SIMULTANEOUS CONTROLLED RELEASE OF MULTIPLE COMFORT MOLECULES AND THE PRODUCTION OF NOVEL HIGH COMFORT CONTACT LENS MATERIALS THROUGH BIPHASIC MOLECULAR IMPRINTING

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. The most popular modalities of wear in the current and near future for lens wearers within the US market are extended and daily disposable wear lenses.

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 materials capable of controlled delivery of diverse comfort molecules including 120 KDa hydroxypropyl methylcellulose (*HPMC*), trehalose, ibuprofen, prednisolone, aspirin, chloramphenicol, and other comfort molecules selected to provide comfort across a diverse range of propagators. The comfort molecules selected

for use in this work were chosen as a group to address multiple propagators of discomfort and control over the mass release rate from the lens was demonstrated releasing both individually and simultaneously from the same imprinted lens. The release rate was controlled by engineering the lens formulation according to principles of biomimetic molecular imprinting. This is the first instance controlled and tailorable release of multiple ~~simultaneous~~ ocular therapeutics from contact lenses. Release of multiple diverse comfort molecules is the most promising method of ensuring true high comfort in contact lenses during the full duration of lens wear.

Special care was taken to develop novel correlations between the mass release rate of comfort agents and *in vivo* levels of ocular comfort. Novel index values were developed from evaluation and analysis of comfort agent physical and solution properties. It was shown that the comfort contribution of comfort agent solutions depends strongly on both the comfort agent solution concentration, comfort agent molecular weight, and the precorneal contact time between the comfort agent and the ocular surface/tear fluid. The development of the index values was based on the rheological and physical behavior of static comfort agent solution concentrations and did not account for the gradual loss of concentration with time due to the natural flow of tears. Thus, the index values provided high value for the field by allowing comparison between diverse comfort agent eye drop solutions for the first time and resulted in a method to resolve many discrepancies in the clinical literature. In addition, a statistical meta-analysis of the clinical literature allowed us to accurately model the comfort agent concentration profile within the ocular tear film. It is hypothesized that the comfort contribution can be found and compared among any delivery vehicle with high degree of confidence by comparing the product of the specific

comfort index value for a specific comfort agent/solution in and the calculated area under the *in vivo* comfort agent concentration profile.

Our Lab has pioneered the use of both large volume, static sink models and small volume, continuous flow sink devices, referred to as microfluidic devices, to accurately determine the release kinetics from drug-eluting contact lenses and to predict the mass release profile under physiological conditions. The most recent published device design has represented a major contribution to the field. However, there are several drawbacks of the design that could be improved upon with the design of a novel device. The conception, development, fabrication, programming, and evaluation of a novel heat exchanger-based automaton for the performance of *in vitro* dynamic mass release studies is described in this work. A novel automaton device was designed and fabricated to incorporate solutions to these drawbacks. The automaton was based upon a custom heat exchanger design and a servo-based mechanism to reproduce the blinking motion as well as a method to allow for controlled, variable flow rates of release media through the device.

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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, antiglaucoma, 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 noncovalent 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 co-monomers 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 numerous comfort molecules including 120 KDa hydroxypropyl methylcellulose (*HPMC*), an macromolecular ocular comfort agent, trehalose, a simple disaccharide, and other pharmaceutically active comfort molecules. 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.

Chapter 2 is primarily a review and discussion of the current status and future developments within the comfort product and palliative market. Within the chapter, currently available comfort molecules and solutions are presented, discussed, reviewed, and evaluated according to sales and consumer preferences presented within the literature, research updates, corporate statements and press releases, as well as other independent market reports. To promote a greater understanding of the needs, demands, and developments within the field, it was necessary to provide a review of basic causes and medical conditions that result in sensations of ocular discomfort for both the contact lens wearing population and for non-lens wearers, including a gross review of basic ocular anatomy and tissues, including general descriptions of the eye, the anatomical barriers to effective ocular drug delivery, and differences in the transport of certain classes of molecules within the tear film and within the ocular tissues. With this basic understanding, the behavior and properties of common comfort molecules and their respective solutions are reviewed. In addition, the most promising comfort molecules undergoing clinical and regulatory evaluation for use in commercial and medical products are presented.

