 40-70 KDa have the highest retention times in the eye [**5.60**], however as the diameter of particles rises to 50 nm, light scattering interferes with vision [**5.69**]. Drugs are eliminated from the vitreous humor via: 1) the anterior chamber by diffusion across the vitreous to the posterior chamber and elimination via the aqueous turnover and iris blood vessels or 2) across the blood-retina barrier into systemic circulation [**5.8**]. Sub-

conjunctival injections can deliver drug into the sclera while bypassing the epithelial barriers. The drug can diffuse laterally through the sclera and reach the choroid and the retina.

5.3.3. Effect of Drug Nature on Bioavailability and Penetration. Drug selection can be used to overcome anatomical resistance to diffusion by selecting drugs that are more likely to be absorbed by the barrier tissues. As discussed below, drugs of different natures favor different methods of delivery and permeate the tissues at different rates. Selection of drugs with similar natures as the targeted tissue aids the overall effectiveness of treatment.

5.3.3.1. Obstacles to the Transport of Hydrophobic Drugs. Highly lypophilic drugs cannot be formulated in an aqueous medium and need to be prepared as emulsions or suspensions. These formulations often suffer stability problems. Particle size should be under 10 μm in diameter for maximum comfort and minimize irritation and reflex tearing [**5.70**]. The discomfort they cause in the patients may lead to blinking and lacrimation, hence the loss of a considerable amount of drug. The remaining drug on the pre-corneal surface will have to diffuse into the lacrimal fluid before it can penetrate through the corneal barriers [**5.2, 5.71**].

The transcellular pathway is the main route of lypophilic drug transported from the lacrimal fluid to the aqueous humor [**5.8, 5.59**]. At the corneal epithelium, lypophilic drugs can transport quickly through the transcellular route due to the lypophilic nature of the barrier. For the most lypophilic drugs, the stroma is a rate limiting barrier. This is not due to the hydrophilic nature of the stroma, but rather to the slow partitioning of lypophilic compounds from the epithelium to the stroma. However, for highly lypophilic

drugs, crossing the stroma is the rate limiting step, thereby determining corneal permeability. With some drugs, the stroma can act as a reservoir from which the drug will be slowly delivered to the aqueous humor [**5.17, 5.61**].

5.3.3.2. Obstacles to the Transport of Hydrophilic Drugs. Hydrophilic drugs can be easily presented as aqueous eye-drop solutions; however, they encounter some difficulties in passing from the tear film to the corneal/conjunctival epithelium, having a low residence time over the pre-corneal surface [**5.71**].

The paracellular pathway is the most common transport for hydrophilic drugs through corneal and non-corneal (conjunctival/scleral) epithelium [**5.69**]. The intercellular spaces at the most superficial corneal epithelial cells have tight junctions that serve as a selective barrier between adjacent cells, thus, this paracellular route is limited to very low molecular weight of hydrophilic compounds or ions (< 350 Da) [**5.7, 5.17, 5.72**]. Regarding the absorption by the non-corneal route, many studies have shown that the conjunctiva is a leakier epithelium, which plays an important role in the absorption of large hydrophilic drugs such as proteins and peptides (i.e., poor corneal permeability compounds) [**5.60, 5.37, 5.73**]. The conjunctiva may allow the permeation of hydrophilic compounds with a molecular weight up to 20 KDa [**5.17**], whose molecular radius is around 4.9 nm [**5.74**], and the sclera may allow permeation of a molecular size up to 70 KDa [**5.5**]. Finally, the endothelium presents large intercellular junctions, which does not make it a rate limiting barrier for hydrophilic compounds. It has been estimated that drugs with molecular diameter up to 20 nm can diffuse across normal endothelium [**5.74**].

The non-corneal pathway is favored for delivery of hydrophilic drugs, bypassing the anterior chamber and permitting direct access to the intraocular tissues of the

posterior segments. These ocular barriers limit the utility of hydrophilic drugs in ocular therapies. Different attempts have been tried for increasing the residence time of these types of drugs, using mucoadhesive polymers (e.g. polysaccharides), in situ gel-forming systems and viscosity enhancers (e.g. cellulose derivatives). Since hydrophilic drugs penetrate much easier via paracellular pathway, transcellular transport is possible by using a limited range of transporters present on the corneal and conjunctival epithelial cells [**5.7**].

5.3.3.3. Obstacles to the Transport of Ionizable Drugs. Permeation of an ionizable drug (weak bases and weak acids) depends on the chemical equilibrium between the ionized and unionized molecules of the drug [**5.32**]. The unionized molecule usually penetrates the lypophilic membranes more easily than the ionized ones. In the case of ionized molecules, the charge of the molecule also affects their corneal permeation [**5.75**]. The corneal epithelium is negatively charged at physiological pH (or above its isoelectric point: 3.2); as a result, negatively charged molecules permeate slower than positively charged and neutral molecules [**5.75**].

5.4. Tables and Figures.

Table 5.1. Ancient Egyptian Recipes for Ocular Treatments.*

Condition	Common Ingredients for Treatments
Poor Vision	Asafetida, balsam resin, marrow, myrrh, malachite, galena
Eye Trauma and Tumors	Aloe, balm of mecca, blood, dung, frankincense, red ochre, yellow ochre, malachite, galena
Inflammation	Aloe, galena, malachite, myrrh, red and yellow ochre, ink-powder
Conjunctivitis	(*Paste*) incense, myrrh, lead salt, sodium hydroxide, lead and honey
Chronic Conjunctivitis (known as Hetae)	(*Ointment*) malachite, gazelle dung, white oil. To be applied topically with a vulture feather and covered with a bandage for four days
Constriction or Occlusion of the Pupil	Saltpeter and ebony wood shavings
Calcifications in Meibomian Glands	Topical mixture of red lead, fuller's earth, sodium hydroxide, and antimony
Blow to the Eye	Apply to the eyelid a fluid containing honey and dried excrement from a child
Corneal Scars	Turtle brain mixed with honey
Bleeding in the Eye	Drip into the eyes palm fruit powder mixed with milk of a woman just delivered of a boy then wash the powder mixed with cow's milk
Night Blindness	Liver of ox, roasted and crushed
White Spots	Reciting a prayer over gall of a tortoise
Burning Eyes	Bone marrow from an ass jaw or tooth, with water to form a cream and apply to the temple
Pterygium	Mixture of sate, frankincense, and pelicans dung or mixture of stibium, honey and lizards dung

*Table is compiled from data in references [**5.1, 5.3**].

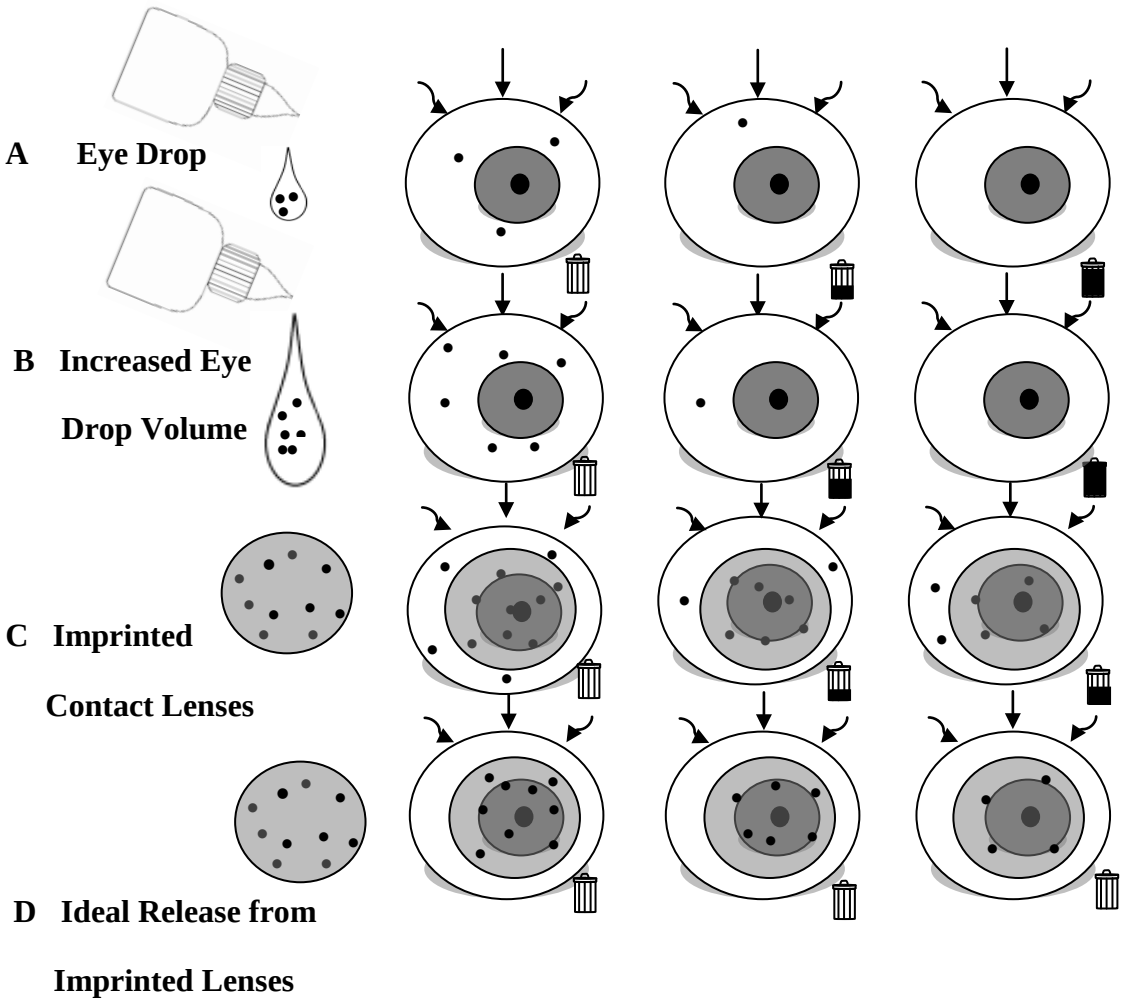


Figure 5.1. Delivery Options and Drug Loss.

Drugs delivered through typical tear drop volume (**A**) are typically removed in 15 minutes with only 1-7% of the drug absorbed productively by the eye. (**B**) Increasing drop volume of same drug concentration corresponds to a linear increase in the tear drainage rate resulting in similar or lower bioavailability with more drug lost reaching systemic circulation (represented by trash cans). (**C**) Delivery via imprinted contact lenses increases residence time of the drug on the eye surface and extends delivery time increasing productive absorption and decreasing drug loss. (**D**) The ideal imprinted

contact with drug release rate correlating with the rate of drug absorption by the eye. The curved arrows represent lacrimation or tear flow rate.

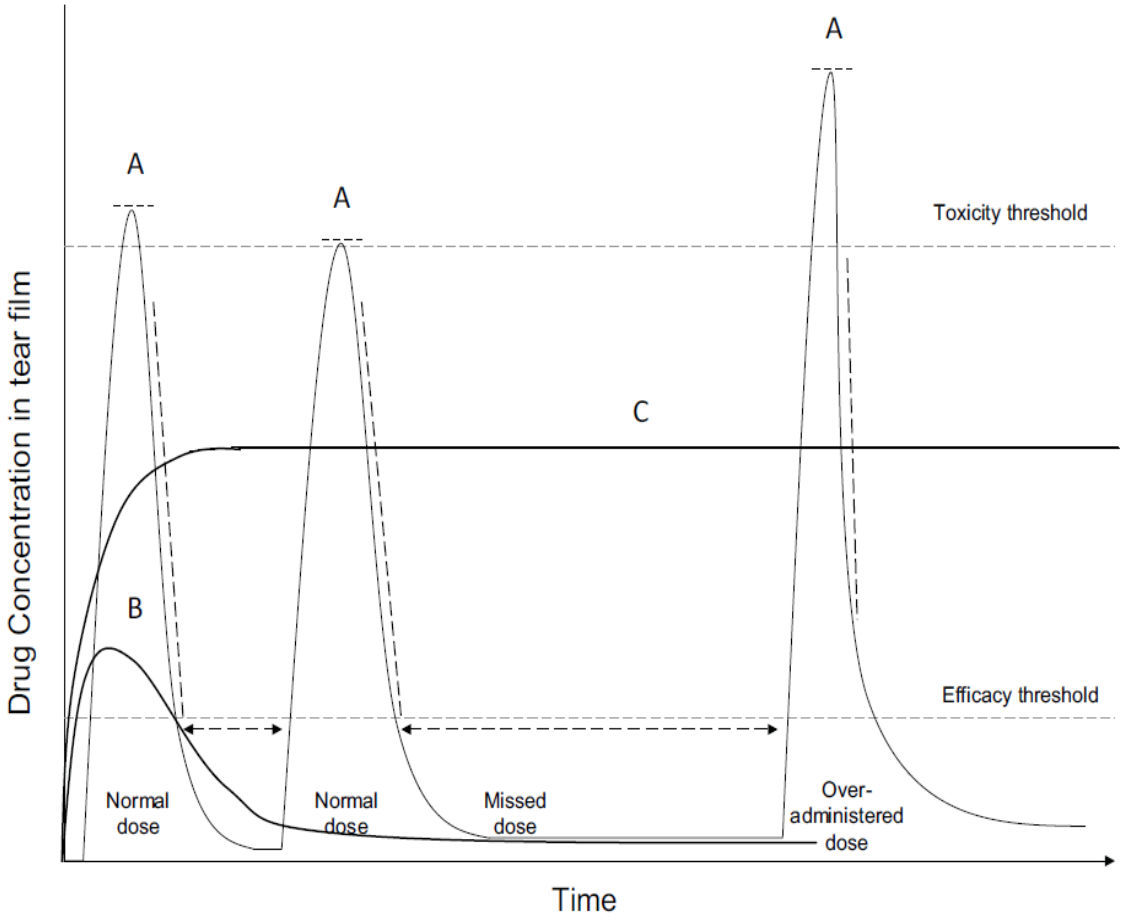


Figure 5.2. Drug Concentration in Ocular Tear Fluid through Delivery Options.

When an eye drop is applied to the eye, the tear film concentration varies with time. (A) Immediately upon application, a maximum concentration is reached which quickly decreases due to lacrimation, drainage, and absorption dropping below the efficacy threshold until another drop is applied. If a dose is delayed or missed, the eye will be without therapeutic levels of drug. Relative heights of the eye drop concentration peak and elimination rate depends on factors such as force on the bottle, angle of application, patient administration, lacrimation, and drainage rate. (B) Drug soaked contact lenses administer small amounts of drug in a very short amount of time, making them virtually ineffective as drug carriers. (C) Imprinted contact lenses provide a controlled and sustained drug release where a constant concentration of drug can be achieved for an extended period of time.

5.5. References.

[5.1] Hirschberg J. History of Ophthalmology, Volume I: Antiquity. Bonne, 1982.

[5.2] Lang J. Ocular Drug Delivery Conventional Ocular Formulations. *Advanced Drug Delivery Reviews*. 1995; 16:39-43.

[5.3] Albert D. History of Ophthalmology. Blackwell Sciences, Inc. Cambridge; 1996.

[5.4] Albert D. Dates in Ophthalmology. Parthenon Publishing Group, New York; 2002.

[5.5] Hughes P, Olejnik O, Chang-Lin J, Wilson C. Topical and Systemic Drug Delivery to the Posterior Segments. *Advanced Drug Delivery Reviews*. 2005;57:2010-2032.

[5.6] Peyman G, Ganiban G. Delivery Systems for Intraocular Routes. *Advanced Drug Delivery Reviews*. 1995;16:107-123.

[5.7] Ali M, Byrne M. Challenges and Solutions in Topical Ocular Drug-Delivery Systems. *Expert Reviews of Clinical Pharmacology*. 2008;1(1):145-161.

[5.8] Urtti A. Challenges and Obstacle of Ocular Pharmacokinetics and Drug Delivery. *Advanced Drug Delivery Reviews*. 2006;58:1131-1135.

[5.9] del Amo E, Urtti A. Current and Future Ophthalmic Drug Delivery Systems: A Shift to the Posterior Segment. *Drug Discovery Today*. 2008;13(3/4):135-143.

[5.10] Mannermaa E, Vellonen K, Urtti A. Drug Transport in the Corneal Epithelium and Blood-Retina Barrier: Emerging Role of Transporters in Ocular Pharmacokinetics. *Advanced Drug Delivery Reviews*. 2006;58:1136-1163.

[5.11] Cunha-Vaz J. The Blood-Retina Barriers Systems. Basic Concepts and Clinical Evaluation. *Experimental Eye Research*. 2004;78:715-721.

[5.12] Raviola G. The Structural Basis of the Blood-Ocular Barriers. *Experimental Eye Research*. 1977;25:27-63.

[5.13] German E, Hurst M, Wood D. Eye Drop Container Delivery: A Source of Response Variation? *Ophthalmic and Physiological Optic*. 1997;17(3):196-204.

[5.14] Rubinstein M, Evans J. Therapeutic Contact Lenses and Eye Drops – Is There a Problem? *Contact Lens and Anterior Eye*. 1997;20(1):9-11.

[5.15] Noecker R. Effects of Common Ophthalmic Preservatives on Ocular Health. *Advances in Therapy*. 2001;18(5):205-215

[5.16] Winfield A, Jessiman D, Williams A, Esakowitz. A Study of the Causes of Non-Compliance by Patients Prescribed Eye Drops. *British Journal of Ophthalmology*. 1990;74:477-480.

[5.17] Jarvinen K, Jarvinen T, Urtti A. Ocular Absorption Following Topical Delivery. *Advanced Drug Delivery Reviews*. 1995;16:3-19.

[5.18] Lederer C, Harold R. Drop Size of Commercial Glaucoma Medications. *American Journal of Ophthalmology*. 1986; 101:691-694.

[5.19] Lee V, Robinson J. Topical Ocular Drug Delivery: Recent Developments and Future Challenges. *Journal of Ocular Pharmacology*. 1986;2:67-108.

[5.20] Zaki I, Fitzgerald P, Hardy J, Wilson C. Comparison of the Effect of Viscosity on the Precorneal Residence of Solutions in Rabbit and Man. *Journal of Pharmacy and Pharmacology*. 1986; 38:463-466.

[5.21] Chrai S, Patton T, Mehta A, Robinson J. Lacrimal and Instilled Fluid Dynamics in Rabbit Eye. *Journal of Pharmaceutical Sciences*. 1973;62:1112-1121.

[5.22] Wichterle O, Lim D. Hydrophilic Gels for Biological Use. *Nature*. 1960;185:117-118.

[5.23] Sedlacek J. Possibilities of Application of Eye Drugs with the Aid of Gel-Contact Lenses. *Cesk Slov Oftalmol*. 1965;21:509-512.

[5.24] Newell F. Ophthalmology, Principles and Concepts, 6th Ed. St Louis, Mo: CV Mosby, 1986.

[5.25] Reinstein D, Silverman R, Rondeau M, Coleman D. Epithelial and Corneal Thickness Measurements by High-frequency Ultrasound Digital Signal Processing. *Ophthalmology*. 1994;101:140-146.

[5.26] Hitzenberger C, Baumgarter A, Drexler W, Fercher A. Interferometric Measurement of Corneal Thickness with Micrometer Precision. *American Journal of Ophthalmology*. 1994;118:468-476.

[5.27] Schoenwald R, Huang H. Corneal Penetration Behavior of β-Blocking Agents I: Physiochemical Factors. *Journal of Pharmaceutical Science*. 1983:72:1266-1272.

[5.28] Grass G, Robinson J. Mechanisms of Corneal Drug Penetration II: Ultrastructural Analysis of Potential Pathways for Drug Movement. *Journal of Pharmaceutical Sciences*. 1988:77:15-23.

[5.29] Liaw J, Robinson J. The Effect of Polyethylene Glycol Molecular Weight on Corneal Transport and the Related Influence of Penetration Enhancers. *International Journal of Pharmaceutics*. 1992:88:125-140.

[5.30] Huang A, Tseng S, Kenyon K. Paracellular Permeability of Corneal and Conjunctival Epithelia. *Investigative Ophthalmology and Visual Sciences*. 1989;30:684-689.

[5.31] Rojanasakul Y, Wang L, Bhat M, Glover D, Malanga C, Ma J. The Transport Barrier of Epithelia: A Comparative Study on Membrane Permeability and Charge Selectivity in the Rabbit. *Pharmaceutical Research*. 1992;8:1029-1034.

[5.32] Liaw J, Rojanasakul Y, Robinson J. The Effect of Drug Charge Type and Charge Density on Corneal Transport. *International Journal of Pharmaceutics*. 1990;16:2595-2612.

[5.33] Sieg J, Robinson J. Vehicle Effects on Ocular Drug Bioavailability II: Evaluation of Pilocarpine. *Journal of Pharmaceutical Sciences*. 1977;66:1222-1228.

[5.34] Maren T, Jankowska L. Ocular Pharmacology of Sulfonamides: The Cornea as Barrier and Depot. *Current Eye Research*. 1985; 4:399-408.

[5.35] Brechue W, Maren T. pH and Drug Ionization Affects Ocular Pressure Lowering of Topical Carbonic Anhydrase Inhibitors. *Investigative Ophthalmology and Visual Sciences*. 1993; 34:2581-2587.

[5.36] Shih R, Lee V. Rate Limiting Barrier to the Penetration of Ocular Hypotensive Beta Blockers Across the Corneal Epithelium in the Pigmented Rabbit. *Journal of Ocular Pharmacology and Therapeutics*. 1990;6:329-336.

[5.37] Ahmed I, Gokhale R, Shah M, Patton T. Physiochemical Determinants of Drug Diffusion Across the Conjunctiva, Sclera and Cornea. *Journal of Pharmaceutical Sciences.* 1987;76:583-586.

[5.38] Wang W, Sasaki H, Chien D, Lee V. Lipophilicity Influence on Conjuctival Drug Penetration in the Pigmented Rabbit: A Comparison With Corneal Penetration. *Current Eye Research*. 1991;10:571-579.

[5.39] Chien D, Sasaki I, Bundgaard I, Buur A, Lee V. Role of Enzymatic Lability inb the Corneal and Conjuctival Penetration of Timolol Ester Prodrugs in the Pigmented Rabbit. *Pharmaceutical Research*. 1991;8:728-733.

[5.40] Schoenwald R, Ward R. Relationship Between Steriod Permeability Across Excised Rabbit Cornea and Octanol-Water Partition Coefficients. *Journal of Pharmaceutical Sciences*. 1978;67:768-788.

[5.41] Jiang J, Geroski D, Edelhauser H, Pausnitz M. Measurement and Prediction of Lateral Diffusion within Human Sclera. *Investigative Ophthalmology and Visual Science*. 2006;47(7):3011-3016.

[5.42] Lee V, Robinson J. Mechanistic and Quantitative Evaluation of Precorneal Pilocarpine Disposition in Albino Rabbits. *Journal of Pharmaceutical Sciences*. 1979;68:673-684.

[5.43] Mishima S, Gasset A, Klyce S, Baum J. Determination of Tear Volume and Tear Flow. *Investigative Ophthalmology*. 1966;5(3):264-276.

[5.44] Lee V, Robinson J. Review: Topical Ocular Drug Delivery: Recent Developments and Future Challenges. *Journal of Ocular Pharmacology*. 1986;2:67-108.

[5.45] Zaki I, Fitzgerald P, Hardy J, Wilson C. A Comparison of the Effect of Viscosity on the Precorneal Residence of Solutions in Rabbit and Man. *Journal of Pharmaceutics and Pharmacology*. 1986;38:463-466.

[5.46] Baeyens V, Gurny R. Chemical and Physical Parameters of Tears Relevant for the Design of Ocular Drug Delivery. *Pharmaceutica Acta Helvetiae*. 1997;72:191-202.

[5.47] Lee V, Robinson J. Review: Topical Ocular Drug Delivery: Recent Developments and Future Challenges. *Journal of Ocular Pharmacology*. 1986;2:67-108.

[5.48] Lee V. Precorneal, Corneal and Postcorneal Factors. Mitra A (Ed) Ophthalmic Drug Delivery Systems. New York:Marcel Dekker,1993.

[5.49] Milder B. The Lacrimal Apparatus. Moses RA, Hart WMJ (Eds). Adlers Physiology of the Eye, Clinical Application. St Louis MO: CV Mosby Company.

[5.50] Lamberts D. Basic Science Aspects: Physiology of the Tear Film. Smoli G,Thoft RA (Eds). The Cornea: Scientific Foundations and Clinical Practice. Boston: Little, Brown anc Company,1987.

[5.51] Mikkelson T . Altered Bioavailability of Drugs in the Eye Due to Drug-Protein Interactions. *Journal of Pharmaceutical Sciences*. 1973;62:1648-1653.

[5.52] Holly F. Formation and Stability of the Tear Film. *International Ophthalmology Clinicals*. 1973;13:73-96.

[5.53] Mishima S. Some Physiological Aspects of the Precorneal Tear Film. *Archives of Ophthalmology*. 1965;73:233-241.

[5.54] Prydal J, Campbell F. Study of Precorneal Tear Film Thickness and Structure by Interferometry and Confocal Microscopy. *Investigative Ophthalmology and Visual Sciences*. 1992;33:1996-2005.

[5.55] Van Haeringen N, Glasius E. Enzymatic Studies in Lacrimal Secretion. *Experimental Eye Research*. 1974;19:135-139.

[5.56] Polanski J, Weinreb R. Anti-Inflammatory Agents: Steroids as Anti-Inflammatory Agents. Sears M (Ed) Pharmacology of the Eye. Heidelberg:Spring-Verlag, 1984.

[5.57] Iwata S. Chemical Composition of the Aqueous Phase. *International Ophthalmology Clinical*. 1973;13:29-46.

[5.58] Rozier. Gelrite: A Novel Ion-Activated, in situ Gelling Polymer For Ophthalmic Vehicles. Effect on the Bioavailability of Timolol. *International Journal of Pharmaceutics*. 1989;163-168.

[5.59] Hosoya K, Lee V, Kim K. Roles of the Conjunctiva in Ocular drug delivery: a Review of Conjunctival Transport Mechanisms and Their Regulation. *European Journal of Pharmaceutics and Biopharmaceutics*. 2005; 60(2):227-240.

[5.60] Gaudana R, Jwala J, Boddu S, Mitra A. Recent Perspectives in Ocular Drug Delivery. *Pharmaceutical Research*. 2009; 26(5):1197-1216.

[5.61] Prausnitz M, Noonan J. Permeability of Cornea, Sclera, and Conjunctiva: A Literature Analysis for Drug Delivery to the Eye. *Journal of Pharmaceutical Sciences*. 1998; 87(12):1479-1488.

[5.62] Schoenwald R. Ocular Drug Delivery: Pharmacokinetic Considerations. *Clinical Pharmacokinetics*. 1990; 18(4):255-69.

[5.63] Maurice D, Mishima S. Ocular Pharmacokinetics. Sears M (Ed). Handbook of Experimental Pharmacology. Berlin-Heidelberg: Springer-Verlag; 1984: 19-116.

[5.64] Duvvuri S, Majumdar S, Mitra A. Role of Metabolism in Ocular Drug Delivery. *Current Drug Metabolism*. 2004; 5(6):507-15.

[5.65] Pitkanen L, Ranta V, Moilanen H, Urtti A. Permeability of Retinal Pigment Epithelium: Effects of Permeant Molecular Weight and Lipophilicity. *Investigative Ophthalmology and Visual Science.* 2005; 46(2):641-6.

[5.66] Hornof M, Toropainen E, Urtti A. Cell Culture Models of the Ocular Barriers. *European Journal of Pharmaceutics and Biopharmaceutics*. 2005; 60(2):207-225.

[5.67] Hosoya K, Tachikawa M. Inner Blood-Retinal Barrier Transporters: Role of Retinal Drug Delivery. *Pharmaceutical Research*. 2009; 26(9):2055-65.

[5.68] Tamesis R, Rodriguez A, Christen W, Akova Y, Messmer E, Foster C. Systemic Drug Toxicity Trends in Immunosuppressive Therapy of Immune and Inflammatory Ocular Disease. *Ophthalmology*. 1996; 103(5):768-75.

[5.69] Ghate D, Edelhauser H. Ocular Drug Delivery. *Expert Opinion on Drug Delivery*. 2006; 3(2):275-87.

[5.70] Prankerd R, Stella V. The Use of Oil-in-Water Emulsions as a Vehicle for Parenteral Drug Administration. *Journal of Parenteral Science and Technology*. 1990; 44(3).

[5.71] de la Fuente M, Raviña M, Paolicelli P, Sanchez A, Seijo B, Alonso M. Chitosan-based Nanostructures: A Delivery Platform for Ocular Therapeutics. *Advanced Drug Delivery Reviews*. 2010;62(1):100-117.

[5.72] Geroski D, Edelhauser H. Transscleral Drug Delivery for Posterior Segment Disease. *Advanced Drug Delivery Reviews*. 2001; 52(1):37-48.

[5.73] Schoenwald R, Deshpande G, Rethwisch D, Barfknecht C. Penetration into the Anterior Chamber via the Conjunctival/Scleral Pathway. *Journal of Ocular Pharmacology and Therapeutics*. 1997; 13(1):41-59.

[5.74] Horibe Y, Hosoya K, Kim K, Ogiso T, Lee V. Polar Solute Transport Across the Pigmented Rabbit Conjunctiva: Size Dependence and the Influence of 8-Bromo Cyclic Adenosine Monophosphate. *Pharmaceutical Research*. 1997; 14(9):1246-1251.

[5.75] Rojanasakul Y, Robinson J. Transport Mechanisms of the Cornea: Characterization of Barrier Permaselectivity. *International Journal of Pharmaceutics*. 1989; 55(2-3):237-246.

[5.76] Arrington G. A History of Ophthalmology. MD Publications, New York; 1959.

[5.77] Heitz R. The History of Contact Lenses, Volume One: Early Neutralizations of the Corneal Dioptric Power. Bonne, 2003.

[5.78] Heitz R. The History of Contact Lenses, Volume Two: Keratoconus and the Use of Early Contact Lenses (1888-1920). Bonne, 2003.

[5.79] White C, Byrne M. Molecularly Imprinted Therapeutics Contact Lenses. *Expert Opinion on Drug Delivery*. 2010;7(6):765-780.

CHAPTER 6

CONTACT LENSES AS DRUG DELIVERY PLATFORMS

The concept of effective drug delivery from combination devices dates back to Egyptian and Roman eras [**6.1-6.2**]. Early attempts to create such devices capable of providing therapeutic to the eye in an efficient manner (i.e. overcoming the natural barriers of the eye and supplying medication in a continuous dose) used cloth bandages soaked in therapeutic solutions (e.g. honey). The linen served as the diffusion barrier to delay the release of the therapeutic reservoir and extend the residence time on the eye. This device is a unsophisticated attempt to gradually release a drug reservoir to the eye. The first description of drug delivery through soft hydrogel contact lenses was first presented by Otto Wichterle in 1965 [**6.3-6.4**].

Adolf Fick developed the first modern incarnation of contact lenses from blown glass in 1887 [**6.5, 6.6**]. However, the glass contacts were uncomfortable and easily broken and could be worn only for short periods of time before eye damage occurred. At the time, the importance of oxygen and ion transport to the eye was not understood, but the impermeability of glass to oxygen and water caused considerable distress to the eye. Additionally, protein and lipid attachment to the surface of the glass decreased lens clarity and caused increased biofouling, increasing the discomfort felt by the lens wearer. Attempts were made to coat the glass with a hydrophilic material to make it more comfortable, but this was a temporary result which was ultimately futile. The push to

make lenses more comfortable led to the development of polymethyl methacrylate (PMMA) lenses in 1948 by Kevin Tuohey [**6.7**]. PMMA lenses showed better fitting, increased toughness and were easier to produce. They quickly replaced glass lenses as the lead commercial product. Once again, contacts lenses could be worn only for short periods of time due to low oxygen and water transport through the lens to the eye. Improvements in transport properties were seen due to increased permeability (relative to glass) and that PMMA lenses could be designed to float in the tear fluid, allowing transport around and under the lenses. Attempts were made to make the lenses more comfortable and less damaging to the eye by adding hydrophilic co-monomers, such as N-vinyl pyrrolidone (NVP) or methacrylic acid (MAA), or by coating the surface to increase wettability [**6.8**]. Other attempts included the alteration of lens shape and diameter [**6.9**] to increase the transport of tear flow and oxygen under the lens. Also, lens thickness was decreased to be as thin as possible to increase gas permeability, often sacrificing mechanical properties.

The first hydrogel lenses were patented by Otto Wichterle and further described in his seminal article published in 1960 [**6.3, 6.10**]. Until the late 1990's, hydrogels (polymers that swell in water without dissolving and usually contain 30-80% water) have dominated the contact lens industry. Hydrogel lenses demonstrated the highest comfort and best fitting and were soon prescribed for extended, continuous wear to meet consumer demand for "natural vision" (i.e. vision when waking) [**6.7**]. However, it was found in the 70's and 80's that continuous wear of these lenses damaged the eyes through oxygen starvation. As a result, the FDA rescinded all 30 day continuous wear lenses in

1989 [**6.11**]. Since then, there has been high interest in oxygen permeability of lens materials [**6.12**].

The importance of oxygen transport through lenses cannot be overstated. Oxygen reaches the cornea directly from the atmosphere but when a lens is placed on the eye, a barrier to oxygen transport exists. Insufficient oxygen flux causes discomfort to the wearer and, eventually, eye fatigue, corneal edema and severe damage to the cornea. Oxygen permeability (represented as Dk) is characteristic to lens materials regardless of thickness. It is reported in barrers, which is equivalent to $1x10^{-10}$ cm^3 [STP]/(sec cm^2 [cm Hg]) [**6.11**]. Dk/t or Dk/l is commonly used to normalize oxygen permeability to thickness and generally expressed as barrers/millimeter. Dk/t should be maintained between 87-125 barrer/mm to maintain health in normal open eyes. Below 80 barrers/mm, damage occurs with prolonged wear [**6.13**]. When eyes are closed, oxygen transport is negligible and the minimum Dk/t should be at least 85 barrers, though recent research indicates that a Dk/t of 125 barrers is more accurate [**6.14**]. Each new material has shown a marked increase in Dk/t and remains one of the more important limiting factors in lens wear. Each year more lenses become available that show increased oxygen permeability as shown in **Figure 6.1**. **Figure 6.1** was been compiled from *Physician's Desk Reference for Ophthalmology* [**6.15, 6.16**] and *Contact Lens Spectrum* [**6.17-6.25**].

The first soft contact lenses had Dk values ranging from 8-20 barrers [**6.11**]. The first attempts to improve the Dk increased the water content in lenses. However, this method is by necessity one of diminishing returns. Starting at the Dk of the pure polymer (water content = 0), a linear increase can be approximated as the fraction of polymer in the lens decreases [**6.26, 6.27**]. However, as the water content approaches 1, the Dk levels

off at ~80 barrers, which is that of pure water [**6.11**]. Lenses with up to 90% water have been developed, but mechanical properties of the lens are often poor. The drive for a highly permeable material resulted in the development of polydimethyl siloxane (Dk = 600 barrers) [**6.11**].

This novel material was first introduced to the commercial contact lens market by Dow Corning in 1980 [**6.28**]. The material was highly permeable to oxygen due to the bulkiness and flexibility and movement of the polymer backbone [**6.11**]. But since it had very low water content, this lens lacked necessary transport properties for water, proteins and ions. Since an entirely silicone lens is highly hydrophobic, increased lens fouling and disruption of the lipid layer necessitated treating the surface with a hydrophilic coating to provide more comfort to the wearer and to prevent lens adhesion to the cornea. Currently, there is only one brand of purely silicone contact lens available on the market. The silicone lenses have been entirely replaced by highly oxygen permeable polymers based on polydimethyl siloxane (PDMS) macromers. These lenses are typically copolymers of PDMS macromers, TRIS and some other hydrophilic monomer usually DMA. As a result, silicone hydrogel lenses (SiHy) are not as hydrophobic as the purely silicone lenses and allow some ion permeability. The ratio of hydrophobic to hydrophilic components in the lens can be adjusted to attain Dk values greater than 100 barrers and promote wear comfort [**6.29**].

The first silicone hydrogels appeared on the market in 1998 [**6.30**]. Popular with consumers, silicone hydrogel lenses seemed to initially meet the demand for more “natural vision”(i.e. vision upon waking) and have proven through clinical studies to be more comfortable than traditional hydrogels [**6.11**]. The development of silicone

hydrogel materials made safe extended wear contact lenses possible. CIBA's Focus Night and Day and Bausch and Lomb's PureVision were approved by the FDA for 30 day continuous wear in late 2001 [**6.30**]. Many of the adverse effects of continuous wear hydrogels, but not all, are eliminated by the use of silicone hydrogels [**6.11, 6.35**].

6.1. Controlled Release Methods from Soft Contact Lenses.

The progression from glass lenses to highly permeable silicone hydrogel lenses has shown that material design can be an effective method of controlling adverse events associated with contact lens wear. However, consumers still report dissatisfaction with contact lenses. Bacterial colonization, contact lens induced dry eye (CLIDE), and end of day discomfort are still observed in many wearers. End of day discomfort is reported by up to 80% of contact lens wearers in the US [**6.31-6.34**]. Incidents of microbial keratitis still occur with undesirable frequency [**6.35**]. It is possible, however, to overcome many of these problems with drug delivery from contact lenses. **Table 6.1** demonstrates the incredible variety of drugs demonstrated in the literature to release from contact lenses for treatment for an equally diverse array of conditions. However, wide spread use of TSCls has not yet merged into commercial lenses. This is due to several factors, including materials and release time. To successfully integrate with commercial lenses, drug releasing lenses must be developed correlating to the trends in the current market such as silicone hydrogels and tailoring release times to overlap with the current wear times (**Chapter 3**).

6.1.1. Diffusion Controlled Release. Typically, diffusion control lenses have a high initial rate of release (sometimes referred to as a burst release) and short delivery times typically much less than 12 hrs and often release is complete within 1 hr. The

diffusion process occurs with minor control over release rates and dose and is considered to be a passive method of controlling release. Different lens materials often yield different release rates of the drug due to drug solubility within the polymer lens and water content as well as crosslink density. In traditional hydrogels, water content had to be high due to comfort and oxygen permeability and other requirements. As water content increased, the transport of drugs through the lens would mimic that of diffusion through water. Diffusion methods such as drug soaked lenses remain popular due to the ease of manufacture and loading of the drug though no viable commercial therapeutic lens can be produced with such a mechanism to control drug elution.

6.1.1.1. Drug Soaked Lenses. However, diffusion controlled and drug soaked lenses have been the predominant forms of therapeutic contact lenses to date. It is worth noting, however, that while diffusion controlled lens delivery has been unsuccessful in producing commercially viable products, the variety of drugs demonstrated to load into lenses highlights the potential for growth in the field. Also, many clinical trials using drug soaked lenses have been performed in both human and rabbit models and have implied or explicitly demonstrated increased drug bioavailability from contact lenses compared to eye drops.

The first published account of drug release from hydrogel contact lenses occurred by replacing the water used as solvent in the lens prepolymer with 50 milligrams of 1% homatrope solution in 1965 [**6.36**]. Homatrope is used for nerve paralysis and pupil dilation in ocular procedures. Testing on 25 eyes showed complete pupil dilation for about 10 hours while wearing the lens. In addition, the first indications that delivery from hydrogels is more effective and increases bioavailability compared to contact lenses was

demonstrated when a lens formulated with a 1% mesocaine solution instead of water relieved sensation in the cornea in less time than 1% solution applied through eye drops [**6.36**]. The procedure of loading contact lenses through dispersing the drug in the lenses prepolymer solution and polymerizing the network trapping the drug is referred in this review as direct embedding.

Pilocarpine is an anti-glaucoma treatment shown to reduce intraocular pressure (IOP) and has been well documented in release from hydrophilic therapeutic contact lenses (**Table 6.1**). Pilocarpine was loaded into afocal Sauflon (vinyl pyrrolidone and acrylic copolymer) lenses for use as bandage lenses by soaking in 1% pilocarpine solution for at least 3 days [**6.37**]. Intraocular pressure was observed to drop an average of 36% within 30 min of lens placement and remained effective for at least 2 hours. After 2 hours, the average drop in IOP was found to be 55% compared to the 50% drop in IOP in patients treated with 4% pilocarpine eye drops [**6.37**]. The lenses were found to contain 400-500 μg pilocarpine after soaking for 24 hours and released for 2 hours [**6.37**]. Further testing with Sauflon lenses demonstrated similar results (i.e. release time = 2 hrs and loading of 700 μg pilocarpine/ lens) where release strongly correlated to water content where Sauflon (which is 70-90% water) delivered more pilocarpine to the eye and loaded in 3-12 hours after being dried [**6.38**].

Bionite lenses were investigated with similar results with 90% of the loaded drug from 0.5, 1 and 4% pilocarpine solutions released within 4 hrs in both in vitro (3 mL DI water) and in vivo (10 human eyes) models [**6.39**]. Poly(hydroxylethylmethacrylate) (PHEMA) lenses were shown to deliver less pilocarpine and require longer soak times to saturate with pilocarpine [**6.40**]. An attempt to prolong residence time of pilocarpine by

applying 1% pilocarpine drops while wearing lenses (the hypothesis suggested that the lens would absorb pilocarpine from the drop before draining and the lens would slowly elute the absorbed drug) reduced IOP for up to 24 hrs [**6.84**]. However, the results were variable and were undoubtedly difficult to repeat. Though pilocarpine was heavily investigated with therapeutic lenses, uncertainty as to toxic concentrations, insignificant release times and the development of more effective anti-glaucoma therapeutics rendered these devices uninteresting from a treatment perspective. However, the published data showed that bioavailability increased when lower concentrations of pilocarpine were delivered from contact lenses than higher concentrations of pilocarpine delivered via eye drops.

Many other drugs have been loaded and released via drug soaked lenses and are summarized in **Table 6.1**. Polymyxin B and phenylphrine both showed increased effectiveness when delivered from hydrophilic contact lenses under human and leporine models [**6.84**]. Other drugs such as acetazolamide [**6.115**], ciprofloxacin [**6.91-6.93, 6.104, 6.119]**, cromolyn sodium [**6.42, 6.92**], dexamethasone [**6.114**], dexamethasone sodium phosphate [**6.42**], flurbiprofen [**6.47, 6.116, 6.117**], gentamycin [**6.104**], fluorescein [**6.41**], hyaluronic acid [**6.113**], idoxuridine [**6.92**], kanamycin [**6.104**], ketorolac tromethamine [**6.42**], ketitofen fumarate [**6.42**], lomefloxacin [**6.112, 6.121**], ofloxacin [**6.104, 6.121**], phenylephrine [**6.84**], prednisolone [**6.92**], norfloxacin [**6.121**], timolol [**6.47, 6.115**] and tobramycin [**6.104**] have been released from different materials and under a variety of conditions and represent a wide variety of molecular weights and solubility values. However, many of these results are redundant and simplistic so the reader is recommended to **Table 6.1** for more detail.

To emphasis the low potential for drug soaked lenses, the uptake and release of cromolyn sodium, ketotifen fumarate, keterolac tromethamine and dexamethasone sodium phosphate were compared between silicone hydrogel lenses and traditional hydrophilic lenses [**6.42**]. This paper was overwhelming evidence that both drug soaked silicone hydrogel lenses and traditional hydrogels lack the significant control over drug release rates necessary for the production of therapeutic contact lenses. Drug release was performed in 2 mL of saline. Regardless of material, the uptake of cromolyn sodium, ketorolac tromethamine and dexamethasone sodium phosphate was rapid and release was complete in less than an hour. Ketotifen fumarate demonstrated slower uptake and release was complete in approximately 5 hours.

6.1.1.2. Supercritical Solvent Soaked Lenses. In recent years, supercritical solvents have been of interest for many applications and supercritical CO_2 recently been used to load contact lenses [**6.47**]. Supercritical carbon dioxide was used to load four commercially available lenses with timolol maleate and flurbiprofen. Timolol maleate was selected as a model hydrophilic drug, which to treat glaucoma, while flurbiprofen, a non-steroidal anti-inflammatory drug (NSAID), was selected as a hydrophobic drug. Loading was achieved by soaking the lenses in a concentrated supercritical CO_2 solution. While release was not really explored, loading is shown in **Table 6.1**. The cumulative mass release of flurbiprofen from methafilcon A lenses impregnated by soaking in supercritical CO_2 was 5-6x greater than the mass released from lenses soaked in a conventional aqueous solution [**6.47**]. This method controls release via diffusion and did not extend drug elution time beyond control lenses but serves interest as a method to enhance loading. This method of loading lenses was further explored by the same authors

to separately load timolol and acetazolamide into balafilcon A (silicone hydrogel) contact lenses. The release profile was similar to traditional drug soaked lenses with 90%of the loaded drug released within 1 hr [**6.115**]. By altering the supercritical solvent used to load acetazolamide from water to ethanol, loading increased from 20 to 50 μg/ lens, a trivial increase in loading. However, a much more substantial increase was seen in the loading of timolol maleate in the same transition from supercritical water to supercritical ethanol in a 17-fold increase. Comparing the loading from supercritical ethanol to traditional methods of loading drug soaked lenses, loading increased by a factor of 20 [**6.115**]. This method increased the loading of timolol (~600 μg/ lens) and was slightly higher than other published values but acetazolamide loading was minor (~100 μg/ lens), which was beaten by previous work (~1500 μg/ lens) [**6.82**].

Flurbiprofen was loaded into a variety of lenses to a concentration of 80-1200 μg/ lens by supercritical CO_2 impregnation [**6.116**]. It was demonstrated that flurbiprofen-loading with a mixture of supercritical solvents was increased 10-fold in methafilcon A lenses compared to traditional aqueous loading techniques, yet the release profile was unaffected, indicating that this method is not truly a mechanism to control release [**6.116**]. The works in [**6.47, 6.115, 6.116**] demonstrate that supercritical solvents may be an effective method to increase loading of some drugs, but no control over release rate was observed indicating this method has no true benefit over drug soaked lenses in the development of controlled drug delivery. To incorporate supercritical fluids into a commercial process, significant alteration to plant design would suggest this method to be impractical. The application of supercritical fluid loading in addition to a controlled drug delivery method, such as molecular imprinting as described in [**6.116-6.117]**, could

prove to be a powerful combination. In references [**6.116-6.117**], however, molecular imprinting failed to delay the release rate. Flurbiprofen was loaded into Hilafilcon B to a concentration of 1,200 μg/ lens, increasing the loaded mass by a factor of 3. Regardless of concentration in the lens, release was complete in 2-3 hours [**6.117**].

6.1.1.3. Reptation Controlled Lenses. Currently, there is only one marketed commercial lens formulated with sustained release technology. CIBA Vision's Focus Dailies® are designed to release a hydrophilic macromolecule (PVA) to sequester water on the anterior surface of the eye. During the blinking motion, water is forced out of the polymer replenishing the tear layer. Release is controlled via solubility and reptation of the PVA in the Nelfilcon A network (based on a PVA macromer). The reported release rate is ~1 day, where the lens is then discarded and a new lens is placed on the eye [**6.48, 6.49**]. As the first marketed lens with drug release, it is a milestone in the industry and several clinical trials [**6.126-6.127**] have shown it to be more effective in treating contact lens induced dry eye than topical eye drops [**6.128-6.130**] and, very significantly, other comfort oriented lenses that sequester re-wetting inside the lens [**6.131**]. Other diffusion controlled mechanisms of release demonstrate very low loading and very short release times of macromolecular comfort agents [**6.113**]. It is notable and exciting that the application of controlled release technologies provides increased control over loading and release and can be used to provide greater comfort.

6.1.1.4. Barrier Molecules. In a recent work, the concept of drug soaked lens was altered by the application of a diffusion barrier to slow release of loaded drug. In theory, a lens can be loaded by soaking it in a drug solution, but the elution is slowed by a large diffusion barrier. Such a lens was created when vitamin E was loaded into 5 different

commercial lenses through soaking in a concentrated solution for 24 hours [**6.50**]. As a large molecule, the vitamin E was worked to constrain the free movement of timolol, dexamethasone 21-disodium phosphate, and fluconazole and, thereby, increasing the residence time of the drug within the lens. To work as a diffusion barrier, vitamin E must be loaded into the lens in sufficient quantities to eliminate the free volume within the lens removing the unhindered transport of loaded drug. By necessity, loading of the barrier drug decreases volume available for any secondary drug resulting in lower mass uptake which is repeatedly demonstrated by the report [**6.50**]. The rate of release is strongly dependent on the concentration of the diffusion barrier. However, the barrier molecule is also diffusing from the lens and as time increases, the effectiveness of the blockage will decrease.

Loading of vitamin E is lens dependent with the greatest vitamin E affinity occurring with Acuvue Oasys. Loading vitamin E into Acuvue Oasys was reported as 8.7 mg/ lens. Release rates of vitamin E into 2 mL of PBS were found in all cases to be decaying delivering lower doses over time. Oasys lenses were found to load ~6.5 mg Vitamin E. The release rate decreased exponentially releasing ~3.5 mg in the first 24 hrs, ~1.5 mg in the second 24 hours, and the balance (~1.5 mg) over 20 days. Furthermore, the vitamin e barriers were ineffectual in controlling the release of timolol, dexamethasone 21-disodium phosphate, and fluconazole. Regardless of the vitamin E concentration or drug concentration, 90% of the drug was released in the first 24 hours [**6.50**]. Investigation of the loading and release of dexamethasone in a second article by the same authors demonstrated similar trends as [**6.50**], and a mathematical model was

developed to describe the kinetics of release [**6.86]**. Elution of dexamethasone reached 90% completion within a day of release [**6.86**].

6.1.1.5. Summary of Diffusion Control Techniques. Though much work has been done with drug soaked lenses, very few accounts in the literature demonstrate any potential to meet the demands placed on therapeutic lenses. The applications of controlled delivery techniques, as discussed in the rest of the chapter, have repeatedly shown greater potential in lenses than drug soaked lenses.

6.1.2. Molecular Imprinting. Molecular imprinting is the most promising and versatile method to control drug delivery from contact lenses and has received considerable attention as a delivery mechanism. Much outstanding work has been done with imprinting methods since its introduction to the field of ocular drug delivery. The reviews [**6.51-6.53**] and articles [**6.43-6.46, 6.55-6.63**] put forth by these authors are recommended as background to the method.

The principle of molecular imprinting exploits the natural associations between drug and monomers, namely through non-covalent interactions such as hydrogen bonding or ionic attractions, to create macromolecular memory sites. Drug templates and functional monomers are selected to promote intermolecular interactions. When polymerization occurs, resulting polymer network has memory segments where the drug particles have been templated into the hydrogel with functional monomers oriented to bind template drug. Thus each, various chains have recognitive properties capable of binding drug after the template drug has been removed. The orientation of the monomer functional groups creates active sites within the network that interact with the template molecule as it diffuses past. The drug undergoes Brownian motion as it diffuses in the

network and each interaction between imprinting monomer and the drug causes the drug to be temporarily held by chains, increasing the transport time as well as increasing the mean path length between the drug and the surface of the lens. However, it is not sufficient to add functional monomers to a pre-polymer and drug solution as it will not necessarily create an imprinted lens. Also, the functional monomers must be in sufficient concentration to create the interactions in sufficient quantity to retard diffusion through the gel. If the functional monomer is too low, monomers will be too sparsely spread or too distant from the template, mimicking the non-imprinted hydrogel. Also, molecular weight between crosslinks (Mc), or the molecular weight between junction point, must be at the optimal size as to allow drugs to easily pass through the network and small enough to allow interactions as the drug diffuses.

Molecular imprinting typically depends on drug molecules being dissolved instead of aided into the monomer formulation through use of a third molecule. Any surfactant or emulsifier can, in theory, prevent the orientation of monomers around the drug molecule. Also, best results for large molecules, especially macromolecules, can be seen if the drug is in the conformation as it would be seen in the bulk polymer network. Many factors exist to control the conformation of drug in solution and in polymer network. As a result, the best results in molecular imprinting occur with miscible drugs and polymers, especially in contact lenses where optical clarity is of paramount importance, though use of immiscible drugs is not necessarily prohibited. Once the drug is dispersed throughout the solution and the polymer network formed, release depends on the interactions between the drug and the functional monomer(s) polymerized into the network. Any observed differences in release of molecular weights are then based on the

diffusion among crosslinks and steric influences. The drug can be dispersed into the prepolymer solution and can be loaded further by soaking in a concentrated drug solution or reloaded with once the reservoir is depleted or loaded with a different drug if the original drug is a model. Model drugs may be used if the gel must be washed, sterilized, or purged and the intended drug is costly or difficult to remove.

The first imprinted hydrogel contact lens showing potential for contact lens industry was published in 2002 [**6.60**]. The lens released timolol to treat glaucoma by lowering the intraocular pressure. PHEMA hydrogels were formulated with methacrylic acid (MAA) or methyl methacrylate (MMA) as imprinting monomers. Complete release of the loaded timolol was released in artificial lacrimal solution between 6 and 10 hours which correlated to a Fickian release profile. The exciting results of this paper showed increased loading of timolol over unimprinted lenses, especially in lenses containing 100 mM MAA which loaded 12 mg of timolol / g of dry hydrogel. This was a 3 fold increase in loading over control PHEMA lenses.

Timolol release was once again explored with variations in the backbone polymer network based on relative hydrophilicity at similar ratios and formulations with varying concentrations of crosslinkers [**6.61**]. Results showed 300 μm thick lenses or greater capable of releasing 90% of the loaded timolol in a Fickian manner for 16 hours or 4 hours. Conclusions focused mainly on the minimum crosslinking concentration for effective imprinting and the nature of the backbone polymer chain and the effect of swelling on release. However, the article failed to demonstrate and difference in the shape of the mass release curve compared to the mass release from unimprinted lenses though loading was increased in the imprinted lenses and the amplitude of release curves

displayed high correlation to imprinting monomer. Diffusion coefficients were not shown to be affected in any significant manner. In 2005, M/T ratio (the ratio of imprinting monomer concentration to template drug concentration) was shown to affect release rate of imprinted lenses [**6.62**]. Comparison of release rates showed a slower in vitro release rate over 3 days with 50% of the loaded mass released. This is the first paper to relate M/T ratio, an important imprinting variable, to contact lenses.

Interactions between the imprinting monomers and template drugs are vital to successful control of release. At high M/T ratios, more interactions occur and slow template transport. At very high M/T ratios, there is no organized orientation of the monomers and the functional groups are randomly oriented and no difference is seen in imprinted and unimprinted lenses. At low M/T ratios, functional monomers are spread widely apart and the number of interactions is low enough that no effect is seen in template transport. These trends are relevant whether a single monomer or multiple functional monomers are employed. However, greater control can be gained by including several different functional monomers which interact differently. When multiple monomers are used, very stable bonding complexes are formed, much more stable than single monomer complexes. In 2005, it was demonstrated in contact lenses that four different imprinting monomers loaded 8 times the amount of drug from single imprinted monomer networks [**6.43, 6.45**]. The multiple monomers outperformed single monomers and loaded 6 times the amount of ketotifen fumarate over control lenses. Using these lenses for in vitro releases in artificial lacrimal solution, controlled release of therapeutically relevant concentrations was demonstrated for 5 days [**6.45**].

The development of a novel microfluidic device is of great interest to more closely correlate flow rate and flow volume of the eye. One such device resulted in a constant zero order release of ketitofen fumarate using the best performing lenses from the 2005 paper [**6.44**]. Extrapolating to complete release, it would be possible to extend release 150 days or 10-15 day from lenses corresponding to commercial thickness. Tumbling hypothesis was proposed by analyzing the one-dimensional template transport which showed imprinting delays release through interactions and not through network changes or porosity [**6.43**].

Hyaluronic acid was also used in imprinted lenses, and this was the first time imprinting was shown for a large molecular weight macromolecule within a hydrogel lens [**6.55-6.56**]. Films and lenses of ~120 μm thickness lenses were composed of CIBA Vision's Nelfilcon A, acrylamide, N-vinyl pyrrolidone and 2-(diethylamino) ethyl methacrylate (DEAEM) and controlled release of HA was demonstrated for 24 hours. Effective control of the diffusion coefficient for HA was demonstrated by varying the concentration and variety of imprinting monomers. This diffusion coefficient with diverse monomers was lowered 1.5 times compared to a single monomer and 1.6 over unimprinted lenses. Altering the M/T ratio reached a critical value which sequestered HA chains inside the lens and did not release until the pH was altered to interfere and disrupt the HA-DEAEM interactions. Such devices were designed to deliver a therapeutic amount of HA to the eye to treat CLIDE symptoms and increase wettability and the comfort of lenses.

Most recently, diclofenac sodium, which is used to treat inflammation, was released from imprinted hydrogels formulated from living polymerization reactions. The

imprinting of living polymerization formed networks led to 54% increase in loading over traditionally formed (uncontrolled free radical polymerization) contact lenses and a 269% increase in loading over non-imprinted lenses [**6.58**]. Controlled living imprinting delayed release for 5 days with release profiles approaching zero order release. The controlled polymerizations slowed the polymerization reactions and lead to chain orientation around the template [**6.58, 6.64, 6.65**].

To date, the only in vivo release from imprinted contacts was published in 2005 showing the release of timolol in rabbit eyes using 14 mm wide diameter, 80 μm thick lenses (which are comparable to commercial lenses) [**6.63**]. Imprinted lenses showed higher timolol concentration in the tear layer of the rabbits but did not manage to extend release past the 90 minute release shown for the control lens. However, since then more effective imprinted contact lenses have been developed and soon to be published work will demonstrate increased control over the release rate of drug from imprinted lenses.

Molecular imprinting has been experimentally verified as a successful method for producing contact lenses with high drug loading and controllable release. Progress in the field has mostly included low molecular weight therapeutics in the middle of the hydrophilic/lipophilic spectrum used to treat anterior eye disorders. Control in loading and delay of release has been established with careful attention of the functional monomer/template ratio, the diversity of functional monomers, and the polymer backbone and crosslinking structure. Experimental work has also demonstrated that macromolecular memory and not structural phenomena are responsible for delayed template release kinetics. Current methods can produce lenses of suitable thickness, water content, and mechanical and optical properties compared to lenses on the market today.

In comparison to topical alternatives, imprinted lenses provide an increased residence time of therapeutic at the surface of the eye leading to increased bioavailability and more convenient and efficacious therapy.

There has been exciting progress in the field since the first experimental evidence appeared in 2002, but clearly this field is in its adolescence with only a handful of researchers demonstrating success with increased therapeutic loading and delayed transport in-vitro. In-vivo success and validation of therapeutic contact lenses has not been sufficiently demonstrated to date and is a significant aim of the field. This primarily concerns matching release duration with the wear time of the lens and maintaining suitable drug concentration. Also, a wide spectrum of therapeutics has not been experimentally demonstrated; however it is expected to be a platform technology for most ocular hydrophilic drugs, hydrophilic comfort molecules, and drugs of slight to moderate lipophilicity. For more lipophilic molecules, modification or inclusion complexes may be incorporated to increase the applicability of the imprinting approach. Constraints on optical clarity, oxygen transfer, and mechanical properties add some hurdles to network design in some systems, but these issues can be overcome. It is important to note for all the drugs that have been experimentally demonstrated, the presence or release of drug did not affect lens optical clarity or mechanical properties. Considering the timeframe of drug release from lenses and that large concentrations of drug are not needed, it is expected that lens clarity, modulus, or surface properties, such as wettability, will not be adversely affected by drug in the lens. Imprinted lenses can be produced via UV free-radical polymerization in molds and sterilized post-synthesis with no degradation or reaction of drug during the process. In the HA imprinted lenses, the

steam sterilization protocol decreased HA degradation when in the lens compared to HA in solution [**6.55-6.56**]. Sterilization is not expected to be a significant problem for most drugs, but post-sterilization aseptic loading is an alternative.

Drug loading was the first major issue to be studied using imprinted lenses and groundbreaking work has been conducted. For example, it is interesting to note that the earliest produced imprinted gels were much thicker than contact lenses on the market today and contained marginal concentrations of water. Contemporary imprinted lenses are an order of magnitude thinner and equivalent to lenses in the market, contain copious amounts of water, and drug loading has substantially increased. In early systems, drug loading was moderately higher for the imprinted lenses over non-imprinted lenses, but since the duration of release was low on the order of hours, high loading was not needed. Increased drug loading became crucial to success as the duration of the release challenge increased. Thus, the rate of drug needed and the duration of release are important design parameters. It is now evident that a therapeutically relevant amount of drug can be loaded for release to occur over multiple days, which allows the technique to be applied to extended-wear lenses on the market. This is predominantly due to using a diversity of non-covalent interactions to provide imprinting control. To date, these systems have shown the highest loading levels [**6.44, 6.46**].

Current trends in the contact lens market divide soft contact lens wear into three major categories: extended, continuous-wear, daily-wear, and daily-disposable lens wear. Daily wear lens account for ¾ of lens fittings making daily wear the dominant product in the market. Daily disposable are responsible for 8% of lens fitting. Extended wear lens form the minority with 7% of lens wearers [**6.126**]. However, contact lenses capable of

drug delivery and the additional desire by consumers for more natural vision lenses should cause daily disposable and extended wear lenses to grow into a more substantial share of the market. All imprinted lenses in the literature fall into the daily-wear category. The advent of silicone hydrogel lenses to the lens market in the 1990s has made extended, continuous-wear lenses practical and safe. Silicone hydrogels provide extremely high levels of oxygen permeability and movement of the lens on the eye surface allowing continuous wear for up to 30 days. No imprinted lenses of this type have been experimentally demonstrated, and this is a natural progression of the field along with integrating the technique into existing manufacturing techniques. Silicone hydrogels may require additional understanding of the partitioning of the drug, but they can be imprinted with drug. For all lens types, the flux of drug from the imprinted lens must be controlled so the reservoir of drug inside the lens is not depleted before the lens is removed. Thus, it is expected that extended delivery of a wide variety of drugs will increase in all modalities of contact lens wear.

The ideal situation is not having to reload drug or lose drug in a wash/disinfecting medium. Thus, daily-disposable imprinted lenses would be inserted, deliver drug, and discarded. For the extended-wear category, imagine a patient receiving a drug releasing lens in the doctor's office and having it removed on a follow-up visit two weeks later. The lens could release drug in a controlled manner during the interim period between visits. This type of lens and delivery may be better suited for the elderly or for patients that need continuous delivery. Daily-wear lenses that are taken out before sleeping require disinfection and cleaning, which would lead to small amounts of drug lost to the cleaning solution and potential for adverse interactions with the drug.

Considerable attention has also been given to controlling the rate of therapeutic release from contact lenses. Release profiles from drug-soaked lenses, the first generation of drug eluting contact lenses, were Fickian in nature (i.e., concentration dependent) and very short in duration with all drug being released in less than an hour. Release profiles from the first reported imprinted lenses were also Fickian, with most drug being released in approximately 9 hours. This led to discussion on reloadable contact lenses, but the contact lens market and progress in the field has made this type of lens obsolete before it was even developed. Thus, the only significant advantage to imprinted lenses was that drug release rates were higher, but the shape of the drug release curve was the same for the non-imprinted lenses. In the last few years, differences in the release curves have been obtained with imprinting delaying release. Thus, the therapeutic release can be controlled and the shape of the release curve moved from Fickian release closer to more constant, zero-order release, compared to the non-imprinted systems. This was a significant accomplishment of the field demonstrating that imprinting was directly related to delayed template release when comparing imprinted and non-imprinted lenses with similar network structures and free volume. In an ocular flowrate, with limited tear turnover, release rates will decrease due to significant drug concentration boundary layers.

Given the control demonstrated over release rate, there is enormous potential for ideal release rates to be designed considering specific ocular drug absorption rates. This is also a significant challenge of the field, and it would result in the best possible ocular delivery with the least amount of drug entering the systemic circulation. Such achievements may only be possible with imprinted lenses and inserts, which can

specifically control the rate that the drug is delivered into the eye. While there will also be some variation in drug release from imprinted lens based upon a person's tear volumetric flowrate and volume, it is not a limitation of the technology. This variation exists in other forms of topical delivery, including eye drops, and a faster tear flowrate would lead to higher levels of drug released.

It is apparent that imprinted lenses are ideally suited to treat anterior diseases of the eye. All experimental work to date has included these types of therapeutics, and future progress will begin to target posterior delivery. It is difficult to deliver medications to these regions without systemic delivery or invasive procedures, which have many drawbacks [**6.107**]. Topical posterior eye delivery is hampered by low penetration of the drug into the eye due to transport barriers and removal of drug from the eye which reduce the amount of drug available. This limitation can be overcome in theory by the addition of permeation enhancers to temporarily ease transport. Work demonstrating the versatility of multiple monomer systems, high drug loading levels, and the effectiveness in controlling drug release has potential to aid this direction of work. Lenses designed to release two or more molecules at specified rates could allow a molecule to aid the transport of a second molecule and deliver it to the desired area.

Loading levels are now high enough that multiple therapeutics could be delivered from the same lens, mimicking some successful dual-therapeutic eye drop formulations. Also, it is important to note that imprinted lenses can be produced as corrective or non-corrective drug delivery devices and several variations of cosmetic, non-refractive contacts and bandage lenses are currently sold. Thus, bandage lenses or non- vision altering lenses would be significantly improved by using imprinted methods.

The value proposition of imprinted, drug-releasing contact lenses targets consumers, ophthalmologists and optometrists, contact lens manufacturers, and pharmaceutical companies. For consumers, it has the potential to deliver over-the-counter or prescription eye medication more effectively delivering a more constant and optimal therapeutic concentration. It will be more convenient eliminating multiple daily drops with less systemic absorption, side effects, adverse reactions, and toxicity. Thus, ophthalmologists and optometrists will be able to provide better care for their patients. For contact lens manufacturers, there is additional opportunity to enhance existing product lines as well as create new contact lens products. Significant opportunities exist for pharmaceutical companies to address additional consumer needs in an integrated solution. There is also potential to protect or extend existing patent rights on existing drugs close to patent expiration exploiting imprinted drug delivery systems. Thus, the future is indeed bright for the field which will see a sharp increase in the number of ocular therapeutics imprinted within lenses as well as in-vivo studies. In-vivo validation will take center stage, which will significantly increase the commercialization and clinical translation of these systems.

6.1.3. Carrier Mediated Release (CMR) and Surfactant Mediated Release (SMR). Encapsulants are commonly used as drug delivery devices to increase solubility of drugs and as carriers to deliver drugs to specific targets. Emulsifiers and surfactants are commonly used in ocular formulations, especially in eye drops as preservatives and stabilizers. However, the use of emulsifiers and surfactants as well as liposomes has found application in topical delivery from contact lenses to control release rate and increase loading. Drug is encapsulated into thermodynamically stable micelles or drug

particles and mixed with a lens prepolymer solution. The encapulsation process can be formulated as emulsions (macro, micro, mini, nano), colloids, suspensions, and particulates or can be embedded into some sort of carrier. The carriers can then elute from the hydrogel and release the drug. Work with these carriers has been explored in many fields, but carriers within contact lenses have been limited to liposomes. The conceptual understanding of release from colloid and emulsion laden lenses and release of drug carrying liposomes are comparable mechanisms of release, though many reviews of the field discuss colloids, emulsions and liposomes separately. To highlight progress in the field and alleviate the inconsistencies in the literature, the term carrier-mediated release (CMR) is coined by this work as an inclusive mechanism of release combining any method involving one phase dispersing into another through surfactants, emulsifiers or dispersants, or any soluble compound or carrier that disperses an otherwise insoluble molecule. A more specific term SMR (surfactant mediated release) will also be used to discuss a subset of CMR-based devices that use surfactant as the carrier.

Carriers are best employed in release where high partitioning occurs between two phases. Drug release is controlled by the rate-limiting step of drug diffusion from the minor phase to the continuous phase. As a result, CMR-based lenses are conceptually limited to release of hydrophobic drugs from hydrophilic lenses or the reverse. Attempts to release hydrophilic drugs from hydrophilic lenses ultimately fail as the partitioning of the drug is too weak to form a stable CMR. CMR-based mechanisms are most commonly encountered from PHEMA based lenses, which have released hydrophobic drugs such as lidocaine [**6.66-6.68**], timolol [**6.69**] and cyclosporine A [**6.70**]. Lidocaine has uses as anti-arrhythmic drug commonly used for heart patients but was selected as an

inexpensive model drug due to its hydrophobic nature. The octanol-water partition coefficient for lidocaine is 245 [**6.71**]. Timolol is an anti-glaucoma treatment used to control the intraocular pressure on the optic nerve. Cyclosporine A can be used to treat ocular ulcers or keratoconjunctivitis.

In the lens prepolymer, the drug particles are evenly distributed throughout the solution when the lens is formed. Loading the drug and forming a stable drug particle often requires the addition of an oil phase, e.g. octadecyltrimethoxysilane and hexadecane. This oil phase, essential for many CMR devices, affects clarity of the hydrogel lenses in a similar manner as emulsions and colloids. Refractive index values differ greatly between the oil and aqueous phase. When light enters the continuous phase, it bounces off the minor phase particles due to refractive index differences reducing the clarity of lenses and making the lenses appear white. This effect is characteristic of any biphasic system but can be controlled by controlling particle size, loading, and materials. Loading of the minor phase must be kept low to prevent clarity loss. If the nanoparticle size and loading are sufficiently low (the exact value depends on the refractive index mismatch between the gel and particles), the particle loaded lenses remains transparent. This is of great concern considering drug delivery from lenses. It may not be possible to load sufficient drug to deliver effectual drug concentrations more than 2-3 days. Once the encapsulation is complete, a polymer network is formed around the suspended drug particles, embedding the drug in the hydrogel. The finished gel is then a drug loaded contact lens ready to release to the user.

However, CMR has several drawbacks that hinder it from being a dominant mechanism of ocular delivery. The entire method of release is dependent on the presence

and concentration of a carrier. Typically, the carrier is not covalently linked to any part of the polymer network, and it also elutes from the lens. The carrier can then cause irritation to the eye or toxicity. The loss of the mechanism of release is detrimental to the release rate, which decays as release approaches completion. Conceptually, as the release rate is controlled through the slow step of drug migration from areas of high solubility in the minor phase through the major phase where it is poorly soluble, release rate will decrease greatly as the concentration gradients that force the migration dwindle. Drug may also be sequestered in the particles for long periods. Published work in the field has shown poor control over release over time with a large fraction of the drug eluting quickly and quickly dropping below effective values.

Also, molecular weight of the drug is important to CMR-based releases. A small molecule will not grant the same control of release as well as a large molecule, and if a drug is too large, the particle will not form around the drug or cannot be fit into the carrier. Without the stable structure, CMR is not an effective method of release. Many CMR studies, especially SMR-based vehicles, have shown sensitivity to the presence of ionic species present in lacrimal fluid. Prolonged release times of experiments conducted in de-ionized water are reduced dramatically in saline solutions and phosphate buffers. The ions interact with the surfactant and collapse the particle.

In 2004, a PHEMA based lens was used to release hydrophobic lidocaine [**6.66**]. The lidocaine, typically insoluble in hydrophilic materials was encapsulated in the lenses with Brij 97 and the addition of an oil phase hexadecane and octadecyltrimethoxysilane. Lenses were 1,000 μm thick and took 24 hrs to polymerize. Loading was minor with 200 μg lidocaine/ gram lens. Lenses containing between 3 and 0.55 wt% oil released ~100 μg

lidocaine (50%) in less than 6 hours, ~70% release at one day, after which the rate of release dropped to ~10 μg lidocaine/day for 4 days. Addition of crosslinkers to the formulation did not significantly affect the release probably due the mesh size of the hydrogel being much larger than the 50 nm particles. It was clear that the release was not significant after 2-3 days. There are a few problems with this work. A release in DI water may be much different than a release done in salt solution. Also, the films were much too thick for practical lens design. Scaling the thickness down to an appropriate thickness would greatly reduce the loading these systems and reduce release time.

A later article investigated liposomes to deliver lidocaine from PHEMA based lenses [**6.67**]. The liposome serves as a physical encapsulation mechanism where the lidocaine is trapped in the core of the liposome. Release rate of the liposome is then controlled. When the liposome elutes from the lens, the lidocaine is released. The 1,000 μm thick films were oven cured for 24 hours. Using liposomes, extremely high loading of lidocaine was measured for PHEMA lenses with levels approaching 5,000 μg lidocaine/g lens. This is a drastic improvement over the 2004 article where loading of lidocaine was restricted to 200 μg lidocaine. After 3-4 days however, release levels off at around 65% indicating either that the liposomes are sequestered in the lens, or that theoretical loading was not as high as expected or that the release medium of 20 mL of DI water was too small a volume for perfect sink conditions after the first day, where 40% of the loaded lidocaine (600 μg) was released. Different concentrations of lidocaine in the lenses did not affect the release.

The following year, published data showed improvements in loading and release of lidocaine from PHEMA lenses with a few modifications to the 2004 formulation

[**6.67**]. Additional surfactants and oils were added to the formulation to improve the release observed in the previous SMR article. Four types of SMR solutions were formulated using (i) canola oil, Tween 80 and Panodam SDK (ii) canola oil, Tween 80, Panodam SDK and octadecyltrimethoxysilane (OTMS) (iii) hexadecane and Brij 97 and (iv) hexadecane, Brij 97 and OTMS. The OTMS was added to provide a silica shell around the SMR particle to further partition the drug. The best performing lens were the fourth type. A 200 μm thick lens released 1,200 μg lidocaine in 5-6 days in 40 mL DI water, with 50% released in less than 6 hours. Increasing film thickness to 1,200 μm did not significantly affect release though release rate did decrease. Release was negligible until day 4 where 65% of the load mass was measured at an average rate of 200 μg /day. This 3 day period of minor or undetected release can be assumed to be due to the presence of the silicone shell since any delay in release is not observed in type (iii) lenses. Type (i) based lenses were not structurally stable and were not tested. Altering the lidocaine concentration between 300, 450 and 2,000 μg loaded into the lens did not statistically alter the mass release profile. The results showed a large decay in release that delivered correspondingly lower mass as time progressed.

Timolol, an anti-glaucoma treatment, was released from PHEMA lenses [**6.69**]. The SMR solution was composed of Pluronic F127 and sodium caprylate as co-surfactant with ethyl butyrate oil to serve as the minor phase. Four different SMR solutions were prepared. Formulations (i) and (ii) were of similar composition except the ratio of timolol to ethyl butyrate (T/E) was higher in (ii) with T/E ratio of 0.15 instead of 0.1. Formulation (iii) was of similar compositions to (i) and (ii) but did not include ethyl butyrate. Lenses of the fourth type were the same composition as (i) but with higher oil,

timolol, and surfactant levels per lens. Lenses were formed to a thickness of 200 μm and submerged in 3 mL of DI water, which was replaced daily, or in 3 mL of phosphate buffered saline (PBS) solution. PHEMA lenses directly loaded with timolol through direct embedding (done by dissolving the timolol directly in HEMA monomer before photo-curing step). Release of timolol in DI water demonstrated a release time of at least 50 days. However, switching the release medium from DI water to PBS solution, release time was shortened to less than a day. Timolol partitioning in PBS is about 5 regardless of concentration, but much higher in DI water with values of about 100. The difference is partitioning explains the difference seen in release. Release of timolol through a medium of DI water showed that the presence of surfactant and the oil phase speeds release of timolol, reaching completion in 20 days. Removing the oil phase in the third series matched the release profile of pure HEMA lenses for the first 40 days indicating the surfactant did not affect release. Using a post-cure sanitizing step by soaking the lens in a concentration drug solution for 5 days resulted in drug loss and affected the release time since up to 90% of the loaded drug could be lost in the step. Timolol releases performed in PBS or saline solutions reached completion in less than a day. The SMR system underwent total failure in the salt solutions, and it was concluded that the timolol-laden lenses were not feasible in SMR lenses. The only benefit the SMR system displayed was extremely high loading. Previous work published in 2002 and 2005 with molecular imprinting showed similar trends in loading and release, reaching completion in 4 and 16 hours. The benefit of the imprinted lenses was the ability to reload timolol into the lens after the sanitization step [**6.54**]. By the time the SMR-based lens was developed, the technology was obsolete.

Cyclosporine A, dexamethasone and dexamethasone acetate were loaded into 100, 200, 400 and 800 μm thick PHEMA lenses [**6.70**]. Release was performed in 3.5 mL of PBS solution. Brij 78, 97, 98, and 700 surfactants were used to stabilize the drug particles. Loading of cyclosporine A into the PHEMA gels was 50 μg /lens and delivery in PBS solution from PHEMA control lenses was measured to be 5 μg /day for ~10 days. Some of the SMR based delivery from the surfactant laden gels managed to extend the release times though loading remained the same. Minor differences in rate were observed as Brij 78 concentration was increased from 4-8 wt%. Increasing surfactant concentration seemed to decrease loading of cyclosporine A while extending release though, release rate was not significantly altered. Release of cyclosporine from Brij 78 lenses delivered ~0.7-1 μg /day when loaded with 8 wt% and 2 wt%, respectively. Less control over delivery was observed in the Brij 97 laden lenses. The addition of 2 and 8 wt% Brij 97 extended release by 7-10 days beyond the control and rates of mass release were 3 μg /day and 2 μg /day. Brij 700 followed similar trends to Brij 78. Release rates of Brij 700 laden lenses at 2 wt% concentration were indistinguishable from control lenses. Rates for 8 and 4 wt% delivered ~1.5 μg and ~1.75 μg cyclosporine /day respectively. Release rate variation from the control lens was greatest for Brij 78 laden lenses, and the release behavior of Brij 97 and 700 was similar. However, release was not largely affected by increasing concentration of surfactant. Typically, increasing the surfactant ratio decreased release rate by 0.3 μg/day. Such negligible differences in release rates are not of great interest, but it would be feasible match a desired mass release rate with a unique formulation and surfactant (i.e., using Brij 78 to deliver at 1 μg/day and Brij 700 to

deliver at 2 μg/day). Release of DMS and DMSA found no significant effect of surfactant on release curves.

The trend of lenses releasing only 50-70% of the calculated mass loaded is another concern of relying on this system. It is unclear whether the failure of cyclosporine A to completely release is due to the surfactant-laden lenses sequestering up to 40% of the reservoir, the decaying release rate with the release of the remaining reservoir at undetectable rates, or failure of the lenses to load as much mass as theoretically calculated. The decaying release rate is common for SMR-based systems and is a major concern for application as combination devices. Surfactant-laden systems are concentration dependent and deliver variable doses of drug over the lifetime of the device. Several articles promote the use of SMR technology as extended release options for ocular devices, but all the published material involves the release of hydrophobic drugs from hydrophilic (PHEMA) lenses. Commercial extended wear contact lenses are silicone hydrogel materials which are hydrophobic in nature and have much lower water content. Drug partitioning, which is vital for SMR based release, would not be possible in silicone hydrogels with the drugs used in the past. With most of the published work, low release rates were observed after a high initial rate of release (up to 60% of the release occurred in 6 hours) and up to 90% of drug was lost in sanitation steps which need to be controlled before this technology can be applied to commercial products.

6.1.4. Network Design for Size Exclusion Release. Several types of mechanisms such as controlling the mesh size, pH sensitive structures, network degradation or degradation of a scaffold within another polymer and interpenetrating networks, can be included together under network design. The common thread is that each of these

methods controls the flux of drug through size exclusion. As drug molecules travel through a network, the motion can be modeled as particles travelling through a field of random obstacles, where obstacles are the crosslinks between polymer chains. As the concentration of these obstacles increases (i.e. the mesh size decreases), more constraint is seen in the diffusion of the particle. Eventually, as the crosslink density approaches infinity, no movement of the drug is observed. Steric interferences between the network and drug prevent the transport of the drug. However, the relative sizes of most networks are far too large to effectively prevent all but large macromolecular drugs from eluting. For lenses, constraining the mesh size has yet to be shown in the literature as an independently effective method of controlling release.

Using steric interferences to control release could be used at low crosslinking density through the use of pH-sensitive networks. Hydrogel networks (especially at high mesh size) are remarkable for the flexibility of the polymer and have been designed to expand and collapse at desired pH values. Such technology could be applied to lenses so that in the expanded state, drugs can be loaded into the network with collapse at ocular pH. The folding of the chains between crosslinks would serve to restrict movement of the drug due to steric interactions. To the authors' knowledge, no lens has been produced from this technology at the time of this publication but results from comparable hydrogel formulations show promise in this method [**6.72**]. However, clarity may be a significant issue.

Controlling release through controlled polymer degradation follows by controlling the mesh size initially preventing all drug elution through size exclusion but as the polymer degrades, mesh size increases allowing more drug to elute. Such materials are

usually poly(lactic acid-co-glycotic acid) or poly(lactic acid) (PLGA and PLA, respectively) as the degradation can be controlled quite well and the degraded polymer is not harmful to the body.

Recent work with biodegradable scaffolding as the mechanism for controlled release from lenses with PLGA core infused with ciprofloxacin with a PHEMA shell [**6.73**]. The inner core of PLGA measured 200-250 μm thick and was placed in another mold with HEMA monomer and cured, resulting in a PLGA center sandwiched between two layers of PHEMA. Thus, complete lenses were 450 μm thick (mold thickness) and release was performed in 15 mL of PBS solution. However, the practicality of these lenses is questionable. The PLGA core is white and opaque and has a clear 5 mm wide aperture in the center over where the lens would sit over the pupil. Typically in well lit environments, the aperture of the pupil is 3-4 millimeters in diameter, while in darker situations the pupils dilate to 5-9 mm. This means that when dilated, the PLGA core would block up to half of the pupil greatly impairing sight. However, the article is of interest as very high loading of ciprofloxacin into the PLGA phase was measured (up to 20 mg ciprofloxacin). The release was less exciting though. Zero order release (concentration independent release, ideal for release devices) was reported by the authors for both ciprofloxacin and fluorescein but significant deviation in measurement was observed. Significant deviation in measurements, however, makes any confident conclusions difficult to accept [**6.73, 6.74**].

As discussed above, small molecules undergo Brownian motion as they diffuse through a material. The direction the molecule undergoes is the vector sum of the random movement of each constituent atom in the molecule, but most molecules are small

enough and the atoms composing them constrained enough that the entire molecule can be thought of as moving in concert. With macromolecules and polymers, the case is much different. In a sufficiently long polymer, the two ends can be thought of as moving independently of each other. In fact, assuming a Gaussian polymer coil, each coil can move with little relation to the main body of the polymer. For this reason, polymeric motion has long been thought of as wormlike or a statistical motion of coils and known as reptation. For release, network design has a much larger effect on reptation than on diffusion of small molecules. In an excellent article, Briber et al correlated hydrodynamic volume of a polymer to crosslink density [**6.75**] demonstrating that as Mc approaches tail to tail length of a polymer, the reptation of a polymer is severely reduced or eliminated. Work by Alvarez-Lorenzo explored the release of PVP from PHEMA materials for use as lenses with EGDMA as crosslinker [**6.76**]. The work demonstrated release of PVP for ~3 days.

6.1.5. Ion-Exchange Lenses. Ion-exchange lens has been used as controlled release materials. This mechanism depends on the ionic exchange of salt molecules between similarly charged molecules. Published work with azulene and naphazoline have demonstrated controlled release through ion-exchange. However, this method, which can greatly extend release in DI water, is dramatically limited in the presence of other ions, especially among those ions common in lacrimal fluid. The ions can overwhelm the ionic interactions on a purely statistical basis as there is no selectivity between the network ion and drug ion pair. Any ion absorbed from the ocular environment can interact with the drug, ionic monomer or both, preventing the pairing essential to the delay of release for this method.

In work similar in concept to molecular imprinting, naphazoline, a cationic drug, was loaded into lenses composed of HEMA and methacrylamide (MAm) with 2-Methacryloxyethyl phosphate (MOEP) or Methacrylic Acid (MAA) as ionic monomer [**6.77**]. The presence of the MAA increased loading in lenses at all concentrations yet loading was minor. Naphazoline was loaded by soaking the lenses in a drug solution. At 10 wt% ionic monomer, loading of the drug was found to be ~23 μmol and ~18 μmol with MAA and MOEP respectively. Naphazoline released into saline from 3 mol% monomer containing lenses reached completion in 4 hours (MAA) and 12 hours (MOEP). This work is interesting as it combines release through drug soaking and ion interaction and relates to imprinting, though the small loading of the drug. The duration of release, while short, is interesting as the release was performed in a salt solution where ions could disrupt the complexation points between drug and pendant groups. Higher loading could be achieved by dissolving naphazoline into the prepolymer mixture. The inclusion of the ionic monomer capable of interacting with the drug is a principle of molecular imprinting where the drug and monomer can orient to each other and form memory sites. The ionic monomer in this system was randomly oriented and as a result interactions between drug and ionic groups were inefficient. Application of this technology as imprinting and alteration of ionic monomer to template ratio could have produced a better performing lens and significantly increased loading. Work done by the same authors with azulene demonstrated similar patterns including low drug uptake and quick release time into saline [**6.78**].

6.1.6. Covalently Attached Drugs and Drug Coated Lenses. Drugs can be covalently attached to the polymer backbone or individual monomers before the polymer

matrix is formed. The covalent bond, designed to be reversible, dissociates at a certain rate, freeing drug molecules to move through the gel. This method, however, can be impractical due to excess steps needed to load drugs and clean the lens, as well as the inefficacy of the loading. Also, it requires monomers to be used that can be readily used to attach drugs to in a concentration large enough to allow a high enough drug loading to release for extended periods of time. Also, the rate of drug-monomer dissociation can be difficult to control and predict. However, work in delivering comfort agents to the eye can be promising by using this method. Many of these drugs are not designed to penetrate the eye but to stay sequestered on the surface. Drugs covalently (permanently or temporarily) attached to the surface or coated on the surface are held in direct contact with the eye, increasing the probability of absorption. Coated drugs can be attached to the surface or to structures inside the lens, which then dissolve and diffuse to the eye. However these methods can be difficult and inefficient, especially for an industrial process.

Other methods of drug delivery to the eye are through the use of pro-drugs, which are drugs that are chemically altered to allow for controlled release and increased ocular penetration. Once the drug penetrates the outer hydrophobic membranes of the eye, it reverts to its therapeutic form which can easily penetrate the eye. This method of delivery is more about optical penetration than controlled release, though the chemically modified drug may make the drug more suitable for use in a particular material or for use with a specific method of controlled release.

Attaching liposomes to the surface of hydrogel lenses was investigated as a controllable method to deliver ophthalmic drugs. PEGylated liposomes were attached to

premade Hioxifilcon B lens and measured to release fluorescein. Predicted future work would load the liposomes with drug before attachment and release. To attach the liposomes, a series of chemical reactions converted surface hydroxyl groups into neutravidin attachment points for liposomes [**6.79**].

6.1.7. Cyclodextrin Controlled Release. Cyclodextrins have been used in ophthalmic formulations [**6.80**] and recently been formulated into contact lenses and hydrogels [**6.81-6.83**]. Only one article present cyclodextrins as a method to control release from contact lenses [**6.81**]. Cyclodextrins are capable of forming high affinity complexes with certain drugs due to high concentration of hydroxyls inside the ring structure. Cyclodextrins were grafted into PHEMA lenses by reacting functional groups of the cyclodextrins with the glycidal groups of co-monomer glycidal methacrylate (GMA) and loaded with diclofenac. Release reached completion in 8-11 days. The best releasing lens was observed to release 8 mg diclofenac/g lens with 276 μmol GMA/g. The general trend is that as GMA increases from 0 to 360 μmol GMA/g lens, the loading increases and the mass of diclofenac delivered from the lens increased and increased release time from 1 day to ~11 days.

6.1.8. Comparative Evaluation of the Drug Delivery Methods. There is not any strong indication that drug-soaked diffusion control lenses are viable platforms for contact lens drug delivery devices. Yet there continues to be many published literature articles demonstrating release from drug soaked lenses, most of which fail to release significant concentrations beyond thirty minutes. For the field of ocular drug delivery to continue to advance and integrate into the commercial lens market, drug soaked diffusion controlled lenses should be abandoned as controlled release methods. Molecular

imprinting represents the method of release with the greatest potential. Comparing release data of the same drugs between different methods, no other method shows better control over release than molecular imprinting and no other method has been able to control release over as wide a set of drugs of varying molecular weight and solubility. With the work in this thesis, molecular imprinting is the first method of controlled release to be applied in both hydrophilic hydrogel and silicone hydrogel contact lenses.

6.2. Tables and Graphs.

Table 6.1. Comparison of Drug Delivery Methods.

Drug/Molecule Class; MW [Log P]	Method of Release	Lens Material [Thickness] (μm)	Loaded Drug/Molecule Released	Release Time (Medium)	[Ref]
Acetazolamide Anti-Glaucoma; 222 [-0.26]	Cyclodextrin	Poly(PVAMA▪) (200)	~1,500 μg/ lens	~4 days (5 mL Saline)	**[6.82]**
	Diffusion (Drug Soaked)	Sauflon PW	Not Reported	Up to 7.5 hrs (*in vivo* Leporine)	**[6.101]**
	Diffusion (Drug Soaked)	Balafilcon A	100 μg/ lens	30 mins (10 mL Saline)	**[6.115]**
Azulene Anti-allergen; 128.19 [3.45]	Ion-Exchange	Poly(HEMA-co-EGDMA-co-MAPTAC-co-MAA) (300)	20 mg/ lens†	8 hrs (5 mL Saline)	**[6.78]**
Carbenicillin Antibiotic; 378 [1.01]	Diffusion (Drug Soaked)	Sauflon 70	30-80 μg/ mL (tissue concentration)	Up to 2 hrs (*in vivo* Human)	**[6.96]**
		Sauflon 85	60-150 μg/ mL (tissue concentration)	Up to 4 hrs (*in vivo* Human)	
Chloromycetin Antimicrobial; 323	Diffusion (Drug Soaked)	Sauflon 70	10-20 μg/ mL (tissue concentration)	Up to 2 hrs (*in vivo* Human)	**[6.96]**
		Sauflon 85	20-30 μg/ mL (tissue concentration)	Up to 4 hrs (*in vivo* Human)	
Chloropheniramine Anti-Histamine 275 [3.39]	Diffusion (Drug Soaked)	Not Reported	8-12 mg/ lens	1 hr (3 mL PBS♦)	**[6.125]**
Ciprofloxacin Anti-Microbial; 331 [0.65]	Biodegrade; Diffusion between Core/Shell	Poly(lactic acid-co-glycotic acid) [core] Poly(HEMA-co-EGDMA) [shell] (450)	20 mg/ lens	6 mg over 30 days (15 mL PBS♦)	**[6.73]**
	Diffusion (Drug Soaked)	Vifilcon A	Not Reported	8-12 hrs (*in vivo* Human)	**[6.93]**
		Etafilcon A	944 μg/ lens	3 hrs (3 mL Saline)	**[6.92]**
		Vifilcon A	710 μg/ lens		
		PHEMA	417 μg/ lens		
		Polymacon	206 μg/ lens (11%)[α]	24 hrs[α] (2 mL Saline)	**[6.91]**
		Alphafilcon A	117 μg/ lens (6%)[α]		
		Omafilcon A	21 μg/ lens (12%)[α]		
		Etafilcon A	150 μg/ lens (8%)[α]		
		Vifilcon A	150 μg/ lens (8%)[α]		
		Lotrafilcon A	65 μg/ lens (4%)[α]		
		Balafilcon A	80 μg/ lens (5%)[α]		
		Balafilcon A	Not Available	10 mins (PBS♦)	**[6.119]**
		Lotrafilcon A	16 μg/ lens		
		Etafilcon A	420 μg/ lens		
		Etafilcon A	~1,000 μg/ lens	1.5 hrs (3 mL Saline)	**[6.104]**

Cromolyn Sodium Anti-Histamine; 484 [-4.3]	Diffusion (Drug Soaked)	Polymacon	7,264 µg/ lens	≤ 1 hr (2 mL Saline)	**[6.42]**
		Alphafilcon A	9,301 µg/ lens		
		Omafilcon A	7,958 µg/ lens		
		Etafilcon A	7,342 µg/ lens		
		Vifilcon A	7,663 µg/ lens		
		Lotrafilcon A	7,981 µg/ lens		
		Balafilcon A	7,640 µg/ lens		
		Not Reported	8-12 mg/ lens	1 hr (3 mL PBS♦)	**[6.125]**
		Etafilcon A	~1,000 µg/ lens	30 mins (3 mL Saline)	**[6.92]**
		Vifilcon A	~700 µg/ lens	1 hr (3 mL Saline)	
		PHEMA	~350 µg/ lens	3 hrs (3 mL Saline)	
Cyclosporine A Immunosuppressant; 1202 [2.66]	SMR	Poly(HEMA-co-EGDMA) and Brij 98 (100 µm)	50 µg/ lens	~10 days (3.5 mL PBS♦)	**[6.85]**
		Poly(HEMA-co-EGDMA) and Brij 97/Brij 78/ Brij 700 (200 µm)	50 µg/ lens	~10 days (3.5 mL PBS♦)	**[6.70]**
Dexamethasone Anti-inflammatory; 392 [1.87]	SMR	Poly(HEMA-co-EGDMA) and Brij 78 (100 µm)	~7 µg/ lens	5 hrs (3.5 mL PBS♦)	**[6.70]**
	Vitamin E (Diffusion Barrier)	Senofilcon A	80-120 µg/ lens	80-90% in 1-7 days (2 mL PBS♦)	**[6.86]**
		Lotrafilcon A			
		Lotrafilcon B			
	Diffusion (Drug Soaked)	Alphafilcon A	118 µg/ lens	<4 hrs (3 mL PBS♦)	**[6.114]**
		Lotrafilcon A	100 µg/ lens		
		Galyfilcon	34 µg/ lens		
	Vitamin E (Diffusion Barrier)	Silicone Hydrogel (100 µm)	~100 µg/ lens	200 days (2 mL PBS♦)	**[6.87]**
Dexamethasone Acetate Anti-inflammatory; 434 [2.96]	SMR	Poly(HEMA-co-EGDMA) and Brij 78 (100 µm)	~7 µg/ lens	5 hrs (3.5 mL PBS♦)	**[6.70]**
Dexamethasone 21-Disodium Phosphate Anti-inflammatory; 516	Diffusion (Vitamin E Barrier)	Silicone Hydrogel (100 µm)	~10-20 µg/ lens†	~60 Day (2.5 mL PBS♦)	**[6.87]**
	Vitamin E (Diffusion Barrier)	Senofilcon A	27 µg/ lens	34 Days (2 mL PBS♦)	**[6.50]**
		Lotrafilcon A	20 µg/ lens	15 Days (2 mL PBS♦)	
		Lotrafilcon B	27 µg/ lens	15 Days (2 mL PBS♦)	
		Balafilcon A	45 µg/ lens	6 hrs (2 mL PBS♦)	
Dexamethasone Sodium Phosphate Anti-inflammatory; 516	Diffusion (Drug Soaked)	Alphafilcon A	58 µg/ lens	≤ 1 hr (2 mL Saline)	**[6.42]**
		Omafilcon A	76 µg/ lens		
		Etafilcon A	88 µg/ lens		
		Vifilcon A	67 µg/ lens		
		Lotrafilcon A	48 µg/ lens		
		Balafilcon A	66 µg/ lens		
Diclofenac Sodium NSAID; 318	Cyclodextrins	Poly(HEMA-co-EGDMA-co-GMA) (900)	~1,500 µg/ lens†	5 days (10 mL ALS•)	**[6.81]**
	Molecular Imprinting	Poly(HEMA-co-DEAEM-co-PEG200DMA) (400)	70% in 11 hrs	5 days (1000 mL ALS•)	**[6.58]**

Dimystroyl Phosphatidylcholine Liposomes (*lidocaine*) Carrier (*Model*); (*234*) [*245*]*	CMR	Poly(HEMA-co-EGDMA) (1,000)	550 μg lidocaine/ lens	3-5 Days (20 mL DI Water)	**[6.67]**
Fluconazole Anti-Fungal; 306 [0.5]	Vitamin E (Diffusion Barrier)	Senofilcon A	70 μg/ lens	90% in 2 Days (2 mL PBS•)	**[6.50]**
		Lotrafilcon A	20 μg/ lens	90% in 10 Days (2 mL PBS•)	
		Lotrafilcon B	27 μg/ lens	90% in 5 Days (2 mL PBS•)	
Flurbiprofen NSAID; 244 [4.12]	Diffusion (Drug Soaked$^{\beta}$)	Methafilcon A	~100 μg/ lens†	< 1 hr (10 mL Saline)	**[6.47]**
		Nelfilcon A	~80 μg/ lens†	Not Reported	
		Omafilcon B	~800 μg/ lens†	Not Reported	
		Hilafilcon A	~500 μg/ lens†	Not Reported	
		Hilafilcon A	~300 μg/ lens	3 hrs (10 mL ALS•)	**[6.116]**
		Hilafilcon B	~800 μg/ lens†	3 hrs (80 mL DI Water)	**[6.117]**
Gentamicin Antibiotic; 478 [-2.12]	Diffusion (Drug Soaked)	Etafilcon A	186 μg/ lens	20-30 mins (3 mL Saline)	**[6.104]**
		Sauflon 85	10-30 μg/ mL Tissue Concentration	Up to 2 hrs (*in vivo* Human)	**[6.96]**
Fluorescein Model; 332 [3.57]	Diffusion (Drug Soaked)	Bionite	0.1% Fluorescein Solution	3.5 hrs (*in vivo* Leporine)	**[6.41]**
		Soflens			
Homatrope Ocular Paralytic;	Diffusion (Drug Soaked)	Sauflon	50 mg of 1% Solution	~10 hrs (*in vivo* Human)	**[6.36]**
Hyaluronic Acid Therapeutic Comfort Agent, Corneal Healing Aid;	Molecular Imprinting	Nelfilcon A (127)	200 μg/ lens	40 hrs (20 mL ALS•)	**[6.55, 6.56, 6.65]**
	Diffusion (Drug Soaked)	Polymacon	15 μg/ lens	~6-12 hrs (Saline at 3.8 μL/ min)	**[6.113]**
		Alphafilcon A	25 μg/ lens		
		Etafilcon A	25 μg/ lens		
		Balafilcon A	18 μg/ lens		
		Lotrafilcon B	37 μg/ lens		
		Lotrafilcon A	40 μg/ lens		
		Galyfilcon A	20 μg/ lens		
		Senofilcon A	20 μg/ lens		
		Comfilcon A	22 μg/ lens		
Idoxuridine Antiviral; 354 [0.33]	Diffusion (Drug Soaked)	Etafilcon A	150 μg/ lens	30 mins (3 mL Saline)	**[6.92]**
		Vifilcon A			
		PHEMA			
Kanamycin Antibiotic; 484 [-2.58]	Diffusion (Drug Soaked)	Etafilcon A	230 μg/ lens	20-30 mins (3 mL Saline)	**[6.104]**
Keterolac tromethamine NSAID;	Diffusion (Drug Soaked)	Polymacon	101 μg/ lens	≤ 1 hr (2 mL Saline)	**[6.42]**
		Alphafilcon A	123 μg/ lens		
		Omafilcon A	110 μg/ lens		
		Etafilcon A	90 μg/ lens		
		Vifilcon A	107 μg/ lens		
		Lotrafilcon A	60 μg/ lens		
		Balafilcon A	111 μg/ lens		

Ketotifen Fumarate Anti-histamine; 425	Diffusion (Drug Soaked)	Polymacon	151 µg/ lens	≤ 1 hr (2 mL Saline)	**[6.42]**
		Omafilcon A	105 µg/ lens		
		Etafilcon A	213 µg/ lens		
		Vifilcon A	227 µg/ lens		
		Balafilcon A	154 µg/ lens		
		Alphafilcon A	133 µg/ lens	~ 5 hrs (2 mL Saline)	
		Lotrafilcon A	101 µg/ lens		
		Balafilcon A	154 µg/ lens	≤ 1 hr (2 mL Saline)	
		Silicone Hydrogel	1,500 µg/ lens†	13 hrs (in vivo leporine)	**[6.118]**
	Molecular Imprinting	Poly(HEMA-co-PEG200EGDMA-co-AA-co-AA-AM-co-NVP)	50 µg/ lens	3.5 days (ALS• flow at 3 µL/ min)	**[6.44, 6.65]**
		Poly(HEMA-co-PEG200EGDMA-co-AA-co-AM-co-NVP) (400 µm)	2200 µg/ lens	5 days (30 mL ALS•)	**[6.43, 6.46, 6.57 6.65]**
		Poly(HEMA-co-AA-co-AM-co-NVP) (400 µm)	900 µg/ lens†	5 days (30 mL ALS•)	**[6.45, 6.65]**
Levocabastine Antihistamine; 421 [4.29]	Diffusion (Drug Soaked)	PHEMA (200)	33 µg/ lens	6 days (*in vivo* Leporine)	**[6.109]**
		Poly(HEMA-co-VP) (200)	2.7 µg/ lens		
Lomefloxacin Antibiotic; 351 [2.43]	Diffusion (Drug Soaked)	Etafilcon A	150 µg/ lens	1 hr (20 mL Saline)	**[6.121]**
		PHEMA	100 µg/ lens		
		Vasurfilcon A	700 µg/ lens		
		Etafilcon A	750 µg/ lens	8 hrs (*in vivo* Leporine)	**[6.112]**
Lidocaine Model; 234 [245]*	SMR	Poly(HEMA-co-EGDMA) and Brij 97 or Tween 80 (200)	1,000-2,000 µg/ lens	5-6 days (DI Water)	**[6.68]**
		Poly(HEMA-co-EGDMA) and Brij 97 or Tween 80 (1000)	10-50 µg/ lens	3 days (DI Water)	**[6.66]**
Methazolamide Anti-Glaucoma; 236 [-1.5]	Diffusion (Drug Soaked)	Sauflon PW	Not Reported	(*in vivo* Leporine)	**[6.101]**
Naphazoline Vasoconstrictor; 210 [3.88]	Ion-Exchange	Poly(HEMA-co-Mam-co-MOEP-co-EGDMA) (300)	2500 µg/ lens	4 hrs (10 mL Saline)	**[6.77]**
Norfloxacin Antibiotic; 319 [1.09]	Diffusion (Drug Soaked)	Etafilcon A	200 µg/ lens	1 hr (20 mL Saline)	**[6.121]**
		PHEMA	200 µg/ lens		
		Vasurfilcon A	500 µg/ lens		
Norfloxacin Antibiotic; 319 [1.09]	Molecular Imprinting	Poly(HEMA-co-AA or NVP-co- EGDMA) (400)	100 µg/ lens†	24 hrs (10-15 mL ALS•)	**[6.90]**
Ofloxacin Antibiotic; 361 [-0.34]	Diffusion (Drug Soaked)	Etafilcon A	200 µg/ lens	10 mins (3 mL Saline)	**[6.104]**
		Etafilcon A	180 µg/ lens	1 hr (20 mL Saline)	**[6.121]**
		PHEMA	100 µg/ lens		
		Vasurfilcon A	300 µg/ lens		

PEGylated liposomes (*fluorescein*) Carrier (*Model*); *332* *[3.57]*	Surface Attachment	Bionite	2 eye drops added while lens was worn	7 hrs (*in vivo* Human)	**[6.79]**
Phenylphrine Pupil Dilator; 167 [-0.03]	Diffusion (Drug Soaked)	PMMA	2 eye drops added while lens was worn 400-500 µg	0 hrs (*in vivo* Human)	**[6.84]**
		Soflens		6 hrs (*in vivo* Human)	
		Sauflon		~2 hrs (*in vivo* Human)	
Pilocarpine Anti-Glaucoma; 208 [-0.1]	Diffusion (Drug Soaked)	Sauflon (200)	700 µg	~2 hrs (*in vivo* Human)	**[6.37 6.38]**
		Bionite	0.5, 1, 4% Pilocarpine solution	4 hrs (3 mL DI Water)	**[6.39]**
			0.5, 1% Pilocarpine Solution	3-4 hrs (*in vivo* Human)	**[6.39]**
			1% drops added while lens was worn	Up to 24 hrs (*in vivo* Human)	**[6.84]**
		Not Reported	4% Pilocarpine Solution	Not Reported (*in vivo* Human)	**[6.40]**
		Bionite	400 µg/ lens	~3 hrs (*in vivo* Primate)	**[6.88]**
		PHEMA	1,200 µg/ lens	30 mins (5 mL DI Water)	**[6.108]**
		Sauflon (70% water)	2,300 µg/ lens		
		Sauflon (85% water)	1,750 µg/ lens		
		Etafilcon A	~3,000 µg/ lens	30 mins	**[6.92]**
		Vifilcon A			
		PHEMA			
		Sauflon	Not Reported	Effective for 7 hrs (*in vivo* Human)	**[6.122]**
			700 µg/ lens	2 hrs (*in vivo* Human)	**[6.38]**
Polymyxin B Antibiotic; 1200 [2.03]	Diffusion (Drug Soaked)	Bionite	0.25% Polymyxin Solution	Not Reported (*in vivo* Leporine)	**[6.84]**
Poly(Vinyl Alcohol) Re-Wetting Agent; 40000-65000	Diffusion (Reptation)	Nelfilcon A (100)	6 µg/ lens	24 hrs (DI water)	**[6.49]**
		Nelfilcon A (100)	-	16 hrs (*in vivo* Human)	**[6.48]**
Poly(Vinyl Pyrrolidone) Re-Wetting Agent; 44,000-54,000	Diffusion (Reptation)	Poly(HEMA-co-EGDMA) (900)	100 µg/ lens†	30 days (20 mL DI Water)	**[6.76]**
Prednisolone Corticosteroid; 360 [1.49]	Diffusion (Drug Soaked)	Etafilcon A	~3,600 µg/ lens	< 90 mins (3 mL Saline)	**[6.92]**
		Vifilcon A			
		PHEMA		~2 hrs (3 mL Saline)	
		Helfilcon A	2-3x increase over eye drops	1 hr (*in vivo* Leporine)	**[6.95]**
Puerarin Anti-Glaucoma; 416 [1.97]	Cyclodextrin	Poly(HEMA-co-βCD-co-TMATMP) (53)	385-1,000 µg/ lens	~6 hrs (*in vivo* Leporine)	**[6.110]**
		Poly(PVAMA▪) (200)	~1,300 mg	8 hrs (5 mL Saline)	**[6.82]**

Timolol Anti-Glaucoma; 316 [0.68]	pH Responsive Lenses	Poly(HEMA-co-MAA-BIS) (1,000)	~300 μg/ lens	~5 hrs (10 mL PBS♦)	**[6.72]**
	Vitamin E (Diffusion Barrier)	Silicone Hydrogel	100 μg/ lens†	50 days	**[6.87]**
	SMR	Poly(HEMA-co-EGDMA) (200 μm)	70 μg/ lens	2 days (3 mL PBS♦)	**[6.69]**
	Vitamin E (Diffusion Barrier)	Galyfilcon A	60-100 μg/ lens	80% in 0-4 days (2 mL PBS♦)	**[6.50]**
		Senofilcon A			
		Lotrafilcon A			
		Lotrafilcon B			
	Molecular Imprinting	Poly(HEMA-co-MAA-co-EGDMA)/ Poly(HEMA-co-MMA-co-EGDMA) (700)	500 μg/ lens†	9 hrs (5 mL PBS♦)	**[6.89]**
		Poly(DEAA-co-MAA-co-EGDMA) (300)	~2.5 increase over non-imprinted lenses	8-24 hrs	**[6.60]**
		Poly(HEMA-co-EGDMA) Poly(SiMA-co-DMAA-co-EGDMA) Poly(MMA-co-DMAA-co-EGDMA) Poly(DEAA-co-EGDMA) (300)	Not Reported	10 hrs	**[6.61]**
		Poly(MAA-co-EGDMA) (300)	Not Reported	1-3 hrs	**[6.62]**
		Poly(DEAA-co-MAA-co-EGDMA) (300)	35 μg/ lens	30 min -1 hr (*in vivo* Leporine)	**[6.63]**
	Diffusion (Drug Soaked)	Nelfilcon A	~100 μg/ lens†	Not Reported	**[6.47]**
		Omafilcon A	Not Reported		
		Methafilcon A	~400 μg/ lens†		
		Hilafilcon B	Not Reported		
		Balafilcon A	600 μg/ lens	30 mins (10 mL Saline)	**[6.115]**
Tobramycin Antibiotic; 467 [3.58]	Diffusion (Drug Soaked)	Etafilcon A	239 μg/ lens	10 mins (3 mL Saline)	**[6.104]**

Abbreviations: Acrylic Acid (AA); Artificial Lacrimal Solution (ALS); Acrylamide (AM); N,N-Methylene Bisacrylamide (BIS); Cyclodextrin (CD); 4-Tertiary Butyl-2-Hydroxycyclohexyl Methacrylate (CMA);N,N-Diethylacrylamide (DEAA); Diethylaminoethyl Methacrylate (DEAEM); Dimethylacrylamide (DMA or DMAA); Ethylene Glycol Dimethacrylate (EGDMA); Glycotic Acid (GA); Glycidyl Methacrylate (GMA); 2-Hydroxyethyl Methacrylate (HEMA); Lactic Acid (LA); Methacrylic Acid (MAA); Methacrylamide (MAm); Methacrylaminopropyltrimethylammonium Chloride (MAPTAC); Methyl Methacrylate (MMA);2-Methacryloxyethyl Acid Phosphate (MOEP); N-Vinyl Pyrrilidone (NVP); Phosphate Buffered Solution (PBS); Poly(Ethylene Glycol 200 Dimethacrylate) (PEG200DMA);Poly(Methyl Methacrylate) (PMMA); Poly(Vinyl Alcohol) (PVA); Poly(Vinyl Alcohol) Macromer (PVAMA); Poly(Vinyl Pyrrilidone) (PVP); 1-(Tristrimethyl-Siloxysilylpropyl)-Methacrylate (SiMA); Trimethylolpropane Trimethacrylate (TMATMP); Methacryloxypropyl-Tris-(Trimethylsiloxy) Silane (TRIS); Beta-Cyclodextrin (βCD) **Materials:** Lotrafilcon A (polyTRIS-co-DMA-co- silicone macromer); Alphafilcon A - poly(TRIS-co-DMA-co- silicone macromer); Balafilcon A - poly(TRIS-co-DMA-co- silicone macromer); Comfilcon A - poly(TRIS-co-DMA-co-silicone macromer); Etafilcon A - poly(HEMA-co-MA); Galyfilcon A - PHEMA; Hilafilcon A - poly(HEMA) Hilafilcon B - poly(HEMA) Lotrafilcon A - poly(TRIS-co-DMA-co- silicone macromer); Lotrafilcon B - poly(TRIS-co-DMA-co- silicone macromer); Nelfilcon A – PVA Omafilcon A - Poly(HEMA-co-PC); Omafilcon B,poly(HEMA-co-PC) Polymacon - PHEMA; Senofilcon - poly(TRIS-co-DMA-co- silicone macromer); Sauflon - PHEMA; Soflens - PHEMA; Vifilcon A - poly(HEMA-co-MA-co-NVP); Molecular Weight and Log P values were calculated through ACD Labs Chemsketch Software; * Log P is from [6.71]; † Assuming lens weight is 40 mg swollen (approximate commercial average); [α] Release was stopped at 24 hrs regardless of release; [β] Soaked in Supercritical Fluid; ▪ PVAMA is derived from monoacrylated β-cyclodextrin and GMA.

Table 6.2. Descriptions of Lens Materials Mentioned in Table 6.1.

Division I			Low Water (<50% H2O) Non-Ionic Hydrogel Polymer		
Material Water Content		Dk	Brands Available in 2010		
Hydrogel	Helfilcon A&B 45%	12	Continental Toric Flexlens	Flexlens Toric Optima Toric	Flexlens Aphakic
	Polymacon 38%	9	Allvue	Horizon 38	Occasions
			Biomedics 38	Hydron Mini	Optima 38
			Clearview	Hydron Zero 4 SofBlue	PS-45 Multifocal
			CustomEyes 38	Hydron Versa Scribe	Simulvue 38
			EpconSOFT	LifeStyle MV2	Sof-form II
			Esstech PS	Ideal Soft	Soflens
			Esstech PSD	Lifestyle Xtra	Soflens 38
			Esstech SV	LifeStyle 4Vue	Soflens Multifocal
			Frequency 38	LifeStyle Toric Bifocal	Softics
			HD	LL38	SoftView
			HD-T	Metrosoft II Multifocal	Unilens 38
			HDX	Metrosoft Toric	Westhin Toric
			HDX-T	Natural Touch	
Silicone Hydrogel	Comfilcon A 48%	128	Biofinity	Biofinity Toric	

Table 6.3. Descriptions of Lens Materials Mentioned in Table 6.1.

Division II			High Water (>50% H20) Non-Ionic Hydrogel Polymers		
Material Water Content		Dk	Brands Available in 2010		
Hydrogel	Nelfilcon A 69%	26	Dailies AquaComfort Plus Focus Dailies Focus Dailies Toric	Focus Dailies Progressive Freshlook One-Day Synergy	Freshlook One-Day Synergy Triton
	Omafilcon A 59%	33	Biomedics XC Proclear 1-Day Proclear EP	Proclear Multifocal Proclear Multifocal Toric Proclear Sphere	Proclear Toric
Silicone Hydrogel	Galyfilcon A 47%	60	Acuvue Advance	Acuvue Advance for Astigmatism	
	Lotrafilcon A 24%	140	Air Optix Night & Day Aqua		
	Lotrafilcon B 33%	110	O_2Optix	Air Optix for Astigmatism	Air Optix Aqua Multifocal
	Senofilcon A 38%	103	Acuvue Oasys	Acuvue Oasys for Astigmatism	Acuvue Oasys for Presbyopia

Table 6.4. Descriptions of Lens Materials Mentioned in Table 6.1.

Division III			Low Water (<50% H2O) Ionic Hydrogel Polymers
Material Water Content		Dk	Brands Available in 2010
Silicone Hydrogels	Balafilcon A 36%	112	PureVision
			PureVision Multi-Focal
			PureVision Toric

Table 6.5. Descriptions of Lens Materials Mentioned in Table 6.1.

Division IV			High Water (>50% H20) Ionic Hydrogel Polymers
Material Water Content		Dk	Brands Available in 2010
Hydrogel	Etafilcon A 58%	28	Acuvue
			Acuvue 2 Colours
			1-Day Acuvue Moist
			Acuvue 2
			Acuvue 2 Colours
			Acuvue Bifocal
	Vilfilcon A 55%	16	Acuvue Bifocal
			Focus Monthly Softcolors

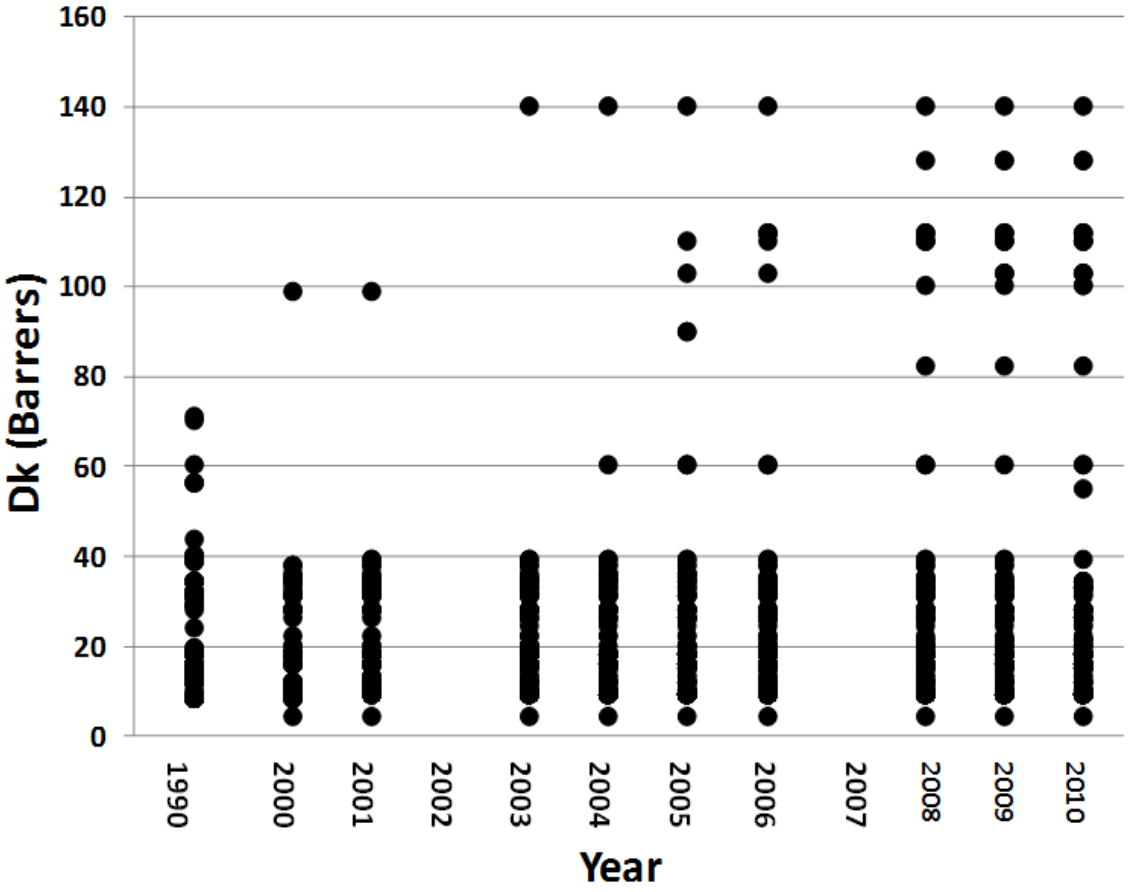


Figure 6.1. Trends in Oxygen Transport Values (Dk) of US Commercial Lenses in Hydrogel and Silicone Hydrogel Lenses

A prevailing commercial trend over the last two decades is the production of highly permeable lens to promote ocular health and comfort. The achievement of 100+ Dk lenses allowed the use of extended, continuous wear lenses without ocular trauma. When silicone hydrogel lenses were introduced in 1998, high Dk values can be achieved beyond that seen in traditional hydrogels. In recent years, a large number of lenses have been produced that have high Dk values, and the trend is expected to continue. Figure 6.1 was compiled from data within references [**6.15-6.25**].

6.2. References.

[6.1] Hirschberg J. History of Ophthalmology,Volume I: Antiquity. Bonne, 1982.

[6.2] Albert D. History of Ophthalmology. Blackwell Sciences, Inc. Cambridge; 1996.

[6.3] Wichterle O, Lim D. Hydrophilic Gels for Biological Use. *Nature*. 1960;185:117-118.

[6.4] Arrington G. A History of Ophthalmology. MD Publications, New York; 1959.

[6.5] Heitz R. The History of Contact Lenses, Volume One: Early Neutralizations of the Corneal Dioptric Power.