In addition to the traditional review and discussion, **Chapter 2** provides a fundamental analysis and novel conclusions. For the first time within the comfort literature, **Chapter 2** attempts to provide a complete definition of ocular comfort, comfort agents, and classifications among comfort molecules, defining and distinguishing the molecules according to similarities in structure, mechanism of action, and properties (*both physical and solution properties*). One such distinction is between comfort promoters (*molecules that contribute to ocular comfort through a single, specific effect or property*), pharmagents (*pharmaceutically active comfort molecules*), and comfort agents (*molecules that*

contribute to ocular comfort via multiple, diverse effects or properties). In addition, the analysis of the current trends within the field provided rationale for prediction of the future of the field.

In **Chapter 3**, the physical and solution properties of comfort agents and comfort agent solutions are discussed. There are numerous advantages for incorporating comfort agents into formulations and/or ocular devices. However, not all comfort agents are equal. Each comfort agent has unique mechanisms of action that make it difficult to compare the levels of comfort between agents. In addition, there is a strong dependence on molecular weight and comfort agent concentration. The clinical data available is often incapable of effectively comparing different comfort agents at different concentrations and/or molecular weights and does little to contribute to the general understanding of comfort agent effectiveness. Furthermore, these studies are very poor models for the development of comfort devices. Therefore, this paper introduced a novel investigation of common ocular comfort agents.

Comfort agent material and solution properties known to correlate to the reduction in ocular discomfort, such as water retention and viscosity, were selected and evaluated for dependence on concentration and molecular weight. It was found that the selected properties varied depending on molecular weight, concentration, and comfort agent species. Through experimentation, polysaccharides were found to be more effective than acrylic comfort agents. More specifically, hyaluronic acid (*HA*), hydroxypropyl methylcellulose (*HPMC*), carboxymethylcellulose (*CMC*) were the three most effective comfort agents, respectively. Though several material properties depended strongly on charge, no clear dependence on polyelectrolyte or neutral classification was apparent in the

overall ranking of comfort agents. In addition, it was found that calculation of the numerical area under the curve for each property versus molecular weight and concentration resulted in a convenient index value for ranking comfort agent effectiveness at different molecular weights and concentrations. The calculated index values led to a greater understanding of general trends found within the clinical data and can be potentially used to resolve numerous contradictory published clinical trials.

Chapter 4 provides valuable contributions to the field by analyzing the comfort contribution of comfort agent solutions delivered to the ocular tear film. The index values developed from the comfort agent physical and solution properties of static solutions in **Chapter 3** were expanded to predict the *in vivo* tear fluid concentration. The analysis required the review of the clinical literature to determine novel correlations between ocular residence time of comfort agents and the two independent variables comfort agent molecular weight and solution concentration. These expressions allowed for the prediction of contact time of comfort agents with the precorneal tear film. Overall, the polysaccharide comfort agents had a much longer residence time than the acrylic molecules, providing further explanation as to the difference in performance between the two classes of comfort agents.

An exhaustive list of lenses, drugs, and methods are presented in this **Chapter 5** of drug releasing contact lens literature. This review highlights how far the field has progressed since 1965 even though there are few drug releasing lens products on the market. However, most of the exciting developments have occurred within the past ten years, and these efforts have revitalized the field.

The majority of work to date has involved release of drug from drug-soaked lenses. Drug-soaked lenses have shown that bioavailability is increased when drugs are delivered from contact lenses compared to topical eye drops. However, it is clear that the benefit in bioavailability is not balanced by the very short release durations of drug-soaked lenses. Also, secondary to release duration is the significant time needed to load drug via soaking which can be much longer than the actual release time. Thus, topical eye drops still maintain 90% market share of ophthalmological treatments. The development of novel release mechanisms is making therapeutic contact lenses a convenient and commercially superior alternative to topical administration methods. The potential for growth in the field is outlined in **Chapter 5**.

It is important to provide a comparative evaluation of the best strategies. While the methods were delineated by mechanism in the text, Table II allows direct comparison of methods relating to particular drugs indicating the relative effectiveness of each method. For example, timolol release has been shown for all major methods discussed in this paper, and ketotifen fumarate and hyaluronic acid have also been used in various methods. Molecular imprinting is consistently one of the best methods in terms of enhanced loading and tailorable control over release rate when factors are balanced such as lens thickness, material, and release media and conditions. The breakthrough of molecular imprinting technologies within drug-eluting contact lenses shows that tailorable and extended release for any duration of lens wear is no longer beyond the grasp of the field. Imprinting extends the drug release profiles providing more constant drug release for longer times while simultaneously increasing the potential drug reservoir within the lens to provide therapeutic

amounts of drug over the duration of release. This has been the goal of drug-eluting contact lens research since 1965.