[6.6] Heitz R. The History of Contact Lenses, Volume Two: Keratoconus and the Use of Early Contact Lenses (1888-1920).

[6.7] DeCarle J. Developing Hydrophilic Lenses for Continuous Wearing. *Australian Journal of Optometry.* 1972;55(9):343–346.

[6.8] Beavers E. Lens With Hydrophilic Coating. 1987; US Patent:4,663,233.

[6.9] Lloyd A, Faragher R, Stephen Denyer. Ocular Biomaterials and Implants. *Biomaterials*. 2001;22(8):769-785.

[6.10] Wichterle O, Lim D. Cross-linked Hydrophilic Polymers and Articles Made Therefrom. US Patent: 3220960; 1965.

[6.11] Vogt J, Nicolson P. Soft Contact Lens Polymers: An Evolution. *Biomaterials*. 2001;22(24):3273-3283.

[6.12] Dillehay S. Does the Level of Available Oxygen Impact Comfort in Contact Lens Wear? A Review of the Literature. *Eye and Contact Lens*. 2007;33(3):148-155.

[6.13] Holden B, Mertz G. Critical Oxygen Levels to Avoid Corneal Edema for Daily and Extended Wear Contact Lenses. *Investigative Ophthalmology and Visual Sciences*. 1984;25(10):1161-1167.

[6.14] Harvitt D, Bonanno J. Re-evaluation of the Oxygen Diffusion Model for Predicting Minimum Contact Lens Dk/t Values Needed to Avoid Corneal Anoxia. *Optometry and Visual Sciences*. 1999;76(10):712-719.

[6.15] Physicians' Desk Reference for Ophthalmic Medicines. Medical Economics Company,Inc: Thomson Healthcare: Montvale NJ;1990

[6.16] Physicians' Desk Reference for Ophthalmic Medicines. Medical Economics Company,Inc: Thomson Healthcare: Montvale NJ; 2001

[6.17] White P, Scott C. Contact Lenses & Solutions Summary. *Contact Lens Spectrum* Supplement. 2000 July.

[6.18] White P, Scott C. Contact Lenses & Solutions Summary. *Contact Lens Spectrum* Supplement. 2001 July.

[6.19] White P, Scott C. Contact Lenses & Solutions Summary. *Contact Lens Spectrum* Supplement. 2003 August.

[6.20] White P, Scott C. Contact Lenses & Solutions Summary. *Contact Lens Spectrum* Supplement. 2004 July.

[6.21] White P, Scott C. Contact Lenses & Solutions Summary. *Contact Lens Spectrum* Supplement. 2005 July.

[6.22] White P, Scott C. Contact Lenses & Solutions Summary. *Contact Lens Spectrum* Supplement. 2006 July.

[6.23] White P, Scott C. Contact Lenses & Solutions Summary. *Contact Lens Spectrum* Supplement. 2008 July.

[6.24] White P, Scott C. Contact Lenses & Solutions Summary. *Contact Lens Spectrum* Supplement. 2009 July.

[6.25] White P, Scott C. Contact Lenses & Solutions Summary. *Contact Lens Spectrum* Supplement. 2010 July.

[6.26] Refojo M, Leong F. Water-Dissolved-Oxygen Permeability Coefficients of Hydrogel Contact Lenses and Boundary Layer Effects. *Journal of Membrane Science*.1978-1979;4:415-426.

[6.27] Maruyama K, Yokoi N, Takehisa Y, Kinoshita S. Effect of Environmental Conditions on Tear Dynamics in Soft Contact Lens Wearers. *Investigative Ophthalmology and Vision Sciences*. 2004;45(8):2563-2568.

[6.28] Dumbleton K. Adverse Events with Silicone Hydrogel Continuous Wear. *Contact Lens and Anterior Eye.* 2002;25(3):137-146.

[6.29] Hu H, Briggs C, Nguyen T, Tran H, Rossberg F. Contact Lenses. US Patent: 7279507 B2;2007.

[6.30] Van Beek M, Weeks A, Jones L, Sheardown H. Immobilized Hyaluronic Acid Containing Model Silicone Hydrogels Reduce Protein Adsorption. *Journal of Biomaterials Science, Polymer Edition*. 2008;19(11):1425-1436.

[6.31] Fonn D. Targeting Contact Lens Induced Dryness and Discomfort: What Properties Will Make Lenses More Comfortable. *Optometry & Vision Science*. 2007;84(4):279-285.

[6.32] Maruyama K, Yokoi N, Takehisa Y, Kinoshita S. Effect of Environmental Conditions on Tear Dynamics in Soft Contact Lens Wearers. *Investigative Ophthalmology and Vision Sciences*. 2004;45(8):2563-2568.

[6.33] Begley C, Chalmers R, Mitchell G, Nichols K, Caffery B, Simpson T, DuToit R, Portello J, Davis L. Characterization of Ocular Surface Symptoms from Optometric Practices in North America. *Cornea*. 2001;20(6):610-618.

[6.34] Pritchard N, Fonn, Brazeau D. Discontinuation of Contact Lens Wear: A Survey. *International Contact Lens Clinicals*. 1999;26(6):157-162.

[6.35] Schein O, McNally J, Katz J, Chalmers R, Tielsch J, Alfonso E, Bullimore M, O'Day D, Shovlin J. Incidence of Microbial Keratitis Among Wearers of a 30-Day Silicone Hydrogel Extended Wear Contact Lens. *Ophthalmology*. 2005;112(2):2172-2179.

[6.36] Sedlacek J. Possibilities of Application of Eye Drugs with the Aid of Gel-Contact Lenses. *Cesk Slov Oftalmol*. 1965;21:509-512.

[6.37] Hillman J. Management of Acute Glaucoma with Pilocarpine-soaked Hydrophilic Lens. *British Journal of Ophthalmology*. 1974;58(7):674-679.

[6.38] Hillman J, Marsters J, Broad A. Pilocarpine Delivery by Hydrophilic Lens in the Management of Acute Glaucoma. *Transactions of the Ophthalmological Society of the United Kingdom*. 1975;95(1):79-84.

[6.39] Podos S, Becker B, Asseff C, Hartsein J. Pilocarpine Therapy with Soft Contact Lenses. American Journal of *Ophthalmology*. 1972;73(3):336.

[6.40] North D. Treatment of Acute Glaucoma. *Canadian Medical Association Journal*. 1971;105:561.

[6.41] Waltman S, Kaufman H. Use of Hydrophilic Contact Lenses to Increase Ocular Penetration of Topical Drugs. *Investigative Ophthalmology*. 1970;9(4):250.

[6.42] Karlgard C, Wong N, Jones L, Moresoli C. In vitro Uptake and Release Studies of Ocular Pharmaceutical Agents by Silicon-containing and PHEMA Hydrogel Contact Lens Materials. *International Journal of Pharmaceutics*. 2003;257:141-151.

[6.43] Venkatesh S, Saha J, Pass S, Byrne M. Transport and Structural Analysis of Molecularly Imprinted Hydrogels for Controlled Drug Delivery. *European Journal of Pharmaceutics and Biopharmaceutics*. 2008;69(3):852-60.

[6.44] Ali M, Horikawa S, Venkatesh S, Saha J, Hong J, Byrne M. Zero-Order Therapeutic Release from Imprinted Hydrogel Contact Lenses Within in-vitro Physiological Ocular Tear Flow. *Journal of Controlled Release*. 2007;124(3):154-162.

[6.45] Venkatesh S, Sizemore S, Zhang J, Byrne M. Therapeutic Contact Lenses: A Biomimetic Approach Towards Tailored Ophthalmic Extended Delivery. *Polymer Materials Science Engineering Preprints*. 2006;94:766-767.

[6.46] Venkatesh S, Sizemore S, Byrne M. Biomimetic Hydrogels for Enhanced Loading and Extended Release of Ocular Therapeutics. *Biomaterials*. 2007;28(4):717-724.

[6.47] Costa V, Braga M, Guerra J, Duarte A, Duarte C, Leite E, Gil M, de Sousa H. Development of Therapeutic Contact Lenses Using a Supercritical Solvent Impregnation Method. *Journal of Supercritical Fluids*. 2010;52(3):306-310.

[6.48] Peterson R, Wolffsohn J, Nick J, Winterton L, Lally J. Clinical Performance of Daily Disposable Soft Contact Lenses Using Sustained Release Technology. *Contact Lens and Anterior Eye.* 2006;29(3):127-134.

[6.49] Winterton L, Lally J, Sentell K, Chapoy L. Elution of Poly(vinyl alcohol) from a Contact Lens: The Realization of a Time Release Moisturizing Agent/Artifical Tear. Journal of Biomedical Materal Research Part B: Applied Biomaterials. 2007;80B:424-432.

[6.50] Peng C, Kim J, Chauhan A. Extended Delivery of Hydrophilic Drugs from Silicone-Hydrogel Contact Lenses Containing Vitamin E Diffusion Barriers. *Biomaterials*. 2010;31(14):4032-4047.

[6.51] Salian V, Byrne M. Molecular Imprinting within Hydrogels II: Progress and Analysis of the Field. *International Journal of Pharmaceutics*. 2008;364(2):188-212.

[6.53] Byrne M, Park K, Peppas N. Molecular Imprinting within Hydrogels. *Advanced Drug Delivery Reviews.* 2002;54(1):149-161.

[6.54] White C, Byrne M. Molecularly Imprinted Therapeutics Contact Lenses. *Expert Opinion on Drug Delivery*. 2010;7(6):765-780.

[6.55] Ali M, Byrne M. Controlled Release of High Molecular Weight Hyaluronic Acid from Molecularly Imprinted Hydrogel Contact Lenses. *Pharmaceutical Research*. 2009;26(3):714-726.

[6.56] Ali M. Therapeutic Contact Lenses for Comfort Molecules, Master's Thesis. Auburn University Thesis; 2007.

[6.57] Venkatesh S, Sizemore S, Byrne M. Biomimetic Hydrogels for Enhanced Loading and Extended Release of Ocular Therapeutics. *Biomaterials*. 2007;28(4):717-724.

[6.58] Vaughan A, Zhang J, Byrne M. Enhancing Therapeutic Loading and Delaying Transport Via Molecular Imprinting and Living/Controlled Polymerization. *AICHE Journal*. 2010;56(1):268-279.

[6.59] Alvarez-Lorenzo C, Hiratani H, Concheiro A. Contact Lenses for Drug Delivery: Achieving Sustained Release with Novel Systems. *Journal of Pharmaceutical Sciences. American Journal of Drug Delivery*. 2006;4(3):131-151.

[6.60] Hiratani H, Alvarez-Lorenzo C. Timolol Uptake and Release by Imprinted by Imprinted Soft Contact Lenses Made of N,N-Diethylacrylamide and Methacrylic Acid. *Journal of Controlled Release*. 2002;83(2):223-230.

[6.61] Hiratani H, Alvarez-Lorenzo C. The Nature of Backbone Monomer Determines the Performance of Imprinted Soft Contact Lenses as Timolol Drug Delivery Systems. *Biomaterials*. 2004;25(6):1105-1113.

[6.62] Hiratani H, Mizutani Y, Alvarez-Lorenzo C. Controlling Drug Release from Imprinted Hydrogels by Modifying the Characteristics of the Imprinted Cavities. *Macromolecular Biosciences*. 2005;5(8):728-733.

[6.63] Hiratani H, Fujiwara A, Tamiya Y, Alvarez-Lorenzo C. Ocular Release of Timolol From Molecularly Imprinted Soft Contact Lenses. *Biomaterials*. 2005;26(11):1293-1298.

[6.64] Salian V, Byrne M. Using Living/Controlled Polymerization Strategies to Enhance Binding Parameters of Imprinted Polymers. *MIP2010: The Future of Molecular Imprinting*; 2010.

[6.65] White C, Tieppo A, Byrne M. Creating Macromolecular Memory in Hydrogels for Drug Delivery. *MIP2010: The Future of Molecular Imprinting*; 2010.

[6.66] Gulsen D, Chauhan A. Ophthalmic Drug Delivery through Contact Lenses. *Investigative Ophthalmology and Visual Science*. 2004;45(7):2342-2347.

[6.67] Gulsen D, Li C, Chauhan A. Dispersion of DMPC Liposomes in Contact Lenses for Ophthalmic Drug Delivery. *Current Eye Research*. 2005;30(12):1071-1080.

[6.68] Gulsen D, Chauhan A. Dispersion of Microemulsion Drops in HEMA Hydrogel: a Potential Ophthalmic Drug Delivery Vehicle. *International Journal of Pharmaceutics*. 2005;292(1-2):95-117.

[6.69] Li C, Abrahamson M, Kapoor Y, Chauhan A. Timolol Transport from Microemulsions Trapped in HEMA Gels. *Journal of Colloid and Interface Science*. 2007;315(1):297-306.

[6.70] Kapoor Y, Thomas J, Tan G, John V, Chauhan A. Surfactant-laden Soft Contact Lenses for Extended Delivery of Ophthalmic Drugs. *Biomaterials*. 2000;30(5):867-878.

[6.71] Lee P, Sunami A, Fozzard H. Cardiac-Specific External Paths for Lidocaine, Defined by Isoform-Specific Residues, Accelerate Recovery from Use-Dependent Block. *Circulation Research*. 2001;89:1014-1021.

[6.72] Garcia D, Escobar J, Noa Y, Bada N, Hernaez E, Katime I. Timolol Maleate Release from pH-sensible poly(2-hydroxyethyl methacrylate-co-methacrylate acid) Hydrogels. *European Polymer Journal*. 2004;40:1683-1690.

[6.73] Ciorlino J, Hoare T, Iwata N, Behlau I, Dohlman C, Langer R, Kohane D. A Drug-Eluting Contact Lens. *Investigative Ophthalmology and Visual Science*. 2009;50(7):3346-3352.

[6.74] Ciolino J, Kohane D. General Considerations in Designing a Drug-Eluting Contact Lens. *Expert Reviews in Ophthalmology*. 2009;4(6):569-571.

[6.75] Briber R, Liu X, Bauer B. The Collapse of Free Polymer Chains in a Network. *Science, New Series*. 1995;268(5209):395-397.

[6.76] Yanez F, Concheiro A, Alvarez-Lorenzo C. Macromolecule Release and Smoothness of Semi-Interpenetrating PVP-PHEMA Networks for Comfortable Soft Comfortable Soft Contact Lenses. *European Journal of Pharmaceutics and Biopharmaceutics*. 2008;69(3):1094-1103.

[6.77] Sato T, Uchida R, Tanigawa H, Uno K, Murakami A. Application of Polymer Gels Containing Side-Chain Phosphate Groups to Drug-Delivery Contact Lenses. *Journal of Applied Polymer Science*. 2005;98:731-735.

[6.78] Uchida R, Sato T, Tanigawa H, Uno K. Azulene Incorporation and Release by Hydrogel Containing Methacrylamide Propyltrimethylammonium Chloride, and Its Application to Soft Contact Lens. *Journal of Controlled Release*. 2003;92:259-264.

[6.79] Danion A, Brochu H, Martin Y, Vermette P. Fabrication and Characterization of Contact Lenses Bearing Surface-Immobilized Layers of Intact Liposomes. *Journal of Biomedical Research*. 2007;82A(1):41-51.

[6.80] Loftssona T, Jarvinen T. Cyclodextrins in Ophthalmic Drug Delivery. *Advanced Drug Delivery Reviews*. 1999;36(1):59-79.

[6.81] dos Santos J, Alvarez Lorenzo C, Silva M, Blasa L, Couceiro J, Torres-Labandeira J, Concheiro A. Soft Contact Lenses Functionalized with Pendant Cyclodextrins for Controlled Drug Delivery. *Biomaterials*. 2009;30(7):1348-1355.

[6.82] Xu J, Li X, Sun F, Chao P. PVA Hydrogels Containing Cyclodextrin for Enhanced Loading and Sustained Release of Ocular Therapeutics. *Journal of Biomaterials Science, Polymer Edition*. 2010;21(8-9):1023-1038.

[6.83] Van Beek M, Jones L, Sheardown H. Hyaluronic Acid Containing Hydrogels for the Reduction of Protein Adsorption. *Biomaterials*. 2008;29(7):780-789.

[6.84] Kaufman H, Uotila M, Gasset A, Wood T, Ellison E. The Medical Uses of Soft Contact Lenses. *Transactions of the American Academy of Ophthalmogy and Otolaryngology*. 1971;75(2):361-373.

[6.85] Kapoor Y, Chauhan A. Drug and Surfactant Transport in Cyclosporine A and Brij 98 laden p-HEMA Hydrogels. *Journal of Colloid and Interface Sciences*. 2008;322(2):624-633.

[6.86] Kim J, Peng C, Chauhan A. Extended Release of Dexamethasone from Silicone-Hydrogel Contact Lenses Containing Vitamin E. *Journal of Controlled Release*. 2010;148(1):110-116.

[6.87] Kim J, Conway A, Chauhan A. Extended Delivery of Ophthalmic Drugs by Silicone Hydrogel Contact Lenses. *Biomaterials*. 2008;29(14):2259-2269.

[6.88] Asseff C, Weisman R, Podos S, Becker B. Ocular Penetration of Pilocarpine in Primates. *American Journal of Ophthalmology*. 1973;75(2):212-215.

[6.89] Alvarez-Lorenzo C, Hiratani H, Gomez-Amoza J, Martinez-Pacheco R, Souto C, Concheiro A. Soft Contact Lenses Capable of Sustained Delivery of Timolol. *Journal of Pharmaceutical Sciences*. 2002;91(10):2182-2192.

[6.90] Alvarez-Lorenzo C, Yanez F, Barreiro-Iglesias R, Concheiro A. Imprinted Soft Contact Lenses as Norfloxacin Delivery Systems. *Journal of Controlled Release*. 2006;113(3):236-244.

[6.91] Karlgard C, Jones L, Moresoli C. Ciprofloxacin Interaction with Silicon-Based and Conventional Hydrogel Contact Lenses. *Eye and Contact Lens*. 2003;29(2):83-89.

[6.92] Lesher G, Gunderson G. Continuous Drug Delivery Through the Use of Disposable Contact Lenses. *Optometry and Vision Science*. 1993;70(12):1012-1018.

[6.93] Kalayci D, Basci N, Kortunay S, Hastripi H, Bozkurt A. Penetration of Topical Ciprofloxacin by Presoaked Medicated Soft Contact Lenses. *CLAO Journal*. 1999;25(3):182-184.

[6.94] Omafilcon A (Proclear) Soft Contact Lenses in a Dry Eye Population. *CLAO Journal*. 1999;25(1):40-47.

[6.95] Hull D, Edelhauser H, Hyndiuk R. Ocular Penetration of Prednisolone and the Hydrophilic Contact Lens. *Archives of Ophthalmology*. 1974;92(5):413-416.

[6.96] Jain M. Drug Delivery Through Soft Contact Lenses. *British Journal of Ophthalmology*. 1988;72(2):150-154.

[6.97] McDermott M, Chandler J. Therapeutic Uses of Contact Lenses. *Survey of Ophthalmology*. 1989;33(5):381-384.

[6.98] Zhao Y, Pitt W, Jack D, Nelson J, Pruitt J. Controlled Release of a Phospholipid From Contact Lenses. *AICHE Poster Presentation*. Salt Lake City, 2010.

[6.99] Peng C, Chauhan A. Cyclosprin A Delivery by Commercial Contact Lenses for Chronic Dry Eye Treament. *AICHE Poster Presentation*. Salt Lake City, 2010.

[6.100] Peng C, Chauhan A. Effect of Composition on Ion Permeability of Silicone Hydrogels as Extend[sic]-Wear Contact Lens. *AICHE Poster Presentation*. Salt Lake City, 2010.

[6.101] Friedman Z, Allen R, Ralph S. Topical Acetazolamide and Methazolamide Delivered by Contact Lenses. *Archives of Ophthalmology*. 1985;103(7):963-969.

[6.102] Silbert J. A Review of Therapeutic Agents and Contact Lens Wear. *Journal of the American Optometry Association*. 1996;67(3):165-171.

[6.103] Christie C. Therapeutic Contact Lenses. *Contact Lens and Anterior Eye*. 1999;22(1):s20-s25.

[6.104] Hehl E, Beck R, Luthard K, Guthoff R, Drewelow B. Improved Penetration of Aminoglycosides and Fluoroquinolones Into the Aqueous Humour of Patients by Means of Acuvue Contact Lenses. *European Journal of Clinical Pharmacology*. 1999;55(4):317-323.

[6.105] Lim L, Tan D, Chan W. Therapeutic Use of Bausch and Lomb PureVision Contact Lenses. *CLAO Journal*. 2002;27(4):41-46.

[6.106] Byrne M, Ventatesh S. Contact Drug Delivery System. United States Patent 2006; US Patent: 0177483 A1.

[6.107] Ali M, Byrne M. Challenges and Solutions in Topical Ocular Drug-Delivery Systems. *Expert Reviews in Clinical Pharmacology*. 2008;1(1):145-161.

[6.108] Ruben M, Watkins R. Pilocarpine Dispensation for the Soft Hydrophilic Contact Lens. *British Journal of Ophthalmology*. 1975;59(8):455-458.

[6.109] Momose T, Ito N, Kanai A, Watanabe Y, Shibata M. Adsorption of Levocabastine Eye Drops by Soft Contact Lenses and Its Effects in Rabbit Eyes. *CLAO Journal*. 1997;23(2):96-99.

[6.110] Xu J, Li X, Sun F. Cyclodextrin-Containing Hydrogels for Contact Lenses as a Platform for Drug Incorporation and Release. Acta *Biomaterialia*. 2010;6(2):486-493.

[6.111] Lang J. Ocular Drug Delivery Conventional Ocular Formulations. *Advanced Drug Delivery Reviews*. 1995;16(1):39-43.

[6.112] Tain X, Iwatsu M, Kanai A. Disposable 1-Day Acuvue Contact Lenses for the Delivery of Lomefloxacin to Rabbits' Eyes. *CLAO Journal*. 2001;27(4):212-215.

[6.113] Scheuer C, Fridman K, Barniak V, Burke S, Venkatesh S. Retention of Conditioning Agent Hyaluronan on Hydrogel Contact Lenses. *Contact Lens and Anterior Eye*. 2010;33(supplement 1):S2-S6.

[6.114] Boone A, Hui A, Jones L. Uptake and Release of Dexamethasone Phosphate from Silicone Hydrogel and Group I, II and IV Hydrogel Contact Lenses. *Eye and Contact Lenses: Science and Clinical Practice*. 2009;35(5):260-267.

[6.115] Costa V, Braga M, Duarte C, Alvarez-Lorenzo C, Concheiro A, Gil M, de Sousa H. Anti-Glaucoma Drug-Loaded Contact Lenses Prepared Using Supercritical Solvent Impregnation. *Journal of Supercritical Fluids*. 2010;53(1-3):165-173.

[6.116] Braga M, Yanez F, Alvarez-Lorenzo C, Concheiro A, Duarte C, Gil M, de Sousa H. Improved Drug Loading/Release Capacities of Commercial Contact Lenses Obtained by Supercritical Fluid Assisted Molecular Imprinting Methods. *Journal of Controlled Release*. 2010;148(1):e102-e104.

[6.117] Yanez F, Martikainen L, Braga M, Alvarez-Lorenzo C, Concheiro A, Duarte C, Gil M, de Sousa H. Supercritical Fluid-Assisted Preparation of Imprinted Contact Lenses for Drug Delivery. *Acta Biomaterialia*. 2011;7(3):1019-1030.

[6.118] Xu J, Li X, Sun F. In vitro and in vivo Evaluation of Ketotifen Fumarate-Loaded Silicone Hydrogel Contact Lenses for Ocular Drug Delivery. *Drug Delivery*. 2011;18(2):150-158.

[6.119] Hui A, Boone A, Jones L. Uptake and Release of Ciprofloxacin-HCl From Conventional and Silicone Hydrogel Contact Lens Materials. *Eye and Contact Lens*. 2008; 34(5):266-271.

[6.120] Danion A, Doillon C, Giasson C, Djouahra S, Sauvageau P, Paradis R, Vermette P. Biocompatibility and Light Transmission of Liposomal Lenses. *Optometry and Vision Science*. 2007;84(10):954-961.

[6.121] Tian X, Iwatsu M, Sado K, Kanai A. Studies on the Uptake and Release of Fluoroquinolones by Disposable Contact Lenses. *CLAO Journal*. 2001;27(4):216-220.

[6.122] Marmion V, Jain M. Role of Soft Contact and Delivery of Drugs. *Transactions of the Ophthalmological Society of the United Kingdom*. 1976;96(2):319.

[6.123] Karlgard C, Jones C, Moresoli C. Survey of Bandage Lens Use in North America, October-December 2002. Eye and Contact Lens. 2004;30(1):25-30.

[6.124] Fahmy M, Long B, Giles T, Wang C. Comfort-Enhanced Daily Disposable Contact Lens Reduces Symptoms Among Weekly/Monthly Wear Patients. *Eye and Contact Lens*. 2010;36(4):215-219.

[6.125] Kanemoto M, Sato T, Aoyama A, Matsunaga T, Uno K, Toshida H, Murakami A. Interaction and Compatibility Between a Soft Contact Lens and an Ophthalmic Drug. *Eye and Contact Lens*. 2006;32(4):192-196.

[6.126] Morgan P, Woods C, Tranoudis I et al. International Contact Lens Prescribing in 2009. *Contact Lens Spectrum*. 2010;24(2):30-35,53.

CHAPTER 7

MOLECULAR IMPRINTING WITHIN HYDROGELS AND DELIVERY OF MACROMOLECULAR COMFORT AGENTS

Although there is a large unmet need for effective ocular dry eye treatments, there have only been three separate systems involving comfort agent releasing contact lenses in the literature and only one commercial lens available to US consumers. Thus far, all the release molecules have been from hydrophilic lens platforms, using imprinting and reptation as the rate control method. To date, no silicone hydrogel lens has been demonstrated to release comfort agents.

7.1. Description of Hydrogels.

Hydrogels are crosslinked three-dimensional polymer networks generally swollen in water that contain high water content. Hydrogels are insoluble, crosslinked polymer network structures composed of hydrophilic homo- or heteropolymers, which have the ability to absorb significant amounts of water and retain their shape without dissolving. Crosslinks (also known as tie-points or junctions) can be covalent bonds, permanent physical entanglements, non-covalent interactions, or microcrystalline regions incorporating various chains and are primarily responsible for preventing the dissolution

of the polymer in water [**7.1**]. Due to the high water content, most hydrogels display a high biotolerance and biocompatibility with tissues in the body, making them an ideal platform for in vivo drug delivery. Moreover, hydrogels can be designed to respond to environmental changes including pH, temperature, electromagnetism, and osmolarity.

7.2. Diffusion of Drug in Hydrogels.

Reservoirs of drug can be loaded into hydrogel lenses and diffusion occurs between areas of high to low concentration. In solvents, there are little or no barriers to drug transport. On a microscopic level, drug molecules undergoing Brownian motion have enough space so it can be assumed that no interactions occur, resulting diffusion coefficients can be quite large. Diffusion coefficients of small molecules in water are on the order of 10^5 cm^2/sec [**7.2**]. However, when molecules are loaded into hydrogels, the polymer chains form constraints on drug motion. Drug motion can be modeled as point motion in a field of random obstacles, where crosslinks form the obstacles. When the obstacles are far apart, the motion is similar to that of drugs in free solvents. However, as molecular weight between crosslinks (Mc) decreases, the obstacles are closer together and drug transport is limited. As the Mc approaches the molecular diameter or persistence length of the polymer, the drug is likely to be sterically hindered. The average molecular weight between crosslinks (Mc) can be used to calculate the mesh size. The steric effects on transport from mesh size can be likened to size exclusion based transport, where molecules much smaller than the mesh easily pass through the network and larger molecules fit through with greater difficulty. As a result, the diffusion coefficient is proportional to the mesh size.

Polymeric drugs are even further constrained by network crosslinks. The polymeric coils can wrap around crosslinks hindering the bulk transport of the drug. Adding to the difficulty seen in transport of a polymer in a network, if a polymer is sufficiently long, the head and tail of the chain can be assumed to be moving independently of each other. With each section of the chain undergoing Brownian motion, polymer transport is often a statistical movement of coils. Conformation of the polymer drug and hydrodynamic volume of the drug often dictate the diffusion coefficients among the crosslinked network. If the chain conformation is approximately linear, the movement of the chain is referred to as reptation, which is much like worm or snake movements. If the conformation is more coiled or spherical and the mesh size sufficiently constraining, conformation changes or squeezing must be undertaken before the drug can move through the network. Conformation, solubility and volume are typically dependent on molecular weight and must be taken into account in macromolecular comfort agent selection. Increasing the number of interactions between polymer chains and the drug can decrease diffusion coefficients. This is one principle imprinting uses to control drug elution.

7.3. Release of HA via Biomimetic Imprinting.

Previous work by Byrne and coworkers has shown release of hyaluronic acid (HA) using biomimetic imprinting within daily disposable Nelfilcon A lenses [**7.2, 7.3**]. Biomimetic molecular imprinting is the selection and use of functional comonomers that resemble the natural amino acid receptors and binding moieties within the human body. In addition, the use of both high and low affinity selected comonomers can be used to modify the way the drug molecules interact with the polymer network as it diffuses,

granting a high level of control to the rational design of therapeutic contact lenses. To prepare a hydrogel via imprinting, the monomers are mixed with the template drug and allowed to reach equilibrium where the drug-monomer complexes reach a thermodynamically stable orientation. After polymerization occurs, the monomers are templated around the drug forming a macromolecular memory site that remains even after the template drug is removed. The process is represented by **Figure 7.1**. This molecular memory enhances affinity for the drug in the network and slowing the release. This technique has been demonstrated for ketotifen fumarate [**7.4-7.7**], hyaluronic acid [**7.2, 7.3**], and diclofenac sodium [**7.8**].

Focus DAILIES^{TM} imprinted HA films were developed by Byrne and Ali that release HA over the course of 2 days under large volume infinite sink conditions [**7.3**]. The films can be formulated as a daily disposable lenses. The lenses used for this platform is known as Nelfilcon A, which is a polyvinyl alcohol based material [**7.9]** and is shown in **Figure 7.2**. Nelfilcon hydrogels were formulated with a variety of HA concentrations but 6.5 mg HA/g lens was identified as the optimum loaded concentration. Exploiting the hydrogen bonding tendency between HA and the functional monomers, acrylamide, N-vinyl pyrrolidone, and (diethylamino)ethyl methacrylate, biomimetic imprinting was used control and optimize the release rate, producing rates approaching zero-order (**Figures 7.3, 7.4**). By altering the M/T ratios, Byrne and Ali also managed to completely sequester the HA in the lens [**7.2-7.3**].

The results of the project were extremely promising and exciting. The principle of biomimetic imprinting was shown to be extremely effective in imprinting macromolecular comfort agents in contact lenses. However, daily disposable lenses are

merely one type of contact lenses and not the most popular among consumers. The success of the HA-Nelfilcon A project formed the foundation of the current work. The current research seeks to develop a similar technology to the daily disposable lens but, in order to meet the demands of the current commercial lens market (**Chapter 3**). A continuous extended wear lens capable of releasing the re-wetting agent for 30 days is needed.

7.4. Tables and Figures.

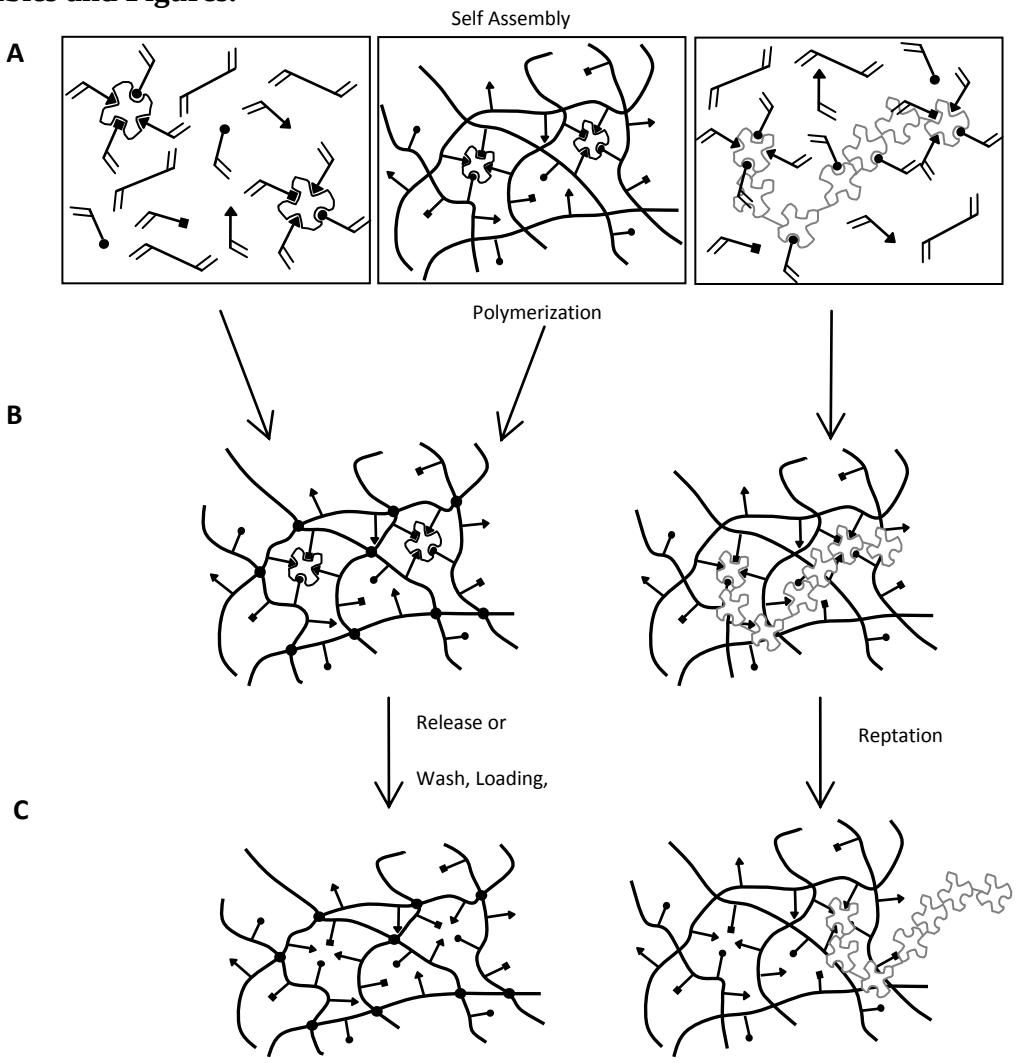


Figure 7.1. Creation of Macromolecular Memory in Hydrogels Through Molecular Imprinting.

Non-covalent self-assembly of the functional monomer drug complexes within the pre-polymerization solution. This can be in the form of monomeric species (left box) or oligomers/polymers that have pendant double bonds or are reacted to other chains by other molecules (•) (middle box) with small or large molecular weight templates (right box, macromolecule). B. Formation of an idealized macromolecular network with

recognition sites consisting of functional chemistry on differing polymer chains. C. Release of drug with or without wash steps. The transport of long molecular weight molecules (ocular comfort molecules) can also be controlled by imprinting mechanisms. Whereas the size of the macromolecule and conformation as well as the polymer mesh size will influence release, imprinting leads to an extra level of control to delay release or turn release on and off.

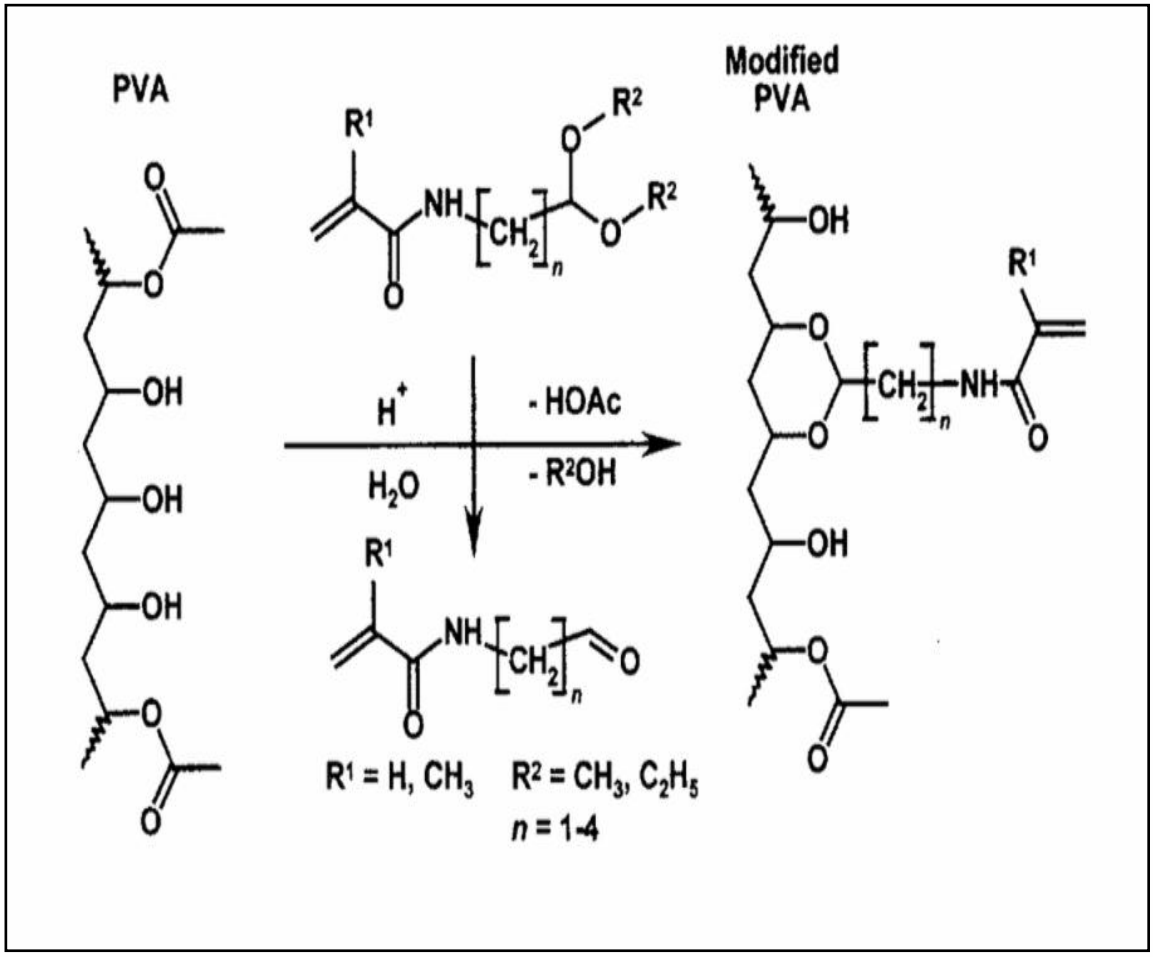


Figure 7.2. Synthesis of Nelfilcon A Macromer from PVA.

Nelfilcon A is a hydrophilic contact lens material used for daily wear contact lenses. The proprietary macromer is created by forming a trans-acetal linkage between the PVA chain and N-acryloyl-aminoacetaldehyde-dimethylacetal (NAADA). NAADA then acts as a crosslinker between the PVA chains during polymerization. All other components (i.e. the visibility tint and radical initiator) can be attached via an ether or acetal linkage in the synthesis process and is easily purified by diafiltration. The figure was used with permission from [**7.2**]

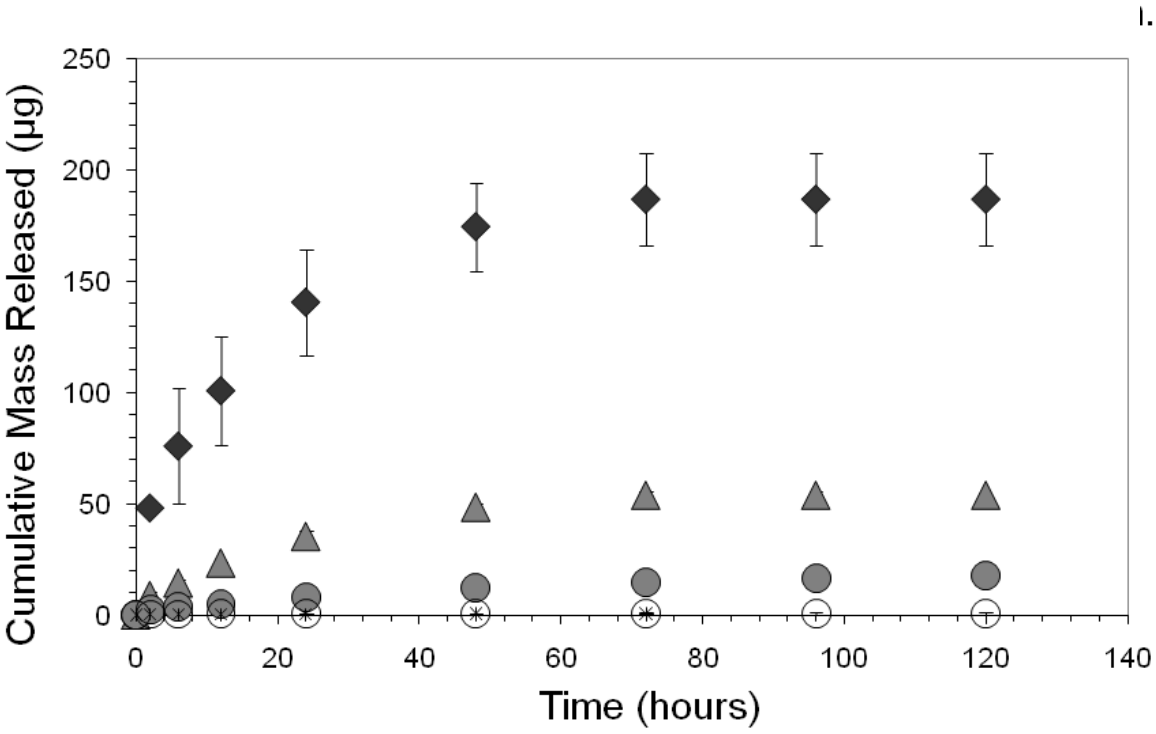


Figure 7.3. Tailorable Hyaluronic Acid Release from Nelfilcon A lenses.

Acrylamide (AM), N-Vinyl Pyrrolidone (NVP), 2-(diethylamino) ethyl methacrylate (DEAEM) were used in Nelfilcon A lenses to control the rate of release of 1.2 million Da HA at a ratio of [1:1:2] respectively. The lenses were formulated with various weight fractions of functional monomers ranging from (♦) 0%, (▲) 0.125%, (●) 0.25% (X) 1% and (○) 5 wt%. Release was performed in 20 mL of artificial lacrimal fluid at 35ºC at a rotation speed of 30 rpm. After measurement, the lacrimal fluid was completely replaced and release continued at the specified conditions. It was found that HA was completely sequestered in the lens at a function monomer concentration between (●) 0.25 wt% and (X) 1 wt%. The figure was used with permission from [**7.2**]

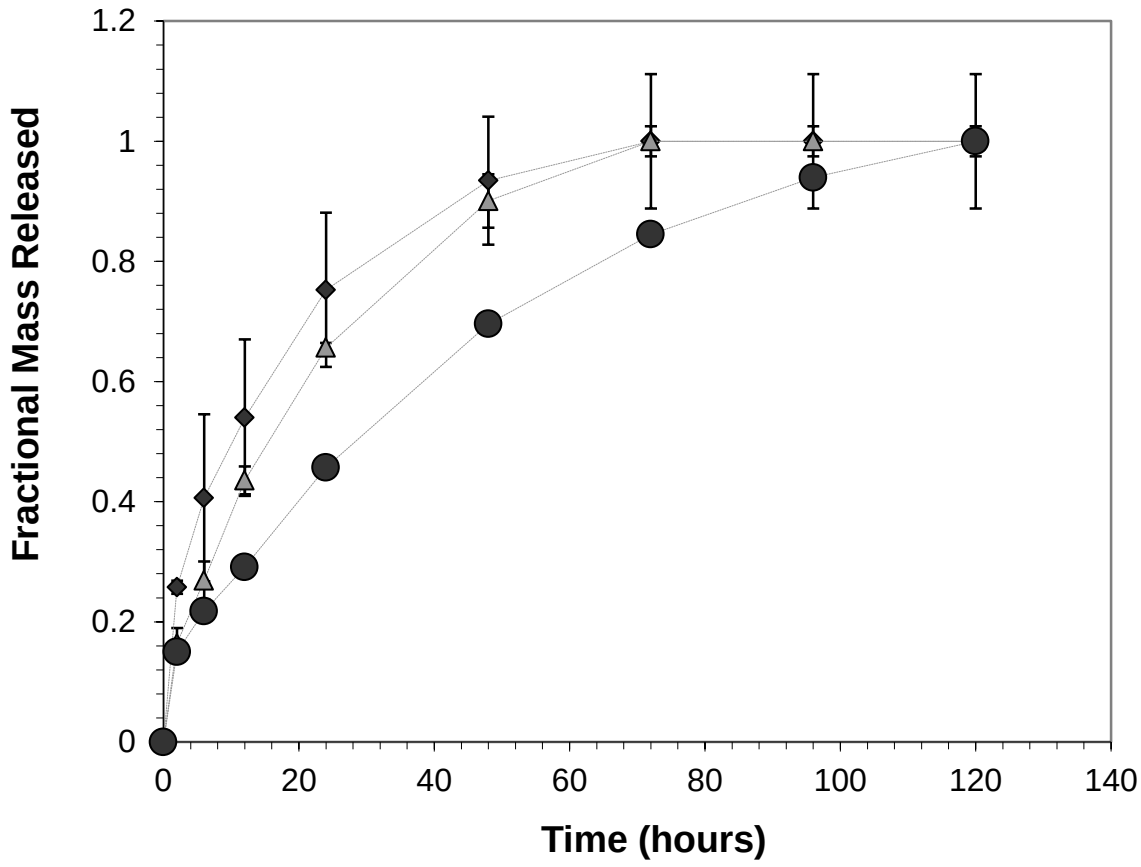


Figure 7.4. Fractional Mass Release of HA.

Release rates approaching zero order release (concentration independent release) were observed with increasing M/T values. Increasing M/T values from (♦) 0% to (▲) 0.125% to (●) 0.25% of the lens showed a definite decrease in release order and continuing to increase the monomer content in the [1-1-2] ratio (AM-NVP-DEAEM) could provide the ideal release rate. The figure was used with permission from [**7.2**]

7.5. References.

[7.1] Byrne M, Park K, Peppas N. Molecular Imprinting within Hydrogels. *Advanced Drug Delivery Reviews*. 2002;54(1):149-161.

[7.2] Ali M. Therapeutic Contact Lenses for Comfort Molecules, Master's Thesis. Auburn University Thesis; 2007.

[7.3] Ali M, Byrne M. Controlled Release of High Molecular Weight Hyaluronic Acid from Molecularly Imprinted Hydrogel Contact Lenses. *Pharmaceutical Research*. 2009;26(3):714-726.

[7.4] Venkatesh S, Saha J, Pass S, Byrne M. Transport and Structural Analysis of Molecularly Imprinted Hydrogels for Controlled Drug Delivery. *European Journal of Pharmaceutics and Biopharmaceutics*. 2008;69(3):852-860.

[7.5] Ali M, Horikawa S, Venkatesh S, Saha J, Hong J, Byrne M. Zero-Order Therapeutic Release from Imprinted Hydrogel Contact Lenses Within in-vitro Physiological Ocular Tear Flow. *Journal of Controlled Release*. 2007;124(3):154-162.

[7.6] Venkatesh S, Sizemore S, Zhang J, Byrne M. Therapeutic Contact Lenses: A Biomimetic Approach Towards Tailored Ophthalmic Extended Delivery. *Polymer Materials Science Engineering Preprints*. 2006;94:766-767.

[7.7] Venkatesh S, Sizemore S, Byrne M. Biomimetic Hydrogels for Enhanced Loading and Extended Release of Ocular Therapeutics. *Biomaterials*. 2007;28(4):717-724.

[7.8] Vaughn A, Zhang J, Byrne M. Enhancing Therapeutic Loading and Delaying Transport Via Molecular Imprinting and Living/Controlled Polymerization. *AICHE Journal*. 2010;56(1):268-279.

[7.9] Bühler N, Haerri H, Hofman M, Irrgang C, Mühlebach A, Müller B, Stockinger F. Nelfilcon A, a New Material for Contact Lenses. *CHIMIA International Journal for Chemistry*. 1999; 53(6):269-274.

[7.10] White C, Byrne M. Molecularly Imprinted Therapeutics Contact Lenses. *Expert Opinion on Drug Delivery*. 2010;7(6):765-780.

CHAPTER 8

SILICONE HYDROGELS MADE FROM LOTRAFILCON B AND COMMERCIAL PRODUCTION

The development of silicone hydrogels has revolutionized the contact lens industry. Traditional hydrogel lenses could not be worn for long times due to inadequate oxygen permeability and discomfort comfort. Traditional hydrogels have typically been made of hydrophilic monomers and have high water content. To maintain comfort and oxygen permeability requirements, traditional hydrogel lenses contain 70-90% water and often sacrifice certain physical properties.

8.1. Composition of Silicone Hydrogels.

Silicone hydrogels lenses are fundamentally different in makeup compared to traditional hydrogel lenses. Instead of purely hydrophilic monomers, silicone hydrogels are a mixture of both hydrophilic and hydrophobic monomers with the central material a silicone-based macromer. The result is a biphasic system, much more complex than the traditional hydrogels. The silicone or highly hydrophobic section is responsible for the high oxygen permeability values. The hydrophilic sections are designed to transport ions, proteins and enzymes through the lens. When swollen, the silicone phases tend to migrate to the surface of the lens where the hydrophobic material can disrupt the lipid layer and can adhere to the epithelial cells. For this reason, it is required to add a hydrophilic or plasma coating to the surface of the lens making the lens more comfortable and compatible to the ocular environment. Typical formulations for silicone hydrogel lenses

include proprietary silicone based macromers, TRIS as a chain extender for the hydrophobic section, and some acrylic, hydrophilic monomer to control both mechanicalproperties and ion, water and protein transport. The hydrophilic monomer is typically dimethyl acrylamide (DMA). As a result, the low water content of the lens reduces potential loading of hydrophilic therapeutics due to low solubility and decreased volume for the drug to reside. In addition, if the drug resides in the hydrophobic section of the lens, hydrophobic interactions are nonspecific and difficult to control. The structures of the silicone hydrogel monomers, crosslinkers and imprinting monomers used in this work are presented in **Figure 8.1**.

In the course of the project, the base material was Lotrafilcon B (LFB), which is composed of specific ratios of DMA, TRIS, and macromer (**Figure 8.2**). Relative concentrations of the comonomers could be adjusted, different monomers could be added, and the DMA completely replaced with another hydrophilic monomer if so desired as long as physical properties were met. Monomers added to the formulation during the course of this research included ethylene glycol (EGDMA), polyethylene glycol 200 dimethacrylate (PEG200DMA), surfactants, methacrylic acid (MAA), acrylic acid (AA), and N-vinyl pyrrolidone (NVP). For imprinting, DMA and AA were selected as low and high affinity binding monomers respectively. The acrylic acid possesses carboxylic acid functional groups that can hydrogen bond with HPMC hydroxyl groups. DMA possesses both a carboxyl group and an amine both of which are capable of hydrogen bonding, though steric interference from the methyl substituents on the amine and electron delocalization between the carboxyl and amine groups makes strong, stable hydrogen bonds unlikely. Turbidity test were conducted on LFB lenses, and the LFB

formulation demonstrated increased optical clarity as DMA and AA content was increased, indicating that some interactions occur between the HPMC macromonomer and the AA and DMA monomers.

8.2. Commercial Lens Production.

It was initially and understandably desired for the laboratory formulation and synthesis procedure to mimic the commercial process as closely as possible. However, it was not possible to completely match the industrial procedure. The LFB formulation includes ethanol as a diluent and solvent to ensure good mixing of the lens components. Afterward, a liquid extraction step is performed on the lens to ensure all unreacted monomer and ethanol is removed for a period of 30 mins. The surface modification is then applied and the lens sterilized and stored in the package. By the time the lens arrives to the wearer, only a trace amount of solvents (not including water) is detected in the lens. It was found in the course of this work that this was not a realistic goal of the laboratory research. The solvent removal process could not be accurately performed in the laboratory setting and the presence of the solvent affected the release rate of the HPMC. When solvent was present within the lens, HPMC release was slowed due to partitioning between the two phases. The ethanol slows the elution rate of HPMC to negligible quantities. To overcome this, the solvent and the liquid extraction step were completely removed from the procedure. This ensured that any solvent effects were eliminated from the release data.

8.3. Comparison Between Commercial and Laboratory Lens Synthesis.

The justification for solvent removal required experimentation in four different formulations to isolate and optimize the formulation. The original material used was the

pre-made LFB formulation received directly from CIBA Vision, Inc. including the blue visibility tint used in the final lens. Due to incompatibilities between the tint and loaded comfort agents, a second phase series of experiments premade tint free formulation was received and used. In a third phase of experiments, ethanol was extracted from the lens by vacuum evaporation. In commercial production ethanol is completely removed from the lens before the product is shipped to the consumer. Removing the ethanol was discovered to induce lens swelling and a reduction in optical clarity. Moreover, it was observed that inclusion of ethanol affected release rate in a deleterious fashion. The decision was made to completely remove the solvent from the lens formulation.

In the course of further research, additional functional and divinyl monomers were added to control swelling, release, and clarity. This required the lens formulations to be mixed individually. The formulations were mixed in the order of Betacon Macromer, TRIS, DMA, HPMC, crosslinkers (if desired), functional monomers (if desired), and photo-initiator.

8.4. Tables and Figures.

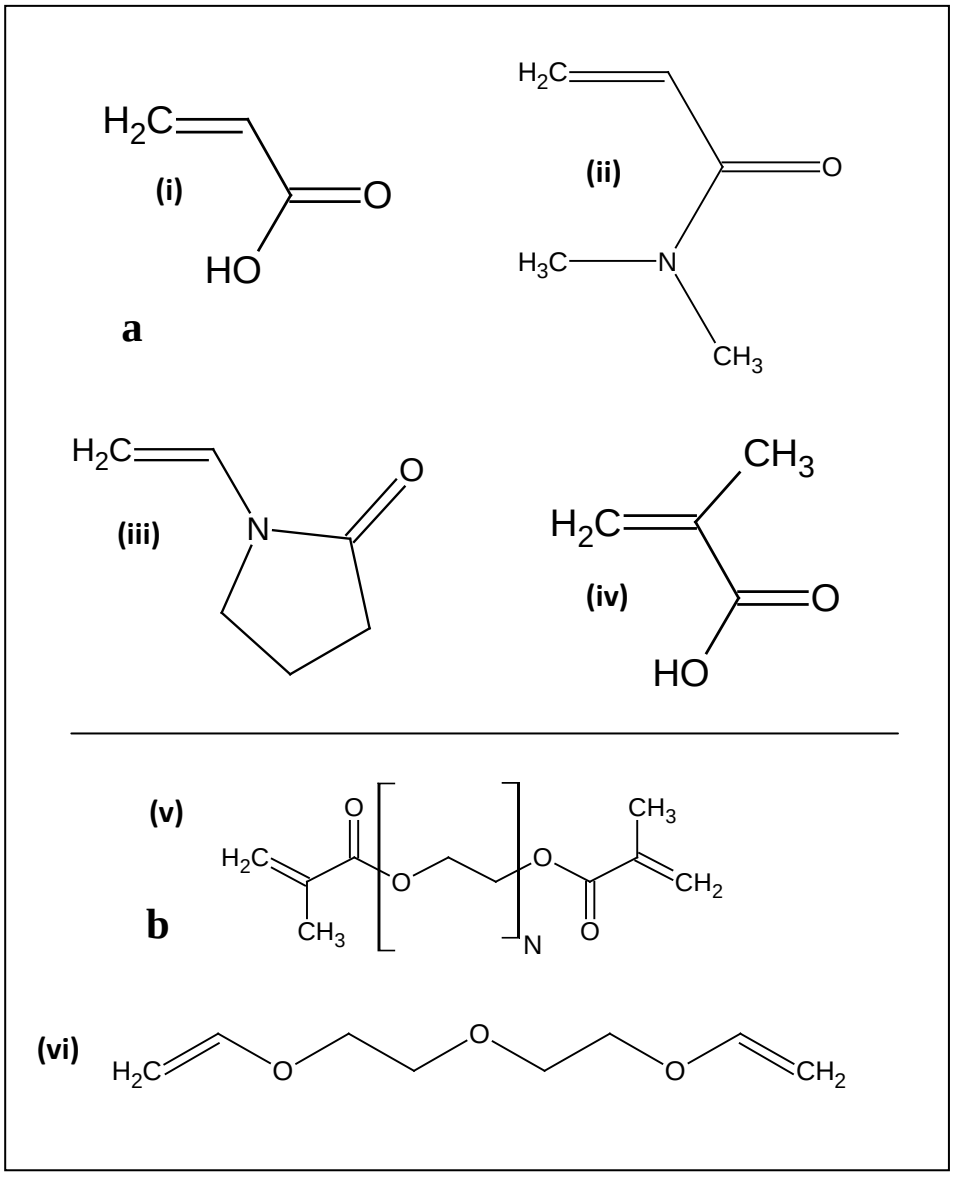


Figure 8.1. Monomers Used in the Development of the HPMC-Imprinted Lenses.

a: Monomers Used in the Imprinting Process. The structures are of the various monomers used to create macromolecular memory sites for HPMC in LFB lenses. All monomers were chosen for the presence of functional groups capable of hydrogen bonding with hydroxyl sites on the HPMC macromolecule. The structures represented are

(i) acrylic acid (AA), (ii) dimethyl acrylamide (DMA), (iii) N-vinyl pyrrilidone (NVP), and (iv) methacrylic acid (MAA). **b: Crosslinkers .** Various lengths of poly(ethylene glycol) dimethacrylates were used to control mechanical properties, clarity and swelling in the HPMC-laden lenses. The generic structure of (v) PEG-N-DMA is represented as well as the structure for (vi) divinyl ethylene glycol. The length of N varied between ethylene glycol dimethacrylate (N~1), tetraethylene glycol dimethacrylate (N~4), polyethylene glycol 200 dimethacrylate (N~4.5), polyethylene glycol 400 dimethacrylate (N~6.5), and polyethylene glycol 600 dimethacrylate (N~9.5).

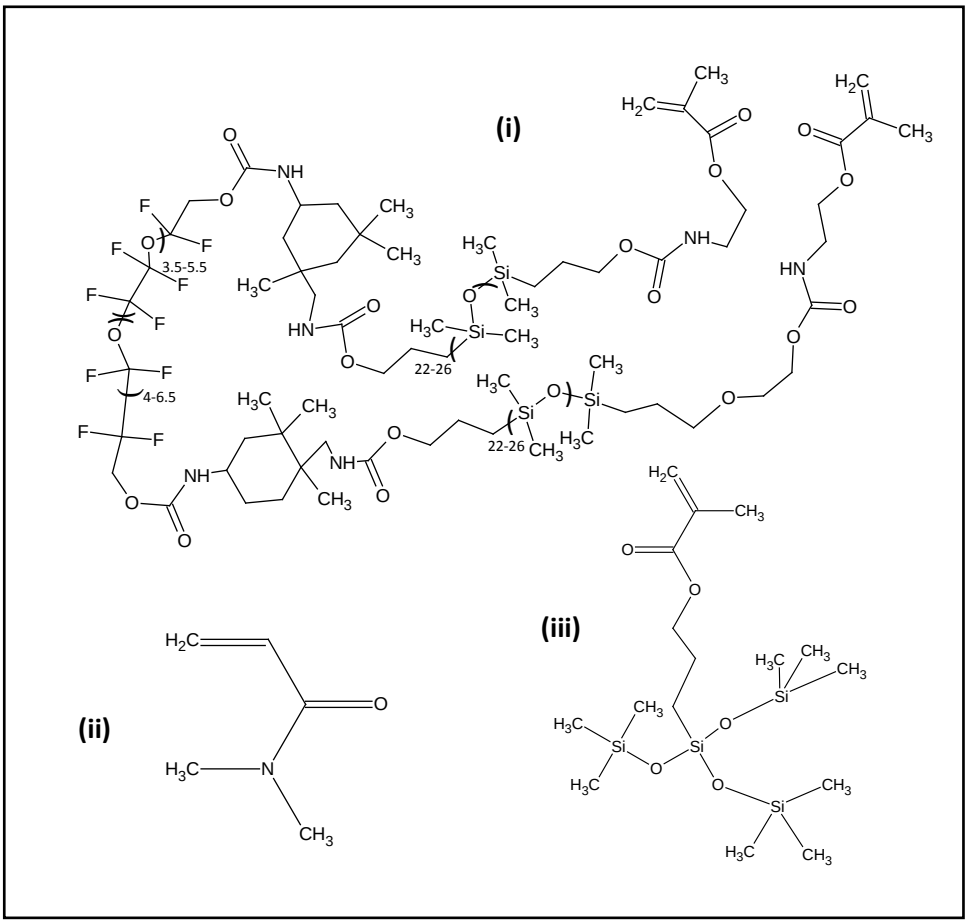


Figure 8.2. Monomers in the LFB Formulation.

The silicone hydrogel contact lens formulation, Lotrafilcon B, is made up of three major components **(i)** 26% Betacon Macromer, **(ii)** 30% DMA, and **(iii)** 19% TRIS. The balance of the formulation is initiator and solvent TRIS and the macromer is the hydrophobic section of the lens and responsible for oxygen permeability. DMA makes up the hydrophilic, ion permeable phase of the lens.

CHAPTER 9

EXPERIMENTAL MATERIALS AND METHODS

For this work, the predominant material used is the proprietary formulation, Lotrafilcon B (CIBA Vision, Inc.). LFB is a mixture of methacryloxypropyl-tris-(trimethylsiloxy) silane (TRIS), dimethyl acrylamide (DMA), and CIBA Vision's Betacon macromer (referred hereafter as macromer). Two different pre-formulated standard mixtures were generously provided by CIBA Vision. One of the pre-formulated standard mixtures contained the blue visibility tint [Cu/P] (referred to in this work as the tinted formulation) and the other did not contain the tint (referred to as the untinted formulation). In addition, DMA was purchased from Sigma Aldrich (Milwaukee, WI), and the TRIS and macromer were provided by CIBA Vision, Inc and used as received. Darocur 1173, used as UV photo-initiator, was purchased from Sigma Aldrich (Milwaukee, WI). Acrylic acid (AA), methacrylic acid (MAA), N-vinyl pyrrolidone (NVP), poly(ethylene glycol) (n) dimethacrylate (PEG-*MW*-DMA) where *MW* = 4, 200, 400, and 600, poly(ethylene glycol) diacrylate (PEG-DA), hydroxypropyl methylcellulose (HPMC) (MW = 10, 90, and 120 KDa), and ethanol were purchased from Sigma Aldrich (Milwaukee, WI) and used as received. All monomers were kept refrigerated at 4°C until use.

9.1. Synthesis of LFB Lenses.

To produce lenses, an aliquot of the formulation was measured into a 50 mL centrifuge tube. Then monomers were added to the mixture according to pre-determined weight ratios, and comfort agent (either HPMC, PVA, or HA) was added. Non-imprinted lenses were produced using the LFB CIBA Vision formulation with and without tint. Functional monomers, crosslinkers, surfactants and other components were added and then the comfort agent was added. The mixture was stirred and sonicated until all components were evenly dispersed. A fixed volume was pipetted into the polypropylene (PP) lens molds provided by CIBA Vision, Inc. (Series No.: EV86-100 and EV86-BCBP). The mass of formulation pipetted varied between 100 to 200 mg depending on the concentration of comfort agent. The lens was polymerized via UV polymerization using a UV light source (Novacure 2100, Exfo) with an intensity of approximately 25 mW/cm^2 for a duration of 1.5 minutes. The lenses were then removed from the mold, and the molds were washed and reused. The lenses were placed in a vacuum oven (30ºC at -30 mm Hg) on aluminum foil for thirty minutes to extract ethanol.

Lenses were also produced using individual component of monomers of the LFB formulation. They were kept refrigerated under the same conditions as the complete, premade LFB formulation. A typical formulation consisted of 1,300 mg of Betacon macromer, 1,300 mg of TRIS, and 1,300 mg of DMA. Thus, the base formulation was equal parts of these monomers and used to calculate ratios of other components. Formulations of individual components ranged from 1,000-1,500 mg of Betacon macromer, 1,000-1,500 mg of TRIS, 1,000-1,500 mg of DMA. EGDMA and PEG200DMA were added at a desired concentration anywhere between 0 and 10 wt% of

the base formulation. Imprinting monomers were then added between 0 and 10 wt% of the base formulation. Darocur 1173 was added to the solution to a concentration of 1% of the base formulation. The samples were thoroughly mixed by sonication for 30 minutes and then the comfort agent was added to the desired concentration. After the comfort agent was added, the sample was sonicated and mixed until evenly dispersed. Polymerization of the lens was performed at the same conditions as the complete, pre-made LFB formulation lenses. As no ethanol was used in the formulation of these lenses, no extraction step was performed. Out of mold lenses were ~220 μm thick (center thickness) and water swollen lenses were ~350 μm thick (center thickness) unless otherwise noted.

9.2. Comparison of Drug Release Methods.

One interest of this work compares to compare the effectiveness of four different loading and controlled delivery methods. This is done by formulating lenses according to each method and directly comparing the loading and release time and rates of drug elution. Factors such as swelling, optical clarity, and mechanical properties were not measured within this series of experiments, other than qualitative notation. If qualitative physical properties were significantly reduced, the method was considered to be inferior to other methods and eliminated from consideration. Each method of loading and release had characteristic alternations to the method listed in **Section 9.1** and any alterations are noted below.

9.2.1. HPMC, PVA and HA Drug Soaked Lenses. LFB films were synthesized from the both the tinted and untinted pre-made formulation. The films were photo-polymerized between two glass slides, separated by a 125 μm thick Teflon mold. A cork

borer was then used to cut samples 10 mm in diameter. The cut samples were weighed, and this was known as the out of mold or pre-extract weight. Half of the sample films created underwent the extraction step in the vacuum oven, while the other half of the films was placed in a separate drug solution without any extraction step. All samples undergoing the extraction procedure were weighed before and after the extraction and the weights referred to as the pre- and post-extraction weight, respectively.

The drug solutions were composed of 5 mL de-ionized water and re-wetting agent (PVA, HA and HPMC) was added until 0.1, 1.0, or 10 wt% concentration was reached. Fresh drug solutions were used for each film to avoid contamination of the drug solution. The lenses were allowed to soak in the drug solution for 1 day, 2 days, and 1 week at room temperature. At the end of each interval, the lens was removed from solution and dabbed in DI water to remove any drug adhering to the surface, dabbed dry with a Kimwipe and weighed. The mass of the loaded drug into the film was calculated from the resulting increase in weight.

9.2.2. Synthesis of Reptation Controlled Diffusion-based Lenses and Films. HPMC was dissolved into the untinted LFB pre-polymer solution to a desired concentration and photo-polymerized in the PP molds. The resulting lenses were taken out of the mold and weighed. Some lenses (depending on the experiment series) may have then undergone the extraction step, while others were placed directly into the dissolution apparatus and release performed in the manner described later in this section. HPMC lenses were also formulated from the individual components in a method similar to that already described. Crosslinkers were added to the formulation, and ethanol was completely removed. Once the components were added to the desired concentration, the

solution was pipetted into a mold and exposed to UV light for 1 min. Since no ethanol was formulated into the solution, no extraction step was performed.

HA-laden lenses were made to a thickness of 500 μm by vigorously mixing HA, DI water and the LFB formulation and immediately placing it between two glass plates and photo-polymerizing for 10 – 40 minutes. Creating films below this thickness was not feasible due to phase separation. Addition of CIBA Vision's macromer, Nelfilcon A, was added as a hydrophilic crosslinker to disperse the HA-aqueous phase. Once formed the films were placed into 50 mL DI water to measure release. PVA was not tested in this procedure.

9.2.3. Synthesis of Surfactant-Mediated Releasing HA and HPMC-laden Lenses. Aliquots of the untinted LFB formulation were measured into a 50 mL centrifuge tubes, and surfactants and comfort agent (HA or HPMC) were added to a desired concentration. For HA-laden systems, de-ionized water was added to certain concentrations. The formulation was exposed to high sheer and sonicated. Films were polymerized between two glass slides by exposing them to UV light for ~5 minutes. The resulting film thickness of HPMC-surfactant systems was 250 μm. A 10 mm cork borer was used to create circular samples. Below 250 μm, HPMC films could not form. Water was necessary to dissolve the HA into the LFB system, yet the presence of water forced the films produced to a diameter of 500 μm. Below this thickness, holes formed in the film where the HA-aqueous portion of the lens phase separated. With thicker films, the LFB phase managed to encapsulate the HA-aqueous phases.

9.2.4. Synthesis of Molecularly Imprinted Lenses. Aliquots of the untinted, premade LFB formulation were added to a centrifuge tube after which any additional

crosslinkers and functional monomers were added. The solution was mixed thoroughly and HPMC was added. HPMC was chosen as the primary template as the other re-wetting agents did not display the necessary solubility. Lens formulations were mixed in accordance with the method described in **Section 9.2.** The formulations were exposed to high shear mixing for up to 1 min and sonicated for at least 15 mins to remove any dissolved air or air bubbles. The formulation was pipette into a PP mold and exposed to UV light to induce photo-polymerization. To form lenses with a center thickness of ~100 μm, a Thomas spherical joint pinch clamp was tightened around the mold.

9.3. Characterization of the Lenses.

Lenses were tested to determine optical clarity, mechanical properties, equilibrium water uptake swelling, and dynamic release studies.

9.3.1. Optical Clarity of Synthesized Lenses. Optical clarity studies were conducted by measuring the percent transmittance of visible light (wavelength range from 450-750 nm) through swollen lenses. Lenses from the molds were cut with a No. 3 cork borer and placed in the bottom of a 96 well plate where absorbance values were measured via spectrophotometric monitoring (Biotek, Winooski, VT). Each sample lens was cut into at least three samples to note any local differences within the lens. All films were fully hydrated in 200 μL of water with care taken that the film was in full contact with the bottom of the well plate and no air bubbles were present. The absorbance value of each well in water was calculated and subtracted from the data. Percent transmission values were calculated from the optical density and absorbance data. Furthermore, in some cases, optical clarity measurements were taken from the pre-polymer mixture, and 200 μL of pre-polymer mixture was placed into a 96 UV well plate. All optical clarity

experiments were carried out in triplicate with three separate lenses (for a total of nine samples for each lens).

9.3.2. Dynamic Mechanical Analysis - Tensile Studies. Hydrogels prepared in strips (in triplicate) were mounted on a dynamic mechanical analyzer (RSA III, TA Instruments) at a gauge length of 30 to 35 mm, and extended at a rate of 4 mm/min. The gels were fully hydrated through the experiment, and hydration was maintained an aerosol diffuser.

9.3.3. Swelling Studies. Equilibrium swelling studies were conducted by placing dried lenses in DI water until they reached equilibrium. The lenses were then removed from the solutions, patted dry with a soft tissue (Kimwipes®), and weighed in air using a balance (Sartorius). For lenses prepared from the LFB formulation, dry weight values were calculated directly after removing from the mold. If ethanol was present in the formulation, the extraction step was performed in the vacuum oven as previously described and then the dry weight was calculated. The equilibrium weight swelling ratio was calculated by the difference between the weight of the fully swollen lens and the weight of the dry lens divided by the weight of the dry lens. Dynamic swelling studies were conducted by placing dried lenses in DI water or lacrimal solution, removing them at designated time intervals, patting them with a soft tissue, weighing them, and then returning them to the solution.

9.3.4. Dynamic Release Studies. Dynamic release studies were conducted to measure how long each therapeutic contact lens would release drug in vitro. The protocol for a kinetic release study begins after the synthesis of hydrogels as described previously. The studies were conducted with the conventional sink model in order to sustain the

greatest driving force, using a Sotax Dissolution Apparatus (Horsham, PA) in which loaded lenses were placed in 200 mL or 250 mL of aqueous solution, such as DI water.

In the Sotax apparatus, the release media was stirred at a constant rate of 30 rpm by paddles and kept at a constant temperature of 34°C. For HPMC containing lenses, the average weight was of the lenses was 35±6 mg. For HPMC release, HPMC concentration was determined via HPLC (Shimadzu, Japan) equipped with a refractive index detector. The mobile phase was deionized water, and a flowrate of 1 mL/min was maintained by the HPLC. A standard curve of refractive index and known HPLC concentration was established. For HA detection, an ELISA assay was used to determine the HA concentration (Corgenix, Denver, CO). The assay kit had a detection range between 20 and 800 ng/ mL, and some samples were diluted to prevent signal saturation.

CHAPTER 10

SILICONE HYDROGEL LENSES FOR DELIVERY OF COMFORT MOLECULES

From the outset of this project, it was decided that the lens material to be engineered into a novel combination device would be the proprietary Lotrafilcon B (LFB), which is already the major component for several commercial lenses. The project was undertaken in full cooperation with and supported by CIBA Vision, Inc., a major international lens manufacturer, who generously provided finished formulations and individual components of the LFB formulation.

10.1. Selection of Appropriate Re-Wetting Agents.

The comfort agent to be released was left to some extent to the discretion of the project investigator, who was able to choose from several common re-wetting agents. Ideally, hyaluronic acid (HA) would be selected as the releasing agent to continue the previously published work. Other common rewetting agents considered were carboxymethyl cellulose (CMC), hydroxypropyl methylcellulose (HPMC), poly(vinyl alcohol (PVA), and poly(vinyl pyrrolidone) (PVP), which are discussed in greater detail in **Chapter 4**. It was eventually found that the preferred macromolecule (HA) was incompatible with the LFB formulation, and HPMC was chosen as the best alternative

10.2. Selection of the Method to Control Comfort Agent Release Rate.

In addition to selecting the re-wetting agent of greatest interest, a high amount of freedom was granted with respect to the method of release and alterations to the composition to the LFB formulation by CIBA Vision. It was of paramount importance to quickly identify the most promising method of controlled re-wetting agent release, neglecting other minor factors, such as clarity and swelling, beyond qualitative measurement. Such properties, it was thought, could be optimized once the desired mechanism of release was identified. A series of experiments was performed comparing four controlled release mechanisms most likely to achieve the extended release. In addition, the experiments managed to highlight the re-wetting agent of greatest potential in the LFB system.

For this reason, during the initial work of this project, four different methods of therapeutic release were selected as the most promising candidates of achieving extended release; these methods included (**10.2.1**) diffusion control via drug soaked lenses, (**10.2.2**) diffusion control via reptation, (**10.2.3**) SMR, and (**10.2.4**) biomimetic molecular imprinting, which are discussed in sections **6.1.1.1, 6.1.1.3, 6.1.3,** and **6.1.2,** respectively. It was of great interest to directly compare the effectiveness of each of these four methods. This is the first time such an analysis has been done within the field of contact lenses, particularly with silicone hydrogels lenses.

10.2.1. Diffusion Control via Drug Soaked Lenses. It was found that measurable quantities of HA or PVA would not directly disperse into Lotrafilcon B films. HPMC displayed significant solubility though optical clarity of the films became a significant issue. Films were synthesized by pipetting the formulation between two glass

plates separated by a 125 μm Teflon sheet, clamping the slides and placing the sample under a UV light source. A 10 mm diameter cork borer was then used to cut samples. The films were then placed into high and low concentrations of re-wetting agent solutions and allowed to reach equilibrium for 24 hrs, 48 hrs and 1 week. Water was used as a solvent in the HA, HPMC and PVA solution. After each time interval, the films were taken from the soaking solution and weighed. The greatest weight gain was observed for 10 KDa HPMC, with a maximum equilibrium swelling weight ratio of 3 wt%. The films were placed in a 50 mL centrifuge tube filled with 50 mL of DI water and placed on an orbital shaker at room temperature and tested for release. Without exception, all detectable release (10 KDa HPMC release was the only detectable release) occurred within 30 minutes of immersion. **Table 10.1** represents the loading of re-wetting agent under each condition of drug soaked loading.

It was observed, then, that loading and controlled release via diffusion in drug-soaked lenses was not achievable. This can be attributed to the thermodynamically unfavorable mechanism of loading for the high molecular weight re-wetting agents. In solution, below a critical concentration, the chains of the re-wetting agents are relatively unrestrained. However, to effectively load, the macromolecule has to move from the bulk phase into the polymer network of the film, which is thermodynamically unfavorable for any measurable quantity, especially to load a concentration sufficient for 30 day release. To eliminate any molecular weight bias, HPMC and HA were tried at varying molecular weights (10, 90, and 120 KDa for HPMC and 10 and 1200 KDa for HA) yet no measurable loading occurred. **Figure 10.1** shows the ineffectual loading and release of 10 KDa HPMC via this method. After the failure of drug soaked films to load any

appreciable quantities of re-wetting agents, the method was eliminated as of no interest to this work. The findings, however, provide validation for conclusions of other researchers within the field (**Table 4.1**). Limited or no control of release via diffusion controlled release has been demonstrated by drug soaked lenses of any molecular weight and should be abandoned.

10.2.2. Diffusion Control via Reptation. A second possible release mechanism was tested for effectiveness in this system. Diffusion control via reptation was only performed on HA and HPMC-laden lenses, as PVA did not demonstrate the necessary solubility for effective study.

To disperse HA, 10 wt% DI Water, 10 wt% NVP, and 10 wt% EGDMA was added to an aliquot of the untinted LFB formulation received from CIBA Vision and aggressively stirred. It was photo-polymerized to produce a film of 500 μm out of the mold. The film contained ~150 μg of HA and was completely opaque. The lens was placed in 20 mL of DI Water in a glass sample tube. Release of HA from the film was immediately visible and lasted for ~10 min (**Figure 10.2**). HA began to swell immediately upon insertion into the water and caused severe damage to the film. The film cracked from the stress of the release of HA, and severe chipping of the film occurred. Pieces of the film were observed to be floating in the medium. A lens of this formulation could not be made, but a 250 μm lens was produced from the PP molds with 10 wt% DI Water, 25 wt% NVP, 25 wt% EGDMA, 20 wt% macromer, 15 wt% TRIS, and 5 wt% DMA. The lens contained only 100 μg of HA, but the lens was again completely opaque and HA release was complete within 10 minutes. The release was performed under the

same conditions as the thinner film. Severe damage occurred to the lens from the pressure developed from the swelling and release of HA.

It was thought that using a more hydrophilic crosslinker, such as the proprietary Nelfilcon A macromer, HA could be loaded into the LFB with the aid of hydrophilic comonomers. However, the Nelfilcon A monomer and HA quickly phase separated when added to the LFB formulation, and it was found that optical clarity values (**Figure 10.3**) and qualitative mechanical properties were extremely poor in 500 μm thick films. Only 100 μg of HA loaded (an insignificant concentration of therapeutic), and that films approximating the thickness of the commercial lenses could not be formed.

For lenses prepared with HPMC in the formulation, 10, 90, and 120 KDa molecular weight HPMC was directly dissolved in the LFB formulation and synthesized in polypropylene lens molds by UV polymerization. The resulting lenses were 14 mm in diameter and 250 μm thick (center thickness when dry). The solubility of the HPMC in the LFB formulation allowed for high loading of HPMC into the lenses. The lenses were then placed in 250 mL of DI water at 33ºC and stirred at 30 rpm. 5 mL aliquots of the release media were taken at various times and tested for HPMC concentration. 5 mL of DI water was then injected into the release media to maintain the 250 mL volume.

It was found that release of HPMC was Fickian in behavior and release time varied based on molecular weight of HPMC, with lenses prepared with 10 KDa reaching complete release within ½ day and 120 KDa reaching 100% release within 3-4 days (**Figure 10.4**). A disperse molecular weight mixture of HPMC was introduced to the untinted LFB formulation and release was performed at the same conditions. It was thought that if the density of HPMC in the lens could be increased, HPMC would

entangle with other HPMC chains and form a barrier to transport for itself. In addition, the lower molecular weights (smaller molecules) will transport out of the hydrogel more quickly than larger molecules. Typically lenses are the most comfortable when first placed on the eye. Release of 120 KDa HPMC within the first day of lens wear would not be necessary to ensure comfort. If the less effective molecular weight (i.e. 10 KDa) were to elute from the lens initially when the least amount of discomfort induced by lens wear was felt by the wearer, it is probable no significant difference in comfort would be noticeable. The release of the molecular weights would ideally conform to the model release presented in **Figure 10.5**. As wear time increased with a corresponding increase in discomfort, the longer and more effective comfort agent would release to the anterior surface of the eye.

Equal weights of 10, 90, and 120 KDa HPMC were mixed into the LFB formulation to a content of ~1,000 μg HPMC/ lens. No significant control was added to the release rate via this method. The release was completed in 3-4 days, as it was in the release of the single molecular weight (120 KDa) HPMC (**Figure 10.6**).

To promote reptation controlled diffusion, crosslinkers of various lengths and concentrations (as described by **Table 10.2** and **Figure 8.1b**) were formulated into the lenses, but little control of the rate of release was granted. By narrowing the polymeric structure of the lenses, it was found that a delay in release could be achieved. The increased number of barriers slowed the diffusion of the HPMC through the hydrogel. However, once release was detected, all HPMC quickly eluted from the lens within 4-6 days regardless of crosslinker concentration as shown in **Figure 10.7**. The release rate of HPMC could not be engineered to extend past the six day period by the addition of

crosslinkers alone, nor could effective control over the rate of release be achieved. Due to the lack of flexibility in designing the release rate, reptation-based controlled release mechanisms were abandoned from consideration.

10.2.3. Surfactant Mediated Release (SMR). Solubility of the re-wetting agents in the LFB formulation proved to be an issue for 2 of the 3 re-wetting agents initially selected for the project. SMR has been shown to increase the loading of hydrophobic drugs within hydrophilic matrices. It was thought that HA and PVA loading could be increased and the qualitative loss of clarity observed in the HPMC-laden lenses by using surfactants to encapsulate and disperse the macromolecules into the hydrophobic sections of the LFB lens. Surfactants were chosen based on FDA approval, HLB values and molecular weight.

To load HA (the preferred releasing agent) and increase clarity of HPMC laden systems, surfactants were added to the LFB formulation to increase HA solubility in a manner similar to a water-in-oil emulsion. The surfactant would emulsify the aqueous phase inside the hydrophobic phase and partition the drug between the two phases. Hydrophilic drugs will reside mostly inside the micelle and drug transport would be limited by the solubility of the drug in the continuous phase. If micelle size and concentration are sufficiently low, the loaded lens remains transparent. Thus, the addition of surfactant controls the rate of release and may increase the clarity of the lens.

An additional advantage of using surfactants is that as free molecules, the surfactants are not covalently attached to the network. Increased control over release rate was to be gained through molecular imprinting while surfactant would be used to increase loading and maintain optical clarity. Using a series of FDA approved surfactants,

it was found that inclusion of the surfactants resulted in unacceptable losses in optical clarity except at very low HLB values and low concentrations of surfactant in both the HA and HPMC systems (**Appendix E**).

This discouraging observation is explained by the structures formed by the surfactant and polysaccharides in solution. To improve clarity of the HPMC laden lenses, HPMC must be concentrated within the aqueous (inner) phase of the micelle. A stable micelle would disperse the HPMC and limit the volume of HPMC aggregates, isolating them from the network or from interacting with the hydrophobic (outer) phase. This would reduce water uptake into the film and limit swelling. To control release and clarity, a large partition coefficient for the drug is needed or else the drug will not reside exclusively inside the micelle. To affect the loading of HA into the LFB formulation, the polysaccharide must fit inside the micelle structure, and the resulting micelles must be below 100 nm in diameter to produce an optically clear film. In addition, if the micelle concentration is too high, light is scattered inside the lens, lowering clarity. The hydrodynamic volume of HPMC and HA, when solvated, was found to be far too large to fit inside the micelles of the surfactants tested (or micelles could not be formed).

10.2.4. Biomimetic Molecular Imprinting. HPMC was dispersed into the LFB formulation. Functional monomers were analyzed for potential hydrogen bonding interactions with the hydroxyl groups on the HPMC main chains. Hydrophilic monomers, such as NVP, MAA, AA, and DMA, were chosen based on the functional groups most likely to interact with the template. The functional group affinity was determined by examination of carbohydrate binding proteins. Methacrylic and acrylic acid were formulated into the LFB formulation and were observed to slow the release rate of 120

KDa HPMC even at low concentrations. Between M/T ~0.2 and ~0.94, both MAA and AA LFB imprinted lenses extended release beyond the LFB formulation by approximately 2-4 days (**Figure 10.8**). The release rate was also affected, decreasing from 250 μg/ day (M/T 0) to ~100 μg/ day (M/T ~0.94).

10.2.5. Final Selection of Release Method and Rewetting Agent. The work comparing release methods and re-wetting agents demonstrated that the system most likely to produce a useable product would be loading HPMC into the LFB lens via biomimetic molecular imprinting. Loading was orders of magnitude greater in the imprinted lens than in the drug soaked lenses, and release time was significantly increased. Control over the release rate was greater in the imprinted systems than the reptation controlled lenses. Control over transmittance, loading, and qualitative mechanical properties were significantly improved in the imprinted systems compared to the SMR-based systems. The optimal blending of loading, release, and qualitative mechanical and optical properties were demonstrated by the imprinted systems, which simply could not be matched by any other method of controlling release. All further experiments in this work involved the creation of HPMC-laden lenses via molecular imprinting.

10.3. Tables and Figures.

Table 10.1. Theoretical Mass Loading and Release Time of Untinted LFB Lenses Soaked in Aqueous 0.1, 1, 10 wt% Solutions of Various Re-Wetting Agents.

Re-wetting Agent		Theoretical Mass Loaded from Drug Solutions (μg/ lens)									Release Time (7 Day Soaked)
		1 Day Soak			2 Day Soak			7 Day Soak			
		0.1%	1%	10%	0.1%	1%	10%	0.1%	1%	10%	
HA	10 KDa	0.006	0.2	0.1	0.4	0.7	0.6	0.01	0.016	0.04	None Detected
	1800 KDa	0.009	0.09	.005	0.1	0.7	0	0.01	0.8	0	None Detected
HPMC	10 KDa	0.32	4.1	5.4	0.21	3.2	6.9	1.2	5.7	2.9	30 min
	90 KDa	0.09	0.07	0.4	0.09	0.65	0	0.01	0.48	0	None Detected
	120 KDa	0.001	0.003	0.004	0.08	0.04	0.01	0.006	0.2	0.1	None Detected
PVA	500 KDa	.02	.001	0.003	0.04	0.06	0.001	0.009	0.09	.041	None Detected

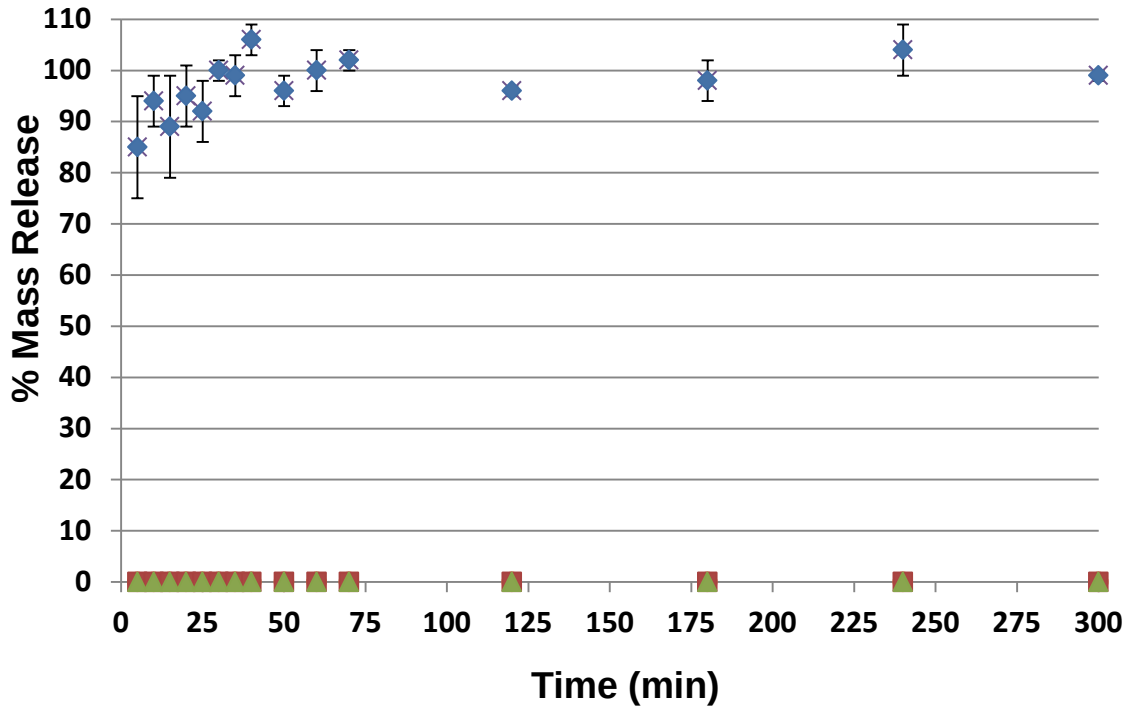


Figure 10.1. HPMC Soaked LFB Lenses: Release from LFB Lenses after Soaking 7 Days in 1 wt% HPMC Solutions.

Untinted LFB lenses (n = 5) were soaked in 5 mL of 0.1, 1 and 10 wt% HPMC solutions for 7 days. No significant difference was seen in loading between the solutions. Loading was determined to be for (♦) 10 KDa to be 2.5 µg ± 2 µg. No loading by the LFB lenses was measured in the (■) 90 and (▲) 120 KDa samples. Release of 10 KDa HPMC reached completion in ~10 mins. Release was performed in 50 mL DI water at room temperature on an orbital shaker.

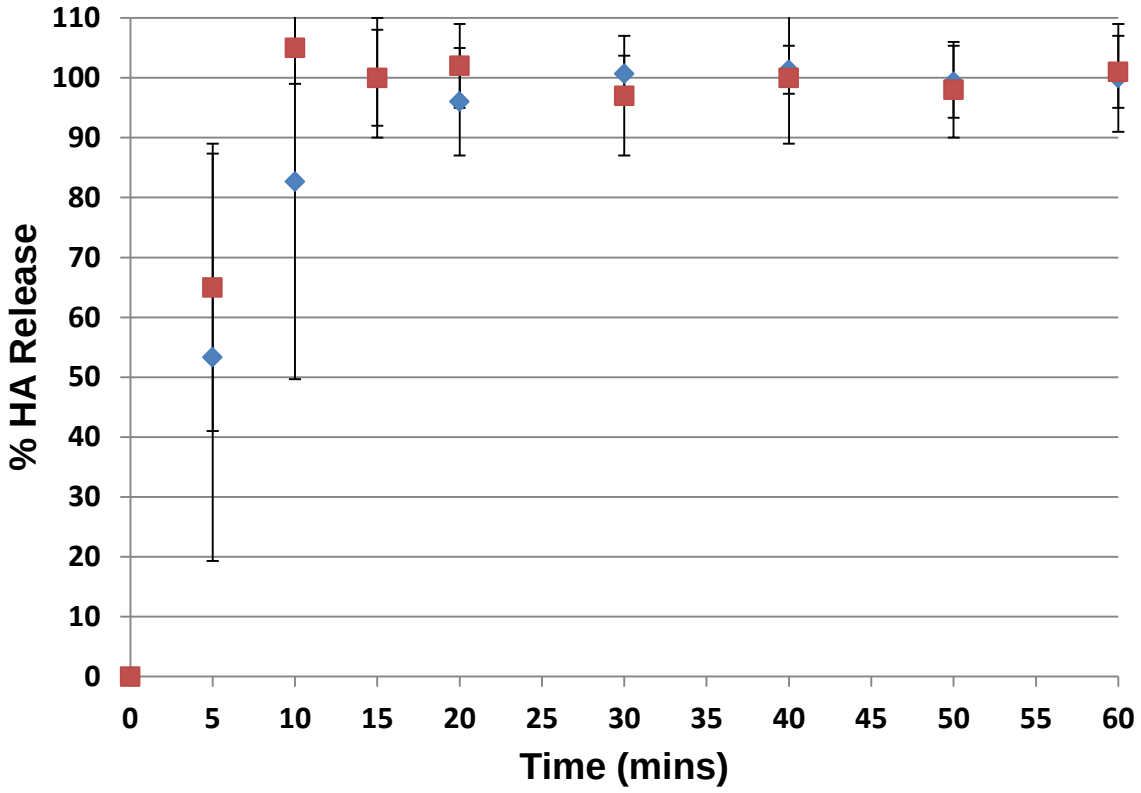


Figure 10.2. Release of HA from LFB Networks Synthesized with HA.

1,800 KDa molecular weight HA was dispersed into a formulation of LFB and 10 wt% DI water, 10 wt% NVP, and 10 wt% EGDMA was added to the mixture to help disperse the HA. The mixture was vigorously stirred and quickly transferred to a mold to avoid phase separation. The ~500 μm thick (♦) film contained ~150 μg HA. A 250 μm lens (■) was produced to contain 100 μg HA. The formulation also contained 10 wt% DI Water, 25 wt% NVP, 25 wt% EGDMA, 20 wt% macromer, 15 wt% TRIS, and 5 wt% DMA. Release was performed in 20 mL DI water at room temperature and took approximately 10 mins to reach completion. Both the film and the lens sample were completely opaque.

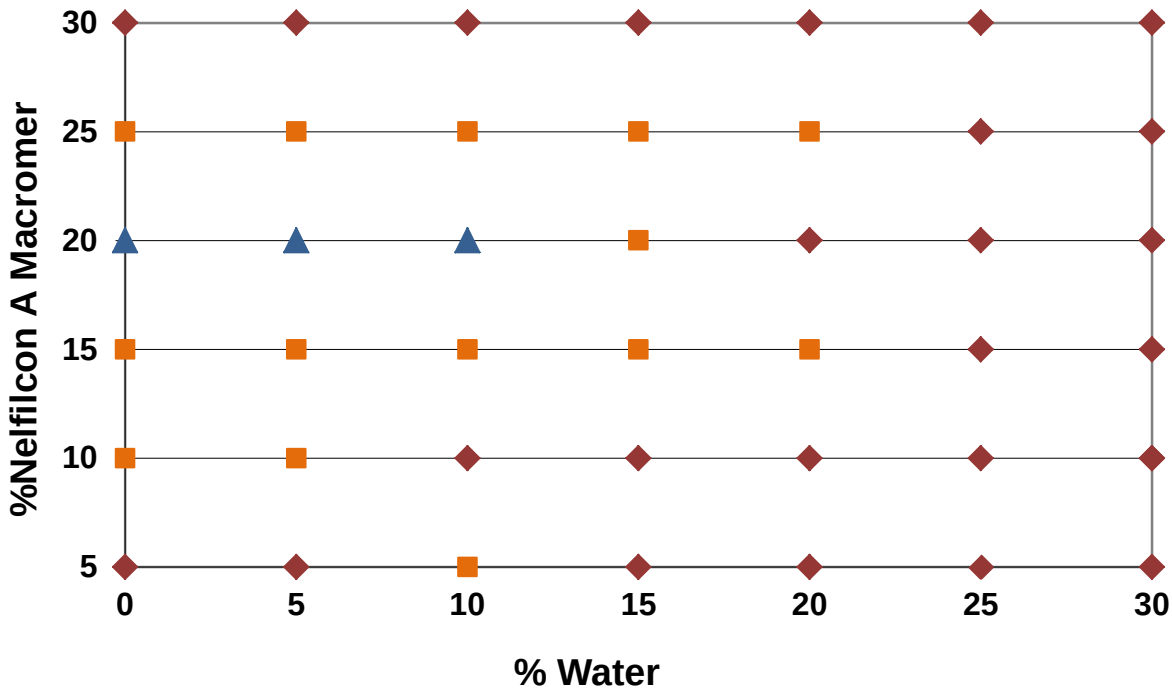


Figure 10.3. Optical Clarity of 500 µm Thick Films Synthesized With ~100 µg of 1800 KDa HA.

CIBA Vision's Nelfilcon A macromer and water were added to the LFB formulation in various ratios to encourage HA solubility in the film. Transmittance was measured for 500 µm thick films and is represented in the plot: (▲) 69% ≥ %T ≥ 60%, (■) 59% ≥ %T ≥ 50%, and (♦) %T ≥ 49%. Transmittance, qualitative mechanical properties, and loading of HA were too low to produce an effective therapeutic contact lens.

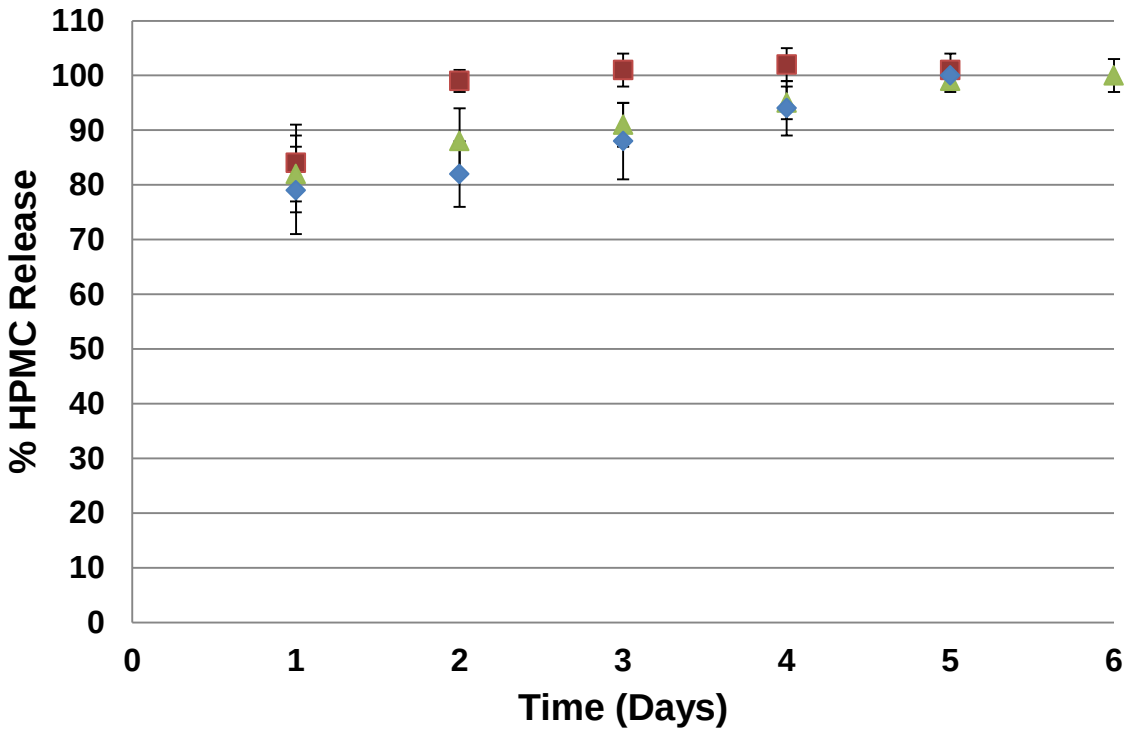


Figure 10.4. Release of 10 KDa, 90 KDa, and 120 KDa HPMC from CIBA Vision LFB Lenses Synthesized with HA.

Release of 800 µg of 120 KDa HPMC from (♦) CIBA Vision's untinted LFB formulation reached completion in ~4-5 days. Release of (▲) 10 KDa HPMC was completed between 1 and 2 days, with (■) 90 KDa falling between the two other molecular weights. A very high initial rate of release was seen due to swelling effects. HPMC release was performed in 250 mL DI water, stirred at 30 rpm at T = 33ºC (n = 3).

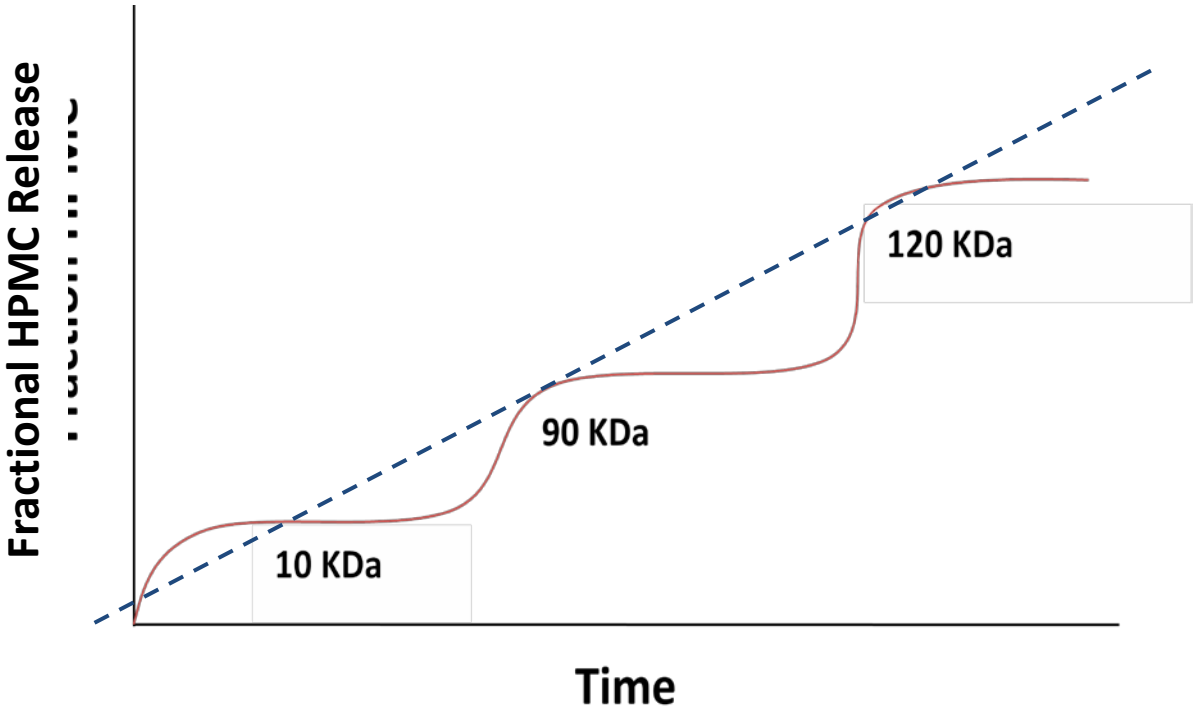


Figure 10.5. Model Release Profiles of Polydisperse Molecular Weight HPMC.

Size exclusion controlled release or (**solid**) reptation based release will result in fractional release corresponding to differences in molecular weight. If reptation based release profile can be extended to 30 days, a (**dashed**) controlled release method could be used to create a linear release profile.

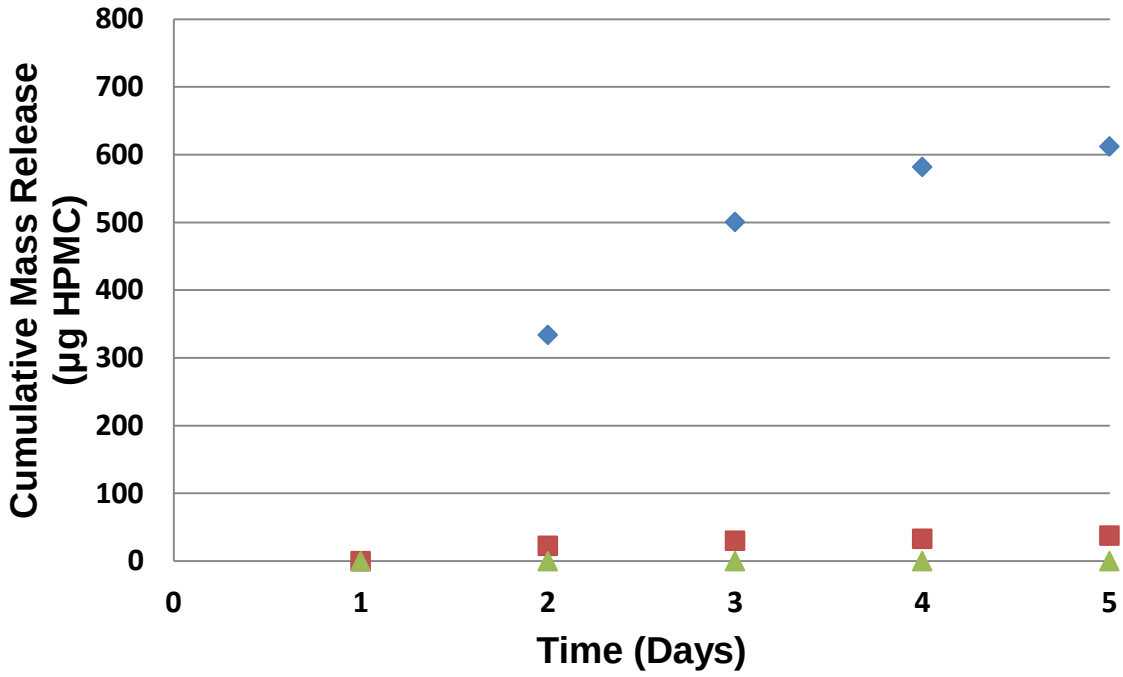


Figure 10.6. Release of Polydisperse Molecular Weight HPMC from LFB Lenses Synthesized with Polydisperse HPMC.

A mixture of (♦) 10 KDa, (■) 90 KDa, and (▲) 120 KDa HPMC was dispersed into a LFB lens. The lower molecular weight quickly eluted from the lens (reaching complete release in 3-4 days). The presence of the lower molecular weight molecules did not alter release beyond what was already observed.

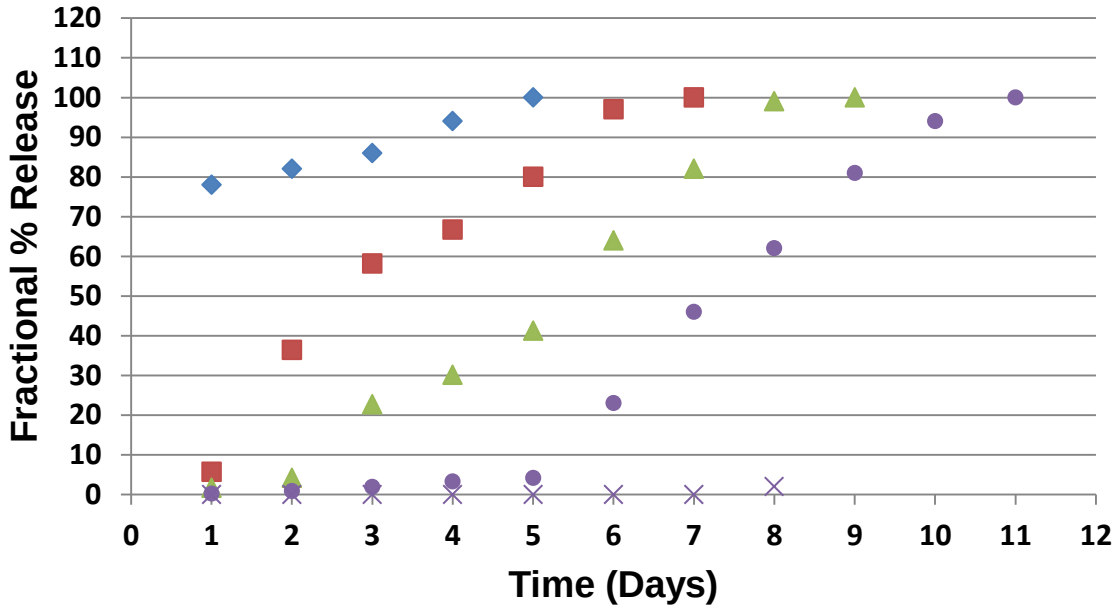


Figure 10.7. The Effect of Crosslinkers on the Release of 120 KDa HPMC from LFB Lenses Synthesized with HPMC.

Crosslinking monomers (xLer) were added to the LFB formulation to control lens swelling of HPMC-laden lenses. Lens compositions were: xLer/T ratio of 0 with 2,750 µg HPMC (♦), xLer/T ratio of 0.019 with 2,800 µg HPMC (■), xLer/T ratio of 0.237 with 2,700 µg HPMC (▲), xLer/T ratio of 1.02 with 2,600 µg HPMC (●), and xLer/T ratio of 1.75 with 2,600 µg HPMC (X). Crosslinks limited the free volume in the lens, thereby altering HPMC release and limiting lens swelling. The presence of crosslinkers in the lens led to significant improvements in clarity with reduced swelling, but they may not be sufficient to properly control HPMC release. By increasing the crosslinking monomer to template ratio (xLer/T), HPMC release is delayed by the decreased mesh size. As the percentage of crosslinker is increased, there is a longer initial delay in release. However, there is not much control over the release rate after the initial delay. This is indicated by

the equivalent rates of release once approximately 5-10% fractional release is achieved. Note: No functional monomers or tint were present in these lenses, T=34 ºC, and N=3.

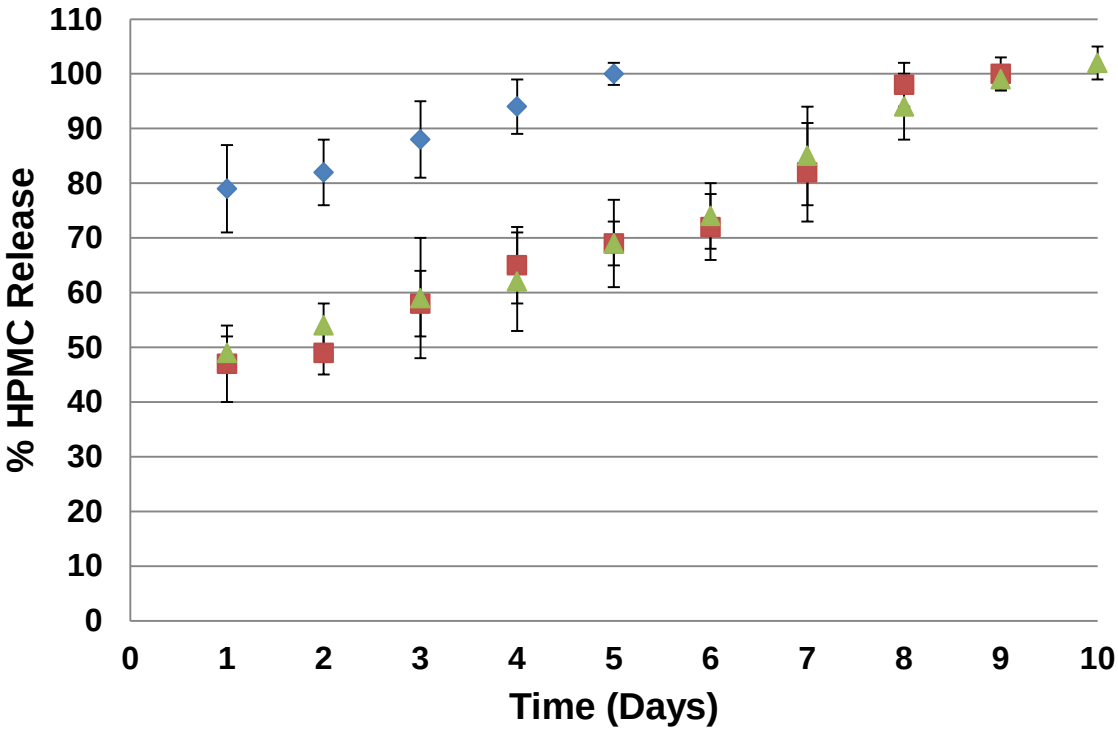


Figure 10.8. Release of 120 KDa HPMC from CIBA Vision LFB Lens and AA and MAA Imprinted Lenses Prepared With MAA and AA.

Release of 700 µg of 120 KDa HPMC from (♦) CIBA Vision's untinted LFB formulation reached completion in ~4-5 days. Adding (■) MAA and (▲) AA to the formulation to create a molecularly imprinted contact lens (M/T ~0.6) increased release time from 4 days to 7-8 days. The lenses contain ~700 µg HPMC with a thickness of 350 µm swollen. HPMC release was performed in 250 mL DI water, stirred at 30 rpm at T = 33ºC (n = 3).

CHAPTER 11

DEVELOPING HPMC IMPRINTED SILICONE HYDROGEL LENSES CAPABLE OF EXTENDED RELEASE

Comparison of different methods of controlled release showed that the method most likely to produce a silicone hydrogel lens capable of releasing a wetting agent for 30 days was molecular imprinting. The only wetting agent of the three explored compatible with imprinting in the silicone hydrogel material was found to be HPMC. HPMC was dispersed into the LFB formulation demonstrating that loading would not be a major concern. However, many factors such as optical clarity, mechanical properties and the efficiency of molecular imprinting depend greatly on the solubility of the macromolecule in the lens. As solubility increases, optical clarity would increase as demonstrated by turbidity testing. If a polymer was introduced to an incompatible system, it would collapse into itself and weaken the hydrogel structure. In polymer solution theory, as polymer solvent interactions increase (i.e. as the solvent becomes a better solvent for the polymer), the polymer conformation becomes extended until it reaches some maximum volume. This volume would provide the most exposed functional groups to interact with macromolecular memory sites. The increased solution volume of the polymer would allow interactions over a long distance in the hydrogel, significantly increasing the effect of imprinting on the reptation time of the HPMC, and delaying release (**Figure 11.1**). As

such, the addition of co-monomers to the LFB formulation and molecular interactions is of great interest to the work as the monomers would increase the loading of HPMC by increasing the solubility, increase the ocular clarity of the lenses as represented by the turbidity test, and serve as molecular imprinting moieties to delay and control release.

11.1. Solubility of Re-Wetting Agents in LFB Formulation.

To understand and confirm the incompatibility between HA and LFB, the solubility of HA was compared to that of the hydrophobic Betacon macromer, the key component of the LFB formulation. Hansen and Hoy solubility parameters are used to relate the solubility of chemical species by comparison of three factors: propensity of a molecule to hydrogen bond, polarity of the molecule, and dispersive forces. No published Hansen and Hoy parameters can be found for the Betacon Macromer. In addition, no accepted parameters are published for HA. Approximate values can be found experimentally by dispersing the unknown species among solvents, which have known values. The unknown values can then be assumed to be near areas of good solvents.

Experimental HA solubility parameters were determined to be near those of water. There appear to be two distinct solubility parameters for the Betacon macomer, due probably to the large size of the macromer and the highly varying nature of the different segments (**Figure 11.2**). As demonstrated in **Figure 11.3**, there appears to be a wide margin separating the soluble regions of either component, indicating that no co-solvent or any direct dissolution method can be used to load HA into the LFB formulation in any significant concentration. PVA is highly miscible in water but displayed poor solubility in the macromer and the LFB formulation. Further testing showed that only minor amounts of PVA could be loaded into the LFB formulation.

Interest in PVA and the other non-cellulose based re-wetting agents was minor however, as they do not provide comparable relief to the eye or stability in the lens manufacturing procedure. Studies comparing the effectiveness of re-wetting agents in providing comfort showed highest interest in HA, followed by HPMC, and last of all PVA [**11.1**].

In a concurrent series of experiments, it was found that the solubility parameter of HPMC was similar to ethanol, the preferred diluent of the LFB formulation and that HPMC displays a wide solubility, dissolving in both water and ethanol. **Figure 11.4** demonstrates the solubility parameter of HPMC as determined by Sigma Aldrich. The parameter is near to that of ethanol, indicating that ethanol would be a good solvent. However, before HPMC laden lenses were swollen in water, the lenses appeared cloudy and stained in spots due to the presence of HPMC sediments. Turbidity tests conducted on the lenses and the pre-polymer formulation showed that as DMA concentration in the LFB formulation increased, cloudiness and haze decreased (**Table 11.1**). Moreover, the sediments of HPMC disappeared. This indicates that some interaction between the HPMC and DMA was occurring to promote solubility in the formulation and the resulting hydrogel.

Examination of the structures of DMA indicates that there exists potential for DMA to serve as a low affinity binding site for HPMC though hydrogen bonding. The electron delocalization between the carboxyl and nitrogen groups would reduce the strength of the hydrogen bonding as well as the steric interactions between the methyl groups and HPMC. The interactions that result in higher clarity by dispersing the HPMC were found by investigation to be too weak to noticeably extend release beyond the control lenses. This was investigated by increasing the concentration of DMA in the LFB

formulation in 10 wt% increments from lenses of 50:50 wt% TRIS:Macromer to 100% DMA comparing it to release data from the CIBA premade formulation. As DMA concentration increased a significant increase in release rate was observed, though it was found to be due to swelling effects of the lens in water (**Table 11.2**).

Release data gathered from lenses formulated from CIBA Vision's pre-made formulation (~30% DMA) indicated a release time of 3-4 days, while release from similar formulations with similar swelling (~50% DMA) demonstrated a slight increase in average release time but was within the standard deviation. While increasing DMA concentration in the formulation and the dry lens increased transmittance, transmittance in the swollen lens was poor. Increasing DMA concentration resulted in a corresponding decrease in the macromer content. The macromer serves as the oxygen permeable phase as well as the crosslinker for the system. When swollen in water, water content in the lens increased due to uptake by HPMC which sequestered water into the lens. This action caused the HPMC and by extension the polymer network to swell like a sponge. The increase in thickness (sometimes up to 8x the dry thickness) caused a significant decrease in clarity (**Figure 11.5**). Therefore, the composition, thickness, and swelling of the HPMC laden lenses were studied to find the optimal formulation.

11.2. Optimizing the Clarity of 350 µm (Swollen) Lenses. A specific aim of this research was to create the novel lens device as close to the factory formulation as possible. For this reason, the project started with a pre-made LFB formulation received from CIBA Vision. In the commercial formulation, a blue Cu/P visibility tint is added to the LFB prepolymer. HPMC (120 KDa) was dissolved directly into the tinted LFB formulation. HPMC displayed good solubility in the formulation, but optical clarity was

significantly reduced. Clarity of lenses was measured at a variety of HPMC concentrations. Upon visual inspection, it was found that the tint and HPMC were not miscible and resulted in the tint appearing as swirls and blotches with uneven patches of clarity. The clarity decreased from approximately 85% clarity in the tinted, unloaded lens to less than 20% clarity in the tinted, loaded lens. It was hypothesized that the reduction in clarity was partly due to the presence of the comfort agent and partially due to the tint. After consulting with CIBA Vision, all future work was conducted with LFB formulation that did not contain the visibility tint. The unloaded lens had an optical clarity of 96±2%, and increased approximately 11% over the tinted lens. An untinted lens created with a similar HPMC concentration as the tinted lens showed an improved clarity by ~34%.