Carrier-mediated release (*CMR*) has been demonstrated to work best for lenses releasing hydrophobic drugs from hydrophilic lenses, and lenses containing inclusion complexes have worked best with the release of hydrophilic drugs from hydrophilic lenses. Thus, these methods have not been proven beyond hydrogel lenses used for daily wear and daily disposable wear. Molecular imprinting has been shown to work for a wider range of drugs for the entire spectrum of lenses from hydrogels to silicone hydrogels, which are used for daily disposable and extended continuous wear, respectively. No other method has demonstrated the tailorability of release and enhanced loading that molecular imprinting demonstrates. Unlike other methods that can reduce lens clarity, molecular imprinting has been shown to produce lenses with excellent optical properties. In addition, imprinted lens have adequate mechanical properties for use as lenses and can be relatively easily incorporated into existing manufacturing schemes compared to other methods.

Therefore, while many controlled drug delivery strategies have not worked, a few have allowed unprecedented control over drug loading and release from contact lenses. There is high potential in the future to treat ocular disease with significantly enhanced efficacy and efficiency.

Chapter 6 demonstrates the potential of release of comfort molecules as the most promising method to ensure high comfort during contact lens wear. For this purpose, novel lens technologies were developed for the controlled delivery of 120 KDa HPMC from both extended and daily wear contact lenses. With the high level of control over the mass release rate demonstrated through the application of molecular imprinting, it was decided that

while HPMC is a superior comfort agent for the relief of the predominant propagators of end of wear, HPMC contributes little comfort for the primary propagators of discomfort experienced during the initial stages of lens wear such as foreign body response and sensations of dryness. As such, additional comfort molecules were selected and incorporated into the lenses to address multiple propagators of discomfort. The two groups of molecules were 120 KDa HPMC, trehalose, prednisolone, and ibuprofen and 120 KDa HPMC, trehalose, aspirin, and chloramphenicol. This technology is a major breakthrough for the field as no other report has shown release of this number and diversity of comfort molecules.

Chapter 7 describes the design, fabrication, and evaluation of a novel device to measure mass release profiles from drug-eluting contact lenses. The prototype was found to be capable of producing flow rates between 0.1 and 10 mL/min and flow could be altered easily through manipulation of the peristaltic pump. The novel design improved upon previous work by as the device is reusable, whereas the previous device had to created specifically for each experiment and discarded afterward, in addition, other improvements included that the device was capable of reproducing vertical fluid flow in a manner similar to that experienced by a lens placed on the eye, eliminating the reservoir of release media volume that surrounds the lens, the addition of a variable blinking action that rewets the lens surface in a similar manner as the eye, ability to set a desired temperature, the attachment of several environmental sensor modules, and other advantages. Varying the flow rate of the device was shown to reproduce release profiles characteristic of large volume, static sinks and of small volume sinks. Release of a diverse set of molecules were demonstrated to release without any complications. Though the potential value was

demonstrated, several observations for potential improvements to the device operation and versatility were found and noted for the creation of future prototypes.

CHAPTER 2

OCULAR DISCOMFORT AND COMFORT AGENTS

2.1. Ocular Discomfort And Dry Eye Syndrome

The occurrence and propagation of ocular discomfort is a complicated and multivariate process (***Figure 2.1***). Unfortunately, there is a wide diversity of causes and conditions that result in discomfort, including environmental, genetic, seasonal, bacterial and viral, age and gender factors, and numerous others. The sensations of discomfort can arise from irritation of the tissue, loss of tear volume and the resulting dryness, degradation of the ocular tissue, photosensitivity, etc. However, dry eye-syndrome and dry eye-related discomfort is the most common cause of consumer complaint.

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.

In general, dry eye sufferers can be divided into two major populations: contact lens wearers and non-lens wearers. Lens wear discomfort is caused by the presence of the contact lens residing in the tear film/on top of the cornea and disrupting the steady state conditions of the eye, resulting in discomfort. The disruption caused by the lens presence can exacerbate or be exacerbated by genetic, seasonal, environmental conditions, etc, but the initial cause of discomfort is the disruption of the tear fluid or foreign body response of the ocular tissue. Contact lens induced dry eye (*CLIDE*) is described in greater detail in **Section 2.1.2.**, while non-lens related dry eye syndrome is discussed in **Section 2.1.1.** Furthermore, **Table 2.1** provides a greater level of detail describing both CLAD and CLIDE and providing a direct comparison identifying the major differences in the two conditions.

2.1.1. Dry Eye Among Non-Contact Lens Wearers

Dry eye syndrome, officially known as keratoconjuctivitis sicca, is caused by insufficient volume of tear fluid or of an unusual composition so that the tear fluid fails to wet the anterior ocular surface **[2.1, 2]**. This condition affects nearly 50 million people in the US **[2.3, 4]**. In addition, there are numerous other genetic diseases, such as Sjögren's syndrome **[2.5-10]** or lipid deficiencies **[2.11-14]**, that affect tear film stability and volume and can result in significant levels of ocular discomfort **[2.11, 15, 16]**. Moreover, there are well documented gender **[2.17-20]** and age-related predispositions **[2.19-22]** for dry eye conditions, as well as environmental and seasonal factors **[2.23]**. Repeated studies have shown, for instance, that computer usage **[2.24]**, airline travel **[2.25]**, seasonal allergies, low humidity **[2.26, 27]** or arid environments **[2.28]**, etc have high correlation with elevated incidents of dry eye discomfort. Ocular surgeries and procedures, including operations like

LASIK **[2.29]**, leave scar tissue that prevents normal tear flow and film formation **[2.30]**. There are very diverse and complicated conditions and causes of dry eye sensations, making dry eye a very difficult condition to ameliorate. To complicate matters, dry eye can be a symptom of any number of other diseases and viruses, ranging from dehydration to sexually transmitted diseases (*STD's*) to glandular conditions and the flu **[2.1, 2, 31, 32]**.

2.1.2. Contact Lens Associated Discomfort (*CLAD*) And Contact Lens Induced Dry Eye (*CLIDE*) Among Contact Lens Wearers

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 **[2.33, 34]**. 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 at least 30% of these wearers suffer from severe discomfort by complete dryness of the tear film **[2.33-36]**. This is a matter of high interest and potential profit for contact lens manufacturers, and CLIDE-related research and products have become a dominant market trend. The primary method of relief is by the application of macromolecular comfort agent eye drop solutions **[2.37]**. These solutions are discussed in greater detail in **Section 2.4**.

The propagation of discomfort due to CLAD and CLIDE occurs through several independent processes. **Figure 2.2** lists these processes as propagators of ocular discomfort. The major propagators discussed in this chapter are broken into four categories CLIDE, the presence of foreign body and the physiological response, biofouling of the lens surface, and disruption of the tear film. Most common relief solutions or products focus on the mitigation of a single process. However, to truly provide high levels of relief to the dry symptoms, methods to mitigate multiple propagators of discomfort need to be devised.

This can be an exceptionally difficult goal to achieve, as the propagators can be very diverse and highly specific to the individual sufferer and can interact between each other to exacerbate the growth of other propagators, resulting in significant levels of discomfort even when a relief method is applied.

As an example of this complex synergy achieved between the propagators of discomfort in lens wear, a lens is applied to the eye and immediately the presence of the contact lens (*a foreign body*) instigates physiological response in the ocular tissue **[2.38-44]**. This response is characterized by the swelling of the cornea due to irritation of the endothelial cells and decreased oxygen flow from the atmosphere and increased production of tear proteins among others. The swelling and oxygen starvation causes perceived sensations of irritation, itching, soreness, and fatigue in short wear durations and can permanently damage tissue during extended wear periods. Also, it can result in a higher rate of blinking **[2.45]**. Lens biofouling is caused by protein, cell, and lipid adhesion to the lens, altering the lens surface, reducing the wettability, and, as protein adhesion increases, the ocular tissue becomes increasingly intolerant of the contact lens **[2.46-53]**. This intolerance increases the foreign body response resulting in greater production of tear proteins to potentially adhere to the lens and higher levels of irritation, propagating the sensations of discomfort in a repeating loop.