It is clear from **Figure 11.6A** that the tint was responsible for a reduction in clarity of around 10%. As the concentration of HPMC increased, the percent transmittance decreased more dramatically. After ethanol extraction, the decrease in clarity due to HPMC concentration was much more dramatic (**Figure 11.6B**). However, the increased clarity gained by removing the visibility tint in the presence of HPMC was still well short of the 80% minimum. It is of interest to note two important, counterintuitive concepts from **Figure 11.6.** The presence of ethanol simultaneously improved clarity in the lenses with high HPMC concentration ($\geq$1000 μg HPMC) compared to ethanol extracted lenses while lenses with low or no HPMC suffered decreased clarity with the presence of ethanol relative to ethanol-extracted lenses. In addition, no significant differences in clarity were observed in the ethanol-extracted untinted lens and the untinted lenses prepared without ethanol.

In the LFB lens manufacturing process, a step is required to remove the residual ethanol used as solvent and any unreacted compounds from the lens. In an attempt to match the industrial process as closely as possible, which contains a liquid extraction step, a liquid extraction was performed using isopropanol and methyl ethyl ketone separately. However, it was found that extraction solvent uptake into the lens affected both release and clarity. Therefore, ethanol was removed from the formulation to prevent any misleading release and clarity values at high HPMC concentration per lens. Ethanol saturates the lenses and prevents a high uptake of water, resulting in lower swelling. In addition, ethanol stays in the lens during release, causing the HPMC to partition between the ethanol- rich lens and the aqueous phase. However, if ethanol is removed, substantial swelling occurs due to high water uptake (**Figure 11.7**).

The swelling and resultant loss of clarity posed a unique problem. Several options were explored for controlling clarity (e.g., emulsions, particulate solutions, and co-solvents) and served as potential solutions. However, it was found that the inclusion of surfactants at a range of HLB values and concentrations decreased clarity. In addition, hydrodynamic volume of 120 KDa HPMC is too large to form stable micelles and is soluble in both hydrophobic and hydrophilic phases and could not partition into the separate phases which is necessary for the formation of emulsions.

To control swelling, the focus shifted toward the addition of crosslinkers to the pre-polymer formulation that would prevent the polymer network from expanding. The crosslinker would serve as physical limitations for the expansion of the matrix (represented by locks on **Figure 11.8c**). Several crosslinking monomers of various molecular weight and concentration were added to the LFB formulation. Their effect on

swelling and clarity is presented in **Figures 11.9, 11.10, & 11.11**. A clarity of 98±2% for HPMC-free lenses was observed for lenses containing 5% PEG200DMA and 5% EGDMA. The addition of HPMC lowered transmittance to 90%, and the equilibrium weight swelling ratio was significantly reduced from 8.5 to 1.4 for lenses containing 700 μg HPMC/lens.

The presence of crosslinkers in the lens led to significant improvements in clarity with reduced swelling, but they may not be sufficient to properly control HPMC release. By increasing the crosslinking monomer to template ratio (xLer/T), HPMC release is delayed by the decreased mesh size. As the percentage of crosslinker is increased, there is a longer initial delay in release. However, there is not much control over the release rate after the initial delay in release. This is indicated by the equivalent rates of release once approximately 5-10% fractional release is achieved.

11.3. Molecular Imprinting within the Hydrophilic Phase.

Three possible functional monomers were selected based on the potential for interaction with the hydroxyl groups of HPMC. The first monomer used was N-vinyl pyrrolidone (NVP), which possesses a carboxyl group capable of hydrogen bonding. In addition, NVP is a very hydrophilic monomer and will reside almost exclusively in the hydrophilic phase of the biphasic contact lens. This is the optimal place to imprint as hydrophobic interactions are nonspecific and difficult to control.

11.4. Molecular Imprinting with NVP and AA as Functional Monomers.

Release studies of HPMC imprinted lenses with NVP as functional monomer were performed at various M/T ratios (**Figure 11.12**). For ethanol-free, post-extract lenses, the most significant effect of NVP incorporation was the high initial rate of

HPMC release. As the M/T ratio increased, there was an increased initial release of HPMC from the lens. For an M/T ratio of 42, the ethanol-free, post-extract lenses lost approximately 25% or 100μg of the loaded HPMC. After this initial burst, release from all lenses was independent of the M/T ratio. For ethanol-rich or pre-extract lenses, there was no initial release of HPMC and all lenses released HPMC at equivalent rates despite differing M/T ratios. As NVP content in the lens increased, the lens imbibed more water (**Figure 11.13A**) and optical clarity decreased (**Figure 11.13B**). Adding approximately 10 wt% NVP (M/T ratio of 1.5), the transmittance decreased from 98% to 75%. The effect was more pronounced as HPMC content increased in the lens. For example, the optical clarity dropped from 73% for the formulation without NVP and 3500 μg HPMC/lens to 49% for a lens containing 10 wt% NVP (M/T ratio of 1.5). The inclusion of NVP also caused the lens to deform with water uptake. Lens deformation was so great that the lens transformed into a thin film with broad peaks and valleys. Equilibrium weight swelling ratios jumped from 0.2 in HPMC-free, NVP-free lenses to 1.0 when 10 wt% NVP was included in the lens (**Figure 11.13A**) without compromising clarity and mechanical properties. If HPMC was added, the maximum loading could not exceed 800 μg HPMC /lens along with 5 wt% NVP. In addition, the lenses (center thickness of ~350 μm wet) could not be scaled down to market standards due to significant losses in the mechanical properties.

A factorial design of experiments was performed to find acceptable clarity and loading by altering crosslinkers concentration, type of crosslinking molecule, and other ratios of the CIBA standard formulation, but it only served to further disqualify NVP as an imprinting monomer.

The failure of NVP as a functional monomer was due more to its incompatibility with the LFB formulation than a failure to hydrogen bond with HPMC. NVP, a very hydrophilic monomer, was incompatible with Betacon macromer and TRIS, two very hydrophobic molecules. Uneven swelling within the lens between the two phases caused by water uptake resulted in deformation of the lens. In the lens, HPMC was likely partitioned between the hydrophobic and hydrophilic phases and interfacial transport of HPMC was likely minor. The immediate HPMC release observed is probably HPMC initially in the hydrophilic phase, and the slow extended release of HPMC is probably from the hydrophobic phase (**Figure 11.13**).

Selection of additional functional monomers included less hydrophilic molecules with carboxylic acid groups. Acrylic acid (AA) and methacrylic acid (MAA) were the most promising alternatives to NVP (**Figure 11.15**). Both molecules are hydrophilic but less hydrophilic than NVP. **Figure 11.16** shows HPMC release from imprinted lenses was linear with 25% HPMC being released in 4 days. Imprinted lenses had equivalent swelling and clarity as lenses prepared without functional monomer, but containing HPMC. Therefore, release was affected by imprinting but not clarity or swelling. As previously mentioned, **Figure 11.16** demonstrates the varied release rates that can be designed by altering the functional monomer to template (M/T) drug ratio. **Figure 11.17** shows release rates at certain days as a function of the M/T ratio.

11.5. Synthesis of Imprinted HPMC LFB Lenses with ~100 µm Swollen Thickness.

Molecular imprinting was shown to control the release rate of 120 KDa HPMC in 350 µm thick lenses. However, these lenses were considered to be out of the desired commercial specifications of clarity, swelling, and thickness. Initial transmittance values

measured for AA imprinted LFB lenses are shown in **Figure 11.18**. The average water equilibrium weight swelling values for the acrylic acid imprinted lenses falls between 1.1 and 2 with the majority falling between 1.4 and 1.5. For the first five days, all lenses are 85+% transparent with some observed haze. After 5 days, when a portion of HPMC is released, clarity drops from 80+% to approximately 60%. During lens synthesis, the HPMC formed aggregates inside the mold while the LFB material formed around the it. When initially swollen in water, the clump became transparent but as HPMC released, the LFB lens maintains the aggregate shape. The HPMC eventually diffuses out of the void, and the void then fills with water. Local refractive index differences in this area caused clarity to drop after the first five days of release.

Producing thinner lenses and reducing the particle clumps of HPMC in the formulation by high shear mixing to reduce HPMC aggregates was proposed as a method to improve clarity while matching the thickness of commercial lenses. A thinner lens would provide less of a barrier to light transport and can reduce observed haze. It was known that reducing thickness would accelerate the release rate of HPMC and that more alterations to the formulation would be needed to adjust the release rate to the desired level. It was surprising though that the thinner lenses provided a lower transmittance than the thicker lenses.

Initially, it was somewhat confusing and counterintuitive that a thinner lens had lower transmittance. It was soon understood by considering that any defect in the lens is magnified when there is less LFB. When LFB is in excess, there is plenty of material to encompass the HPMC molecule. In the thinner lenses however, there is less material to surround the HPMC, making the lens turbid due to local refractive index changes. As a

result of these factors, the composition of the formulation had to be optimized to satisfy transmittance requirements at the lens thickness. To do this, lenses were synthesized at ~980 μg HPMC/ lens ± 127 μg HPMC with varying M/T and xLer/T ratios. As the **Figure 11.19** shows, there is a wide area of acceptable transmittance values corresponding to values $1 \leq xLer/T \leq 3$ and $1.5 \leq M/T \leq 6$.

Lenses formulated to the same M/T and xLer/T as the longest releasing lenses in **Figure 11.16** were placed in the Sotax Dissolution Apparatus. However, since the lens was much thinner, the release rate of HPMC was much higher than in the 350 μm lens, and all HPMC was released were within 10 days (**Figure 11.20**). Though this release time is significantly shorter than 50 day release, it is important to note that the ocular environment contains a much lower volume. Matching the physiological flow and volume would lower the release rate and may mean the desired extended release time of 30 days could be achieved. A novel microfluidic device, pioneered by the Byrne lab, was used to match the ocular flow rate.

11.6. Release in Microfluidic Device.

HPMC was released in both a large volume infinite sink model and through a microfluidic device that mimics the physiological flow of the eye. It was very interesting to see that at ocular flow rates the release is orders of magnitude slower than the release profile of an equivalent lens under infinite sink conditions. This provides some very exciting prospects in tailoring the formulation composition to release at ideal rates and optimizing the lens parameters (i.e. optical clarity).

11.6.1. Formation of the Microfluidic Device. The microfluidic device was created by mixing Sylgard 184 silicone elastomer base and curing agent in a 10:1 ratio.

The mixture was stirred for 3.5 mins and poured onto a glass plate within a circular mold. Within the mold are two needles to create apertures in the device for flow and one hemisphere of a glass marble (created from cutting an 18 mm diameter marble into a segment of 16.5 mm wide x 5.7 mm high). The device is then cured at 60ºC under a vacuum for 6 hours. The PDMS is removed from the mold and the needles and marble removed. A slightly smaller marble hemisphere (15.2 mm wide x 4.35 mm high) is placed under the mold and a syringe pump is used to pump DI water through the mold at the physiological flow rate of 3 μL/ min. The inner chamber contains 175 μL of DI water. A schematic of the microfluidic device is presented in **Figure 11.21**.

11.6.2. Release within Microfluidic Device. A 125 μm thick imprinted LFB lens was created with M/T ~3.5 and xLer/T ~1.5 (corresponding to the 50 day release in the thicker lens in the large volume infinite sink) and ~1000 μg 120 KDa HPMC. **Figure 11.20** showed the release of the same lens with an release time of ~10 days. **Figure 11.22** shows the release profile from the microfluidic device. The release is linear and is completed in 62 days The average daily release rate is ~16 μg/ day.

This release profile is more similar to what could be expected in the eye, though it is hypothesized that under in vivo conditions, release rate would be slower due to decrease aqueous reserve in the eye than in the microfluidic device. It should be noted that other factors such as vertical tear flow, blinking and natural variations in the tear flow are not taken into account by the microfluidic device. Also, there will be an increase in temperature which will lead to faster HPMC transport from the lens. Even with these limitations, the microfluidic device is a powerful optimization device in ths development of therapeutic contact lenses.

11.7. Tables and Figures.

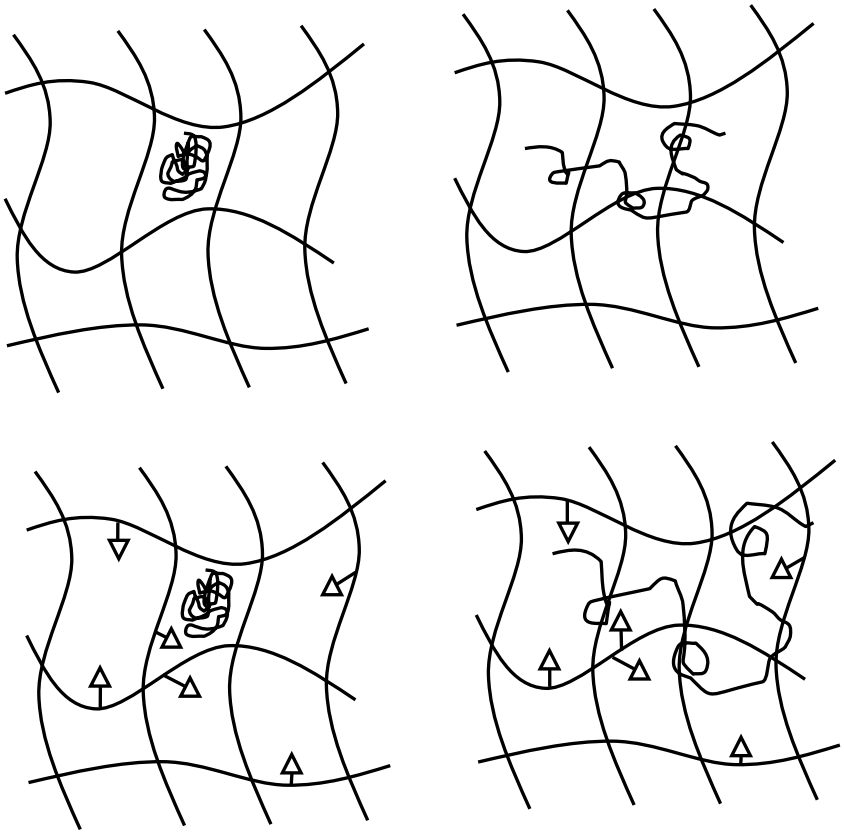


Figure 11.1. Polymer Solubility and Conformation Relating to Transport and Imprinting of Macromolecules.

If a polymer is dispersed into an incompatible crosslinked network (top left), the polymer coil will contract into a tight spherical conformation. As compatibility increases or polymer- network interactions increase (top right), the conformation expands into a wormlike structure and can entangle with the network. If molecular imprinting was applied to the incompatible polymer- network system (lower left), the tight conformation allows minimal interactions between memory sites and the polymer. If a more compatible polymer is imprinted in the network (lower right), the polymer conformation can extend further and interact with several memory sites simultaneously. These interactions slow

the reptation of the polymer and decrease the release rate of the polymer from the network.

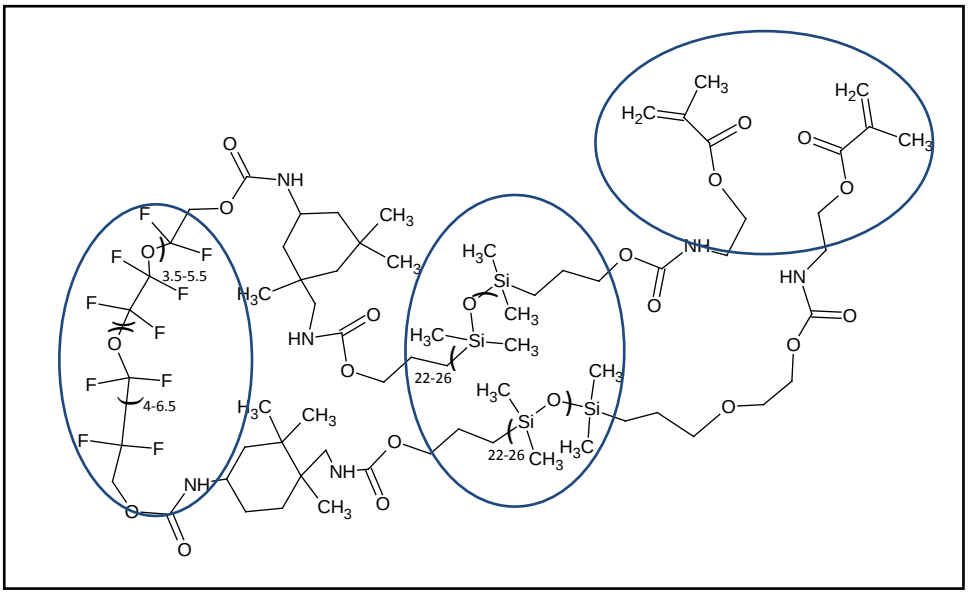


Figure 11.2. Functional Groups in the Betacon Macromer.

The Betacon Macromer is a large molecule with widely diverse component regions. The circled areas demonstrate very different solubility parameters and as a result give the macromer a wide range of possible solvents as shown in **Figures 11.3** and **11.4.**

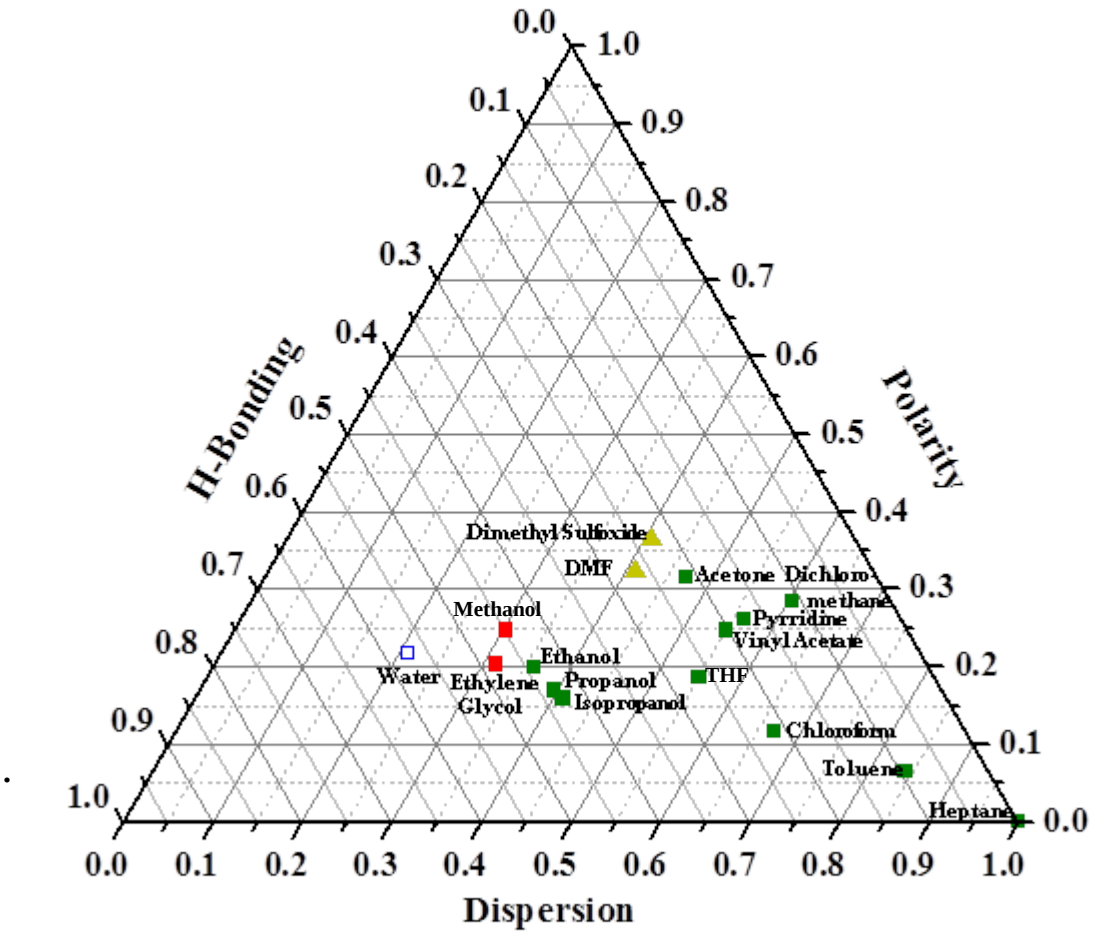


Figure 11.3. HA – Macromer Hansen and Hoy Solubility Chart.

It was of high importance to confirm that HA was immiscible in the LFB solution (i.e. the Betacon Macromer). The only good solvent for HA (□) was found to be water. The good solvents for the Betacon Macromer are represented by (■) and are found to cluster in the lower right corner of the diagram. Bad solvents for both HA and macromer are represented by (■).

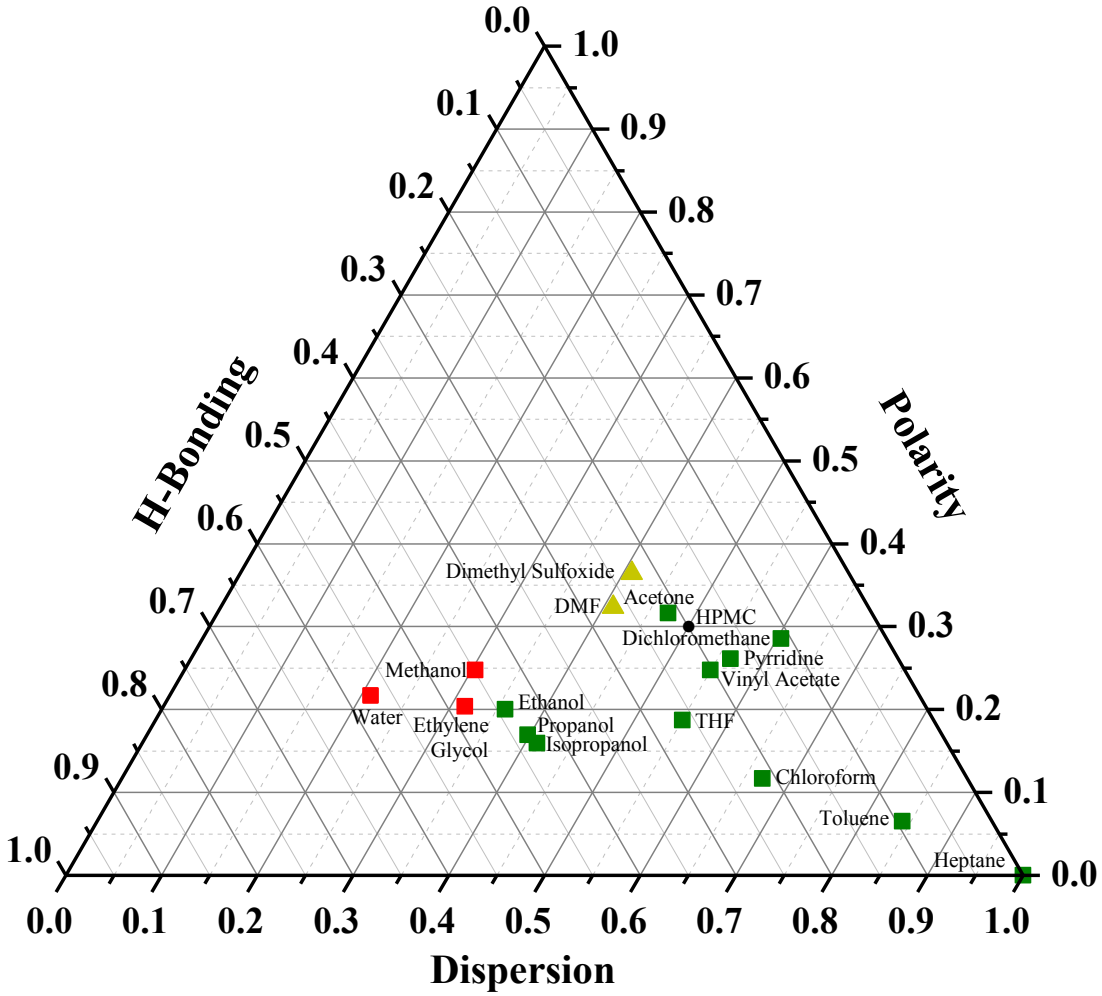


Figure 11.4. HPMC – Macromer Hansen and Hoy Solubility Diagram.

HPMC was found to be highly compatible with the LFB formulation due to its compatibility with a variety range of solvents. HPMC solubility is represented by (●) and is located near the right solubility parameter for the macromer. Water is also a good solvent for HPMC (not represented) making it ideal for loading into LFB and release into the aqueous tear fluid. The parameters for the macromer are divided into good and bad solvents and are represented in the chart. The location of the HPMC parameter and its wide area of solubility indicates it is the best choice for incorporation into the LFB lenses.

Table 11.1. Turbidity Test of LFB Lenses and Lens Formulations

%Transmittance		HPMC Concentration (µg/ lens)	DMA wt% Concentration	TRIS:Macromer wt% Concentration
Formulation	Lens			
36	34	500	0	100
29	46	500	10	90
16	49	500	20	80
19	51	500	30	70
21	56	500	40	60
29	63	500	50	50
34	61	500	60	40
38	65	500	70	30

Table 11.2. Swelling Induced from DMA Concentration.

q	HPMC Concentration (µg/ lens)	DMA wt% Concentration	TRIS:Macromer wt% Concentration
Lens			
0.15	500	0	100
0.2	500	10	90
1.21	500	20	80
1.19	500	30	70
1.34	500	40	60
1.4	500	50	50
1.57	500	60	40
1.7	500	70	30
1.8	500	80	20

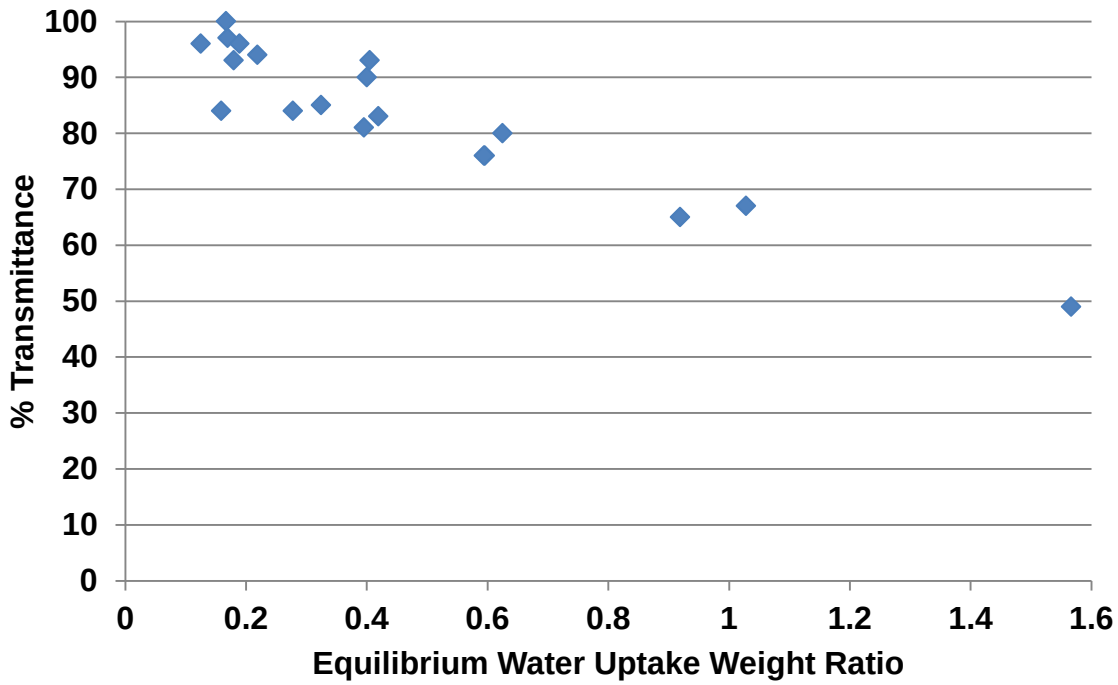


Figure 11.5. The Relationship Between Optical Clarity and Equilibrium Water Weight Swelling Ratio.

There is an inverse correlation between water uptake (swelling) and % transmittance (optical clarity). Samples were made with similar HPMC concentrations and increasing concentration of 50:50 mixture of EGDMA:PEG200DMA crosslinking monomers which correlated to decrease in swelling and a corresponding increase in clarity.

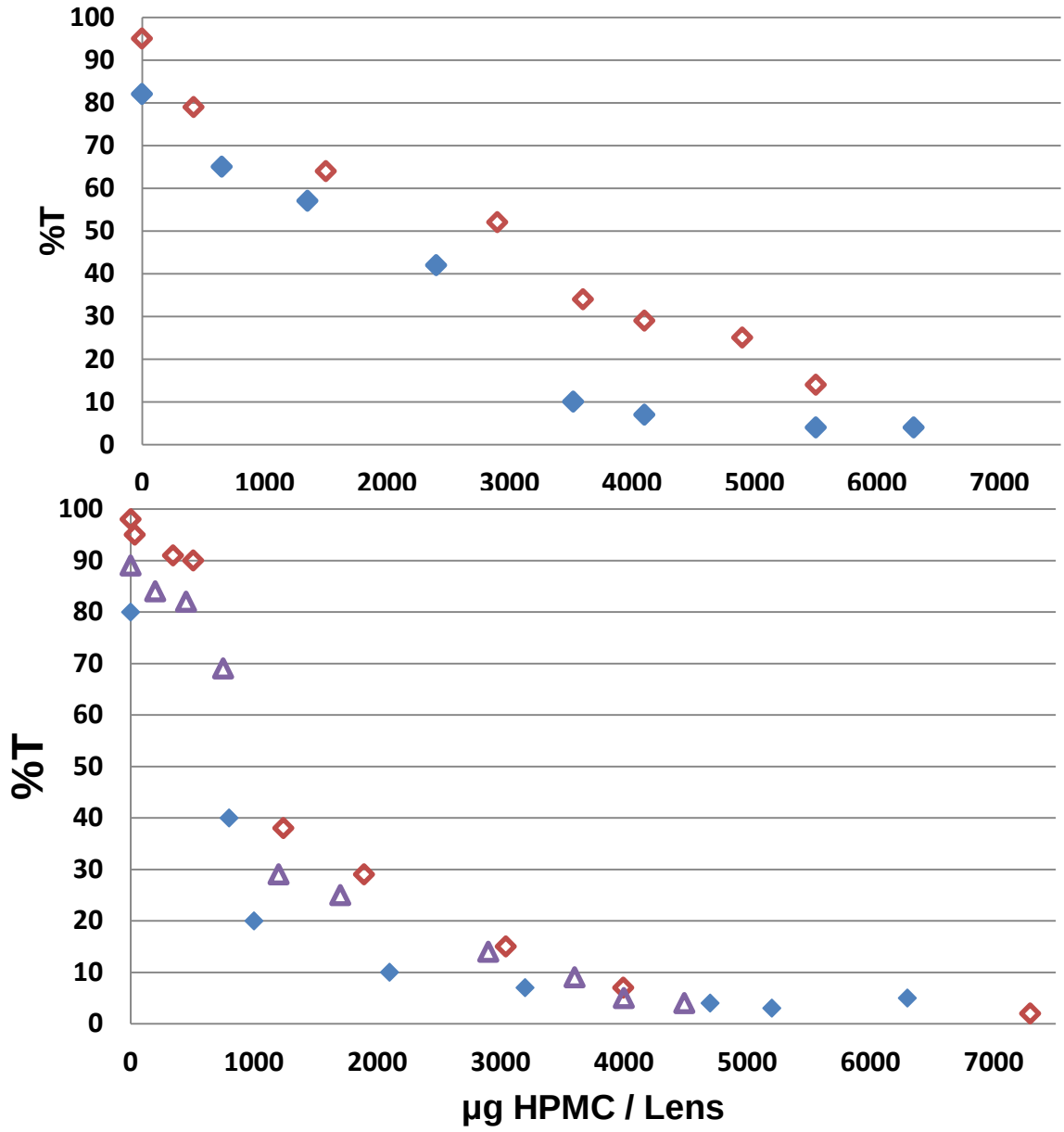


Figure 11.6. Observed Clarity Differences with Removal of Visibility Tint and Ethanol from HPMC-laden LFB lenses.

Optical clarity studies were conducted before ethanol extraction (**a**) and after ethanol extraction (**b**). Tinted lenses are represented by filled points and untinted by hollow points, with the tinted formulation with ethanol before extraction (♦), the untinted before extraction (◊), lenses prepared from LFB formulation containing no ethanol (Δ). It is clear

the tint was responsible for a reduction in clarity of ~10%. As concentration of HPMC increased, the %T decreased more dramatically. After the ethanol extraction, the decrease in clarity due to HPMC concentration is much more dramatic.

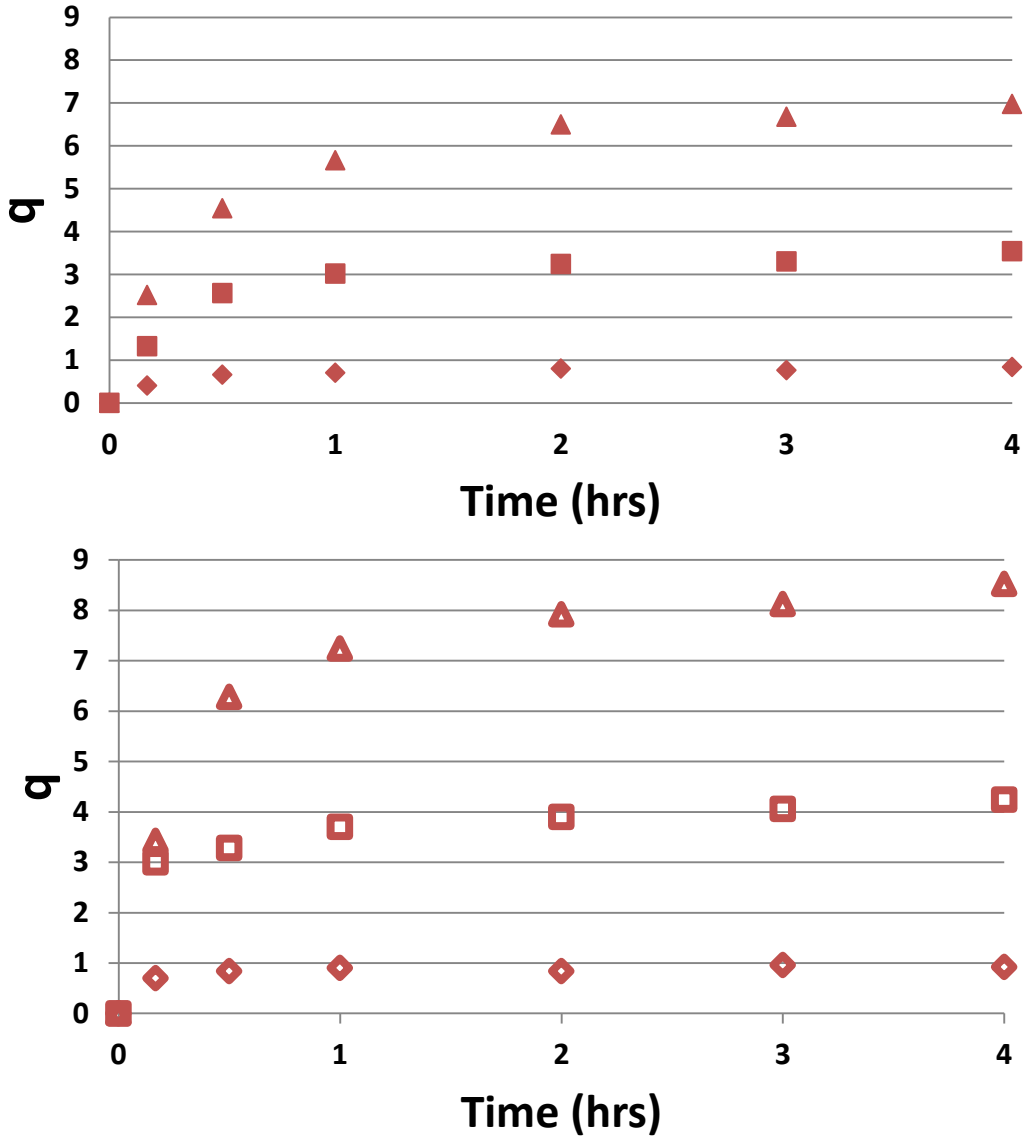


Figure 11.7. Equilibrium Weight Swelling Ratio of LFB Lenses Containing HPMC.

Lenses prepared with HPMC concentrations of 600 µg/lens (▲), 60 µg/ lens (■), and 6 µg / lens (♦). Data from lenses prepared with ethanol in the formulation are filled points and data from lenses with ethanol extracted from the formulation are represented as hollow points. Ethanol saturates the lenses and prevents a high uptake of water, resulting in lower swelling. The ethanol-rich lenses on the left demonstrate lower equilibrium

swelling values than the similar ethanol-free lenses. As HPMC content increases, water uptake in the lenses increases.

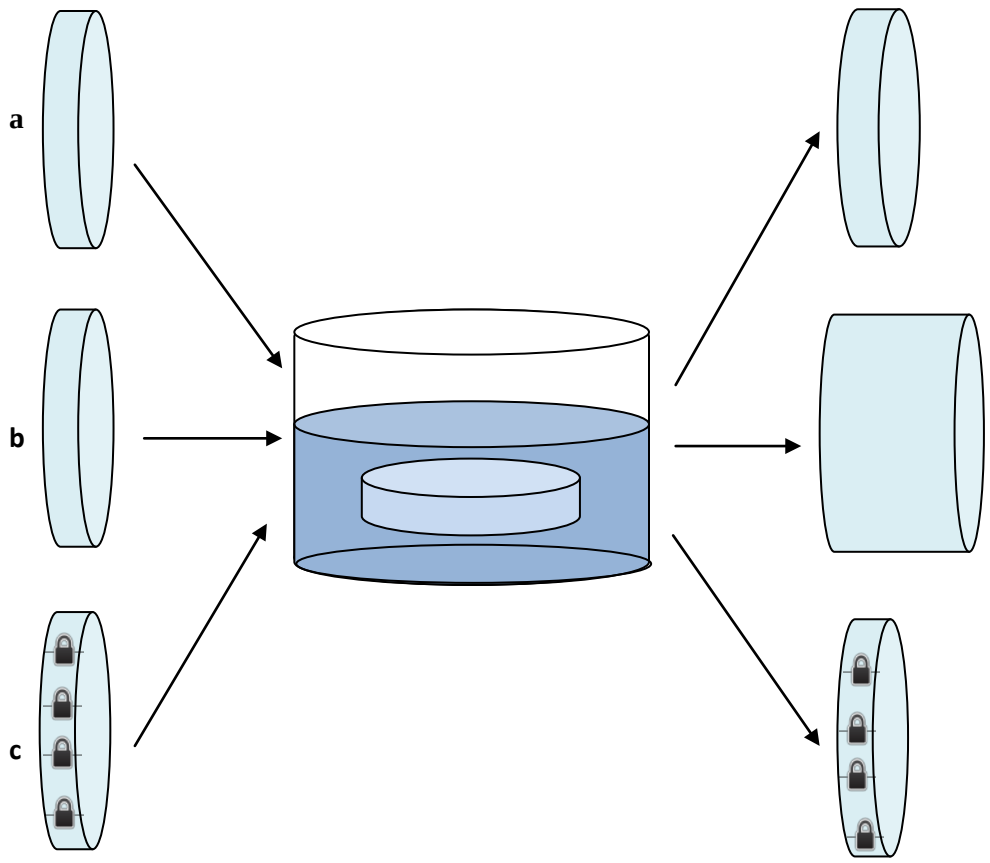


Figure 11.8. Observed Swelling of Various Formulations.

The main hurdles of the project included control of swelling, optical clarity, and release characteristics of HPMC-laden lenses. The LFB formulation contains ethanol that is removed after the lens is prepared. Ethanol was removed from the formulation to prevent any misleading release and clarity values at high HPMC concentrations per lens. Ethanol saturates the lenses and prevents a high uptake of water, resulting in lower swelling **(a)**. In addition, ethanol stays in the lens during release, causing the HPMC to partition between the ethanol-rich lens and the aqueous phase. However, if ethanol is removed, substantial swelling occurs due to high water uptake **(b)**. The addition of crosslinking monomers limit water uptake and as a result, optical clarity can be increased **(c)**.

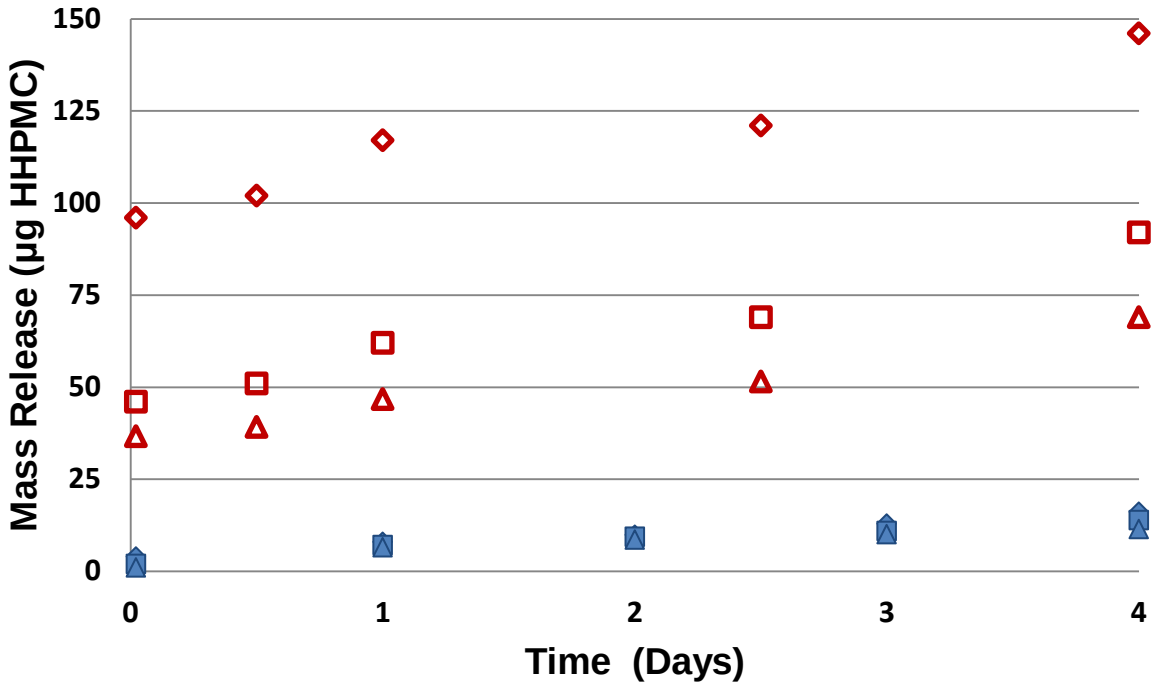


Figure 11.12. Cumulative Mass Release of HPMC from Imprinted LFB Lenses: The Effect of NVP Concentration on Release of 120 KDa HPMC from Ethanol-Rich (Pre-Extract) and Ethanol-Free (Post-Extract) Lenses.

All lenses were prepared with 400 µg HPMC/lens. Data from lenses prepared with ethanol in the formulation are filled points and data from lenses with ethanol extracted from the formulation are represented as hollow points. M/T ratios ranged from 42 (♦), 27 (■),17 (▲). For ethanol-free, post-extract lenses, the most significant effect of NVP incorporation was the high initial rate of HPMC release. As the M/T ratio increased, there was an increased initial release of HPMC from the lens. For an M/T ratio of 42, the ethanol-free, post-extract lenses lost approximately 25% or 100 µg of the loaded HPMC. After this initial burst, release from all lenses was independent of the M/T ratio. For ethanol-rich or pre-extract lenses, there was no initial release of HPMC and all lenses released HPMC at equivalent rates despite differing M/T ratios. T=34ºC, and N=3.

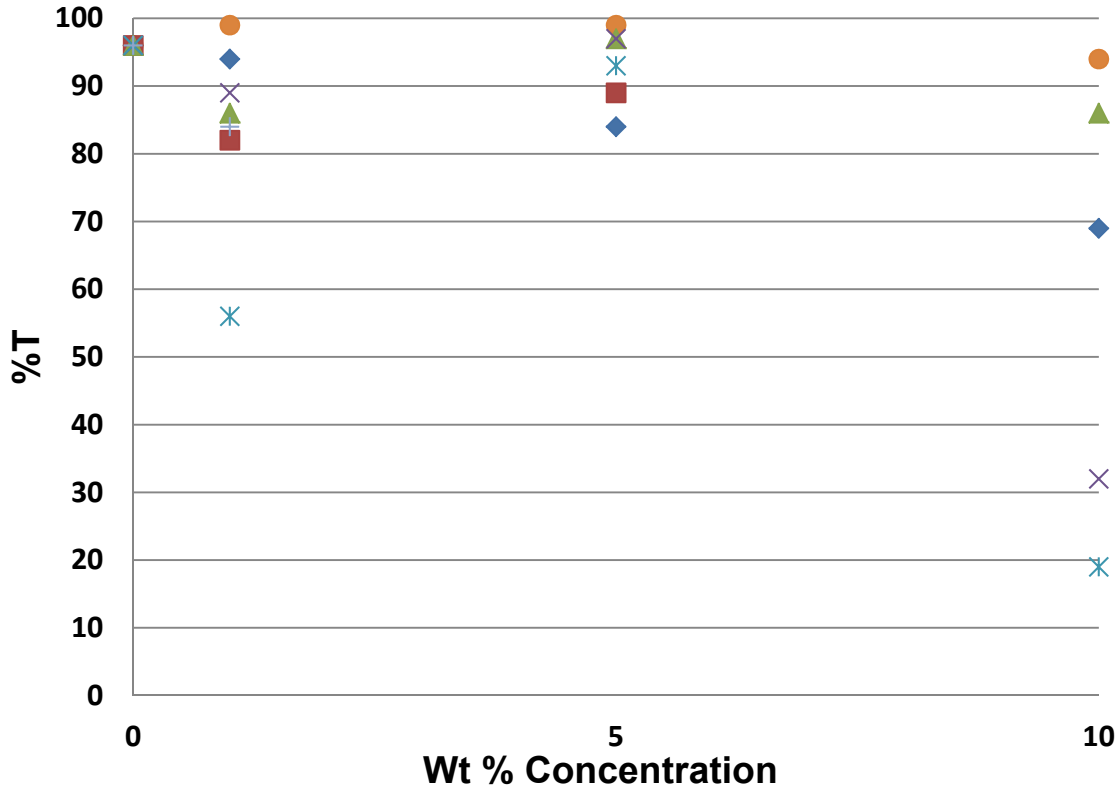


Figure 11.9. Effect of the Addition of Crosslinkers on the Optical Clarity of Untinted LFB Lenses Prepared Without Ethanol

The best clarity was demonstrated by a 50:50 wt. ratio of EGDMA and PEG200DMA (●). The 10% concentration of these monomers in the formulation resulted in lens clarity of 96±2%, and an equilibrium weight swelling ratio of 1.5. Using EGDMA (♦) caused lenses to appear white above 5 wt.% concentration and the lenses were brittle. Using PEG200DMA alone (X) produced a much more flexible lens but the increased length and hydrophilicity caused higher swelling which lowered clarity. Using divinyl ethylene glycol (+) led to problems forming lenses, and lenses did not form after more than 1% concentration of this crosslinking monomer in the formulation. PEG600DMA (□), which was the most hydrophilic crosslinker and longest, allowed for greatest water uptake

which significantly reduced clarity. Tetra-EGDMA (■) was disqualified as the qualitative mechanical properties were poor. Note: HPMC was not present in these lenses.

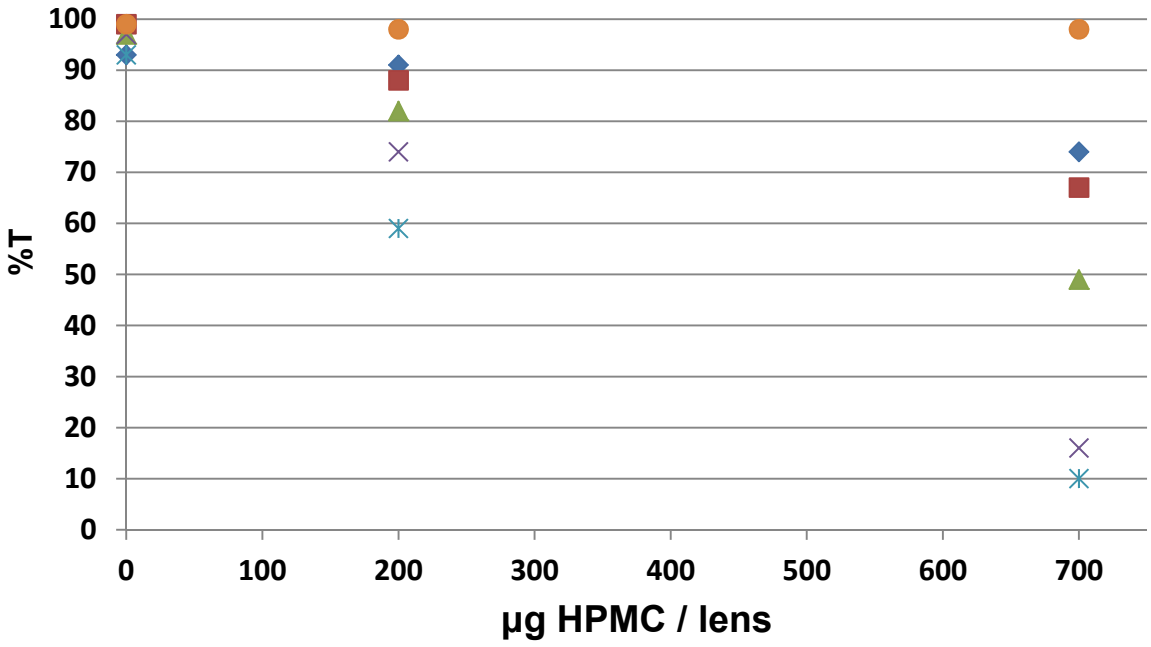


Figure 11.10. Effect of the Addition of Crosslinkers on the Optical Clarity of Untinted LFB Lenses Prepared Without Ethanol and Containing HPMC

All lenses were made with 10 wt% crosslinking monomer. The greatest percent transmittance was obtained for the lenses prepared with EGDMA:PEG200DMA (●), which demonstrated excellent qualitative mechanical properties. For this reason, this mixture was chosen for all following experiments as it had the greatest potential. At 700 µg HPMC, only lenses containing a mixture of EGDMA:PEG200DMA (●) yielded acceptable transmittance values. Lenses containing EGDMA (♦), PEG400DMA (■), PEG200DMA (▲), PEG400DMA (X) and PEG600DMA (□) did not yield suitable transmittance values at higher concentration values of HPMC.

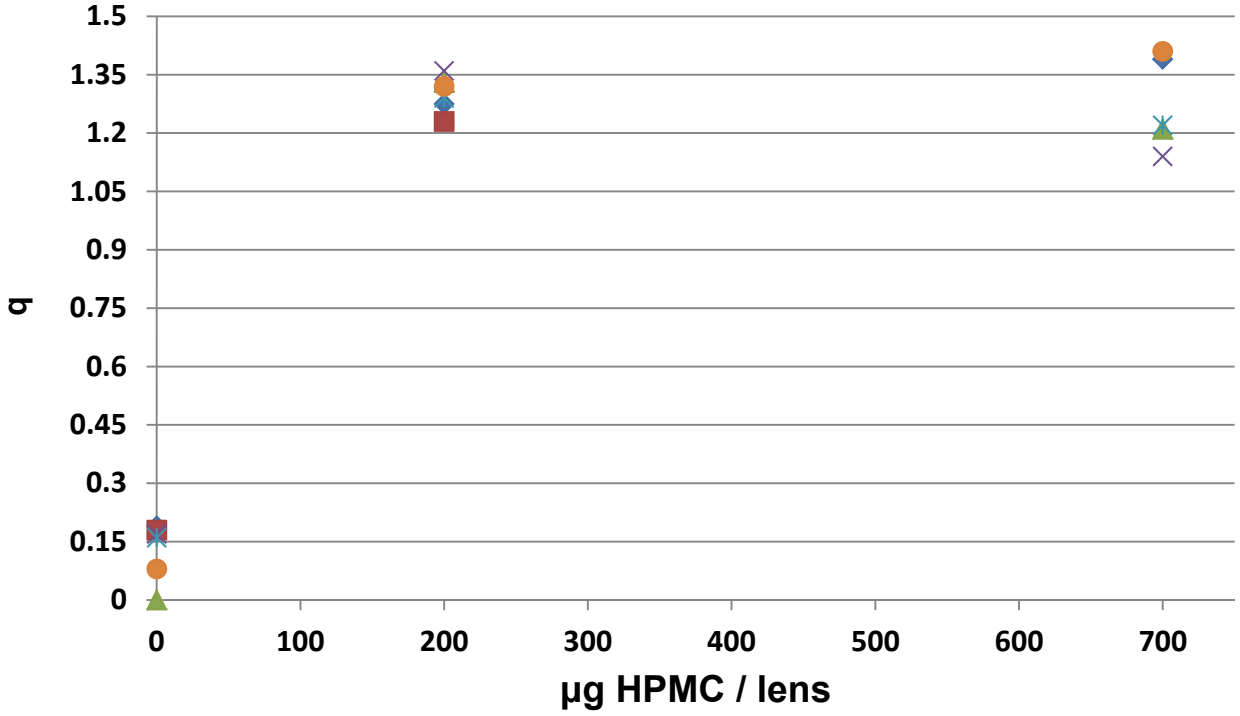


Figure 11.11. Effect of the Addition of Crosslinkers on the Equilibrium Weight Swelling Ratio of Untinted LFB Lenses Prepared Without Ethanol and Containing HPMC.

Lenses were prepared with a 50:50 ratio of EGDMA:PEG200DMA (●), EGDMA (♦), PEG400DMA (■), PEG200DMA (▲), PEG400DMA (X), and PEG600DMA (□). Equilibrium weight swelling values for HPMC free-lenses in DI water ranged from 0–0.2 but increased significantly when HPMC was contained in the lens.

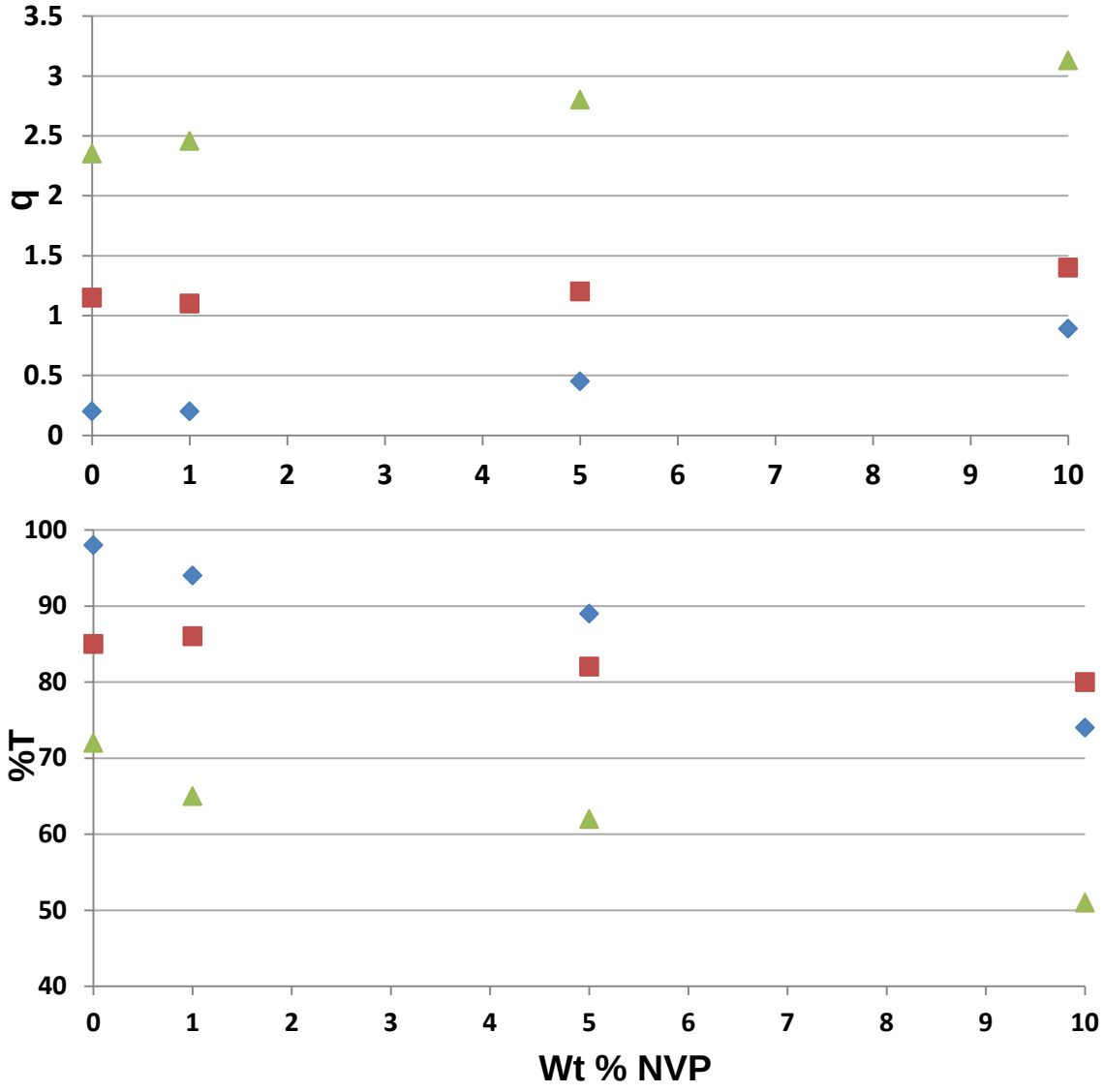


Figure 11.13. Swelling and Optical Clarity of Imprinted LFB Lenses Prepared With NVP and EGDMA:PEG200DMA

Lenses containing 0 µg HPMC (♦), 800 µg HPMC (■), and 3,500 µg HPMC (▲) were formulated at 0, 1, 5 and 10 wt% NVP, (**a**) Equilibrium weight selling ratio and (**b**) percent transmittance. As NVP concentration increases, swelling increases and clarity decreases. However, HPMC concentration has a bigger effect on swelling and clarity. Swollen lenses were ~350 µm thick and had ethanol extracted (N=3).