In addition, the contact lens disturbs the normal laminar flow of the tear film and causes the distinct layers of the tear film (*the structure and anatomy of the tear film is described in* ***Section 2.2.1.***) to rupture **[2.54]**. The outermost of these layers is the lipid layer **[2.55]**. The hydrophobic lipids reduce the rate of tear evaporation, and when the film ruptures, there is a significant increase in the loss of volume of tear fluid from evaporation

[2.15, 56-61]. The turbulence in flow has other ramifications, including shorter intervals before dry spots occur in the tear film [*known as the tear breakup time (TBUT)*], increased tear drainage/loss, increased propensity for tear proteins in solution to denature and adhere to the surface of the lens (*and thereby increasing the biofouling of the lens*), decreased lubrication against the shear stress caused by the blinking action, etc.

The last propagator of discomfort outlined in this work is contact lens induced dry eye (*CLIDE*), or the reduction of tear fluid volume due to the presence of the contact lens **[2.56]**. This occurs through several mechanisms, including a decreased rate of lacrimation due to the lens presence, the lens absorbing tear fluid from the tear film, greater volumes lost due to spillage of tear fluid over the eyelid, etc. Water can be lost through evaporation directly from the lens material (*also known as lens dehydration*). The lens can then replace the lost water by absorbing it from the tear film, acting almost as a pump or wick **[2.56]**.

2.2. Description Of The Ocular Anatomy And Tear Film

There are three distinct sections of the eye to discuss when describing topical ocular drug delivery: the tear film, the anterior segment, and the posterior segment. This section provides a description for all three of these areas with special emphasis placed on the ocular tear film. A cross-sectional representation of the ocular anatomy is shown in **Figure 2.2**.

2.2.1. Gross Description Of Ocular Tissue

A typical adult humans eye has an anterior to posterior diameter of ~24 mm, mass of 7.5 grams, a weight of 0.25 ounce, and is about 6 mL in volume **[2.55]**. A cross-sectional representation of the eye is shown in **Figure 2.3**. The eye can conveniently be divided into three distinct sections: the tear film layer, the anterior chamber/segment, and the posterior chamber/segment **[2.62]**. Approximately 40% of the eye's surface area (*the anterior*

surface) is directly exposed to the atmosphere; the remaining surface is protected by the ocular cavity. The anterior surface is lined by the tear film (*a thin aqueous layer of tear fluid that both lubricates and protects the eye from foreign material and debris*) **[2.63]**. The outermost ocular tissue is composed of the sclera (*the tough, white outer membrane*), the cornea (*the transparent tissue covering the pupil*), the conjunctiva (*thin membrane that covers and lubricates the sclera*), and the associated vascular systems **[2.55]**. The cornea is a transparent tissue that serves to refract and focus light into the eye **[2.64]**. It is 11.7 mm in diameter and possesses a radius of diameter of 7.8 mm **[2.65]**. The thickness is 500-700 μm in thickness and thickest in the center **[2.66, 67]**. The anterior segment is approximately a sixth of the eye's total volume, and the posterior segment composes the balance.

2.2.2. Anatomy And Makeup Of The Tear Film

The tear system is a complex system, and the components are depicted in **Figure 2.3A**. 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 (***Figure 2.3B***) **[2.55]**. A pictorial representation of the tear film system is shown in **Figure 2.3C**. In healthy normal eyes, the tear film is 4-9 μm thick, and the volume is completely replaced approximately every 1-3 minutes **[2.68]**. 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 **[2.3, 69-73]**. Flowing along the mucins is an aqueous layer (*4-9 μm thick*) that allows oxygen transport to the eye along with antimicrobial enzymes **[2.69, 71, 72, 74]**. The final layer (*i.e., the interface between the water and the atmosphere*) is composed of lipids (*0.1 μm thick*) 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 2.3B** represents the normal tear film as it flows over the anterior surface of the eye. **Figure 2.3C** displays the layers of the tear film.

Normally, about 10 μL of tear fluid lines the anterior surface of the eye with an additional reservoir of 7-9 μL stored behind each the lower and the upper lid. When blinking occurs, the reservoir is spread out across the ocular surface and partially replenishes the layer **[2.75]**. 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 **[2.2, 32, 70, 76]**. 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 **[2.3, 70-72]**. 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 tear breakup time (*TBUT*) of less than 10 seconds.

In addition to providing comfort, the tear fluid aids in the transport of oxygen to the eye **[2.77-79]**. 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 **[2.80]**. The rate of oxygen diffusion is approximated to be 7.8 μL/ (cm^2*hr) **[2.81]**. 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 **[2.80]**.

2.3. Ocular Anatomy As Barriers To Topical Ocular Drug Delivery

Nature has provided the eye with various tissues and structures that effectively hinder topical drug administration. Each tissue has characteristic permeability's that make effective diffusion by drugs difficult **[2.82]**. From a drug delivery perspective, the eye can be considered as three distinct 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. The third section, the ocular tear film, lines the anterior surface and is traditionally regarded as predominant barrier to effective topical ocular drug delivery, but the tear film can also be considered as a target for the delivery of topical treatments, such as comfort agents.

2.3.1. Tear Film As A Barrier To Ocular Drug Delivery

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 **[2.83, 84]**. The tear fluid also functions as lubrication between 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 **[2.83]**. The proteins, electrolytes, and enzymes have potential to greatly affect the efficiency of

any delivery system **[2.85]**. 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 **[2.86]**, an aqueous layer containing proteins and salts **[2.78]**, and a mucous layer which coats the epithelium and improves wettability **[2.87]**. 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 **[2.83]**. Enzymes present in the tear film include lysozyme, lactate dehydrogenase, pyruvate kinase, malate dehydrogenase, amylase and esterase **[2.83, 88]**. Electrolytes in the tear fluid include sodium, potassium, calcium and chloride and play an important role in the osmotic pressure of the eye **[2.89]**. These electrolytes can interact with ionic drugs and affect residence time and in some cases affect the mechanism of delivery **[2.90]**. Typical pH values reported for tear fluid are 7.4. The excellent review in reference **[2.82]** is recommended to the reader for greater detail.

When a pharmaceutical-containing eye drop is placed on the surface of the eye, a maximum drug concentration is instantaneously achieved within the tear film **[2.91]**. However, tear flow quickly reduces the drug concentration **[2.73]**. The normal tear volume on the eye is 6-7 μL (*not including the tear volume under the eyelids, etc*), and the normal (*basal*) drainage rate is approximately 1.1 μL/ min **[2.92]**. After an eye drop is applied, the tear volume is greatly increased, but drainage rate increases proportionally to tear volume (*typically up to ~1.5 μL/ min or more depending on the instilled drop size*) **[2.84, 93]**. Under normal, pseudo-steady state conditions, tear fluid is completely exchanged every 5-10 min **[2.68, 94]**. This turnover rate is relatively unchanged after the installation of an eye drop, and some references have demonstrated that the overall turnover rate increases until the mean contact time of the drug on the ocular surface is less than 2 min **[2.93]**.

2.3.2. Anterior Segment As A Barrier To Ocular Drug Delivery

The anterior segment of the human eye is composed of the cornea, iris, ciliary body, and the lens and the surrounding tough white membrane known as the sclera **[2.62, 73]**. The cornea itself is an effective barrier to drug transport due to its structure. The human cornea consists of three layers: the corneal epithelium (*hydrophilic barrier*), the stroma (*hydrophilic barrier*), and the endothelium (*hydrophobic barrier*) which restrict the passage of drug molecules **[2.62, 73]**. 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 <500 KDa can diffuse through the stroma basically unhindered.

Drug permeation is affected by several factors, such as hydrophobicity **[2.95]**, solubility, molecular size and shape **[2.96, 97]**, charge **[2.98]**, and ionization **[2.99-101]**. A highly hydrophilic drug would find the hydrophobic 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 **[2.102]**. 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 hydrophobicity **[2.103-105]**. The optimum octanol/buffer distribution coefficient for permeation through the cornea is between 100-1,000 **[2.95, 106]**.

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 **[2.107]**. Studies of diffusion through the sclera has shown that macromolecules have to attain a molecular weight of up to 800 KDa before diffusion through the sclera is eliminated. Due to low permeability values, rates of drug transport across the cornea and sclera are slow even in the presence of high concentrations.