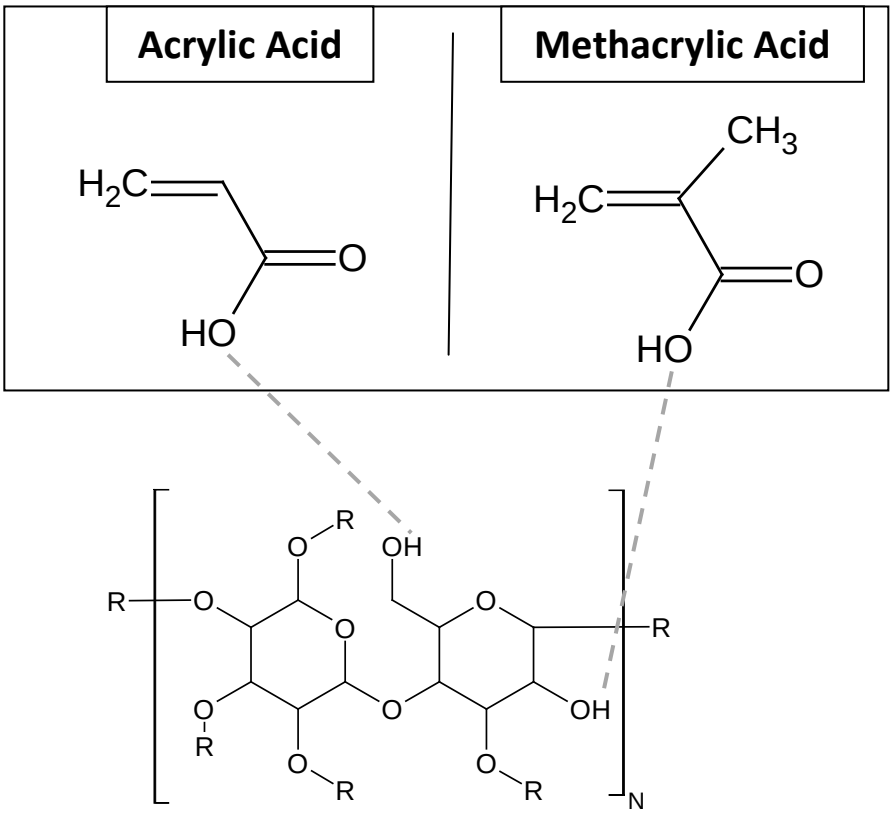


Figure 11.14. Structure of Acrylic Acid and Methacrylic Acid and Hydrogen Bonding With HPMC

The carboxylic acid groups provided by acrylic acid and methacrylic acid potentially hydrogen bond with imprinted memory sites through the above diagram.

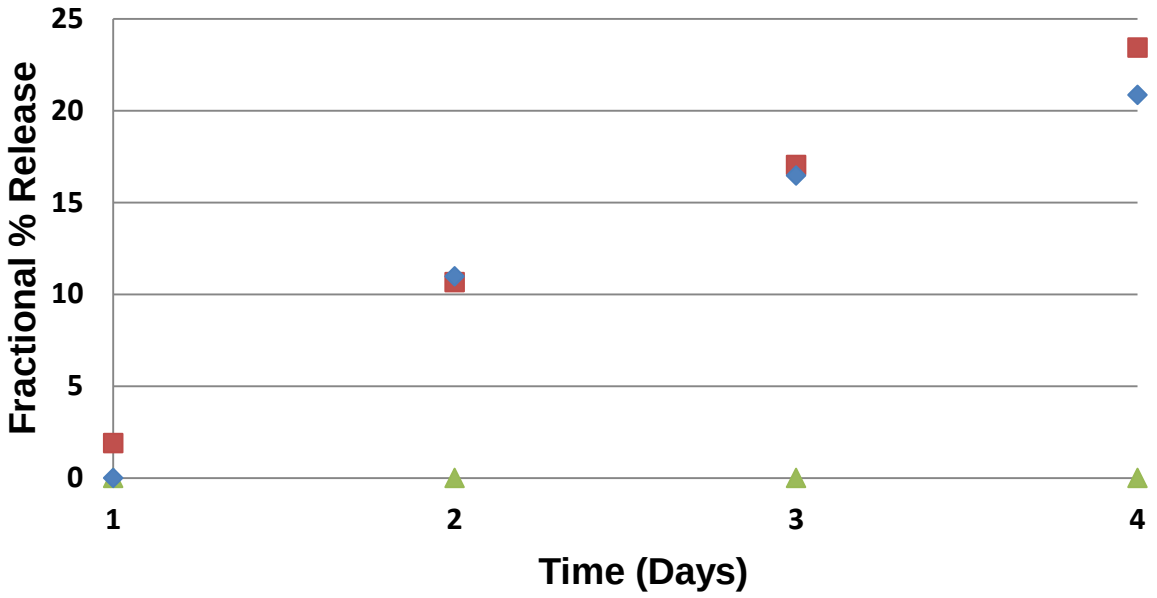


Figure 11.15. Fractional Release of HPMC from Imprinted LFB Lenses with Acrylic Acid and Methacrylic Acid.

Lenses were prepared with 1 wt.% concentration acrylic acid (AA) (■) and 1 wt.% concentration methacrylic acid (MAA) (♦) as imprinting monomers to replace NVP after it was shown that NVP was not a suitable monomer for use in LFB lenses. AA and MAA containing lenses demonstrated low swelling compared to lenses prepared with no functional monomers (▲) and did not affect optical clarity as much as NVP. In the release, no significant differences were seen between the release of HPMC. Lenses were ~400 μm in thickness and contained 600 μg HPMC /lens and contained 10 wt% crosslinker. (T=34ºC, N=3).

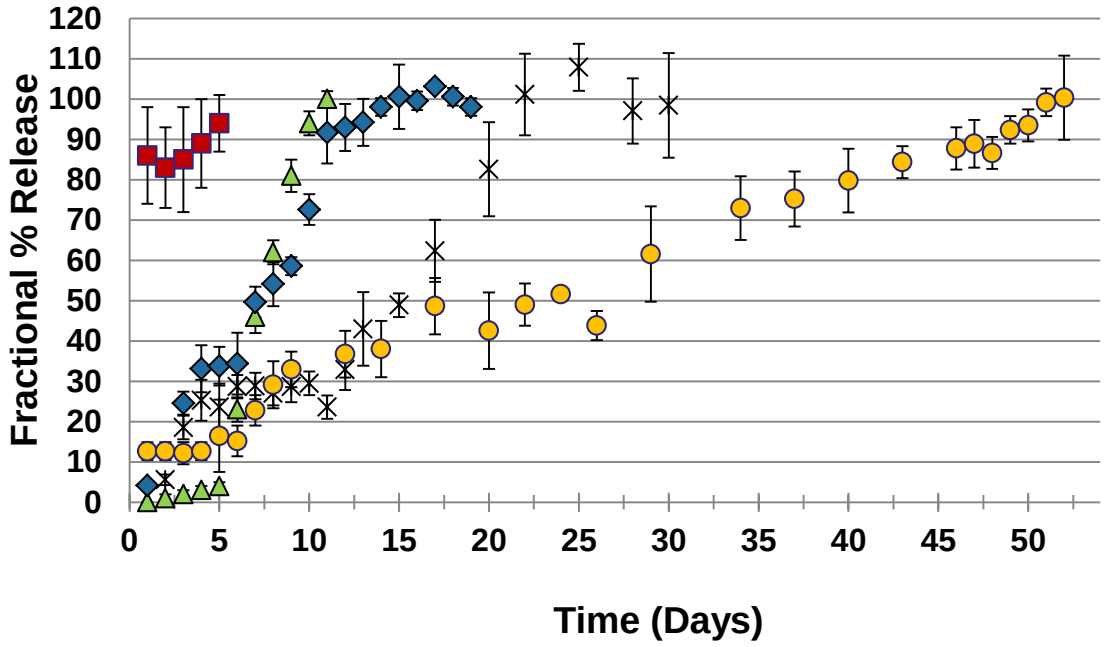


Figure 11.16. Fractional Release of HPMC from Imprinted LFB Lenses: Effect of M/T Ratio on Fractional Release of 120 KDa HPMC.

Release rate in DI water decreases as M/T ratio increases. HPMC was dispersed into the CIBA Vision, Inc, LFB (■) lens to a concentration of 3,000 µg/ lens. The crosslinked LFB formulation (xLer/T~1.5) contained ~2,600 HPMC µg/ lens and released ~250 µg/ day but optical clarity was poor and haze was significant in the swollen lens. The rate of profile for imprinted systems was tested at various M/T ratios. The release rate M/T = 0.2 loaded with ~2,900 µg HPMC (♦) is ~300 µg /day for a duration of 10 days, M/T = 2.8 loaded with ~2,200 µg HPMC (X) delivers ~100 µg /day for 22 days, and M/T = 3.4 loaded with ~2,900 µg HPMC (●) releases 60 µg/day for 50 days. Swollen lenses are ~ 350 µm thick, T = 34ºC, N = 3.

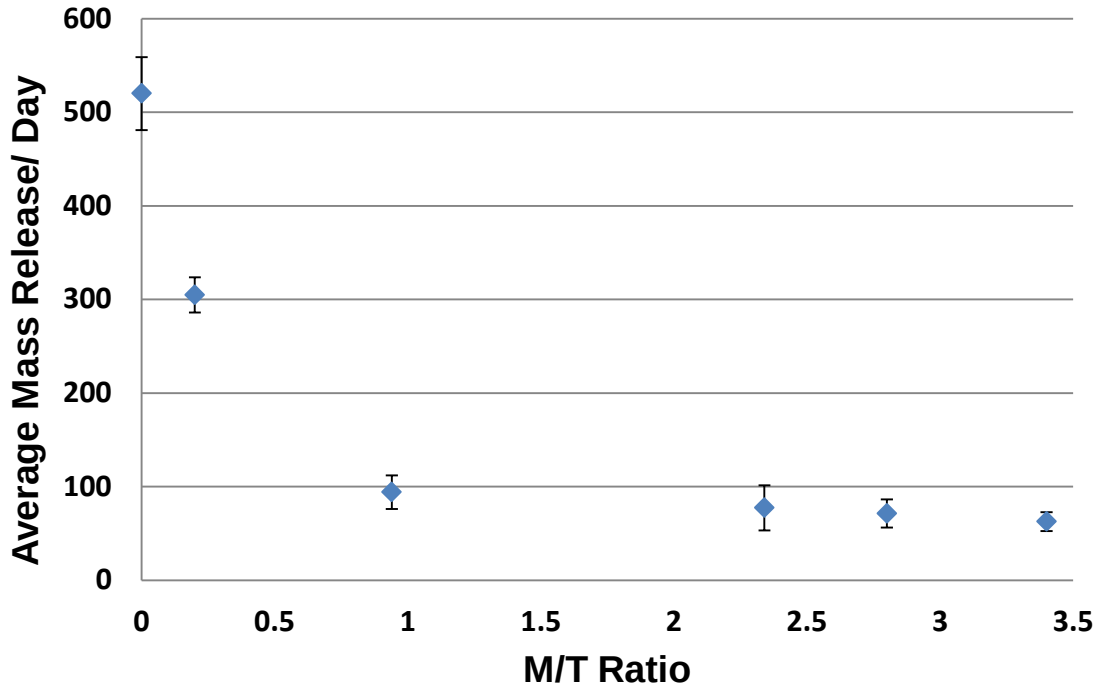


Figure 11.17. Correlation between M/T and Mean Release Rate.

The mean release rate was seen to correlate to the M/T with high accuracy. By extrapolation, it should be possible to determine M/T ratio where HPMC is completely sequestered into the lens. All samples represented has xLer/T ratio between 1-2 and ~2,500 µg HPMC.

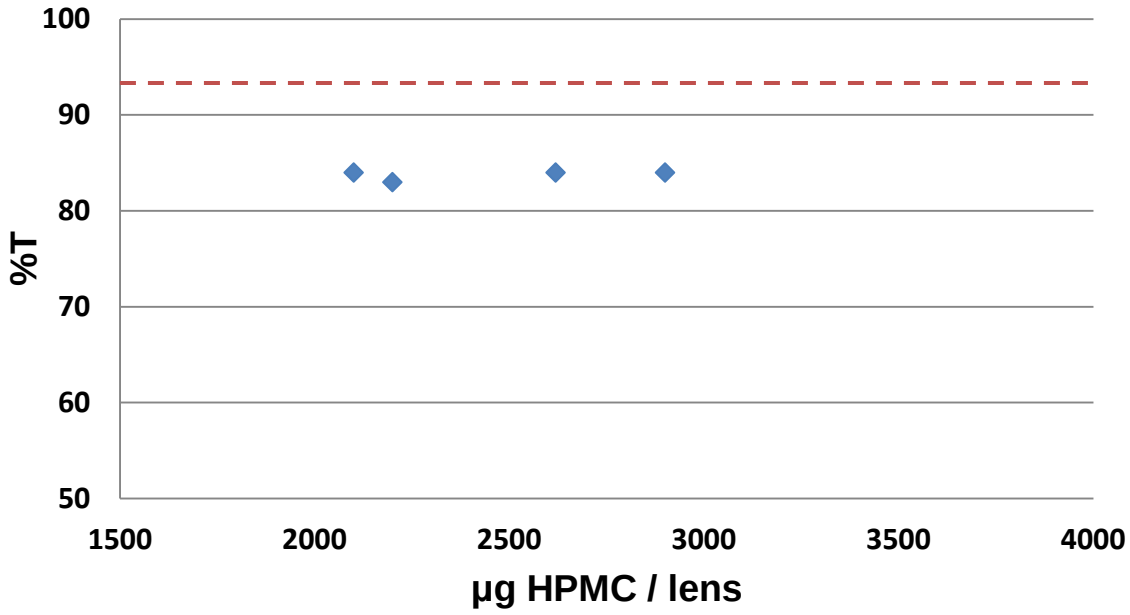


Figure 11.18. Drop in Transmittance of 350 µm Swollen Lenses over Five Days.

Clarity decreased in 350 µm swollen lenses as HPMC release progressed over five days. Transmittance was measured in (♦) lenses after releasing in 250 mL of DI water for 5 days. The dotted line represents the initial transmittance of the lenses (%T ~92). HPMC aggregates in the lenses dissolved and released from the lens leaving voids in the lenses, which filled with water. The change in local refractive index changes caused transmittance to decrease. It was thought producing thinner lenses and subjecting the prepolymer formulation to high shear mixing would reduce aggregate size.

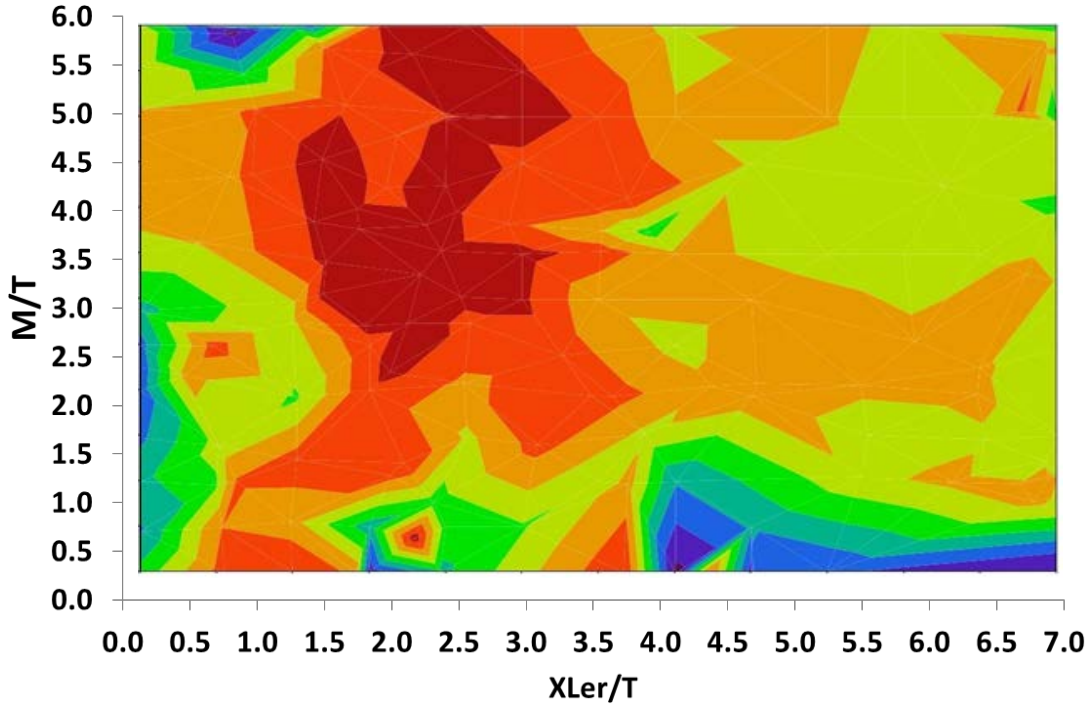


Figure 11.19. Optical Clarity of 120 µm Thick (Swollen) Lenses at Various M/T and xLer/T Ratios.

A series of 250 lenses were formulated at various M/T and xLer/T ratios. Optical clarity was measured and indicated a wide area of high optical clarity between xLer/T of 1.0-2.5, and M/T between 2.5-6. All lenses were formulated to a HPMC concentration of ~1,000 µg HPMC/ lens.

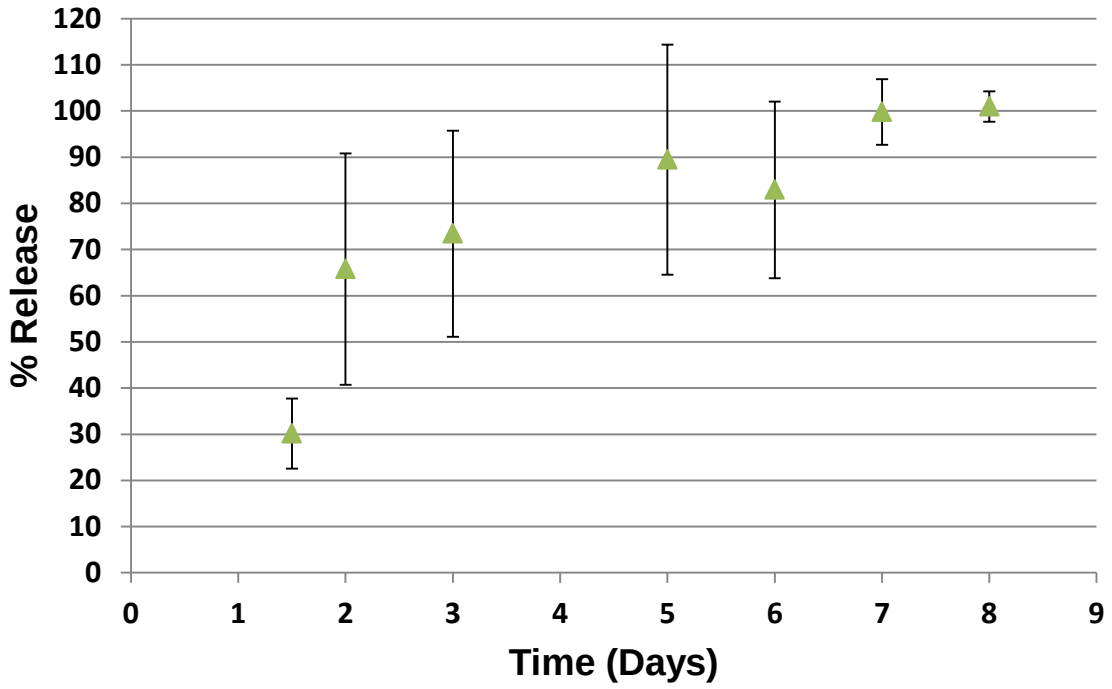


Figure 11.20. HPMC Release from 100 µm Lenses in Large Volume Infinite Sink.

HPMC release was measured from 100 µm lenses (n=3) in 250 mL DI Water (T = 33ºC, 30 rpm). Lenses contained ~1,000 µg of 120 KDa HPMC and were formulated to M/T ~ 3.5 and xLer/T ~1.5. Release reached completion in 4-5 days.

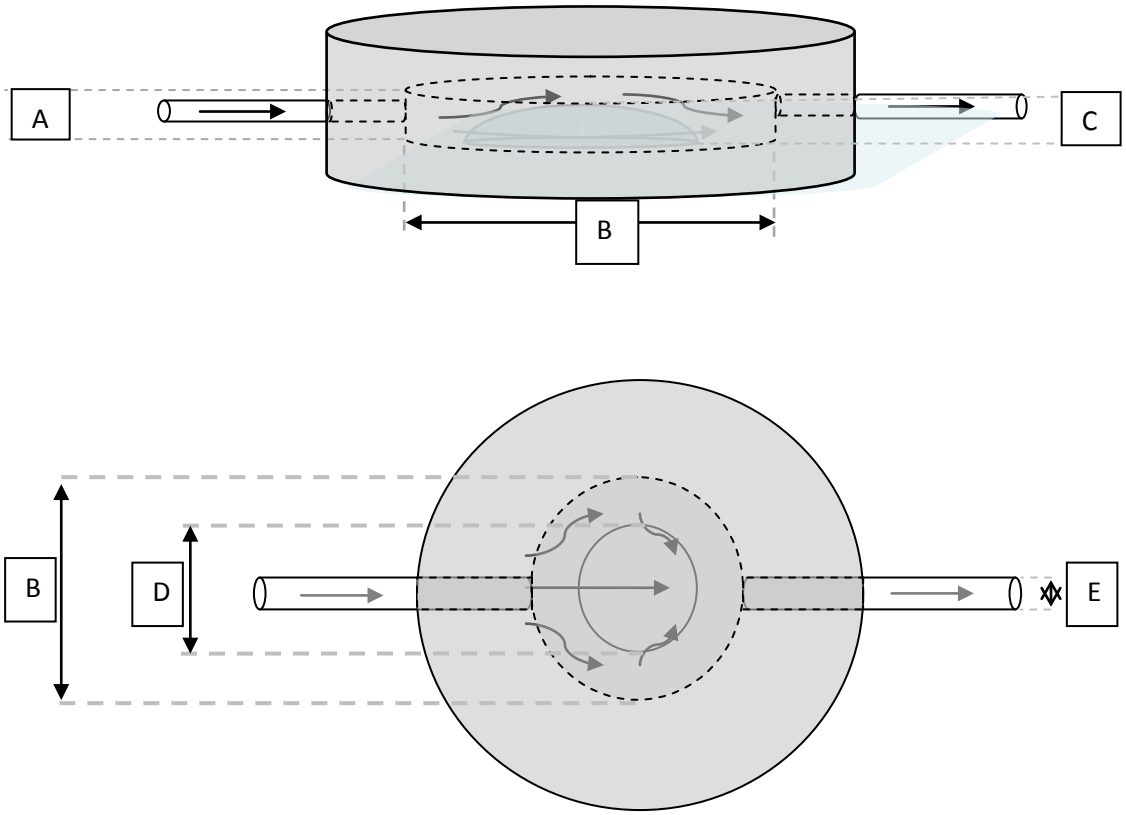


Figure 11.21. Schematic of the Microfluidic Device.

The microfluidic device is a novel device pioneered by our lab. The device is used to mimic the in vivo drug release profiles by duplicating the physiological flow rate of the eye. The inner chamber is formulated by curing Sylgard 184 Silicone Elastomer around a glass marble. The specifications of the inner chamber are (A) 5.7 mm high and (B) 16.5 mm wide. The lens is lightly glued to a glass marble and placed under the mold. The measurements of the marble are (D) 15.2 mm wide and (C) 4.35 mm high. The inner chamber contains 175 μL of DI water. Two needles of (E) 0.125 μm diameter served as the inlet and outlet streams. The arrows represent the flow of DI water through the

device. The continuous flow of water over, around and under the lens ensures that the entire lens is wetted and that the water is refreshed every 60 mins.

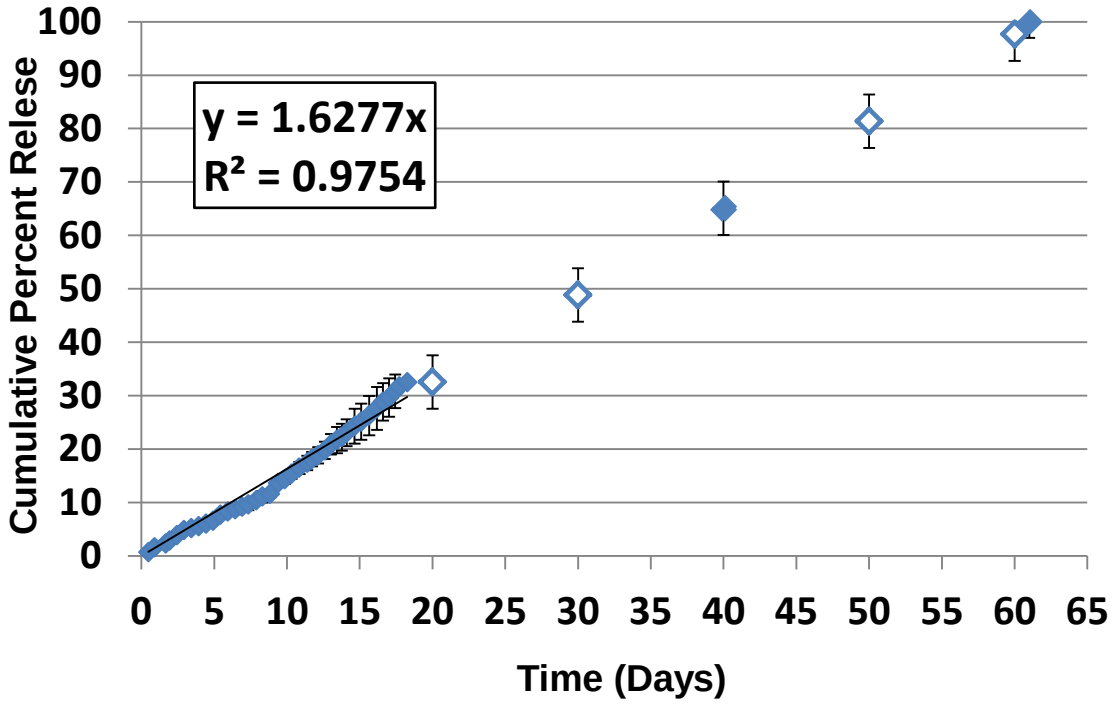


Figure 11.22. Release of HPMC in the Microfluidic Device.

Release of (♦) 120 KDa HPMC was performed in 170 µL of DI water with a flow of 3 µL/min of fresh DI water. The release was linear with a mean release rate of 16 µg HPMC/day. The lens used was M/T ~3.5, xLer/T ~1.5 with 1,000 µg HPMC and 100 µm thick when swollen. Release was completed in 61 days. For clarity, after day 20 the release data was averaged and is represented by (◊). N =2.

CHAPTER 12

CONCLUSIONS

Within this work, molecular imprinting has been shown to be a versatile and valuable method of controlling comfort molecule release from soft, extended wear, silicone hydrogel contact lenses. By adding functional monomers and crosslinking monomers, considerable control has been demonstrated over HPMC release rate, optical clarity, swelling, and mechanical properties. Producing a commercial lens prepared with HPMC added to the formulation resulted in a lens with low optical clarity and a fast release of HPMC of insignificant duration compared to wear time. There was no control over release, and poor optical clarity made the lens unsuitable for commercial use. By applying the principles of molecular imprinting, release rates could be significantly varied by the imprinting effect. Release rates can be tailored to deliver 1,000 μg HPMC over a period of up to 60 days in a constant manner. This work is very exciting for the field as it highlights the tailorable, extended release of a macromolecular re-wetting agent from a silicone hydrogel, extended wear lens. This lens combination device is ideal for combating contact lens induced dry eye and is expected to significantly influence the research and development of future contact lenses as the imprinting technique can be applied as a platform technology to other comfort molecules.

Levels of comfort are not well defined in the literature. Since so little work has been done with continuous release of comfort agents, there are not generally accepted

values defining comfort. Until such data is available, estimates must be made from eye drop formulations. A typical over-the-counter HPMC eye drop delivers 0.125 µg HPMC/drop (assuming a 25 µL drop with 0.2%-0.5% re-wetting agent concentration) [**53-55**]. Drops are applied as needed and 20 drops a day yields a projected cumulative release rate of 2.5 µg HPMC/day. The daily mass delivery rate from the HPMC-imprinted lenses is 6 fold higher than this projected eye drop release rate. Some artificial tears, such as MiniDrops Eye Therapy (Optics Laboratory, Inc.) deliver PVP and PVC at a combined 500 µg comfort agent/drop (20 µg comfort agent/µL assuming a 25 µL drop). With only 2 drops a day, the projected cumulative release rate is 1,000 µg comfort agent/day. Thus, a large range of comfort agent values exist in commercially available products, and our lenses can be designed with varying release rates to prevent CLIDE symptoms. Also, non-corrective, cosmetic HPMC-imprinted lenses could be used to treat other dry eye conditions. With the imprinted lenses, the HPMC release rate and concentration of comfort molecule in the eye would be relatively constant rather than pulsatile with eye drops. In addition, lenses would need to be replaced on a monthly or weekly basis whereas eye drops might need to be applied each hour or as needed.

APPENDIX A

ACRONYMS, TRADITIONAL HYDROGEL LENSES AND THEIR USES, AND COMMERCIAL LENSES

A.1. Acronyms Used in Text.

AA.....Acrylic Acid

ALS.....Artificial Lacrimal Solution

AM.....Acrylamide

BAB.....Blood Aqueous Barrier

BBB.....Blood Brain Barrier

BIS.....N,N-Methylene Bisacrylamide

BRB.....Blood Retina Barrier

CD.....Cyclodextrin

CLIDE.....Contact Lens Induced Dry Eye

CMA.....4-Tertiary Butyl-2-Hydroxycyclohexyl Methacrylate

CMC.....Carboxymethyl Cellulose

CMR.....Carrier Mediatef Release

DEAA.....N,N-Diethylacrylamide

DEAEM.....Diethylaminoethyl Methacrylate

Deff.....Effective Diffusion Coefficient

Dk.....Oxygen Permeability Coefficient

DMA.....Dimethyl Acylamide

DMAA.....Dimethyl Acylamide

EGDMA.....Ethylene Glycol Dimethacrylate

FDA.....Food and Drug Administration

GA.....Glycotic ACid

GMA.....Glycidal Methacrylate

HA.....Hyaluronic Acid

HEMA.....2-Hydroxyethyl Methacrylate

HPLC .....High Performance Liquid Chromatography

HPMC .....Hydroxypropyl methycellulose

KDa .....Kilodalton

LA .....Lactic Acid

LASIK.....Laser Assisted in situ Keratomileusis

LFA .....Lotrafilcon A

LFB .....Lotrafilcon B

M .....Monomer

M/T .....Monomer/Template Ratio

MAA .....Methacrylic Acid

Mam .....Methacrylamide

MAPTAC.....Methacrylaminopropyltrimethylammonium Chloride

MC .....Methylcellulose

Mc .....Molecular Weight Between Crosslinks

MMA.....Methyl Methacrylate

MOEP .....2-Methacryloxyethyl Acid Phosphate

NAADA .....N-acryloyl-Aminoacetaldehyde-dimethylacetal

NSAID .....Non-Steroidal Anti-Inflammatory Drug

NVP.....N-Vinyl Pyrrilidone

OTC.....Over the Counter

OTMS .....Octadecyltrimethoxysilane

PBS .....Phosphate Buffered Solution

PEG200DMA.....PolyEthylene Glycol (n = 200) Dimethacrylate

PEG400DMA.....PolyEthylene Glycol (n = 200) Dimethacrylate

PEG600DMA.....PolyEthylene Glycol (n = 200) Dimethacrylate

PHEMA.....Poly(2-Hydroxyethyl Methacrylate)

PMMA .....Poly(Methyl Methacrylate)

PVA.....Poly(Vinyl Alcohol)

PVAMA .....Polyvinyl Alcohol Macromer

PVP .....Poly(Vinyl Pyrrilidone)

RPE .....Retinal Pigment Epithelium

SCL .....Soft Contact Lens

SiHy .....Silicone Hydrogel

SiMA.....1-(Tristrimethyl-Siloxysilylpropyl)-Methacrylate

SMR .....Surfactant Mediated Release

T .....Template

TMATMP .....Trimethylolpropane Trimethacrylate

TRIS.....Methacryloxypropyl-Tris-(Trimethylsiloxy) Silane

TSCL.....Therapeutic Soft Contact Lens

TSiHyCL.....Therapeutic Silicone Hydrogel Contact Lens

UV.....Ultraviolet

xLer.....Crosslinker

xLer/T .....Crosslinker to Template Weight Ratio

βCD.....Beta-Cyclodextrin

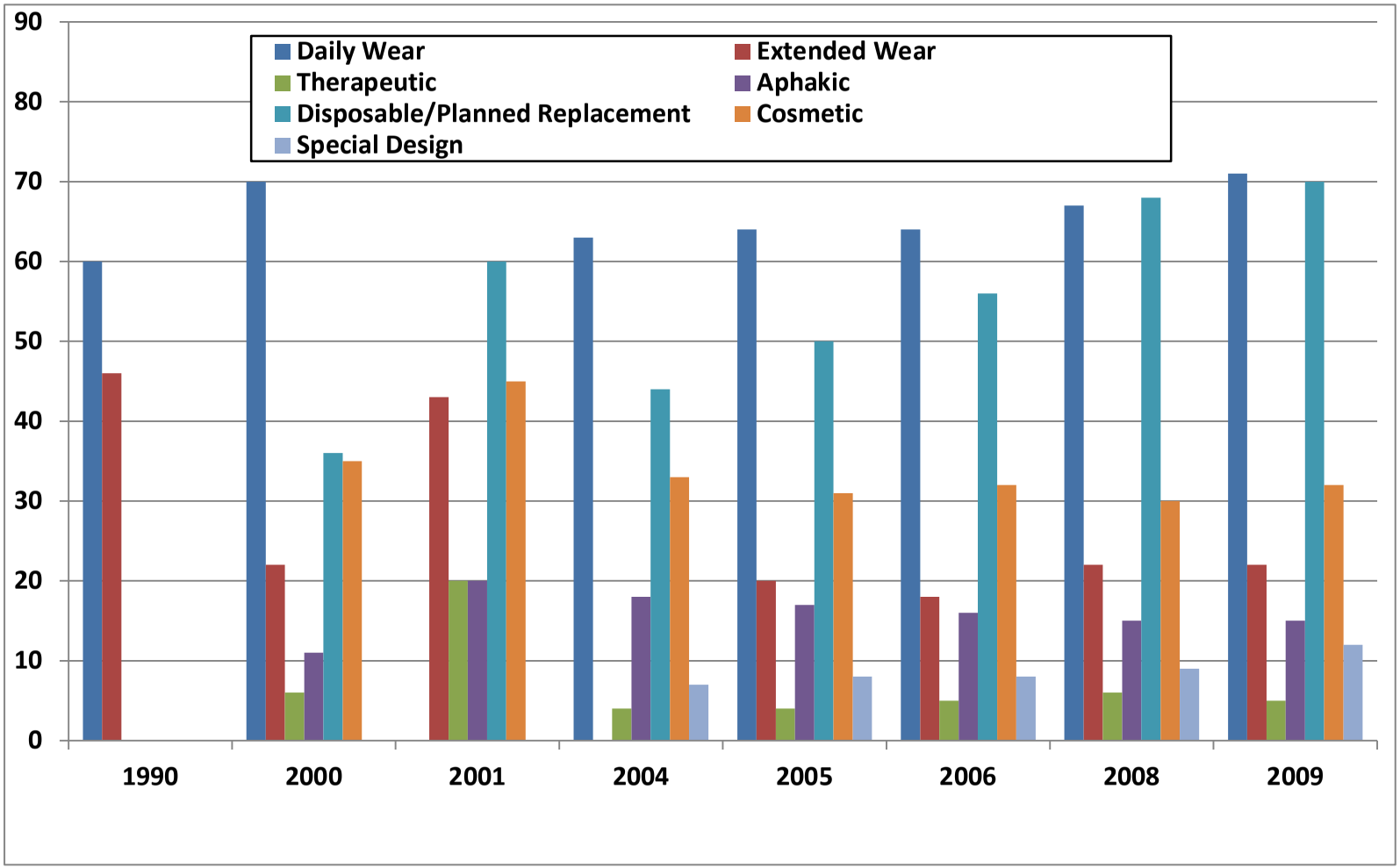


Figure A.1. Traditional Hydrogel Lenses Based on Application.

Different lenses are prescribed for different wear times. **Figure B.3** represents the annual totals for different wear times. The figure was compiled from references [**A.1-A.11].**

Table A.1.a. Table of Lenses based on Material and Wear

Type	1990	2000	2001	2003	2004	2005	2006	2008	2009	2010
Gas Permeable	62	42	50	53	61	60	60	65	63	56
Multifocal		39	47	52	52	59	61	71	75	74
Disposable/Planned Replacement		10	11	12	12	14	15	19	22	22
Daily Wear		23	25	27	27	29	27	29	29	29
Extended/Flexible Wear								2	2	2
Toric		6	11	13	13	16	19	21	22	21
Hydrogel	162	184	178	184	191	194	199	217	227	228
Daily Wear	66	70	68	64	63	64	64	67	71	71
Extended/Flexible Wear	68	22	24	22	22	20	18	22	22	22
Therapeutic		6	6	4	4	4	5	6	5	5
Aphakic	25	11	10	18	18	17	16	15	15	15
Disposable/Planned Replacement	3	36	38	36	44	50	56	68	70	70
Cosmetic		35	27	35	33	31	32	30	32	32
Special Design		4	5	5	7	8	8	9	12	13
Toric		63	73	81	85	93	95	112	114	114
Disposable/Planned Replacement		16	20	21	21	27	27	40	40	40
Daily Wear		34	35	36	39	38	39	40	41	41
Extended/Flexible Wear		7	7	11	12	12	10	11	11	11
Multifocal		6	11	13	13	16	19	21	22	22
Comestic		35	38	35	33	31	32	30	32	32
Daily Wear		11	19	20	17	15	15	14	15	15
Disposable/Planned Replacement		16	11	10	11	11	12	12	13	13
Extended/Flexible Wear		8	8	5	5	5	5	4	4	4
Disposable/Planned Replacement		26	45	32	33	41	42	59	62	62
Toric		16	20	21	21	27	27	40	40	40
Multifocal		10	25	11	12	14	15	19	22	22
Aphakic										

Table A.1.b. Table of Lenses based on Material.

Material	1990	2000	2001	2003	2004	2005	2006	2008	2009	2010
Silicone	3	1	1	1	1	1	1	1	1	1
Hydrogel	120	270	270	270	290	321	324	355	366	366
Silicone Hydrogel		1	1	2	2	7	12	24	25	26
Gas Permeable	52	42	50	53	61	60	60	65	63	56
Total	175	314	322	326	354	389	397	445	455	449

Table was compiled from data in references [**A.1-A.11**].

A.3. References.

[A.1] Physicians' Desk Reference for Ophthalmic Medicines. Medical Economics Company,Inc: Thomson Healthcare: Montvale NJ;1990

[A.2] Physicians' Desk Reference for Ophthalmic Medicines. Medical Economics Company,Inc: Thomson Healthcare: Montvale NJ; 2001

[A.3] White P, Scott C. Contact Lenses & Solutions Summary. *Contact Lens Spectrum Supplement*. 2000 July.

[A.4] White P, Scott C. Contact Lenses & Solutions Summary. *Contact Lens Spectrum Supplement*. 2001 July.

[A.5] White P, Scott C. Contact Lenses & Solutions Summary. *Contact Lens Spectrum Supplement*. 2003 August.

[A.6] White P, Scott C. Contact Lenses & Solutions Summary. *Contact Lens Spectrum Supplement*. 2004 July.

[A.7] White P, Scott C. Contact Lenses & Solutions Summary. *Contact Lens Spectrum Supplement*. 2005 July.

[A.8] White P, Scott C. Contact Lenses & Solutions Summary. *Contact Lens Spectrum Supplement*. 2006 July.

[A.9] White P, Scott C. Contact Lenses & Solutions Summary. *Contact Lens Spectrum Supplement*. 2008 July.

[A.10] White P, Scott C. Contact Lenses & Solutions Summary. *Contact Lens Spectrum Supplement*. 2009 July.

[A.11] White P, Scott C. Contact Lenses & Solutions Summary. *Contact Lens Spectrum Supplement*. 2010 July.

APPENDIX B

CONTACT LENSES AVAILABLE ANNUALLY

Each year, new lenses are introduced to the market. In the following section, the lenses available for each year are listed, along with key characteristics, such as water content and Dk values. The appendix was compiled from data in references [**B.1-B.11**].

B.1. Tables.

Table B.1. Contact Lenses Available in 1990.

Manufacturer	Brand	Material	Water Content	Dk
Allergan Optical	Zero-6	Polymacon	38	8.4
	Z-plus			
	Mini-Lens			
	Hydron Spin-Cast			
Bausch and Lomb	Sofspin	Polymacon	38	8.5
	F			
	N			
	B3			
	B4			
	L3			
	L4			
	U3			
	U4			
	HO3			
	HO4			
	H3			
	H4			
	N			
	F3			
Ciba Vision Care	CibaSoft	Tefilcon	37.5	8
	AOSoft	Tetrafilcon A	42.5	8.5
	Softcon	Vifilcon A	55	16
	Softcon Aphakic		55	16
Coopervision	CooperThin	Polymacon	38	8.4
Lombert Lensees, LTD	Amsof Standard	Deltafilcon B	43	8.4
	Amsof Thin			
	Aquasight Standard			
	Aquasight Thin			
Metro Optics, Inc	Series M	Polymacon	38	8.4
	Metrosoft II			
	Metro 55	Methafilcon A	55	18.8
N&N Contact Lens International	Tresoft Standard	Ocufilcon A	46	16
	Tresoft Thin		46	
	AO Superthin	Tetrafilcon	42.5	8.5
Rynco-Fashion Contacts	Celusoft	Polymacon	38	8.4
Salvatori Ophthalmics	PDC Sof-form II			
	Sof-Form 67	Xyloform A		29
Softsite	Softsite	Helfilcon A	45	12.2
	Custom Pediatric			
	UTC			
Sola/Barnes-Hind	Softmate B	Bulfilcon A	45	12
	Hydrocurve II Regular			
	Hydrocurve II Large			
	CSI	Crofilcon A	38.5	13
	Aztech			
Strieter Labs	Accugel Standard	Droxifilcon	46.6	16
	Accugel Thin Div. 1			
	Div 2			
	Div. P Pediatric			
	Div. 4			
	Div. A			16
Vistakon	Hydromarc Standard	Etafilcon A	43	9
Welsey Jessen	Aquaflex Superthin Minus	Tetrafilcon A	42.5	8.5
	DuraSoft 2 (D2-T3)	Phemfilcon A	38	8.3
Ciba Vision Care	NewVues	Vilifilcon A		
Bausch and Lomb	SeeQuence	Polymacon	38	
Viskaton	Acuvue Disposalens	Etafilcon A	58	28
Allergan Optical	X-70	Lidofilcon A	70	31
	Zero-4	Polymacon	38	8.4
	Zero-4F			

Bausch and Lomb	B&L 70 Minus	Lidofilcon A	70	31
	B&L 70 Low Plus			
	CW79	Lidofilcon B	79	
	B&L 58	Etafilcon A	58	24
	O3	Polymacon	38	8.4
	O4			
	Silsoft Aphakic (Adult)	Elastifocon A	0.2	34
	Ailsoft Super Plus (Pediatric)			
Ciba Vision Care	Softcon EW cosmetic 1-30 days	Vilifilcon A	55	16
	Softcon EW Aphakic			
	CibaThin	Tefilcon	37.5	8
Coopervision	Permaflex UV	Vasurfilcon A	74	38.9
	Permaflex Thin-43	Tetrafilcon	43	8.5
Coopervision	Permalens	Perfilcon A	71	34
	Aphakic Permalens			
	Permalens T-lens (bandage)			
	Permalens XL			
	Permaflex Natural 74	Surfilcon A	74	38.9
Lombert Lenses	Genesis 4	Lidofilcon A	70	31
	Genesis 79 Bandage Lens Therapeutic	Lidofilcon B	79	
	Genesis 79 Aphakic			
	Genesis 79 Therapeutic			
	Genesis 79 Pediatric Aphakic			
N&N Contact Lens International	N&N PW (ped. Aphakia)	Lidofilcon B	79	31
	N&N PW			
	N&N 70	Lidofilcon A	70	31
Softsite	Softsite Ther	Helfilcon A	45	12.2
	Softsite Ther (aphakic)			
	Pediatric Custom UT			
	Bandage Lens			
Softsite		Helfilcon A	45	
Sola/Barnes-Hind	Hydrocurve Elite	Bulfilcon A	55	14.6
	Hydrocurve II			16
	Hydrocurve II High Plus			
	Custom Tinting Avail.			12
				16
	Hydrocurve II High Plus (non-core)			
			45	12
			45 55	12
	Soft Mate II		55	16
	Soft Mate I		45	12
	CSI T	Crofilcon A	38.5	13
Viskaton	Vistamarc	Etafilcon A	58	19.6
Wesley-Jessen	Durasoft 3 Flexiwear (D3-X4)	Phemfilcon A	55	16
	Durasoft 3 Flexiwear (D3-X4)			
Allergan Optical	Allergan Advent	Fluorofocon A (FFP)		10
	Ocusil	Nefocon A		16
	Hyperm	Telefocon A		18.5
	Hyperm II	Telefocon B		43.5
Coopervision	Aquaflex HGP	Itafocon A		14.6
Coopervision	Permaflex HGP	Itafocon B		28.7
Dankerlabs	Dura-Sil	Sil/Acryl Polymer		18
	Dura-Sil Bifocal			
	Meso	CAB		12.3
Firestone Optics	Firestone 721	Telefocon A	18.5	
	Firestone 721W	Nefocon A	16	
	Firestone 721 HDK	Telefocon B	43.5	
Fused Contacts of Chicago	Tangent Streak Bifocal	Optacryl K		32

GBF Contact Lens, Inc	Ellipsoidal (ELS)	Sil/Acryl Polymer		18
	Vari-Ellipsoidal (ELS II)			
	APA-III			
	APA-II			
	Kerato-Aspheric (KAS)			
GT Labs	Fluorex 700	Fluorine/Silicate/Acrylic		70
Optacryl, Inc	Optacryl 60	Sil/Acryl Polymer		18
	Optacryl K			32
	Optacryl K-II			
	UVAsorb-K UV absorbing			
	Optacryl II			18
Paragon Optical	Paraperm 02	Pasifocon A		15.6
	Paraperm EW	Pasifocon C		56
	FluoroPerm	Fluoro/Silicone-Acrylate		18
	FluoroPerm 30			30
	FluoroPerm 60			60
PDC	OxyFlow 39	Pasifocon B		39
	OxyFlow 56	Pasifocon C		56
	OxyFlow EW	Pasifocon C		56
	OxyFlow F	Fluoro/Sil/Acryl		18
Polymer Technology	Boston II Lens	Itafocon A		14.6
	Boston IV Lens	Itafocon B		28.7
	Equalens	Fluoro-Silicone Acrylate		71
Rynco-Fashion Contacts	RX-56	Porofocon A		12.3
	Celuflex			12.3
	TA (Thin Aphakic)			12.3
	Memlite			12.3
	Terget Bifocal RX-56			12.3
Salvatori Ophthalmics	Consta-Vu	Sil/Acryl or Fluorocarbon		18
	Comfort Control	Sil/Acryl or Fluorocarbon		18
Sola Barnes-Hind	Sila Rx (pediatric aphakic)	Dimefocon A (silicon)		13
	Saturn II	Butyl Styrene Center with Hydrophilic Skirt		14
	Polycon II	Silafocon A		12
	Polycon II XT (Extra Thick)	Silafocon A		12
	Polycon II Toric	Silafocon A		12
	Polycon HDK	Silafocon B		40
University Optical	Alges Boston Bifocal	Itafocon A		14.6
	Alges Boston Bifocal	Itafocon B		28.7
Wesley-Jessen	AIRLens	T-butyl Styrene (Arfocon A)		19.3
Bausch & Lomb	C.W. 79	MMA/NVP	79	
	Silsoft	Silicone		
EW Aphakic	Breger Mueller Welt	HEMA/NVP	45	
Sola Barnes-Hind	Hydrocurve II	HEMA/Acrylamide	55	
	Hydrocurve II 55			
N&N	N&N PW	MMA/NVP	79	
Coopervision	Permalens	HEMA/NVP/MMA	71	
CIBA Vision	Softcon	HEMA/PVP	55	
	Softcon EW	HEMA/PVP	55	
Softsite	Softsite	HEMA/NVP	45	
VisionTech	VT 79 Aphakic	MMA/NVP	79	
	VT 79 Pediatric Aphakic	HEMA /NVP	45	
	VT 45 Aphakic			
	VT 45 Aphakic Ultra-Thin			

Table B.2. Contact Lenses Available in 2000.

Group	Material	Water Content	Dk	Product
Low Water (<50% Water) Non-Ionic Polymer	Telfilcon	38	8	Bi-soft
				Cibasoft
				Cibathin
				Illusions
				Softint
				STD
				Torisoft
	Tetrafilcon A	43	9	AOSoft
				Aquaflex Standard
				Aquaflex Super Thin
				CooperClear
				Cooper Toric
				Preference
				Preference Toric
				Vantage Thin Accents
				Vantage
				Vantage Accents
				Vantage Thin
	Crofilcon	38	12	CSI
				CSI Toric
	Helfilcon A&B	45	12	Flexlens
				Gold Medalist Toric
				Optima Toric
				Simulvue
				Unilens
	Mafilcon	33	4	Menicon
	Polymacon	38	9	Alden Classic
				Allvue
				Cellusoft
				Clearview
				Cooper Thin
				CustomEyes 38
				Edge III
				Edge III Thin
				Edge III XT
				EpconSOFT
				Esstech PS
				Esstech PSD
				Esstech SV
				Horizon 38
Low Water (<50% Water) Non-Ionic Polymer	Polymacon	38	9	Hydron Biomedics 38
				Hydron Mini
				Hydron Zero 4
				Hydron Zero 6
				Hydro Toric
				Ideal Soft
				LL38
				Metrosoft II
				Multifocal
				Natural Touch
				Occasions
				Optima 38
				Optima FW
				PS-45 Multifocal
				SeeQuence
				Sof-form II
				Soflens
				Softics
				Softviews
				Westcon Toric

High Water >50% Water Non-Ionic Polymer	Lidofilcon B	79	38	CW 79
				LL 79
	Surfilcon A	74	35	Permaflex
	Lidofilcon A	70	31	Acti FRESH
				CV 70
				LL 70
				N&N 70
				Q&E 70
	Netrafilcon A	65		GentleTouch
	Hefilcon C	57		Gold Medalist Toric
	Alfafilcon A	66	32	Soflens66
	Omafilcon A	59	33	Proclear
	Vasurfilcon A	74	35	Permaflex UV Naturals
				Precision UV
	Hioxifilcon A	59	36	Satureyes Toric And Sphere
	Nelficon A	69	26	Focus Dailies
	Bilafilcon A	70	35	Soflens One Day
Low Water (<50% Water) Non-Ionic Polymer	Polymacon	38	9	Hydron Biomedics 38
				Hydron Mini
				Hydron Zero 4
				Hydron Zero 6
				Hydro Toric
				Ideal Soft
				LL38
				Metrosoft II
				Multifocal
				Natural Touch
				Occasions
				Optima 38
				Optima FW
				PS-45 Multifocal
				SeeQuence
				Sof-form II
				Soflens
				Softics
				Softviews
				Westcon Toric
High Water >50% Water Non-Ionic Polymer	Lidofilcon B	79	38	CW 79
				LL 79
	Surfilcon A	74	35	Permaflex
	Lidofilcon A	70	31	Acti FRESH
				CV 70
				LL 70
				N&N 70
				Q&E 70
	Netrafilcon A	65		GentleTouch
	Hefilcon C	57		Gold Medalist Toric
	Alfafilcon A	66	32	Soflens66
	Omafilcon A	59	33	Proclear
	Vasurfilcon A	74	35	Permaflex UV Naturals
				Precision UV
	Hioxifilcon A	59	36	Satureyes Toric And Sphere
	Nelficon A	69	26	Focus Dailies
	Bilafilcon A	70	35	Soflens One Day
Low Water (<50% Water) Ionic Polymer	Bufilcon A	45	12	Hydrocurve II 45
				Soft Mate
	Deltafilcon A	43	10	Amsoft
				Amsoft Thin
				Comfort Flex
				Custom Flex
				Metrosoft
				Soft Form Toric
	Droxifilcon A	47	17	Accugel
	Phemfilcon A	38	8	DuraSoft 2

				DuraSoft 2 Optifit
	Ocufilcon	44	16	Specialty-T-FRP
	Balafilcon A	36	99	PureVision
High Water (>50% Water) Ionic Polymer	Bufilcon A	55	16	Hydrocurve II
				Hydrocurve II 55 Bifocal
	Perfilcon	71	34	Permalens
				Permalens XL
				Permalens Therapeutic
				Permalens Aphakic
	Etafilcon A	58	28	Acuvue
				1-Day Acuvue
				Acuvue 2
				Acuvue Bifocal
				Acuvue Toric
				Surevue
	Focofilcon A	55	16	Fre-Flex
	Ocufilcon B	53	16	Continental
				Ocu-Flex 53
	Ocufilcon C	55	16	UCL 55
				UCL-Pediatric
	Ocufilcon D	55	19.7	Hydron Biomedics 55
				Hydron Proactive 55
	Ocufilcon E	65	22	Ocuflex 65
	Phemfilcon A Methafilcon A	55	16	DuraSoft 3
				DuraSoft 3 Optifit
		55	18	Additions
				Biocurve Toric & Sphere
				Eclipse
				Edge III 55
		55	18	Flexlens Aphakic
				Flexlens Customs Spheres
				Flexlens Torics
				Frequency 55 Toric & Sphere
				Horizon 55 Bi-Con
				Kontur
				LifeStyle Frequency
				LL 55
				Metro 55
				Multiples Toric & Sphere
				Revolution
				Sof-form 55
				Specialty Choice AB
				Specialty Progressive
				SunFlex
				SunFlex Prism Ballast
				Sunsoft Aphakic
				Sunsoft Toric 15.0
				Westcon Toric & Sphere
	Methafilcon B	55	18	Frequency 55 Toric
				Hydrasoft Sphere
				Hydrasoft Toric
	Vilfilcon A	55	16	Focus
				Softcon
				Spectrum
				Spectrum Bifocal
				Spectrum Toric
				NewVues
				Focus Toric
				Softcon EW

Table B.3. Contact Lenses Available in 2001.

Group	Material	Water Content	Dk	Product
Group 1: Low Water (<50% Water) Non-Ionic Polymers	Tefilcon	38	8.9	Bi-Soft
				CibaSoft
				Cibathin
				Illusions
				Softint
				STD
				Torisoft
	Tetrafilcon A	43	9	AOSoft
				Aquaflex Standard
				Aquaflex Super Thin
				Cooper Clear
				Cooper Toric
				Preference
				Preference Toric
				Vantage Thin Accents
				Vantage Thin
				Vantage Accents
				Vantage
	Crofilcon	38	13	CSI
				CSI Toric
	Helfilcon A&B	45	12	Flexlens
				Flexlens Toric
				Flexlens Aphakic
				Gold Medalist Toric
				Optima Toric
				SimulVue
				Unilens
	Mafilcon	33	4	Menicon
	Polymacon	38	9	Alden Classic
				Allvue
				Cellusoft
				ClearView
				CooperThin
				Custom Eyes 38
Group 1: Low Water (<50% Water) Non-Ionic Polymers	Polymacon	38	9	Edge III
				Edge III Thin
				Edge III XT
				EpconSOFT
				Esstech PS
				Esstech PSD
				Esstech SV
				Horizon 38
				Hydron Biomedics 38
				Hydron Mini
				Hydron Zero 4
				Hydron Zero 6
				Hydron Toric
				Ideal Soft
Group 2 High Water (>50% Water) Non-Ionic Polymer	Lidofilcon B	79	38	CW 79
				LL 79
	Surfilcon A	74	35	Permaflex
	Lidofilcon A	70	31	ActiFRESH
				CV 70
				LL 70
				N&N 70
				Q&E 70
	Netrafilcon A	65	34.5	GentleTouch
	Hefilcon C	57		Gold Medalist Toric
	Alfafilcon A	66	32	Soflens 66
	Omafilcon A	59	33	Proclear

				Proclear Tailor Made Toric
				Proclear Compatibles (62%)
	Vasurfilcon A	74	39.1	Permaflex UV Naturals
				Precision UV
	Hioxifilcon A	59	36	Satureyes Toric and Sphere
	Nelfilcon A	69	26	Focus Dailies
	Hilafilcon A	70	35	Soflens OneDay
Group 3 Low Water (<50% Water) Ionic Polymer	Bufilcon A	45	16	Hydrocurve II 45
				Soft Mate 8
	Deltafilcon A	43	10	Amsoft
				Amsoft Thin
				Comfort Flex
				Custom Flex
				Metrosoft
				Soft Form Toric
	Phemfilcon A	38	9	Durasoft 2
				Durasoft 2 Optifit
	Ocufilcon	44	16	Speciality-T-FRP
	Balafilcon A	36	99	PureVision
Group 4: High Water (>50% Water) Ionic Polymer Group 4	Bufilcon A	55	16	Hydrocurve II
				Hydrocurve II 55 Bifocal
				Hydrocurve 3 Toric
				Sofmate II
	Perfilcon	71	34	Permalens
				Permalens XL
				Permalens Therapeutic
				Permalens Aphakic
	Etafilcon A	58	28	Acuvue
				1-Day Acuvue
				Acuvue 2
				Acuvue Bifocal
				Acuvue Toric
				Surevue
	Focofilcon A	55	16	Fre-Flex
	Ocufilcon B	53	16	Continental
				Ocu-Flex 53
	Ocufilcon C	55	16	UCL 55
				UCL Pediatric
	Ocufilcon D	55	19.7	Hydron Biomedics 55
				Hydron Proactive
	Ocufilcon E	65	22	Ocuflex 65
	Phemfilcon A	55	16	Durasoft 3
				Durasoft 3 Optifit
				Freshlook
				Freshlook Toric
				Prosoft
				WildEyes
	Methafilcon A	55	18	Additions
				Biocurve Toric & Sphere
				Eclipse
				Edge III 55
				Frequency 55 Toric & Sphere
				Horizon 55 Bi-Con
				Kontur
				LifeStyle Frequency
				LL 55
				Metro 55
				Multiples Toric & Sphere
				Revolution
				Sof-Form 55
				Specialty Choice A.B.
				Specialty Progressive
				SunFlex
				Sunflex Prism Ballast
				Sunsoft Aphakic
				Sunsoft Toric 15.0

				Westcon Toric & Sphere
	Methafilcon B	55	18	Frequency 55 Toric & Sphere
				Hydrasoft Sphere
				Hydrasoft Toric
	Vilifilcon A	55	16	Focus 1-2 Week
				Focus Monthly
				Focus Progressives
				Focus Toric Monthly
				Softcon
				Softcon EW

Table B.4. Contact Lenses Available in 2003.