The conjunctiva is a vascularized mucous membrane which covers the anterior part of the sclera and lines the inner surface of the eyelids **[2.73, 108]**. 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*) **[2.109]**. Drug uptake is typically an order of magnitude greater for the conjunctiva than the cornea **[2.72, 110]**. Once absorbed by the conjunctiva, the drug moves throughout the body via 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 an excellent review of permeability ratios for ocular tissues **[2.82]**.

2.3.2. Posterior Segment As A Barrier To Ocular Drug Delivery

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 be present in concentrations sufficient to treat the condition.

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 **[2.73]**. 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, and metabolic enzymes, such as esterases, aldehydes, and keton reductases **[2.111]** 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 **[2.111]**. In the posterior segment, the tissues support the retina. 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 **[2.73]**.

The blood-retinal barrier limits drug distribution from the blood stream to the posterior ocular tissues, and it is a selectively permeable to more hydrophobic molecules **[2.110]**. However, it is impermeable to polar or charged compounds in the absence of a transport mechanism **[2.112]**. 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. 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 **[2.73]**, but in the case of small hydrophobic drugs the sclera and RPE have similar permeability's **[2.113]**. 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 hydrophobic compounds can penetrate more easily **[2.114]**.

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 the choroid and RPE without entering the aqueous humor **[2.103]**. Consequently, they will generally be diluted or eliminated to a sub-therapeutic dosage.

2.3.3. 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.

2.3.3.1. Obstacles To The Transport Of Hydrophobic Drugs

Highly hydrophobic 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 **[2.115]**. 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 **[2.116, 117]**.

The transcellular pathway is the main route of hydrophobic drug transported from the lacrimal fluid to the aqueous humor **[2.71, 108]**. At the corneal epithelium, hydrophobic drugs can transport quickly through the transcellular route due to the hydrophobic nature of the barrier. For the most hydrophobic 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 hydrophobic compounds from the epithelium to the stroma. However, for highly hydrophobic 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 **[2.64, 82]**.

2.3.3.2. 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 precorneal surface **[2.117]**. The paracellular pathway is the most common transport for hydrophilic drugs through corneal and non-corneal (*conjunctival/scleral*) epithelium **[2.118]**. 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*) **[2.64, 73, 119]**. 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*) **[2.103, 110, 120]**. The conjunctiva may allow the permeation of hydrophilic compounds with a molecular weight up to 20 KDa **[2.64]**, whose molecular radius is around 4.9 nm **[2.121]**, and the sclera may allow permeation of a molecular size up to 70 KDa **[2.112]**. 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 **[2.121]**.

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 **[2.73]**.

2.3.3.3. 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 **[2.98]**. The unionized molecule usually penetrates the hydrophobic membranes more easily than the ionized ones. In the case of ionized molecules, the charge of the molecule also affects their corneal permeation **[2.122]**. 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 **[2.122]**.

2.4. Description Of Comfort Agents And Comfort Agent Solutions

Several wetting agents are used in artificial tears and re-wetting drops including acrylic comfort agents like polyvinyl alcohol (*PVA*) and polyvinyl pyrrilidone (*PVP*), or polysaccharides, such as hyaluronic acid (*HA*), carboxymethylcellulose (*CMC*), methyl cellulose (*MC*), and hydroxypropyl methylcellulose (*HPMC*). 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 2.4** shows the chemical structure of common comfort agents.

2.4.1 Definition And Classification Of Comfort Agents

There are many difficulties in defining and differentiating comfort agents. For instance, a number of terms are used to describe them, such as lubricating agents, re-wetting agents, demulcents, mucoprotective agents, etc. While there is no universally

agreed upon definition of comfort or comfort agents within the field, comfort agents augment characteristics of the tear film (*i.e., increase stability and volume of the film*). It is important to note that "comfort agent" does not refer to drugs or molecules that relieve discomfort through pharmacological action, but from material and solution properties that act to prevent disruption of the tear film, prevent loss of tear volume, and/or reduce stress on the corneal epithelium, specifically to alleviate ocular discomfort. The strength of these properties can be highly variable among different comfort agent species, and certain comfort agents provide comfort through multiple properties while others are limited to one property and are often categorized according to the primary mechanism of action. Lubricating agents primarily reduce the shear stress of eyelid movement on the ocular surface. Re-wetting agents primarily restore or retain tear fluid volume to reduce discomfort. Demulcing agents primarily stabilize fluid films that can act as a protective barrier.