Group	Material	Water Content	Dk	Product
Group 1: Low Water (<50% Water) Non-Ionic Polymers	Tefilcon	38	8.9	Cibasoft
				Illusions
				Softint
				STD
				Torisoft
	Tetrafilcon A	43	9	Aquaflex Standard
				Aquaflex Super thin
				CooperClear
				Cooper Toric
				Preference
				Preference Toric
				Vantage Thin
				Vantage Thin
				Vantage Accents
				Vantage Thin Accents
	Crofilcon	38	13	CSI
				CSI Toric
	Helfilcon A&B	45	12	Flexlens
				Flexlens Toric
				Flexlens Aphakic
				Gold Medalist Toric
				Optima Toric
				Simulvue
				Unilens
	Mafilcon	33	4	Menicon
	Polymacon	38	9	Alden classic
				Allvue
				Biomedics 38
				Cellusoft
				Clearview
				CooperThin
				CustomEyes 38
				Edge III Proactive
				Edge III Proactive XT
				Edge III Standard
				Edge III Thin
				EpconSOFT
				Esstech PS
				Esstech PSD
				Esstech SV
	Polymacon	38	9	Horizon 38
				Hydron Echelon
				Hydron Mini
				Hydron Zero 4 SofBlue
				Hydron Zero 6 SofBlue
				Hydron Versa Scribe
				Ideal Soft
				LifeStyle MV2
				LifeStyle Xtra
				LifeStyle 4Vue
				LifeStyle Toric Bifocal
				LL38
				Metrosoft II Multifocal
				Natural Touch
				Occasions
				Optima 38
				Optima FW
				PS-45 Multifocal
				SeeQuence
				Sof-Form II
				Soflens
				Softics
				SoftView
				Westcon Toric

	Hioxifilcon B	49	15	Essential Soft Toric Multifocal
				Ocu-Flex Plus
				Quattro
	Lotrafilcon A	24	140	Focus Night and Day
Group 2: High Water (>50% Water) Non-Ionic Polymers	Lidofilcon B	79	38	CW 79
				LL 79
	Surfilcon A	74	35	Permaflex
	Lidofilcon A	70	31	Acti Fresh
				CV 70
				LL 70
				N&N 70
				Q&E 70
	Netrafilcon A	65	34.5	GentleTouch
	Hefilcon C	57		Gold Medalist Toric
	Alfafilcon A	66	32	Soflens 66
	Omafilcon A	59	33	Proclear
				Proclear Tailor Made Toric
				Proclear Compatibles (62%)
	Vasurfilcon A	74	39.1	Permaflex UV Naturals
				Precision UV
	Hioxifilcon A	59	36	Satureyes Toric and Sphere
	Nelfilcon A	69	26	Focus Dailies
				Focus Dailies Toric
				Focus Dailies Progressive
	Hilafilcon A	70	35	Soflens One Day
	Hilafilcon B	59	22	Soflens 59
Group 3: Low Water (<50% Water) Ionic Polymers	Bufilcon A	45	16	Hydrocurve II 45
				Soft Mate B
	Deltafilcon A	43	10	Amsoft
				Amsoft Thin
				Comfort Flex
				Custom Flex
				Metrosoft
				Soft Form Toric
	Phemfilcon A	38	9	Durasoft 2
				DuraSoft 2 Optifit
Group 4: High Water (>50% Water) Ionic Polymers	Bufilcon A	55	16	Hydrocurve II
				Hydrocurve II 55 Bifocal
				Hydrocurve 3 Toric
				Softmate II
	Perfilcon	71	34	Permalens
				Permalens XL
				Permalens Therapeutic
				Permalens Aphakia
	Etafilcon A	58	28	Acuvue
				1-Day Acuvue
				Acuvue 2
				Acuvue 2 Colours
				Acuvue Bifocals
				Acuvue Toric
				Surevue
	Focofilcon A	55	16	Fre-Flex
	Ocufilcon B	53	16	Continental
				Ocu-Flex 53
	Ocufilcon C	55	16	UCL 55
				UCL Pediatric
	Ocufilcon D	55	19.7	Biomedics Colors
				Biomedics Toric
				Color Girl Colors
				Biomedics 55
				Proactive 55
	Ocufilcon E	65	22	Ocuflex 65
	Ocufilcon F	60	24.3	Hydrogenics 60 UV
	Phemfilcon A	55	16	Durasoft 3
				Durasoft 3 Optifit
				Freshlook
				Freshlook Toric

				Prosoft
				Wildeyes
	Methafilcon A	55	18	Biocurve Toric and Sphere
				Choice A.B
				Edge III 55
				Flexlens
				Frequency 55 Toric & Sphere
				Horizon 55 Bi-Con
	Methafilcon A	55	18	Kontur
				LifeStyle Frequency
				LL 55
				Metro 55
				Sof-Form 55
				Sunsoft Additions
				Sunsoft Eclipse
				Sunsoft Multiples Toric & Sphere
				Sunsoft Revolution
				Sunsoft SunFlex
				Sunsoft SunFlex Prism Ballast
				Sunsoft Sphakic
				Sunsoft Toric 15.0
				Westcon Toric & Sphere
	Methafilcon B	55	18	Frequency 55 Toric
				Hydrasoft Sphere
				Hydrsoft Toric
	Vilifilcon A	55	16	Focus 1-2 Week
				Focus Monthly
				Focus Progressives
				Focus Toric Monthly
				Softcon
				Softcon EW

Table B.5. Contact Lenses Available in 2004.

Description	Material	Water Content	Dk	Brand
Low Water (<50% Water) Nonionic Polymers	Tefilcon	38	8.9	Cibasoft
				Illusions
				Softint
				STD
				Torisoft
	Tetrafilcon A	43	9	CooperClear
				Cooper Toric
				Preference
				Preference Toric
				Vantage Thin Accents
				Vantage
				Vantage Accents
				Vantage Thin
	Crofilcon	38	13	CSI Toric
				CSI
	Helfilcon A&B	45	12	Flexlens
				Flexlens Toric
				Flexlens Aphakic
				Gold Medalist Toric
				Optima Toric
				Simulvue
				Unilens
	Mafilcon	33	4	Menicon
	Polymacon	38	9	Alden Classic
				Biomedics 38
				Allvue
				Cellusoft
				Clearview
				Cooperthin
Low Water (<50% Water) Nonionic Polymers	Polymacon	38	9	CustomEyes 38
				Edge III Proactive
				Edge III Proactive XT
				Edge III Standard
				Edge III Thin
				EpconSOFT
				Esstech PS
				Esstech PSD
				Esstech SV
				Horizon 38
				Hydron Echelon
				Hydron Mini
				Hydron Zero 4 SofBlue
				Hydron Zero 6 SofBlue
				Hydron Versa Scribe
				Ideal Soft
				Lifestyle MV2
				Lifestyle Xtra
				Lifestyle 4Vue
				Lifestyle Toric Bifocal
				LL38
				Metrosoft II Multifocal
				Natural Touch
				Occasions
				Optima 38
				PS-45 Multifocal
				SeeQuence
				Sof-Form II
				Soflens
				Soflens 38
				Softics
				SoftView
				Westcon Toric

	Hioxifilcon B	49	15	Essential Soft Toric Multifocal
				Flexlens
				Quattro
				Ocu-Flex Plus
	Lotrafilcon A	24	140	Focus Night & Day
	Galyfilcon A	47	60	Acuvue Advance
High Water (>50% Water) Nonionic Polymers	Lidofilcon B	79	38	CW 79
				LL 79
	Surfilcon A	74	35	Permaflex
	Lidofilcon A	70	31	Acti Fresh
				CV 70
				LL 70
				N&N 70
				Q&E 70
	Netrafilcon A	65	34.5	GentleTouch
	Hefilcon C	57	-	Gold Medalist Toric
	Alfafilcon A	66	32	Soflens 66
	Omafilcon A	59	33	Proclear
				Proclear Tailor Made Toric
				Proclear Compatibles
	Vasurfilcon A	74	39.1	Permaflex UV Naturals
				Precision UV
	Hioxifilcon A	59	36	Extreme H2O G-60 S
				Extreme H2O G-60 S-Xtra
				Satureyes Toric and Sphere
	Nelfilcon A	69	26	Focus Dailies
				Focus Dailies Toric
				Focus Dailies Progressive
	Hilafilcon A	70	35	Soflens One Day
	Hilafilcon B	59	22	Soflens 59
	Acofilcon A	58	25.5	Flexlens
Low Water (<50% Water) Ionic Polymers	Bufilcon A	45	16	Hydrocurve II 45
		45	16	Soft Mate B
	Deltafilcon A	43	10	Amsoft
				Amsoft Thin
				Comfort Flex
				Custom Flex
				Metrosoft
				Soft Form Toric
	Phemfilcon A	38	9	DuraSoft 2
				DuraSoft 2 Optifit
High Water (>50% Water) Ionic Polymers	Bulfilcon A	55	16	Hydrocurve II
				Hydrocurve II 55 Bifocal
				Hydrocurve 3 Toric
				Softmate II
	Perfilcon	71	34	Permalens
				Permalens XL
				Permalens Therapeutic
				Permalens Aphakic
	Etafilcon A	58	28	Acuvue
				1-Day Acuvue
				Acuvue 2
				Acuvue 2 Colours
				Acuvue Bifocal
				Acuvue Toric
				Surevue
	Focofilcon A	55	16	Fre-Flex
	Ocufilcon B	53	16	Continental
				Ocu-Flex 53
	Ocufilcon C	53	16	UCL 55
				UCL-Pediatric
	Ocufilcon D	55	16	Biomedics Colors
	Ocufilcon D	55	16	Biomedics 55 Premier
				Color Girl Colors
				Biomedics 55
				Biomedics Toric
			19.7	Proactive 55

	Ocufilcon E	65	22	OcuFlex 65
	Ocufilcon F	60	24.3	Hydrogenic 60 UV
	Phemfilcon A	55	16	DuraSoft 3
				DuraSoft 3 OptiFit
				Freshlook
				Freshlook Toric
				Wildeyes
	Methafilcon A	55	18	Biocurve Toric & Sphere
				Choice A.B.
				Edge III 55
				Flexlens
				Frequency 55 Toric & Sphere
				Horizon 55 Bi-Con
				Kontur
				LL 55
				Metro 55
				Sof-form 55
				Sunsoft Additions
				Sunsoft Eclipse
				Sunsoft Multiples Toric & Sphere
				Sunsoft SunFlex
				Sunsoft SunFlex Prism Ballast
				Sunsoft Aphakic
				Sunsoft Toric 15.0
				Westcon Toric & Sphere
	Methafilcon B	55	18	Frequency 55 Toric
				Hydrasoft Sphere
				Hydrasoft Toric
	Vilfilcon A	55	16	Focus 1-2 Week
				Focus Monthly
				Focus Progressives
				Focus Toric Monthly
				Softcon
				Softcon EW

Table B.6. Contact Lenses Available in 2005.

Description	Material	Water Content	Dk	Brand
Low Water (<50% Water) Nonionic Hydrogel Polymers	Tefilcon	38	8.9	Illusions
				Softint
				STD
				Cibasoft
				Torisoft
				LL Bifocal
	Tetrafilcon A	43	9	CooperClear
				Cooper Toric
				Preference
				Preference Toric
				Vantage Thin Accents
				Vantage
				Vantage Accents
				Vantage Thin
	Crofilcon	38	13	CSI
				CSI Toric
	Helfilcon A&B	45	12	Flexlens
				Flexlens Toric
				Flexlens Aphakic
				Gold Medalist Toric
				Optima Toric
				Simulvue
				Unilens
	Mafilcon	33	4	Menicon
	Polymacon	38	9	Alden Classic
				Allvue
				Biomedics 38
				Cellusoft
				Clearview
				Cooperthin
				CustomEyes 38
				Edge III Proactive
				Edge III Proactive XT
				Edge III Standard
				Edge III Thin
				EpconSOFT
				Esstech PS
				Esstech PSD
				Esstech SV
				Horizon 38
				Hydron Echelon
				Hydron Mini
	Polymacon	38	9	Hydron Zero 4 SofBlue
				Hydron Zero 6 SofBlue
				Hydron Versa Scribe
				Ideal Soft
				LifeStyle MV2
				LifeStyle Xtra
				LifeStyle 4Vue
				LifeStyle Toric Bifocal
				LL38
				Metrosoft II Multifocal
				Natural Touch
				Occasions
				Optima 38
				PS-45 Multifocal
				SeeQuence
				Similvue 38
				Sof-form II
				Soflens
				Soflens 38
				Softics

				SoftView
				Unilens 38
				Westcon Toric
	Hioxifilcon B	49	15	Alden HP
				Essential Soft Toric Multifocal
				Flexlens
				Quattro
				Ocu-flex Plus
	Lotrafilcon A	24	140	Focus Night & Day
	Lotrafilcon B	38	110	O2Optix
	Galyfilcon A	47	60	Acuvue Advance
				Acuvue Advance for Astigmatism
	Senofilcon A	38	103	Acuvue Oasys
High Water (>50% Water) Nonionic Hydrogel Polymers	Lidofilcon B	79	38	CW 79
		79	38	LL 79
	Surfilcon A	74	35	Permaflex
	Lidofilcon A	70	31	Acti Fresh
		70	31	CV 70
	Lidofilcon A	70	31	LL 70
				N&N 70
				Q&E 70
				GentleTouch
	Hefilcon C	57		Gold Medalist Toric
	Alfafilcon A	66	32	Soflens 66
	Omafilcon A	59	33	Proclear
				Proclear Tailor Made Toric
				Proclear Compatibles
	Vasurfilcon A	74	39.1	Permaflex UV Naturals
				Precision UV
	Hioxifilcon A	59	36	Exteme H2O G-59 S-Thin
				Exteme H2O G-59 S-Xtra
				Satureyes Toric and Sphere
				Biocurve Gold Sphere and Toric
	Nelfilcon A	69	26	Focus Dailies
				Focus Dailies Toric
				Focus Dailies Progressive
				Synergy
				Triton
	Hilafilcon A	70	35	Soflens One Day
	Hilafilcon B	59	22	Soflens 59
	Acofilcon A	58	25.5	Flexlens
Low Water (<50% Water) Ionic Hydrogel Polymers	Bufilcon	45	16	Hydrocurve II 45
				Soft Mate B
	Deltafilcon A	43	10	Amsoft
				Amsoft Thin
				Comfort Flex
				Custom Flex
				Metrosoft
				Soft Form Toric
	Phemfilcon A	38	9	DuraSoft 2
				DuraSoft 2 OptiFit
	Balafilcon A	36	90	PureVision
				PureVision Toric
High Water (>50% Water) Ionic Hydrogel Polymers	Bufilcon A	55	16	Hydrocurve II
				Hydrocurve II 55 Bifocal
				Hydrocurve 3 Toric
				Softmate II
	Perfilcon	71	34	Permalens
				Permalens XL
				Permalens Therapeutic
				Permalens Aphakic
	Etafilcon A	58	28	Acuvue
				1-Day Acuvue
				Acuvue 2
				Acuvue 2 Colours
				Acuvue Bifocal
				Acuvue Toric

				Surevue
	Focofilcon A	55	16	Fre-Flex
	Ocufilcon B	53	15	Continental
				Ocu-Flex 53
	Ocufilcon C	55	16	UCL 55
				UCL-Pediatric
	Ocufilcon D	55	19.7	Biomedics Colors
				Biomedics 55 Premier
				Color Girl Colors
				Biomedics 55
				Biomedics Toric
				ProActive 55
	Ocufilcon E	65	22	OcuFlex 65
	Ocufilcon F	60	24.3	Hydrogenics 60 UV
	Phemfilcon A	55	16	DuraSoft 3
				DuraSoft 3 OptiFit
				Freshlook
				Freshlook Toric
				Wildeyes
	Methafilcon A	55	18	Biocurve Advanced Asphic
				Biocurve 1-Day
				Biocurve Toric & Sphere
				C-Vue 55
				Choice A.B.
	Methafilcon A	z	18	Edge III 55
				Flexlens
				Frequency 55 Toric & Sphere
				Horizon 55 Bi-Con
				Kontur
				LL 55
				Metro 55
				Sof-form 55
				Sunsoft Additions
				Sunsoft Eclipse
				Sunsoft Multiples Toric & Sphere
				Sunsoft Revolution
				Sunsoft SunFlex
				Sunsoft Sunflex Prism Ballast
				Sunsoft Aphakic
				Sunsoft Toric 15.0
				Westcon Toric & Sphere
	Methafilcon B	55	18	Frequency 55 Toric
				Hydrasoft Sphere
				Hydrsoft Toric
	Vilfilcon A	55	16	Focus 1-2 Week
				Focus Monthly
				Focus Progressives
				Focus Toric Monthly
				Softcon
				Softcon EW

Table B.7. Contact Lenses Available in 2006.

FDA Division	Description	Material	Water Content	Dk	Brand
Division I	Low Water (<50% Water) Non Ionic Hydrogel Polymers	Tefilcon	38	8.9	Cibasoft
					Illusions
					Softint
					STD
					Torisoft
					LL Bifocal
		Tetrafilcon A	43	9	Cooper Clear
					Cooper Toric
					Preference
					Preference Toric
					Vantage Thin Accents
					Vantage
					Vantage Accents
					Vantage Thin
		Crofilcon	38	13	CSI
					CSI Toric
		Helfilcon A&B	45	12	Continental Toric
					Flexlens
					Flexlens Toric
					Flexlens Aphakic
					Gold medalist Toric
					Optima Toric
					Simulvue
					Unilens
		Mafilcon	33	4	Menicon
		Polymacon	38	9	Alden Classic
					Allvue
					Biomedics 38
					Cellusoft
					Clearview
					Cooper Thin
					Custom Eyes 38
					Edge III Proactive
					Edge III Proactive XT
					EpconSOFT
					Esstech PS
					Esstech PSD
					Esstech SV
					Horizon 38
Division I	Low Water (<50% Water) Non Ionic Hydrogel Polymers				Hydron Echelon
					Hydron Mini
					Hydron Zero 4 sofBlue
					Hydron Zero 6 SofBlue
					Hydron Versa Scribe
					Ideal Soft
					Lifestyle MV2
					LifeStyle Xtra
					LifeStyle 4Vue
					Lifestyle Toric Bifocal
					LL38
					Metrosoft II Multifocal
					Natural Touch
					Occasions
					Optima 38
					PS-45 Multifocal
					SeeQuence
					Simulvue 38
					Sof-Form II
					Soflens
					Soflens 38

					Softics
					Softview
					Unilens 38
					Westcon Toric
		Hioxifilcon B	49	15	Alden HP
					Essential Soft Toric Multifocal
					Flexlens
					Ocu-Flex Plus
					Quattro
		Lotrafilcon A	24	140	Night & Day
		Lotrafilcon B	38	110	O2Optix
		Galyfilcon A	47	60	Acuvue Advance
					Acuvue Advance for Astigmatism
		Senofilcon A	38	103	Acuvue Oasys
Division II	High Water (>50% Water) Non-Ionic Hydrogel Polymers	Lidofilcon B	79	38	CW 79
					LL 79
		Surfilcon A	74	35	Permaflex
		Lidofilcon A	70	31	Actifresh 400
					CV 70
					LL 70
					N&N 70
					Q&E 70
		Netrafilcon A	65	34.5	GentleTouch
		Hefilcon C	57		Gold medalist Toric
		Alfafilcon A	66	32	Soflens 66
		Omafilcon	59	33	Biomedics XC
					Proclear Multifocal
					Proclear Sphere
					Proclear Tailor Made Toric
					Proclear Toric
		Vasurfilcon A	74	39.1	Permaflex UV Naturals
					Precision UV
		Hioxifilcon A	59	28	Extreme H2O G-59 S-Thin
					Extreme H2O G-59 S-Xtra
					Satureyes Toric & Sphere
					Biocurve Gold Sphere and Toric
		Hioxifilcon D	54	21	Extreme H2O 54% 13.6
		Nelfilcon A	69	26	Focus Dailies
					Focus Dailies Toric
					Synergy
					Triton
					Focus Dailies Progressive
					Freshlook One-Day
		Hilafilcon A	70	35	Soflens One Day
		Hilafilcon 8	59	22	Soflens 59
		Acofilcon A	58	25.5	Flexlens
Division III	Low Water (<50% Water) Ionic Hydrogel Polymers	Bufilcon A	45	16	Hydrocurve II 45
					SoftMate B
		Deltafilcon A	43	10	Amsoft
					Amsoft Thin
					Comfort Flex
					Custom Flex
					Metrosoft
					Soft Form toric
		Phemfilcon A	38	9	Durasoft 2
					Durasoft 2 Optifit
		Balafilcon A	36	112	PureVision
					PureVision Multifocal
					PureVision Toric
Division IV	High Water (>50% Water) Ionic Hydrogel Polymers	Bufilcon A	55	16	Hydrocurve II
					Hydrocurve II 55 Bifocal
					Hydrocurde 3 toric
					Softmate II
		Perfilcon	71	34	Permalens
					Permalens XL
					Permalens Therapeutic

					Permalens Aphakic
		Etafilcon A	58	28	Acuvue
					1-Day Acuvue
					Acuvue 2
					Acuvue 2 Colours
					Acuvue Bifocal
					Acuvue Toric
					Surevue
		Focofilcon A	55	16	Fre-Flex
		Ocufilcon B	53	16	Continental
					Ocuflex 53
		Ocufilcon C	55	16	UCL 55
					UCL-Pediatic
		Ocufilcon D	55	19.7	Biomedics Colors
					Biomedics 55
					Biomedics 55 Premier
					Biomedics Toric
					Proactive 55
		Ocufilcon E	65	22	Ocuflex 65
		Ocufilcon F	60	24.3	Hydrogenics 60 Uv
		Phemfilcon A	55	16	Durasoft 3
					Durasoft 3 Optifit
					Freshlook
					Freshlook Toric
					Wildeyes
		Methafilcon A	55	18	Biocurve Advanced Asphic
					Biocurve 1-Day
					Biocurve Toric & Sphere
					C-Vue 55
					Choice A.B.
					Edge III 55
					Flexlens
					Frequency 55 Toric & Sphere
					Horizon 55 Bi-Con
					Kontur
					LL 55
					Metro 55
					New Horizons
					Sof-Form 55
		Methafilcon B	55	18	Frequency 55 Toric
					Hydrasoft Sphere
					Hydrasoft Toric
		Vilifilcon A	55	16	Focus 1-2 Week
					Focus Monthly
					Focus Progressives
					Focus Toric Monthly
					Softcon
					Softcon EW

Table B.8. Contact Lenses Available in 2008.

FDA Division	Description	Material	Water Content	Dk	Brand
Division I	Low Water (>50% Water) Nonionic Hydrogel Polymers	Tefilcon	38	8.9	Cibasoft
					Illusions
					Softint
					STD
					Torisoft
					LL Bifocal
		Tetrafilcon A	43	9	CooperClear
					Cooper Toric
					Preference
					Preference Toric
					Vantage Thin Accents
					Vantage
					Vantage Accents
					Vantage Thin
		Crofilcon	38	13	CSI Toric
		Helfilcon A&B	45	12	Continental Toric
					Flexlens
					Flexlens Toric
					Flexlens Aphakic
					Gold Medalist Toric
					Optima Toric
					Simulvue
					Unilens
		Mafilcon	33	4	Menicon
		Polymacon	38	9	Allvue
					Biomedics
					Cellusoft
					Clearview
					CooperThin
					Custom Eyes 38
					EpconSoft
					Esstech PS
					Esstech PSD
					Esstech SV
					Horizon 38
					Hydron Mini
					Hydron Zero 4 SofBlue
					Hydron Zero 6 SofBlue
					Hydron Versa Scribe
					Ideal Soft
					Lifestyle MV2
Division I	Low Water (>50% Water) Nonionic Hydrogel Polymers	Polymacon	38	9	Life Style Xtra
					LifeStyle Toric Bifocal
					LL38
					Metrosoft II Multifocal
					Natural Touch
					Occasions
					Optima 38
					PS-45 Multifocal
					Simulvue 38
					Sof-form II
					Soflens
					Soflens 38
					Softics

					Softview
					Unilens 38
					Westcon Toric
		Hioxifilcon B	49	15	Alden HP
					Essential Soft Toric Multifocal
					Flexlens
					Ocu-Flex Plus
					Quatrro
		Lotrafilcon A	24	140	Night and Day
		Lotrafilcon B	38	110	O2Optix
					Air Optix Aqua
					Air Optix for Astigmatism
		Galyfilcon A	47	60	Acuvue Advance
					Acuvue Advance for Astigmatism
		Senofilcon A	32	82	O2Optix Custom
		Comfilcon A	48	128	Biofinity
		Enfilcon A	46	100	Avaira
		Lidofilcon B	79	38	CW 79
					LL 79
		Surfilcon A	74	35	Permaflex
		lidofilcon A	70	31	ActiFresh 400
Division II	High Water (>50% Water) Nonionic Hydrogel Polymers	Lidofilcon A	70	31	CV 70
					LL 70
					N&N 70
					Q&E 70
		Alfafilcon A	66	32	Soflens Toric
		Omafilcon A	59	33	Biomedics EP
					Biomedics XC
					ProcleaR 1-Day
					Proclear Multifocal
Division II	Group 2: High Water (>50% Water) Nonionic Hydrogel Polymers	Omafilcon A	59	33	Proclear Multifocal Toric
					Proclear Sphere
					Proclear Toric
		Vasurfilcon A	74	39.1	Permaflex UV Naturals
					Precision UV
		Hioxifilcon A	59	28	Extreme H2O Thin
					Extreme H2O 59% Extra
					SaturEyes Progressive
					SaturEyes Toric and Sphere
					Biocurve Gold Sphere and Toric
		Hioxfilcon D	54	21	Extreme H2O 54%
					Extreme H2O 54% Toric
		Nelfilcon A	69	26	Dailies Aquacomfort Plus
					Focus Dailies
					Focus Dailies Toric
					Focus Dailies Progressive
					Freshlook One-Day
					Synergy
					Triton
		Hilafilcon A	70	35	Soflens Daily Disposable

					Soflens One Day
		Acofilcon A	58	25.5	Flexlens
Division III	Low Water (<50% H2O) Ionic Hydrogel Polymers	Bufilcon A	45	16	Hydrocurve II 45
					Soft Mate B
		Deltafilcon A	43	10	Amsoft
					Amsoft Thin
					Comfort Flex
					Custom Flex
					Metrosoft
					Soft Form Toric
		Phemfilcon A	38	9	Durasoft 2
					Durasoft 2 Optifit
		Balafilcon A	36	112	PureVision
					PureVision Multi-Focal
					Pure Vision Toric
Division IV	High Water (>50% Water) Ionic Hydrogels Polymers	Bufilcon A	55	16	Hydrocurve II
					Hydrocurve II 55 Bifocal
					Hydrocurve 3 Toric
					Softmate II
		Perfilcon	71	34	Permalens
					Permalens XL
					Permalens Therapeutic
					Permalens Aphakic
	High Water (>50% Water) Ionic Hydrogels Polymers	Etafilcon A	58	28	Acuvue
					1-Day Acuvue
					1-Day Acuvue Moist
					Acuvue 2
					Acuvue 2 Colours
					Acuvue Bifocal
		Focofilcon A	55	16	Fre-Flex
		Ocufilcon B	53	16	Clearsight 1 Day
					Continental
					Ocu-Flex 53
		Ocufilcon C	55	16	UCL 55
					UCL-Pediatric
		Ocufilcon D	55	19.7	Biomedics 55
					Biomedics 55 Premier
					Biomedics Toric
					ClearSight 1-Day toric
		Ocufilcon E	65	22	Ocuflex 65
		Ocufilcon F	60	24.3	Hydrogenics 60UV
		Phemfilcon A	55	16	Durasoft 3
					Durasoft 3 Optifit
					Freshlook
					Freshlook Toric
					Wildeyes
		Methafilcon A	55	18	Biocurve Advanced Aspheric
					Biocurve 1-Day
					Biocurve Toric and Sphere
					C-Vue 1 Day ASV
					C-Vue 55
					Edge III 55
					Flexlens

					Frequency 55 Toric & Sphere
					Horizon 55 Bi-Con
					Kontur
					LL 55
					Metro 55
					New Horizons
					Sof-Form 55
					Vertex Sphere
					Vertex Toric
		Methafilcon B	55	18	Frequency 55 Toric
					Hydrasoft Sphere
					Hydrasoft Toric
Division IV	High Water (>50% Water) Ionic Hydrogels Polymers	Vilfilcon A	55	16	Focus 1-2 Week
					Focus Monthly
					Focus Progressives
					Focus Toric Monthly
					Soft 55
					Soft 55 EW
					Softcon

Table B.9. Contact Lenses Available in 2009.

Description	Material	Water Content	Dk	Brand
Low Water (<50% Water) Nonionic Hydrogel Polymers	Tefilcon	38	8.9	Cibasoft
				Illusions
				Softint
				STD
				Torisoft
				LL Bifocal
	Tetrafilcon A	43	9	Cooper Clear
				Cooper Toric
				Preference
				Preference Toric
				Vantage Thin Accents
	Crofilcon	38	13	CSI
				CSI Toric
	Helfilcon A&B	45	12	Continental Toric
				Flexlens
				Flexlens Toric
				Flexlens Aphakic
				Gold Medalist Toric
				Optima Toric
				Simulvue
				Unilens
	Mafilcon	33	4	Menicon
	Polymacon	38	9	Allvue
				Biomedics 38
				Cellusoft
				Clearview
				Cooperthin
				CustomEyes 38
				EconSOFT
				Esstech PS
				Esstech PSD
				Esstech SV
				HD
				HD-T
				HDX
				HDX-T
				Horizon 38
				Hydron Mini
				Hydron Zero 4 SofBlue
				Hydron Zero 6 SofBlue
				Hydron Versa Scribe
				Lifestyle MV@
				Ideal Soft
				Lifestyle Xtra
				LifeStyle 4 Vue
				Lifestyle Toric Bifocal
				LL38
				Metrosoft II Multifocal
				Natural Touch
				Occasions
				Optima 38
				PS-45 Multifocal
				Simulvue 38
				Sof-Form II
				Soflens
				Soflens 38
				Softics
				SoftView
				Unilens 38
				Westcon Toric
	Hioxifilcon B	49	15	Alden HP
				Essential Soft Toric Multifocal

				Flexlens
				Ocu-Flex Plus
				Quattro
	Lotrafilcon A	24	140	Air Optix Night & Day Aqua
	Lotrafilcon B	38	110	O_2Optix Aqua
				Air Optix for Astigmatism
	Galyfilcon A	47	60	Acuvue Advance
				Acuvue Advance for Astigmatism
	Senofilcon A	38	103	Acuvue Oasys
				Acuvue Oasys for Astigmatism
				Acuvue Oasys for Presbyopia
	Sifilcon A	32	82	O_2Optix Custom
	Comfilcon A	48	128	Bioinfinity
				Bioinfinity Toric
	Enfilcon A	46	100	Avaira
High Water (>50% Water) Nonionic Hydrogel Polymers	Lidofilcon B	79	38	CW 79
				LL 79
	Surfilcon A	74	35	Permaflex
	Lidofilcon A	70	31	Actifresh 400
				CV 70
				LL 70
				N&N 70
				Q&E 70
	Alfafilcon A	66	32	Soflens Toric
	Omafilcon A	59	33	Biomedics EP
				Biomedics XC
				Proclear 1-Day
				Proclear Multifocal
				Proclear Multifocal Toric
				Proclear Sphere
				Proclear Toric
	Vasurfilcon A	74	39.1	Permaflex UV Naturals
				Precision UV
	Hioxifilcon A	59	28 28	Extreme H@O 59% Thin
				Extreme H2O 59% Extra
				SaturEyes Progressive
				SaturEyes Toric and Sphere
				Biocurve Gold Sphere and Toric
	Hioxifilcon D	54	21	Clartiy H2O
				C-Vue Advanced Custom Toric
				Extreme H2O 54%
				Extreme H2O 54% Toric
	Nelfilcon A	69	26	Dailies AquaComfort Plus
				Focus Dailies
				Focus Dailies Toric
				Focus Dailies Progressive
				Fresh-Look One-Day
				Synergy
				Triton
	Hilafilcon A	70	35	Soflens Daily Disposable
	Acofilcon	58	25.5	Flexlens
Low Water (<50% Water) Nonionic Hydrogel Polymers	Bufilcon A	45	16	Hydrocurve II 45
				Soft Mate B
	Deltafilcon A	43	10	Amsoft
				Amsoft Thin
				Comfort Flex
				Custom Flex
				Metrosoft
				Soft Form Toric
	Phemfilcon A	38	9	Durasoft 2
				Durasoft 2 Opfit
	Balafilcon A	36	112	Purevision
				Purevision Multi-focal
				PureVision Toric
High Water (>50% Water)	Bufilcon A	55	16	Hydrocurve II
				Hydrocurve II 55 Bifocal

Ionic Hydrogel Polymers				Hydrocurve 3 Toric
				Softmate II
	Perfilcon	71	34	Permalens
				Permalens XL
				Permalens Therapeutic
				Permalens Aphakic
	Etafilcon A	58	28	Acuvue
				1-Day Acuvue
				1-Day Acuvue Moist
				Acuvue 2
				Acuvue 2 Colours
				Acuvue Bifocal
	Focofilcon A	55	16	Fre-Flex
	Ocufilcon B	53	16	ClearSight 1 Day
				Continental
	Ocufilcon B	53	16	Ocu-Flex 53
	Ocufilcon C	55	16	UCL 55
				UCL-Pediatirc
	Ocufilcon D	55	19.7	Biomedics 55
				Biomedics 55 Premier
				Biomdics Toric
				ClearSight 1 Day Toric
	Ocufilcon E	65	22	Ocuflex 65
	Ocufilcon F	60	24.3	Hydrogenics 60 UV
	Phemfilcon A	55	16	Durasoft 3
				Durasoft 3 Optifit
				Freshlook
				Freshlook Toric
				Wildeyes
	Methafilcon A	55	18	Biocurve Advanced Aspheric
				Biocurve 1-Day
				Biocurve Toric & Sphere
				C-Vue 1 Day ASV
				C-Vue 55
				Edge III 55
				Elite AC
				Elite Daily
				Elite AC Toric
				Flexlens
				Frequency 55 toric and Sphere
				HD2
				HDX2
				Horizon 55 Bi-Con
				Kontur
				LL 55
				Metro 55
				New Horizons
				Sof-Form 55
				Vertex Sphere
				Vertex Toric
	Methafilcon B	55	18	Frequency 55 Toric
				Hydrasoft Sohere
				Hydrasoft Toric
	Vilfilcon A	55	16	Focus 1-2 Week
				Focus Monthly
				Focus Progressives
				Focus Toric Monthly
				Soft 55
				Soft 55 EW
				Softcon
				Softcon EW

Table B.10. Contact Lenses Available in 2010.

Description	Material (Water Content)	Dk	Brand
Low Water (<50% H2O) Non-Ionic Hydrogel Polymer	Tefilcon (38%)	8.9	Cibasoft
			Illusions
			Softint
			STD
			LL Bifocal
	Tetrafilcon A (43%)	9	Cooper Clear
			Cooper Toric
			Preference
			Preference Toric
			Vantage Thin Accents
			Vantage
			Vantage Accents
			Vantage Thin
	Crofilcon (38%)	13	CSI
			CSI Toric
	Helfilcon A&B (45%)	12	Continental Toric
			Flexlens
			Flexlens Toric
			Flexlens Aphakic
			Optima Toric
	Polymacon (38%)	9	Allvue
			Biomedics 38
			Clearview
			CustomEyes 38
			EpconSOFT
			Esstech PS
			Esstech PSD
			Esstech SV
			Frequency 38
			HD
			HD-T
			HDX
			HDX-T
			Horizon 38
			Hydron Mini
			Hydron Zero 4 SofBlue
			Hydron Versa Scribe
			LifeStyle MV2
Low Water (<50% H2O) Non-Ionic Hydrogel Polymer	Polymacon (38%)	9	Ideal Soft
			Lifestyle Xtra
			LifeStyle 4Vue
			LifeStyle Toric Bifocal
			LL38
			Metrosoft II Multifocal
			Metrosoft Toric
			Natural Touch
			Occasions
			Optima 38
			PS-45 Multifocal
			Simulvue 38
			Sof-form II
			Soflens
			Soflens 38
			Soflens Multifocal
			Softics
			SoftView
			Unilens 38
			Westhin Toric
	Hioxifilcon B (49%)	15	Alden HP
			Alden HP Toric
			Aquaease
			Essential Soft Toric

			Multifocal
			Flexlens
			Quattro
			Satureyes
			Satureyes Toric and Multifocal
	Lotrafilcon A (24%)	140	Air Optix Night & Day Aqua
	Lotrafilcon B (33%)	110	O_2Optix
			Air Optix for Astigmatism
			Air Optix Aqua Multifocal
	Galyfilcon A (47%)	60	Acuvue Advance
			Acuvue Advance for Astigmatism
	Narafilcon B (48%)	55	1-Day Acuvue TruEye
	Senofilcon A (38%)	103	Acuvue Oasys
Low Water (<50% H_2O) Non-Ionic Hydrogel Polymer	Senofilcon A (38%)	103	Acuvue Oasys for Astigmatism
			Acuvue Oasys for Presbyopia
	Sifilcon A (32%)	82	O_2Optix Custom
	Comfilcon A (48%)	128	Biofinity
			Biofinity Toric
	Etafilcon A (46%)	100	Avaira
			Avaira Toric
High Water (>50% H_20) Non-Ionic Hydrogel Polymers	Lidofilcon A (70%)	31	Actifresh 400
			CV 70
	Alfafilcon A (66%)	32	Soflens Toric
	Omafilcon A (59%)	33	Biomedics XC
			Proclear 1-Day
			Proclear EP
			Proclear Multifocal
			Proclear Multifocal Toric
			Proclear Sphere
			Proclear Toric
	Vasurfilcon A (74%)	39.1	Precision UV
			Extreme H2O 59% Thin
			Extreme H2O 59% Extra
			Biocurve Gold Sphere and Toric
	Hioxifilcon D (54%)	21	Clarity H2O
			C-Vue Advanced Custom Toric
			Extreme H2O 54%
			Extreme H2O 54% Toric
	Nelfilcon A (69%)	26	Dailies AquaComfort Plus
			Focus Dailies
			Focus Dailies Toric
			Focus Dailies Progressive
			Freshlook One-Day
			Synergy
			Triton
	Hilafilcon B (59%)	22	SofLens Daily Disposable
	Acofilcon A (58%)	25.5	Flexlens Tricurve Keratoconus
Low Water (<50% H_2O) Ionic Hydrogel Polymers	Bufilcon A	16	Hydrocurve II 45
			Soft Mate B
	Deltafilcon A	10	Amsoft
			Amsoft Thin
			Comfort Flex
			Custom Flex
			Metrosoft

			Soft Form Toric
	Phemfilcon A	9	DuraSoft 2
			DuraSoft 2 Optifit
	Balafilcon A	112	PureVision
			PureVision Multi-Focal
			PureVision Toric
High Water (>50% H_20) Ionic Hydrogel Polymers	Bufilcon A	16	Hydrocurve II
			Hydrocurve 3 Toric
			Softmate II
	Perfilcon	34	Permalens
			Permalens XL
			Permalens Therapeutic
			Permalens Aphakic
	Etafilcon A	28	Acuvue
			1-Day Acuvue
			1-Day Acuvue Moist
			Acuvue 2
			Acuvue 2 Colours
			Acuvue Bifocal
	Focofilcon A	16	Fre-Flex
			ClearSight 1 Day
			Continental
			Ocu-Flex 53
	Ocufilcon C	16	UCL 55
			UCL-Pediatric
	Ocufilcon D	19.7	Biomedics 55
			Biomedics 55 Premier
			Biomedics Toric
			ClearSight 1 Day Toric
	Ocufilcon E	22	Ocuflex 65
	Ocufilcon F	24.3	Hydrogenics 60 UV
	Phemfilcon A	16	DuraSoft 3
			DuraSoft 3 Optifit
			Freshlook
			Freshlook Toric
			Freshlook Colorblends
			Wildeyes
	Methafilcon A	18	Biocurve Advance Aspheric
			Biocurve 1-Day
			Biocurve Toric & Sphere
			C-Vue 1 Day ASV
			C-Vue 55
			Edge III 55
			Elite AC
			Elite Daily
			Elite AC Toric
			Flexlens
			Frequency 55 Sphere & Multifocal
			HD2
			HDX2
			Horizon 55 Bi-Con
			Kontur
			LL 55
			New Horizons
			Sauflon 55 UV
			Sauflon 55 Asphere
			Sof-form 55
			Vertex Sphere
			Vertex Toric
	Methafilcon B	18	Frequency 55 Toric
			Hydrasoft Sphere
			Hydrasoft Toric
	Vilfilcon A	16	Focus 1-2 Week Softcolors
			Focus Monthly Softcolors

			Focus Progressives
			Soft 55
			Soft 55 EW

B.2. References.

[B.1] Physicians' Desk Reference for Ophthalmic Medicines. Medical Economics Company,Inc: Thomson Healthcare: Montvale NJ;1990

[B.2] Physicians' Desk Reference for Ophthalmic Medicines. Medical Economics Company,Inc: Thomson Healthcare: Montvale NJ; 2001

[B.3] White P, Scott C. Contact Lenses & Solutions Summary. *Contact Lens Spectrum Supplement*. 2000 July.

[B.4] White P, Scott C. Contact Lenses & Solutions Summary. *Contact Lens Spectrum Supplement*. 2001 July.

[B.5] White P, Scott C. Contact Lenses & Solutions Summary. *Contact Lens Spectrum Supplement*. 2003 August.

[B.6] White P, Scott C. Contact Lenses & Solutions Summary. *Contact Lens Spectrum Supplement*. 2004 July.

[B.7] White P, Scott C. Contact Lenses & Solutions Summary. *Contact Lens Spectrum Supplement*. 2005 July.

[B.8] White P, Scott C. Contact Lenses & Solutions Summary. *Contact Lens Spectrum Supplement*. 2006 July.

[B.9] White P, Scott C. Contact Lenses & Solutions Summary. *Contact Lens Spectrum Supplement*. 2008 July.

[B.10] White P, Scott C. Contact Lenses & Solutions Summary. *Contact Lens Spectrum Supplement*. 2009 July.

[B.11] White P, Scott C. Contact Lenses & Solutions Summary. *Contact Lens Spectrum Supplement*. 2010 July.

APPENDIX C

TENSILE AND MODULUS VALUES FOR LFB LENSES

C.1. Tables and Figures.

Sample	Modulus (MPa)	N
Tinted Premade LFB With EtOH	1.42 ± 0.44	4
Tinted Premade LFB With EtOH 1,000 μg 120 KDa HPMC	0.79 ± 0.19	3
Untinted Premade LFB With EtOH	1.48 ± 0.25	3
Crosslinked LFB EGDMA:PEG200DMA = 1:1 No EtOH; No HPMC Equivalent xLer/T = 1.5	12 ± 9	3
Crosslinked LFB EGDMA:PEG200DMA = 1:1 No EtOH; Equivalent xLer/T = 1.5	8.91 ± 4.3	3

Sample size was 13 mm x 13 mm x 120 μm square. Literature values for CIBA Air Optix Night & Day Aqua lenses indicate a diameter of 13.8 mm and thickness of 80 μm [**C.1**]. LFB modulus was reported as 1.2 MPa [**C.2, C.3**].

C.2. References.

[C.1] White P, Scott C. Contact Lenses & Solutions Summary. *Contact Lens Spectrum Supplement*. 2010 July.

[C.2] Chou B. Evolution of Silicone Hydrogel Lenses. *Contact Lens Spectrum*. 2008; June Issue.

[C.3] Simard P, Bitton E. Use of High Modulus Silicone Hydrogel (siHy) lens in the Management of Epithelial Defects. *Contact Lens and Anterior Eye*. 2008;31(3):154-157.

APPENDIX D

HPLC CALIBRATION CURVES FOR 10 KDA AND 120 KDA HPMC.

D.1. Figures.

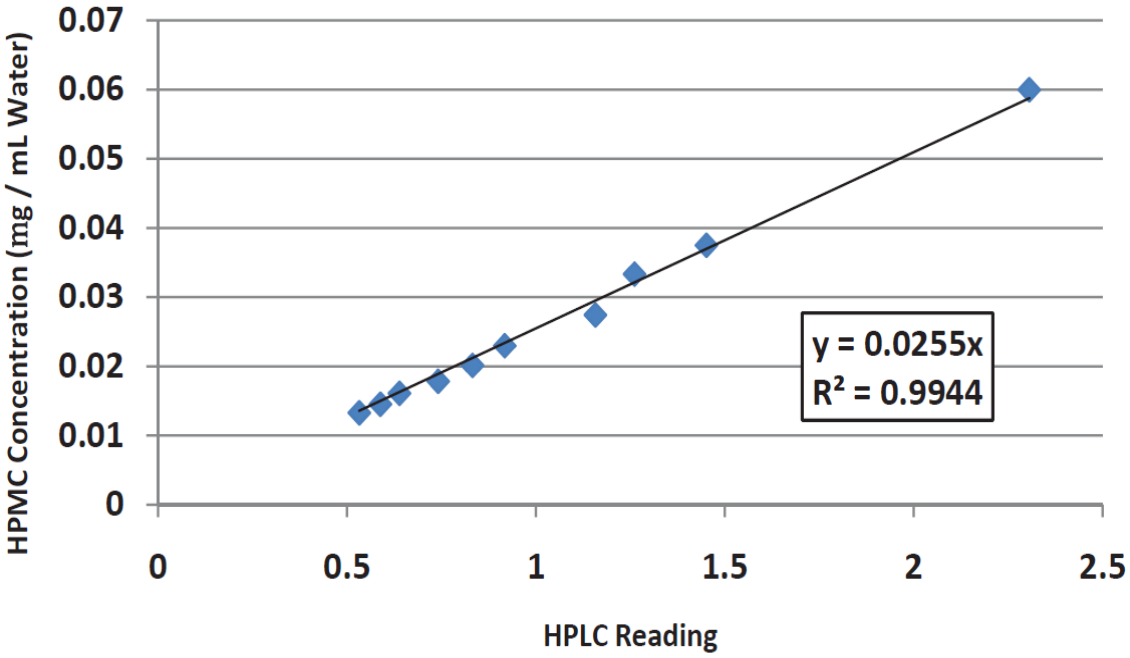


Figure D.1. Calibration Curve for 10 KDa HPMC.

HPMC concentration was measured through refractive index changes. A series of known concentration HPMC-water mixtures were run through the HPLC and the resulting difference in refractive index was recorded. A graph of concentration vs peak height was plotted and a linear regression was performed. The equation relates observed peak height to concentration in mg HPMC/mL DI water.

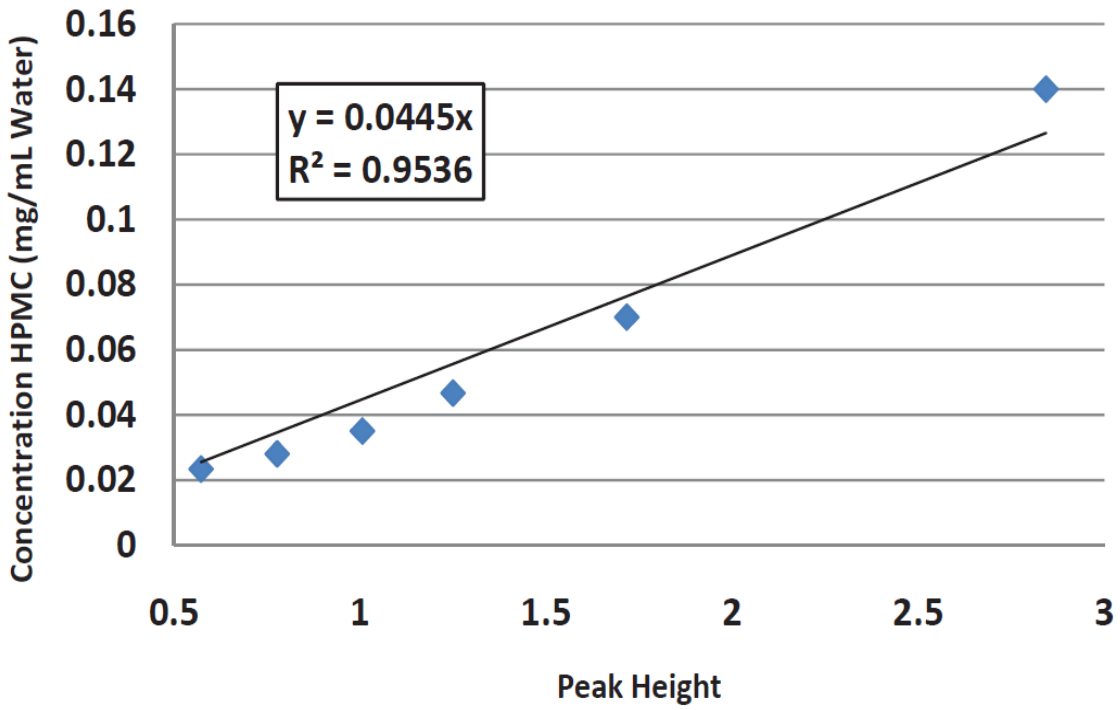


Figure D.2. HPLC Calibration Curve for 120 KDa HPMC.

HPMC concentration was measured through refractive index changes. A series of known concentration HPMC-water mixtures were run through the HPLC and the resulting difference in refractive index was recorded. A graph of concentration vs peak height was plotted and a linear regression was performed. The equation relates observed peak height to concentration in mg HPMC/mL DI water.

APPENDIX E

SURFACTANT STUDY

E.1. Discussion.

As discussed in the main report, producing lenses from the tinted LFB formulation with insignificant quantities of 120 KDa HPMC led to unacceptable losses in optical clarity due to water uptake and swelling. However, surfactants can be used to disperse molecules and have been used to load and control the release of drugs. The surfactant would emulsify the aqueous phase inside the hydrophobic phase and partition the drug between the two phases. Hydrophilic drugs will reside mostly inside the micelle and drug transport is limited by the solubility of the drug in the continuous phase. If micelle size and concentration are sufficiently low, the loaded lens remains transparent. Thus, the addition of surfactant controls the rate of release and may increase the clarity of the lens. An additional advantage of using surfactants is that as free molecules, the surfactants are not covalently attached to the network. Increased control over release rate was to be gained through molecular imprinting while surfactant would be used to increase loading and maintain optical clarity.

To improve clarity, HPMC must be concentrated in the aqueous phase of the micelle. A stable micelle would disperse the HPMC and limit the volume of HPMC aggregates isolating them from the network or from interacting with the hydrophobic (outer) phase. This would reduce water uptake into the film and limit swelling. To control release and clarity, a large partition coefficient for the drug is needed or else the drug will not reside exclusively inside the micelle. In addition, the drug must fit inside the micelle structure and the micelles must be below 100 nm in diameter to produce an optically clear film. In addition, if the micelle concentration is too high, light is scattered among the lens, lowering clarity. The hydrodynamic volume of HPMC and HA, when solvated,

are too large to fit inside the micelles of the surfactants tested. HPMC displays solubility in both the hydrophobic and hydrophilic phase which lowers the partition coefficient to the point where a micelle will not form.

Surfactants used in the study are shown in Table E.1 and were selected based on FDA approval, HLB value, and molecular weight. The effect of each surfactant on clarity of a HPMC-free, untinted, LFB film was tested to eliminate any surfactants before testing with HPMC. It was quickly found that several surfactants were incompatible with the LFB formulation (both with and without ethanol) and/or caused unacceptable losses in optical clarity. With most surfactants, it was observed dissolving 10 wt% surfactant lowered clarity below acceptable values and caused physical property loss. Most surfactant-containing films were clear out of the mold but became opaque after soaking in DI water. Figure E.1. displays the clarity for various films prepared from selected surfactant-LFB mixtures.

Benzalkonium chloride (BAC) (Figure E.2., a) is incompatible with the Lotrafilcon B formulation in even the smallest concentrations. Films containing BAC had a percent transmittance of ~4 and were waxy and easily torn when removed from the mold. It is hypothesized that the cationic nature of the surfactant caused the failure. Further evidence of this theory was demonstrated when DADMAC (a cationic monomer) was added to the LFB formulation and gave similar values for transmittance. The reason the cationic compounds produce this effect has not been investigated, but it is hypothesized that the cationic nature of the compounds inhibits the polymerization of the Betacon macromer and TRIS. Testing with HPMC at several concentrations showed no

improvement in clarity (%T ~0) and a further loss in observed mechanical properties when all BAC-containing films ripped when being removed from the molds.

Tween 20 and 80 (Figure E.2., b and c) were tested up to 20 wt% concentration. Above 10 wt%, films were fragile and easily ripped when removed from the mold. Even at small concentrations of Tween 20 or 80, lenses out of the mold possessed good clarity but decreased when swollen in water (e.g., clarity ~20%).

Films produced with Brij 97 (Figure E.2., d) had acceptable clarity values only at low concentrations (≤5 wt%). At 5 wt% concentration Brij 97, optical clarity was ~85%. At 15 wt% Brij 97, clarity dropped to 50%. Films containing 600 μg HPMC and 5 wt% Brij 97 had a transmittance of 40%. The low transmittance of the HPMC containing films made further investigations obsolete.

Films produced with Span 20 and Span 80 (Figure E.2., e and f) had the greatest clarity even at high concentrations (40 wt%). Up to 20 wt%, Span 20 could be loaded without significant drop in transmittance. Span 80 could be loaded up to 10 wt% without any negative effects on clarity. Due to the large transmittance of films containing Span 20, it seemed to be the optimal surfactant. However, when HPMC was loaded into the formulation, Span 20 did not completely emulsify the solution and phase separation occurred in a short period of time (~10 secs). Improved stability was demonstrated using 5 wt% Span 20 and 5 wt% Span 80 with phase separation occurring in ~60 seconds. Various films containing this mixture of Span surfactants were pursued since they could be kept mixed, transferred to a mold, and cured without significant phase separation. Mixtures of other surfactants were attempted in a factorial fashion with the Spans to improve clarity and slow separation, but no other mixtures extended separation time or

improved clarity. Films containing 1000 μg of 120 KDa HPMC decreased clarity below 50%. A number of Pluronic surfactants (a total of five) were tried to improve clarity. No improvements in clarity were noticed.

Analyzing the results, a correlation was found between optical clarity and HLB values indicating that lower HLB values resulted in higher transmittance (Figure E.3.). Conventional surfactant theory states that surfactants with HLB values between 4 to 6 are best suited as water-in-oil emulsifiers and surfactants with HLB values between 8 to 18 are best used as water-in-oil emulsifiers. Higher HLB values corresponded to the least optically clear films. The best explanation for the experimental observations is likely due to the surfactants causing differences in the biphasic structure of the film. Hydrophobic monomers make up the majority of the LFB formulation with the CIBA macromer, intensely hydrophobic itself, acting as crosslinker for the lens. Oil-in-water emulsifiers would emulsify some of the phobic monomers inside a shell of hydrophilic monomers. The curing process of the system then leaves a high local concentration of phobic monomers, with a disproportionately high crosslink concentration, connected by loosely crosslinked hydrophilic sections. When soaked in water, the hydrophilic region, serving as the lens' continuous phase, swells and loses clarity. The opposite reaction occurs in the water-in-oil systems where hydrophilic monomers are packed into locally concentrated areas with phobic sections serving as the continuous phase. This explanation draws upon existing theory and observations and explains why such large amounts of low HLB surfactants can be added to the solution without drastic losses in clarity. Span 20 (HLB 2) failed to produce an optically clear HPMC laden film. There are few FDA approved surfactants with lower HLB values and the failure of Span 20 to increase clarity caused

all further inquiries in this direction to be abandoned. In addition, to load enough HPMC for 30 day release, the surfactant/HPMC ratio had to be much higher than could be practically loaded into the lens. The micelle concentration would also be too high for optical clarity.

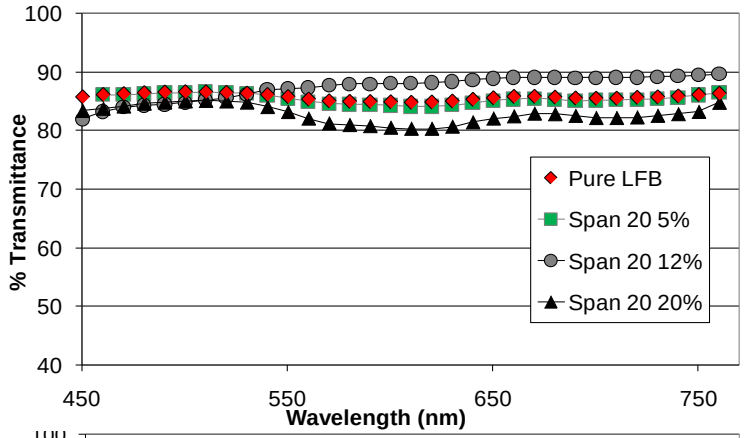
E.2. Tables and Figures.

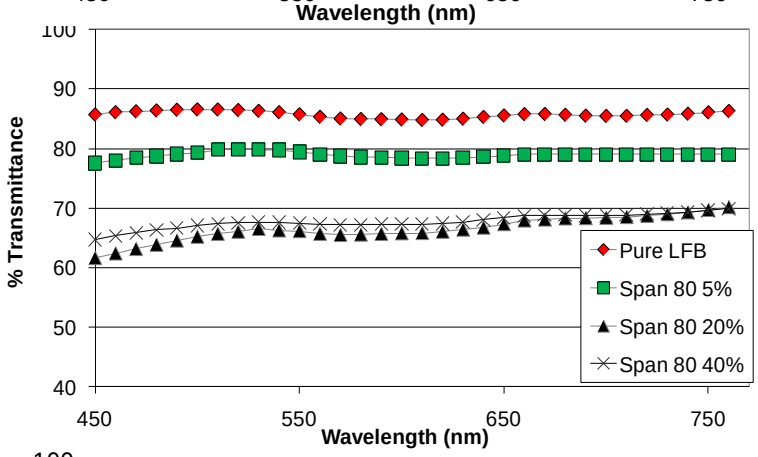
Table E.1. Surfactant Characteristics.

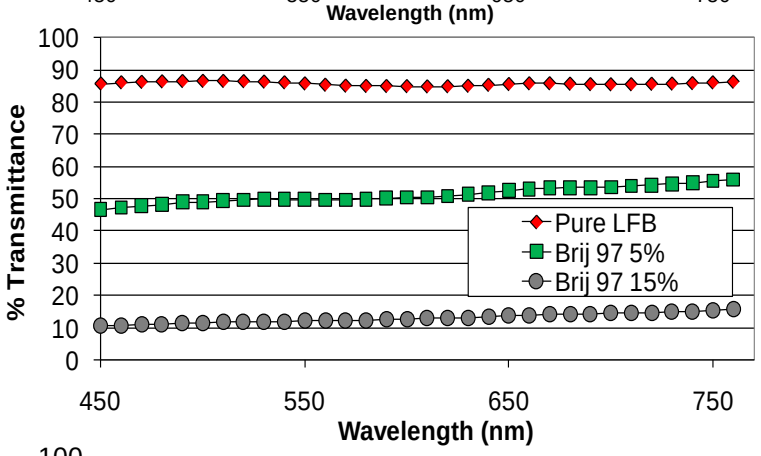
Product Number	Surfactant	MW	HLB
Sigma 16005	Brij 35	~ 627	16.9
Sigma P6136	Brij 97	709	12.4
Pfaltz & Bauch G03260	Glyceryl Monostearate	359	3
Sigma P2443	Pluronic F127	12600	18-23
Sigma S6635	Span 20	~ 400	2
Sigma 388920	Span 40	402	6.7
Sigma 7010	Span 60	~ 416	4.7
Sigma 85547	Span 65	994	2.1
Sigma 6760	Span 80	~ 424	4.3
Sigma 3386	Span 83	~ 426	
Sigma 7135	Span 85	~ 410	1.8
Acros 23336	Tween 20	~ 1200	16.7
Acros 33414	Tween 40	~ 1283	15.6
Acros 27862	Tween 60	-	14.9
Acros 27863	Tween 80	~ 1281	14.9
Acros 33415	Tween 85	-	11
BASF	Pluronic 31R1	3200	1.7
BASF	Pluronic 25R4	3800	14.3
BASF	Pluronic 17R4	2700	16.0
BASF	Pluronic 10R5	1970	21.0

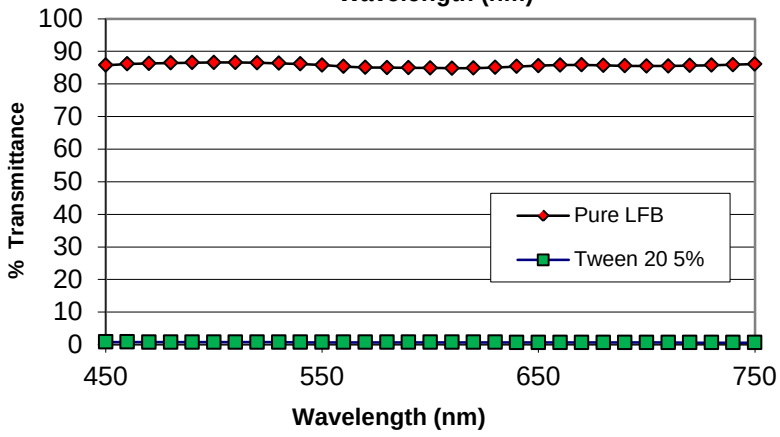
Surfactants were chosen based on FDA approval and current use in medical devices and products. Nine different surfactant systems were tested, with five passing

minimal LFB solubility tests - Tween 20, Tween 80, Span 20, Span 80, and Brij 97. The tested surfactants represented a range of HLB values and molecular weights.


100
90
80
70
60
50
40
% Transmittance
450
550
650
750
Wavelength (nm)
Pure LFB
Span 20 5%
Span 20 12%
Span 20 20%


100
90
80
70
60
50
40
% Transmittance
450
550
650
750
Wavelength (nm)
Pure LFB
Span 80 5%
Span 80 20%
Span 80 40%


100
90
80
70
60
50
40
30
20
10
0
% Transmittance
450
550
650
750
Wavelength (nm)
Pure LFB
Brij 97 5%
Brij 97 15%


100
90
80
70
60
50
40
30
20
10
0
% Transmittance
450
550
650
750
Wavelength (nm)
Pure LFB
Tween 20 5%

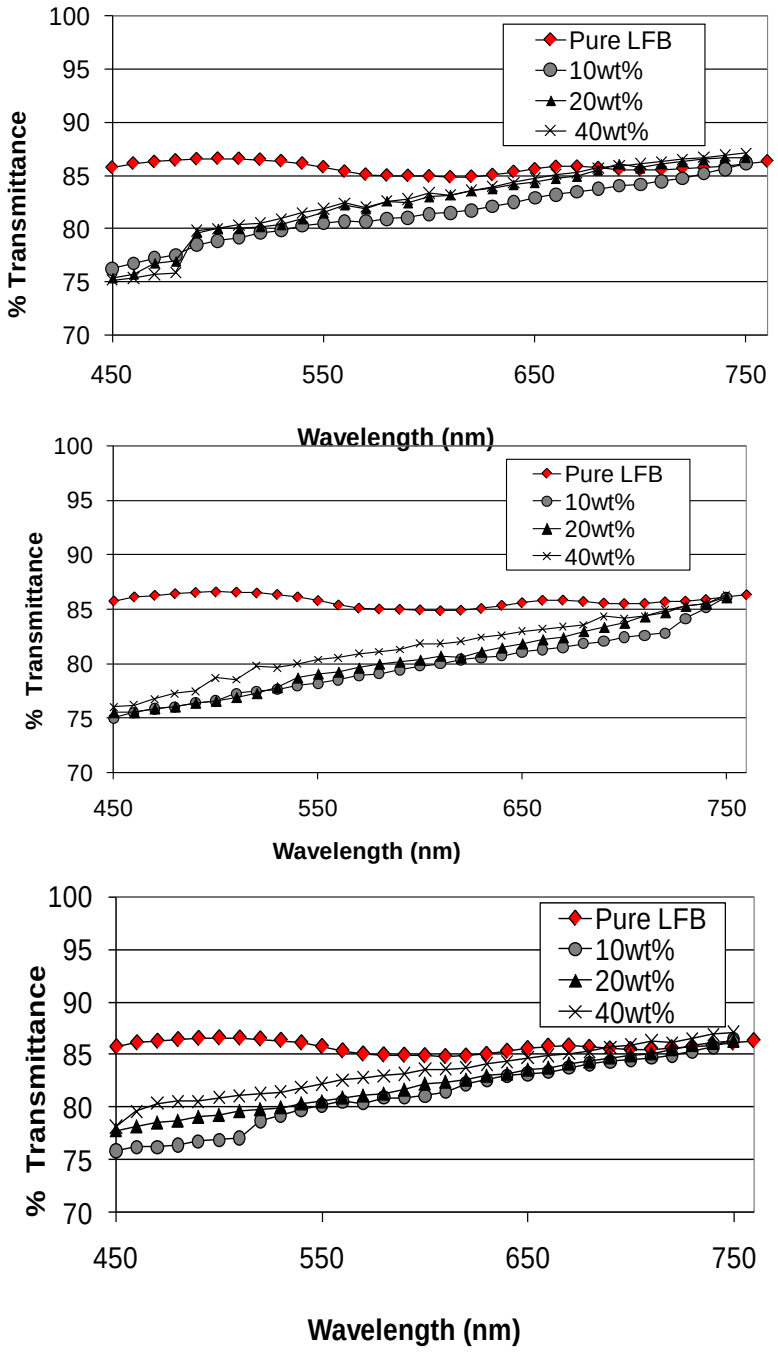


Figure E.1. Optical Clarity for Selected Surfactant-Tinted Ethanol Containing LFB Films.

The Span 20 and Span 80 systems are the best performing systems with respect to optical clarity and qualitative mechanical properties, where 20 wt% concentrations can be added

to the LFB solution without detrimental effects to film clarity. The Tween family of surfactants, however, caused the films to be completely opaque in DI water. Brij 97 could potentially used as surfactant at extremely low concentrations though it is impractical to use Brij 97 as emulsifier as surfactant/HPMC ratio would require more Brij 97 than be reasonably loaded into the lenses.

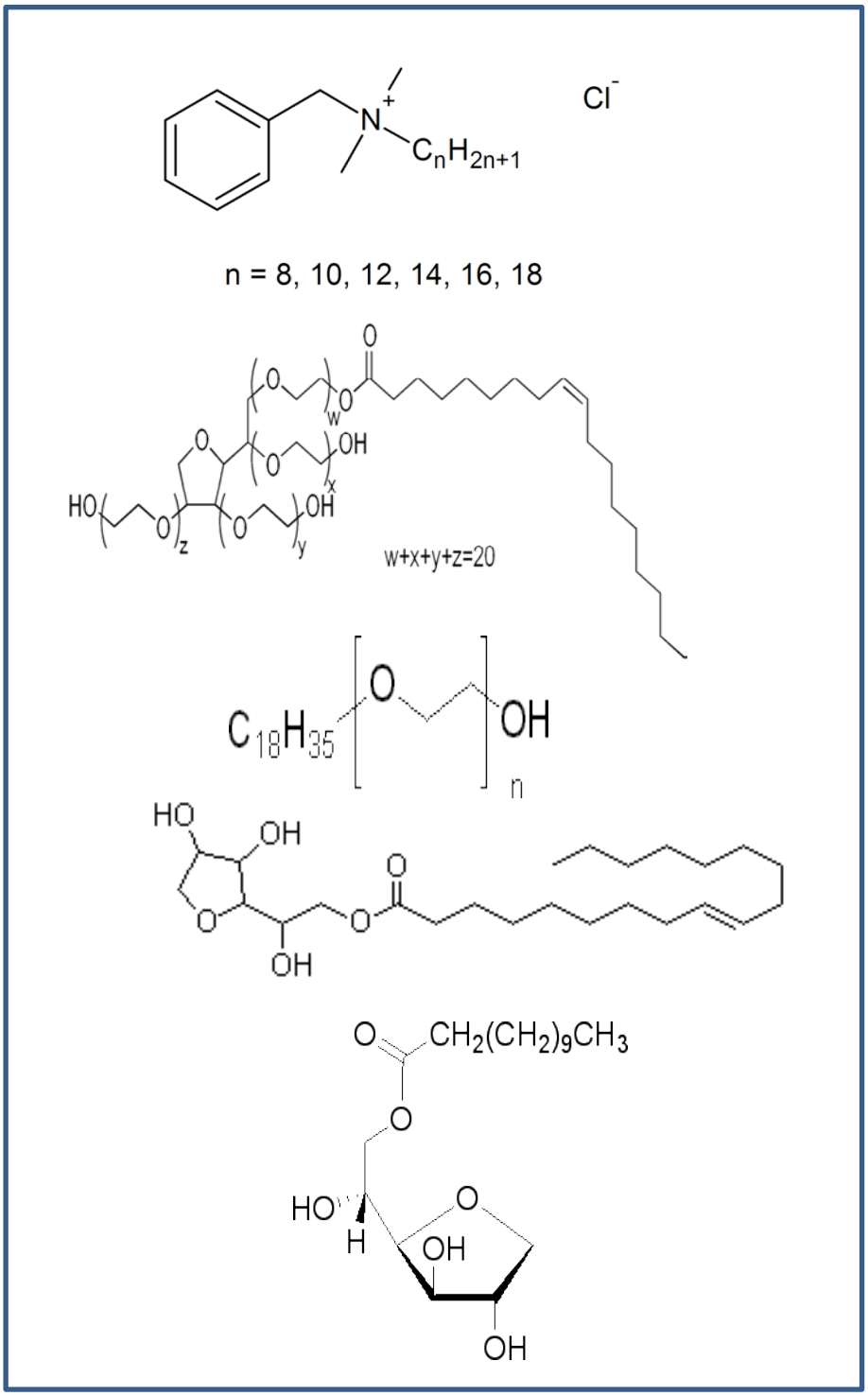


Figure E.2. Chemical Structures of Selected Surfactants

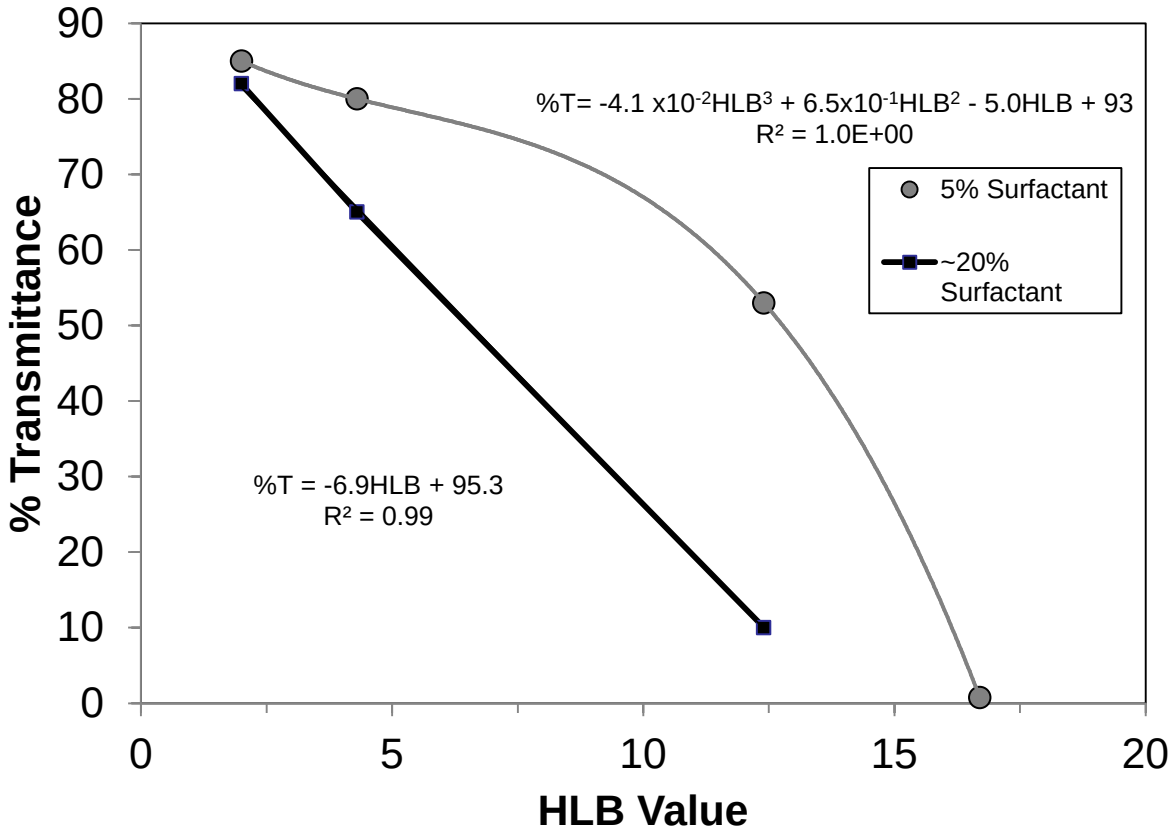


Figure E.3. Correlating Transmittance and HLB Values

A linear correlation is found relating HLB values and transmittance. Lens transmittance increases with decreasing HLB values. At very low HLB values, it is expected that transmittance could be observed above 90%.

APPENDIX F

PERFECT SINK VALIDATION

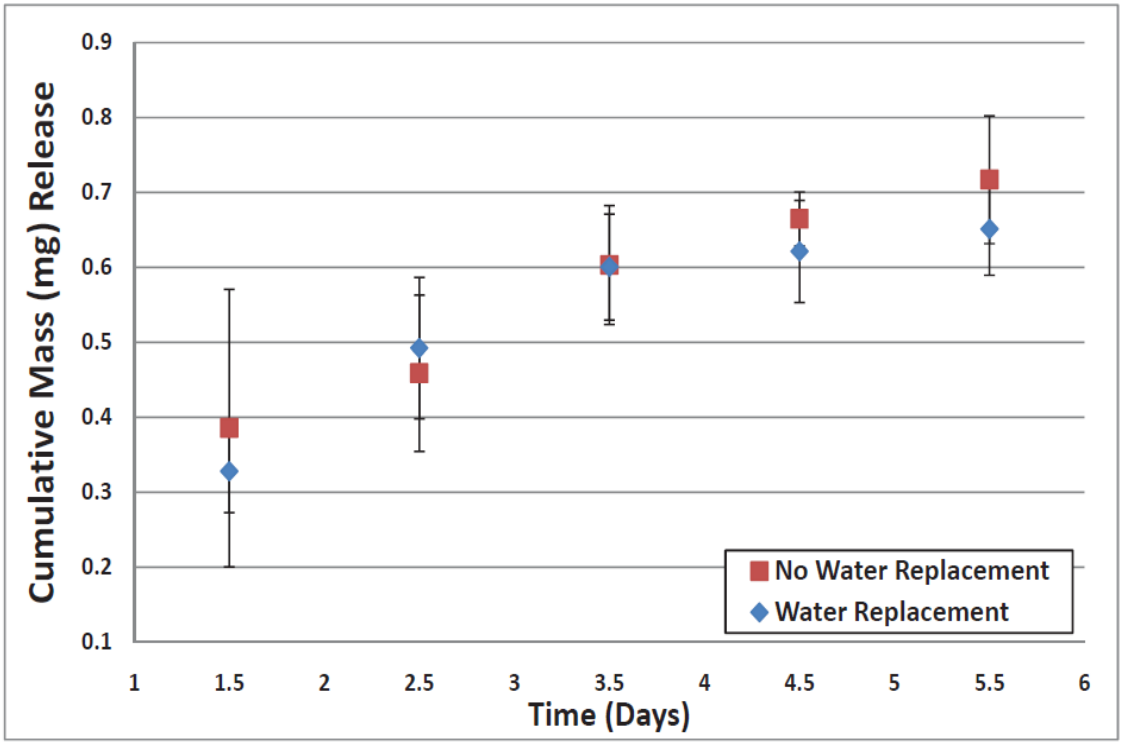


Figure F.1. Perfect Sink Validation.

All release experiments were performed in a Sotax Dissolution Apparatus. A perfect sink condition states that the concentration of solute in solution is effectively zero which negates any equilibrium based release kinetics. The sink condition was verified by studying the release of 120 KDa HPMC from lenses prepared from the ethanol-free untinted LFB formulation in 250 mL DI water without replacing the water and the release from a lens in which the water was replaced after each data point. All data points were within the experimental error, indicating that a 250 mL volume under the release conditions approximates perfect sink conditions.

APPENDIX G

RELEASE OF 10 KDA HPMC FROM LOTRAFILCON B LENSES.

G.1. Discussion.

Contact lenses loaded with 10 KDa HPMC showed much better clarity and much lower water uptake than lenses with 120 KDa HPMC. A lens loaded with 7,000 μg of 10 KDa HPMC (additionally crosslinked lens) resulted in a clarity ~75% while to produce the same clarity the limiting concentration of 120 KDa HPMC is approximately half or ~4,000 μg/ lens.

Figure G.1 shows the effect of the addition of PEG200DMA:EGDMA crosslinkers on the optical clarity of untinted LFB lenses prepared without ethanol and containing 10 KDa HPMC. The PEG200DMA:EGDMA crosslinker was selected since it gave the best results with 120 KDa HPMC. With no crosslinker, HPMC causes increased water uptake into the lens. Increasing the crosslinker content reduces water uptake and results in increased clarity. Even at a low crosslinker content (xLer/HPMC ~2), clarity is within acceptable ranges. At high xLer/HPMC (between 4-10), swelling approaches HPMC free -lens swelling values. Comparisons of similar xLer/HPMC ratios between 10 and 120 KDa HPMC shows that equilibrium weight swelling ratio for 120 KDa HPMC is 4x greater than for 10 KDa. The conclusion is that a lower molecular weight HPMC could be used instead of 120 KDa HPMC to take advantage of the lower swelling and better clarity seen with 10 KDa HPMC. In addition, a positive effect due to the inclusion of crosslinkers is observed in release time. With higher xLer/HPMC ratios, less mass is released per day and the release is prolonged (**Figure G.2**). Use of slightly higher molecular weight HPMC will further delay release. However, crosslinkers cannot be used to control release exclusively but can be effective when paired with molecular imprinting.

Release of 120 KDa HPMC was shown to be extended through application of molecular imprinting with acrylic acid. The successful control of release indicated that the method could be applied to lenses loaded with 10 KDa HPMC. Moreover, more HPMC could be loaded into the lens without a loss of optical and mechanical properties as seen in 120 KDa HPMC lenses. **Figure G.3** correlates AA/HPMC concentration to optical clarity. The trend lines found in **Figures G.2 and G.3** can be used to design optically clear lenses at desired HPMC reservoir. Continuing research into the use of 10 KDa HPMC will use acrylic acid to form imprinted systems and attain extended release. Also, higher ratios of xLer/ 10 KDa HPMC will be investigated to lower release and control optical clarity. This xLer /HPMC ratio will be of use when acrylic acid is added to the formulation.

It is important to note that 10 KDa, being a much smaller molecule than 120 KDa HPMC, does not sequester as much water and as a result will not deliver as much comfort to the surface of the eye as higher molecule weight molecules. The exciting aspect to the investigation of 10 KDa is that molecules of lower molecular weight can be loaded in greater quantities and produce lenses with better properties. Finding a balance between the benefits of using lower molecular weights that do not cause as much swelling in the lens and the increased comfort provided by higher molecular weights is of great interest.

G.2. Tables and Figures.

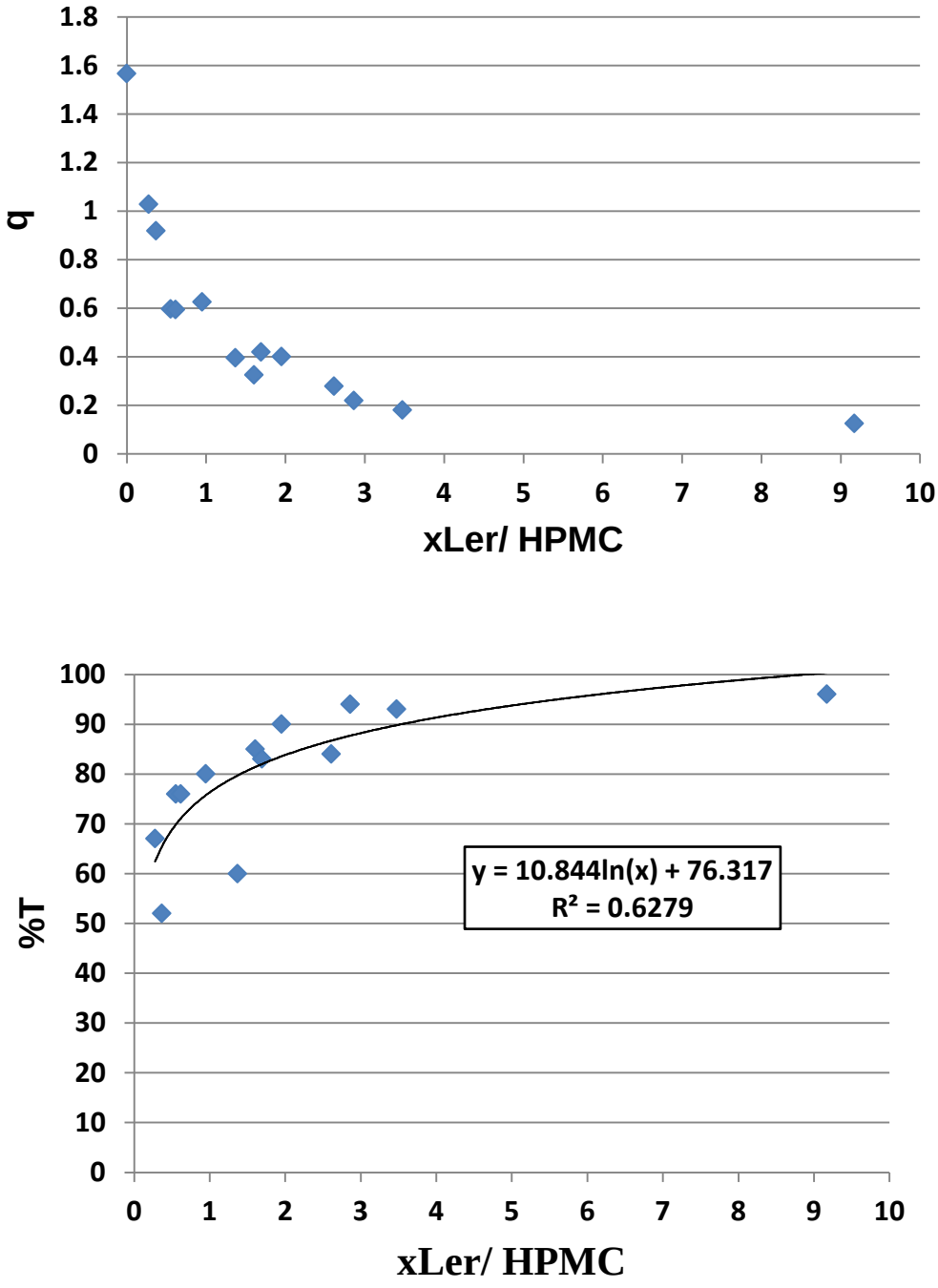


Figure G.1. Effect of the Addition of Crosslinkers on the Equilibrium Swelling and Optical Clarity of Untinted LFB Lenses Prepared Without Ethanol and Containing 10 KDa HPMC

With no crosslinker, HPMC causes increased water uptake into the lens. Increasing the crosslinker content reduces water uptake and results in increased clarity. Even at a low crosslinker content (xLer/HPMC ~2), clarity is inside acceptable ranges. At high xLer/HPMC (between 4-10), swelling approaches HPMC free lens swelling values. Comparisons of similar xLer/HPMC ratios between 10 and 120 KDa HPMC shows that q values for 120 KDa HPMC is 4x greater than for 10 KDa. The conclusion is that the lower molecular weight HPMC could be used instead of 120 KDa HPMC to take advantage of the lower swelling and better clarity seen with 120 KDa HPMC.

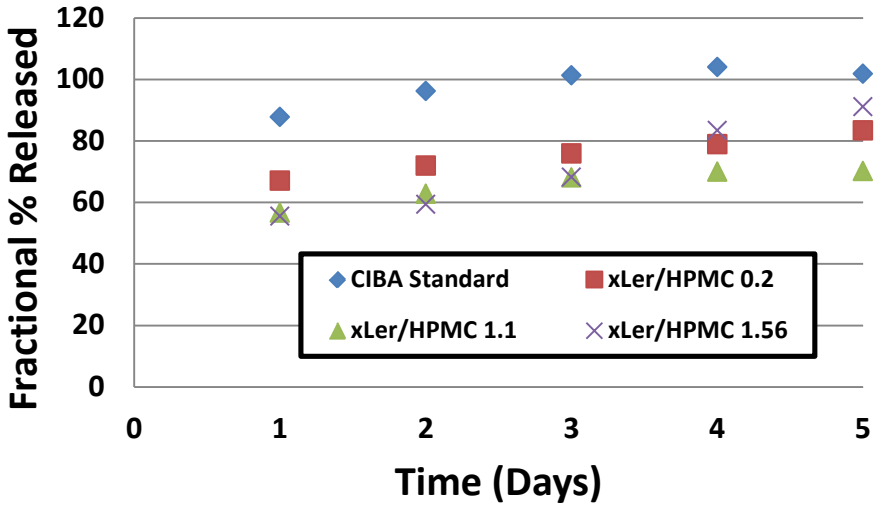


Figure G.2. Effect of the Addition of Crosslinkers on HPMC Release of Untinted LFB Lenses Prepared Without Ethanol and Containing 10 KDa HPMC

There is a correlation between a reduction in total mass released and the increase in crosslinker concentration. The inclusion of crosslinker allows more HPMC be loaded into the lens without effecting clarity and improving mechanical properties, but molecular imprinting will be needed to significantly alter release rates.

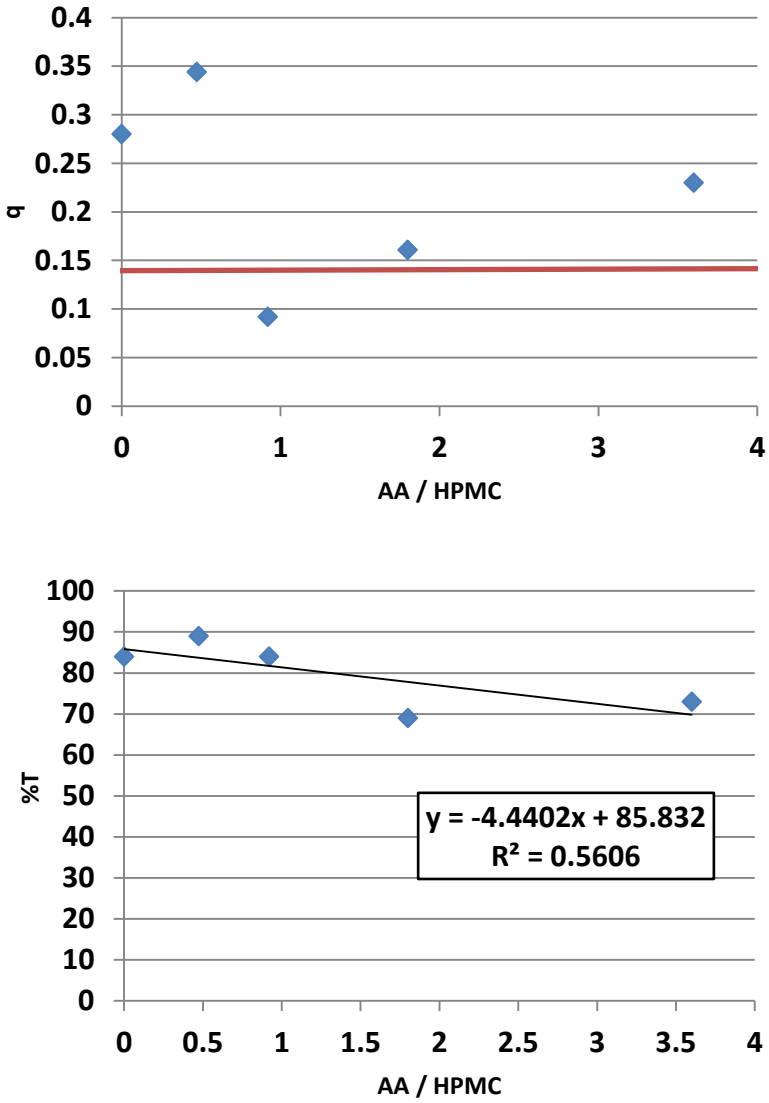


Figure G.3. Effect of the Addition of Crosslinkers on the Equilibrium Swelling and Optical Clarity of Untinted Imprinted LFB Lenses Prepared Without Ethanol and Containing 10 KDa HPMC

Increasing acrylic acid content in the lens results in a downward trend that indicates a M/T between 1 to 2 seems to be the limit before optical clarity is lost in 200 µm (center

thickness) lenses. The red line indicates the swelling value of HPMC-free, AA-free LFB lenses.

APPENDIX H

LENS FORMULATIONS USED

This section outlines most of the lens formulations used in this work.

H.1. Tables and Figures.

Premade, Tinted LFB Formulation

Transmittance was measured before ethanol extraction

Cure Time: 5 min - UV Intensity: 14 mW/cm^2 - Soak Time: 30 min

LFB	HPMC	%T
5999	0	83
7597	7.5	74
8001	80	34
5500	595	20

Untinted, Premade LFB Formulation

Transmittance was measured before and after ethanol extraction

Cure Time: 1.5 min - UV Intensity: 25 mW/cm^2 - Soak Time: 30 min

LFB	HPMC	EtOH Extracted	%T
5996	0	No	95
5994	6.1	No	88
5935	62.3	No	41
5400	603.6	No	30
5935	0	Yes	94
5834	10.3	Yes	86
5334	58.5	Yes	25
5334	594.6	Yes	10

Untinted, Premade LFB Formulation With Added Crosslinkers and NVP

Transmittance was measured after ethanol extraction

Cure Time: 1.5 min - UV Intensity: 25 mW/cm^2 - Soak Time: 30 min

LFB	HPMC	Brij 97	BAC	Span 20	Tween 80	NVP
5094	25	508	0	0	0	0
5009	1011	1011	0	0	0	0
5013	1536	1536	0	0	0	0
5049	25.58	0	50	0	0	0
5001	25.54	0	248	0	0	0
5015	29.57	0	531	0	0	0
5009	25.76	0	0	515	0	0
4995	25	0	0	1020	0	0
5084	25.6	0	0	1505	0	0
5005	28	0	0	0	538	0
5020	25	0	0	0	1008	0
5014	127	0	0	0	0	96
5008	109	0	0	0	0	262
5000	108	0	0	0	0	529

Untinted, Premade LFB Formulation With NVP

Transmittance was measured before and after ethanol extraction

Cure Time: varied - UV Intensity: 25 mW/cm^2 - Soak Time: varied

LFB	NVP	Exp time	Soak Time	EtOH Extracted	%T
4000	0	1.5	10	No	90
4000	0	5	10	No	91
4000	0	10	10	No	88
4000	0	1.5	30	No	92
4000	0	5	30	No	92
4000	0	10	30	No	92
4000	400	1.5	10	No	85
4000	400	1.5	30	No	86
4000	400	5	10	No	78
4000	400	5	30	No	88
4000	400	10	10	No	76
4000	400	10	30	No	87
4000	800	1.5	10	No	80
4000	800	1.5	30	No	72
4000	800	5	10	No	78
4000	800	5	30	No	70
4000	800	10	10	No	64
4000	800	10	30	No	74
4000	1200	1.5	10	No	70
4000	1200	1.5	30	No	64
4000	1200	5	10	No	60
4000	1200	5	30	No	54
4000	1200	10	10	No	75
4000	1200	10	30	No	74
4000	1200	1.5	30	Yes	91
4000	1200	5	30	Yes	92
4000	1200	10	30	Yes	90
4000	1200	1.5	10	Yes	92
4000	1200	5	10	Yes	87
4000	1200	10	10	Yes	54
4000	1200	1.5	30	Yes	87
4000	1200	5	30	Yes	79
4000	1200	10	30	Yes	78
4000	1200	1.5	10	Yes	83
4000	1200	5	10	Yes	83
4000	1200	10	10	Yes	70
4000	1200	1.5	30	Yes	67
4000	1200	5	30	Yes	59
4000	1200	10	30	Yes	44
4000	1200	1.5	10	Yes	79
4000	1200	5	10	Yes	69
4000	1200	10	10	Yes	77
4000	1200	1.5	30	Yes	78

4000	1200	5	30	Yes	34
4000	1200	10	30	Yes	79
4000	1200	1.5	10	Yes	73
4000	1200	5	10	Yes	76
4000	1200	10	10	Yes	74

Untinted, Premade LFB Formulation With NVP

Transmittance was measured before and after ethanol extraction

Cure Time: 1 min - UV Intensity: 28 mW/cm^2 - Soak Time: 1 Day

LFB	HPMC	NVP	%T
5082	80	0	55 ± 5
5000	1200	0	30 ± 11
4500	1400	0	9 ± 2
5056	86	618	47 ± 11
5000	150	600	24 ± 4
5000	250	600	11 ± 48
15659	280	582	17 ± 3
15500	550	550	42 ± 33
15500	800	550	36 ± 13
7707	147	1337	67 ± 4
7700	250	1330	22 ± 6
7700	520	1315	16 ± 4
2018	36	0	67 ± 12
2152	38	0	56 ± 34
2364	47	0	51 ± 21
2110	32	0	42 ± 23
2107	25	0	69 ± 11
2164	27	0	56 ± 19
4900	54	0	12 ± 21
2627	39	0	30 ± 14
2599	33	0	27 ± 16

Untinted LFB Formulation Mixed From Individual Components

Transmittance was measured before and after ethanol extraction

Cure Time:1.5, 15, and 30 mins - UV Intensity: 14 and 25 mW/cm^2 - Soak Time: 10 mins, 30 mins, and 24 hours

Note: Each formulation was tested at each separate condition but it was the standard deviation of the samples overlapped to the extent no definite trend could be estabilished though the mean decreased with increasing intensity and cure time. The response to soak time varied based on ethanol and HPMC concentration. The reported transmittances and standard deviations are overall.

Macromer	TRIS	DMA	NVP	HPMC	EtOH	%T
178	164	168	2303	50.2	703	22 ± 11
49	53	170	566	15	262	55 ± 16
55	50	257	461	15	212	66 ± 9
A53	48	350	358	16	198	79 ± 18

306	102	95	1103	30	401	5 ± 9
294	107	303	915	30	406	26 ± 5
298	98	491	705	31	423	49 ± 23
299	97	695	510	30	406	66 ± 16
505	96	111	901	32	398	11 ± 4
492	104	306	698	30	413	35 ± 12
504	101	499	516	30	402	49 ± 22
502	95	788	234	31	398	75 ± 13
2273	316	406	2264	91	1557	33 ± 15
742	215	382	535	37	432	60 ± 17
761	117	548	441	32	413	87 ± 7
750	150	795	400	30	470	66 ± 14
836	278	768	184	38	447	Failed
700	148	337	624	36	493	66 ± 7
97	100	102	1293	31	402	7 ± 4
91	297	105	1109	33	399	4 ± 12
113	493	95	895	29	396	26 ± 6
102	697	98	701	31	410	13 ± 22
302	105	104	1104	31	405	9 ± 6
297	298	97	904	30	413	17 ± 9
305	503	99	718	30	402	52 ± 26
295	695	106	502	31	399	46 ± 38
815	146	140	790	36	450	46 ± 38
498	360	149	905	32	420	13 ± 12
606	126	113	714	31	429	72 ± 26
525	534	171	548	40	410	62 ± 11
817	750	225	317	47	588	72 ± 8
772	625	400	549	41	430	53 ± 9
608	552	163	367	50	367	28 ± 13
729	725	113	433	34	433	47 ± 20
767	300	195	618	59	618	12 ± 8
5	4.6	4.7	64.6	1.4	19.7	82 ± 4
4.3	4.5	14.9	49.5	1.2	25.5	50 ± 26
5.2	4.8	24.5	43.9	1.4	20.2	33 ± 2
5.2	4.7	34.2	35	1.6	19.4	40 ± 16
15	5	4.7	54.1	1.5	19.7	50 ± 18
14.3	5.2	14.7	44.5	1.5	19.8	60 ± 9
14.6	4.8	24	34.5	1.5	20.7	53 ± 6
14.7	4.8	34.1	25	1.5	19.9	67 ± 8
24.7	4.7	5.4	44.1	1.6	19.5	42 ± 14
24.1	5.1	15	34.2	1.5	20.2	53 ± 10
24.6	4.9	24.3	25.1	1.5	19.6	66 ± 16
24.5	4.6	38.5	11.4	1.5	19.4	62 ± 14
32.9	4.6	5.9	32.8	1.3	22.5	41 ± 12
31.7	9.2	16.3	22.8	1.6	18.4	11 ± 5
32.9	5.1	23.7	19.1	1.4	17.9	49 ± 8
28.9	5.8	30.6	15.4	1.2	18.1	75 ± 16
32.8	10.9	30.1	7.2	1.5	17.5	35 ± 7
29.9	6.3	14.4	26.7	1.5	21.1	42 ± 21

4.8	4.9	5	63.9	1.5	19.9	78 ± 8
4.5	14.6	5.2	54.5	1.6	19.6	5 ± 24
5.6	24.4	4.7	44.3	1.4	19.6	21 ± 11
5	34.2	4.8	34.4	1.5	20.1	36 ± 24
14.7	5.1	5.1	53.8	1.5	19.7	66 ± 34
14.6	14.6	4.8	44.3	1.5	20.3	27 ± 21
14.8	24.5	4.8	34.9	1.5	19.5	49 ± 4
14.5	34.3	5.2	24.8	1.5	19.7	66 ± 13
34.3	6.1	6	33.2	1.5	18.9	26 ± 9
21.1	15.3	6.3	38.3	1.4	17.6	12 ± 9
30	6.2	5.6	35.4	1.5	21.2	66 ± 12
23.6	24	7.7	24.6	1.8	18.4	79 ± 35
29.8	27.3	8.2	11.6	1.7	21.4	64 ± 52
27.4	22.2	14.2	19.5	1.5	15.3	22 ± 6
27.5	25	7.4	16.6	2.3	21.2	7 ± 7
29.1	28.9	4.5	17.3	1.4	18.9	45 ± 3
32.6	12.7	8.3	26.3	2.5	17.6	50 ± 12
1751	953	1460	98	775	151	12 ± 15
1280	945	1449	600	753	163	8 ± 7
864	958	1445	997	781	151	16 ± 23
540	945	1448	1349	765	152	1 ± 11

Untinted LFB Formulation Prepared Without Ethanol

No Extraction Step Was Performed

Cure Time:1.5 min - UV Intensity: 25 mW/cm^2 - Soak Time: 30 mins

Macromer	TRIS	DMA	PEG200DMA	EGDMA	HPMC	AA	MAA	NVP	%T
958	1014	1042	191	162	51	60	0	0	46
794	780	875	139	225	60	25	0	0	52
738	772	802	133	221	67	12	0	0	38
678	748	692	117	200	140	0	25	0	69
623	636	692	123	188	69	0	52	0	76
824	756	643	121	222	51	0	290	0	32
702	774	707	136	160	170	0	0	14	70
1070	1115	1063	219	213	111	0	0	424	50

Untinted LFB Formulation Prepared Without Ethanol

No Extraction Step Was Performed

Cure Time:1.5 min - UV Intensity: 25 mW/cm^2 - Soak Time: 30 mins

Macromer	TRIS	DMA	EtOH	HPMC	Tween 20	Brij 97	Span 20	Span 80	BAC	EGDMA	PEG200 DMA	MAA
213	1404	219	0	0	0	0	0	0	285	0	0	0
205	207	213	0	0	213	410	778	0	338	0	0	0

235	205	208	0	0	0	0	804	0	0	0	0	0
198	216	217	0	208	0	0	0	0	318	0	1011	111
244	202	201	1007	0	206	0	0	155	334	0	0	0
1393	204	217	0	206	0	247	0	0	0	0	0	0
246	213	211	0	0	198	0	0	104	335	1049	0	0
363	1422	203	0	0	0	0	0	0	0	0	0	0
352	347	383	0	0	0	0	0	0	0	353	0	0
825	754	870	0	0	0	0	0	0	0	362	0	0
837	565	557	0	0	0	0	0	0	0	132	0	0
350	354	350	0	1	0	0	0	0	0	360	0	0
371	360	371	0	10	0	0	0	0	0	345	0	0
356	366	356	0	15	0	0	0	0	0	361	0	0
371	364	371	0	58	0	0	0	0	0	356	0	0
358	368	358	0	127	0	0	0	0	0	355	0	0
357	355	357	0	243	0	0	0	0	0	374	0	0

Untinted LFB Formulation Prepared Without Ethanol

No Extraction Step Was Performed

Cure Time: 1.0 min - UV Intensity: 28 mW/cm^2 - Soak Time: 30 mins

Macromer	TRIS	DMA	PEG200DMA	EGDMA	HPMC	AA	%T
670	525	645	0	133	0	0	98
702	541	682	0	342	0	0	96
911	937	911	146	186	0	0	97
771	825	890	136	0	0	0	90
908	949	1015	512	0	0	0	92
713	816	866	832	0	0	0	94
958	1014	1042	191	162	0	0	76
794	780	875	139	225	0	0	52
738	772	802	133	221	0	0	38
678	748	692	117	200	0	0	69
623	636	692	123	188	0	0	76
824	756	643	121	222	0	0	82
702	774	707	136	160	0	0	70
1070	1115	1063	219	213	0	0	50
754	768	805	145	134	0	0	64
909	900	897	15	22	148	0	64
910	897	896	1.5	1.5	149	0	37
910	895	899	82	78	149	0	41
961	947	953	145	141	186	34	51
1800	1999	1999	359	528	254	955	46
1241	1180	1480	335	330	319	1123	24
1419	1427	1480	109	169	49	276	74
984	932	933	185	188	192	200	32
1310	1316	1540	292	310	145	630	36

1083	1099	1098	209	207	99	200	57
1195	1216	1194	202	217	64	128	75
1125	1107	1111	201	238	62	73	85
1073	1064	1065	0	0	155	0	24
1222	1217	1186	91	90	164	0	23
1049	1043	1064	150	153	147	0	21
1361	1358	1351	210	216	83	0	64
1186	1150	1155	0	0	159	163	44
1179	1121	1118	86	78	150	150	32
1069	1056	1014	190	217	150	147	32
1083	1050	1037	186	189	79	83	56

Untinted Premade LFB Formulation Prepared Without Ethanol

No Extraction Step Was Performed

Cure Time: 1.5 min - UV Intensity: 25 mW/cm^2 - Soak Time: 30 mins

Macromer	TRIS	DMA	EGDMA	PEG 200 DMA	AA	HPMC	Pre-Release %T	Post Release %T
1640	1603	1787	32	28	0	216	54	66
1309	1454	1356	128	120	0	181	63	80
1216	1222	1214	201	350	0	269	59	77
1309	1329	1340	220	213	0	222	55	74
1245	1243	1250	105	108	238	161	81	86
1294	1306	1297	212	210	0	763	76	82
985	980	980	158	163	0	35	96	94
1466	1438	1470	235	241	105	222	89	88
1132	1120	1134	185	182	155	168	84	87
1168	1168	1211	196	203	338	184	69	72
1179	1186	1180	199	190	714	199	73	74
1101	1097	1127	187	202	0	0	96	94
1086	1081	1074	179	186	105	105	93	92
1347	1333	1352	235	219	283	283	85	87
1383	1376	1380	241	250	0	188	84	84
1245	1244	1235	112	94	0	0	100	98
1473	1468	1469	116	113	0	80	94	92
12373	1246	1221	104	94	0	117	83	94
1229	1220	1224	95	98	0	203	80	84
1273	1273	1283	107	107	0	347	76	74
1180	1174	1200	108	108	0	588	52	52
1374	1335	1348	224	216	224	231	82	84
1039	1016	1116	0	0	137	137	47	51
1127	1162	1178	100	108	614	613	44	41
1008	1011	1014	151	169	39	34	96	92
1115	110	1117	0	0	280	138	32	36
1343	1335	1353	230	230	576	286	75	74

1370	1343	1329	224	222	462	216	74	78
1051	1069	1038	335	322	238	119	9	24
1613	1643	1632	30	28	517	258	74	71
1262	1242	1233	115	110	0	139	93	91
1155	1146	1137	200	200	0	82	84	88
1172	1205	1132	198	208	123	78	97	96

Untinted Premade LFB Formulation

Transmittance was measured after ethanol extraction

Cure Time: 1.5 min - UV Intensity: 25 mW/cm^2 - Soak Time: 30 mins

LFB	HPMC	%T
1004.46	59.38	40
1058.04	11.8	56
1097.2	29.89	52
4000	143	4
3184	160	46
3159	137	43

Untinted LFB Formulation Prepared Without Ethanol

Transmittance was measured after ethanol extraction

Cure Time: 1.5 min - UV Intensity: 27 mW/cm^2 - Soak Time: 30 mins

Macromer	TRIS	DMA	EGDMA	PEG200DMA	10KDa	90 KDa	120 KDa	%T
1190	1189	1302	442	0	21	17	22	76
840	835	860	150	0	14	33	17	64
998	1002	1000	175	0	41	41	40	54

Surfactant-laden Untinted, Premade Lenses

Transmittance was measured before ethanol extraction

Cure Time: 1.5 min - UV Intensity: 22 mW/cm^2 - Soak Time: 30 mins

LFB wt %	HPMC wt %	BAC wt %	%T
98.81	0.20	0.99	21
97.69	0.39	1.93	25
97.00	0.19	2.81	15
96.01	0.19	3.80	12
95.11	0.19	4.70	7
91.77	0.51	7.71	4
99.04	0.00	0.96	27
91.85	0.00	8.15	4.5

LFB wt %	HPMC wt %	Brij 97 wt %	%T
98	0	2	67

90	0	10	45
93	0	7	52
91	5	5	42
90	5	5	39

LFB wt %	HPMC wt %	Span 20 wt %	%T
91	0	9	76
80	0	20	72
71	0	29	69
73	0	27	71
71	1	27	65
71	4	25	61
66	8	27	55
69	3	28	69
67	6	27	59

LFB wt %	HPMC wt %	Span 80 wt %	%T
99	0	1	92
91	0	9	72
83	0	17	64
72	0	28	61

LFB wt %	HPMC wt %	Tween 20 wt %	%T
99	0	1	65
97	0	3	40
92	0	8	21
90	0	10	26

LFB wt %	HPMC wt %	Tween 80 wt %	%T
98	0	2	62
91	0	9	17
94	0	6	26
96	0	4	33

LFB wt %	HPMC wt %	Pluronic 10R5 wt %	%T
99	0	1	89
97	0	3	82
94	0	6	64

LFB wt %	HPMC wt %	Pluronic 17R4 wt %	%T
99	0	1	95

93	0	7	89
92	0	8	82
81	0	19	75
83	7	10	74
81	9	10	63
88	1	11	76

LFB wt %	HPMC wt %	Pluronic 25R4 wt %	%T
99	0	0.955	85
93	0	6.70	52
92	0	7.80	17

LFB wt %	HPMC wt %	Pluronic 31R1 wt %	%T
99	0	1	94
91	0	9	82
95	0	5	87
92	2	7	79
85	8	7	42
87	7	6	63

LFB wt %	HPMC wt %	Pluronic F127 wt %	%T
98	0	2	82
93	0	7	46
91	0	9	21

Formulations Used to Synthesize Lenses For Figure 11.19.

Transmittance was measured after fully swollen

Cure Time: 5 min - UV Intensity: 14 mW/cm^2 - Soak Time: 30 min

Macromer	TRIS	DMA	HPMC	EGDMA	PEG200DMA	AA
1168	1130	1137	120	124	118	229
1098	1094	1097	122	171	170	235
1116	1119	1133	120	146	152	235
1166	1147	1125	118	114	136	173
1177	1171	1171	119	59	63	236
1062	1056	1051	122	250	236	240
1086	1039	1028	124	315	294	305
2320	2234	2298	268	186	178	255
1274	1209	1293	236	105	162	234
1226	1212	1260	128	89	126	417
1053	1040	1033	112	89	90	485
1148	1044	1062	140	92	102	570
1319	1327	1300	97	81	122	775
1251	1231	1226	120	156	179	0
1128	1139	1057	138	141	159	174
1200	1231	1278	183	250	200	373
1180	1025	1059	170	135	170	531
1310	1320	1392	140	127	158	464
1208	1244	1226	124	152	230	192
900	891	941	108	150	158	697
991	1016	982	112	133	133	577
1125	1188	1163	141	127	145	500
1289	1300	1213	133	60	60	0
1032	1036	1159	126	47	62	640
1850	1940	1865	198	77	81	792
1032	1090	1142	141	85	85	668
1200	1247	1268	154	76	49	165
1160	1118	1204	122	0	0	614
1283	1423	1226	117	68	126	0
1223	1225	1125	104	0	0	775
1601	1729	1738	172	0	0	467
1427	1410	1505	114	0	0	233
1358	1372	1412	152	37	50	496
1170	1186	1184	112	36	38	588
1226	1374	1234	152	42	44	350
1324	1337	1407	156	60	33	0

Macromer	TRIS	DMA	HPMC	EGDMA	PEG200DMA	AA
1364	1337	1325	140	0	0	254
1265	1265	1281	119	137	142	275
1052	1120	1149	116	231	272	500
1700	1719	1719	111	327	317	0
1502	1620	1534	134	216	216	63
1326	1521	1509	119	0	0	0
1623	1602	1640	144	0	0	52
1123	1140	1140	120	0	0	120
1159	1104	1157	115	0	0	474
1178	822	1101	135	0	0	801
1197	1076	1063	127	49	67	225
1018	1071	1012	120	58	62	552
1173	1079	1083	160	33	56	719
1294	1294	1294	118	0	0	0
1275	1275	1275	118	0	0	59
1255	1255	1255	118	0	0	118
1137	1137	1137	118	0	0	471
1059	1059	1059	118	0	0	706
1216	1216	1216	118	29	29	176
1098	1098	1098	118	29	29	529
1235	1235	1235	118	59	59	59
1137	1137	1137	118	59	59	353
1020	1020	1020	118	59	59	706
1235	1235	1235	118	88	88	0
1216	1216	1216	118	88	88	59
1157	1157	1157	118	88	88	235
1137	1137	1137	118	88	88	294
1020	1020	1020	118	88	88	647
1020	1020	1020	118	118	118	588
1049	1049	1049	118	118	118	500
1196	1196	1196	118	118	118	59
1176	1176	1176	118	147	147	59
1078	1078	1078	118	147	147	353
1059	1059	1059	118	147	147	412
1020	1020	1020	118	147	147	529
961	961	961	118	147	147	706
980	980	980	118	176	176	588
1020	1020	1020	118	176	176	471

Macromer	TRIS	DMA	HPMC	EGDMA	PEG200DMA	AA
1059	1059	1059	118	176	176	353
1137	1137	1137	118	176	176	118
1157	1157	1157	118	206	206	0
1118	1118	1118	118	206	206	118
1059	1059	1059	118	206	206	294
1020	1020	1020	118	206	206	412
961	961	961	118	206	206	588
1137	1137	1137	118	235	235	0
1118	1118	1118	118	235	235	59
1020	1020	1020	118	235	235	353
961	961	961	118	235	235	529
1118	1118	1118	118	265	265	0
980	980	980	118	265	265	412
922	922	922	118	265	265	588
882	882	882	118	265	265	706
902	902	902	118	294	294	588
863	863	863	118	294	294	706
961	961	961	118	294	294	412
1039	1039	1039	118	324	324	118
1000	1000	1000	118	324	324	235
941	941	941	118	324	324	412
882	882	882	118	324	324	588
1000	1000	1000	118	353	353	176
902	902	902	118	353	353	471
863	863	863	118	353	353	588
824	824	824	118	353	353	706
1000	1000	1000	118	382	382	118
922	922	922	118	382	382	353
843	843	843	118	382	382	588
804	804	804	118	382	382	706
1020	1020	1020	118	412	412	0
922	922	922	118	412	412	294
843	843	843	118	412	412	529
922	922	922	118	206	206	706
1020	1020	1020	118	59	59	706
1147	1147	1147	118	59	59	324
922	922	922	118	309	309	500

Macromer	TRIS	DMA	HPMC	EGDMA	PEG200DMA	AA
1137	1137	1137	118	153	153	165
922	922	922	118	235	235	647
882	882	882	118	412	412	412
1157	1157	1157	118	0	0	412
1098	1098	1098	118	59	59	471
1059	1059	1059	118	118	118	471
980	980	980	118	235	235	471
941	941	941	118	294	294	471
1294	1294	1294	118	0	0	0
1255	1255	1255	118	0	0	118
1216	1216	1216	118	0	0	235
1176	1176	1176	118	0	0	353
1137	1137	1137	118	0	0	471
1098	1098	1098	118	0	0	588
1059	1059	1059	118	0	0	706
1255	1255	1255	118	59	59	0
1216	1216	1216	118	59	59	118
1176	1176	1176	118	59	59	235
1137	1137	1137	118	59	59	353
1098	1098	1098	118	59	59	471
1059	1059	1059	118	59	59	588
1020	1020	1020	118	59	59	706
1216	1216	1216	118	118	118	0
1176	1176	1176	118	118	118	118
1137	1137	1137	118	118	118	235
1098	1098	1098	118	118	118	353
1059	1059	1059	118	118	118	471
1020	1020	1020	118	118	118	588
980	980	980	118	118	118	706
1176	1176	1176	118	176	176	0
1137	1137	1137	118	176	176	118
1098	1098	1098	118	176	176	235
1059	1059	1059	118	176	176	353
1020	1020	1020	118	176	176	471
980	980	980	118	176	176	588
941	941	941	118	176	176	706
1137	1137	1137	118	235	235	0

Macromer	TRIS	DMA	HPMC	EGDMA	PEG200DMA	AA
1098	1098	1098	118	235	235	118
1059	1059	1059	118	235	235	235
1020	1020	1020	118	235	235	353
980	980	980	118	235	235	471
941	941	941	118	235	235	588
902	902	902	118	235	235	706
1098	1098	1098	118	294	294	0
1059	1059	1059	118	294	294	118
1020	1020	1020	118	294	294	235
980	980	980	118	294	294	353
941	941	941	118	294	294	471
902	902	902	118	294	294	588
863	863	863	118	294	294	706
1059	1059	1059	118	353	353	0
1020	1020	1020	118	353	353	118
980	980	980	118	353	353	235
941	941	941	118	353	353	353
902	902	902	118	353	353	471
863	863	863	118	353	353	588
824	824	824	118	353	353	706
1235	1235	1235	118	88	88	0
1196	1196	1196	118	88	88	118
1157	1157	1157	118	88	88	235
1118	1118	1118	118	88	88	353
1078	1078	1078	118	88	88	471
1039	1039	1039	118	88	88	588
1000	1000	1000	118	88	88	706
1196	1196	1196	118	147	147	0
1157	1157	1157	118	147	147	118
1118	1118	1118	118	147	147	235
1078	1078	1078	118	147	147	353
1039	1039	1039	118	147	147	471
1000	1000	1000	118	147	147	588
961	961	961	118	147	147	706
1275	1275	1275	118	29	29	0
1235	1235	1235	118	29	29	118
1196	1196	1196	118	29	29	235
1157	1157	1157	118	29	29	353

Macromer	TRIS	DMA	HPMC	EGDMA	PEG200DMA	AA
1118	1118	1118	118	29	29	471
1078	1078	1078	118	29	29	588
1039	1039	1039	118	29	29	706
1275	1275	1275	118	0	0	59
1255	1255	1255	118	29	29	59
1235	1235	1235	118	59	59	59
1216	1216	1216	118	88	88	59
1196	1196	1196	118	118	118	59
1176	1176	1176	118	147	147	59
1157	1157	1157	118	176	176	59
1137	1137	1137	118	206	206	59
1235	1235	1235	118	0	0	176
1216	1216	1216	118	29	29	176
1196	1196	1196	118	59	59	176
1176	1176	1176	118	88	88	176
1157	1157	1157	118	118	118	176
1137	1137	1137	118	147	147	176
1118	1118	1118	118	176	176	176
1098	1098	1098	118	206	206	176
1196	1196	1196	118	0	0	294
1176	1176	1176	118	29	29	294
1157	1157	1157	118	59	59	294
1137	1137	1137	118	88	88	294
1118	1118	1118	118	118	118	294
1098	1098	1098	118	147	147	294
1078	1078	1078	118	176	176	294
1059	1059	1059	118	206	206	294
1196	1196	1196	118	147	147	0
1157	1157	1157	118	147	147	118
1118	1118	1118	118	147	147	235
1078	1078	1078	118	147	147	353
1039	1039	1039	118	147	147	471
1000	1000	1000	118	147	147	588
961	961	961	118	147	147	706
1157	1157	1157	118	0	0	412
1137	1137	1137	118	29	29	412
1118	1118	1118	118	59	59	412
1098	1098	1098	118	88	88	412

Macromer	TRIS	DMA	HPMC	EGDMA	PEG200DMA	AA
1078	1078	1078	118	118	118	412
1059	1059	1059	118	147	147	412
1039	1039	1039	118	176	176	412
1020	1020	1020	118	206	206	412
1118	1118	1118	118	0	0	529
1098	1098	1098	118	29	29	529
1078	1078	1078	118	59	59	529
1059	1059	1059	118	88	88	529
1039	1039	1039	118	118	118	529
1020	1020	1020	118	147	147	529
1000	1000	1000	118	176	176	529
980	980	980	118	206	206	529
1078	1078	1078	118	0	0	647
1059	1059	1059	118	29	29	647
1039	1039	1039	118	59	59	647
1020	1020	1020	118	88	88	647
1000	1000	1000	118	118	118	647
980	980	980	118	147	147	647
961	961	961	118	176	176	647
941	941	941	118	206	206	647
902	902	902	118	265	265	647
941	941	941	118	265	265	529
980	980	980	118	265	265	412
1098	1098	1098	118	265	265	59
1059	1059	1059	118	324	324	59
1020	1020	1020	118	324	324	176
902	902	902	118	324	324	529
1067	1067	1067	118	253	253	176
1010	1010	1010	118	265	265	324
980	980	980	118	324	324	294
939	939	939	118	318	318	429
871	871	871	118	318	318	635
922	922	922	118	206	206	706
1078	1078	1078	118	206	206	235
1157	1157	1157	118	206	206	0
855	855	855	118	394	394	529
1012	1012	1012	118	394	394	59
902	902	902	118	394	394	388

Macromer	TRIS	DMA	HPMC	EGDMA	PEG200DMA	AA
1118	1118	1118	118	206	206	118
1039	1039	1039	118	206	206	353
1000	1000	1000	118	206	206	471
941	941	941	118	206	206	647
1246	1246	1246	118	23	23	98
1113	1113	1113	118	69	69	406
1106	1106	1106	118	118	118	328
939	939	939	118	341	341	382
1096	1096	1096	118	167	167	260
1103	1103	1103	118	179	179	215
1176	1176	1176	118	61	61	234
1141	1141	1141	118	117	117	226
1095	1095	1095	118	179	179	239
1062	1062	1062	118	226	226	242
1050	1050	1050	118	283	283	168
1027	1027	1027	118	282	282	237
1002	1002	1002	118	293	293	291
1084	1084	1084	118	229	229	172
1057	1057	1057	118	235	235	243
1042	1042	1042	118	228	228	300
977	977	977	118	407	407	138
1040	1040	1040	118	357	357	49
1080	1080	1080	118	311	311	21
807	807	807	118	396	396	669
851	851	851	118	334	334	663
1050	1050	1050	118	247	247	238
959	959	959	118	385	385	235
970	970	970	118	417	417	139
1067	1067	1067	118	279	279	124
1093	1093	1093	118	302	302	0
1526	1527	1577	160	41	60	100
2158	1973	2128	236	74	71	64
1228	1328	1282	99	95	80	115
1300	1241	1319	123	61	56	173