Additionally, lipids, surfactants, decongestants, proteinases, pharmaceuticals (*anti-histamines, aesthetics, analgesics, anesthetic, antibacterials, antifungals, steroids, anti-inflammatories, anti-irritants, immunosuppressant, vasoconstrictors, etc*), proteins, and more are all used in the field to relieve signs of discomfort. Even water and saline can be used for comfort. A distinction must be made between comfort agents and comfort molecules and indirect comfort providers. This distinction can be made difficult as there is no universally agreed upon definition comfort agents or of comfort within the field. Comfort agents are macromolecules specifically delivered to the tear fluid to augment characteristics of the tear film (*i.e., prevent disruption of the tear film, prevent loss of tear volume, and/or reduce stress on the corneal epithelium specifically to alleviate ocular*

discomfort, stabilize the tear film, increase tear volume, etc). The contributing properties are derived from the physical and solution properties of the comfort agent and not pharmacological action, such as with cyclosporine (*immunosuppressant*), ketotifen fumarate (*antihistamine*), lidocaine (*anesthetic*), naphazoline (*vasoconstrictor*), and other pharmaceuticals. Comfort agents are not absorbed by the ocular tissues, residing only in the tear film until removed via spillage from the eye and normal drainage through the nasal cavity. The comfort agents are only active while residing in the tear fluid, ceasing to promote ocular comfort once removed from the tear fluid. Comfort molecules can promote comfort but do not act on the bulk tear film properties, such as using surfactants or emulsifiers (*increase solubility of proteins, act as antibacterials or antivirals, replace lipids*) or lipids (*prevent tear evaporation*). Comfort providers are molecules (*pharmaceuticals, ions, saline, or water*) that relieve discomfort, such as drugs that act through pharmaceutical action within the ocular tissue or within the inner eye to relieve a specific condition/symptom that results in the cessation of discomfort almost as a side effect. **Table 2.4** and **Table 2.5** demonstrates the classification of molecules according to this criteria. A brief summary of the advantages of incorporating comfort agents into various formulations and ocular devices is provided in **Table 2.6**.

2.4.2. Classes of Comfort Agents

There are two broad classes of polymeric comfort agents: polysaccharide comfort agents and acrylic comfort agents. Polysaccharide comfort agents are macromolecules composed of one or more types of monosaccharide. Most often, polysaccharide comfort agents are typically linear, high molecular weight, and hydrophilic, though substitution along the polymer backbone is common and can affect the overall conformation of the

macromolecule, particularly at high degrees of substitution. These substitutions can be branches, alkyl groups, functional groups, or even salt complexes. In solution, polysaccharides have high hydrodynamic volume and a stiff, rod-like conformation at low molecular weight and adapt a Gaussian coil conformation at higher molecular weight **[2.123-127]**. Solution viscosity of polysaccharide comfort agents is typically high and pseudoplastic in behavior. However, highly diverse and varied properties can be achieved by controlling monosaccharide composition and morphology within the polysaccharide architecture. In general, polysaccharides all have high water affinity and high rheological-modifying properties. These molecules act as thickeners but demonstrate shear-thinning behavior and possess bio-adhesive properties. These properties vary between molecular weights, concentration, and, in particular, comfort agent species. Comfort agents used in the salt form are referred to as polyelectrolytes, and charged polysaccharides are known as polyelectrolyte polysaccharides.

Acrylic comfort agents are linear chains composed of carbon-carbon backbones with regular repeat units, often including at least one functional group. Acrylic comfort agents can be used as polyelectrolytes or in the neutral state. This category also includes polyacids, which are used less often than other agents but have slightly increased water retention properties when compared to neutral acrylic agents.

2.4.3. Description Of Comfort Agent Solutions

Comfort agent eye drops are viscoelastic aqueous solutions containing comfort agents, preservatives, buffer salts, and emulsifiers. An instilled aliquot of solution replenishes the volume of water to the tear film and is spread over the entire area of the eye through the blinking response. The presence of the comfort agent aids to retain the excess

volume within the tear film. Key solution properties of the tear fluid are altered to promote comfort. These properties are discussed in detail and related to comfort agent molecular weight and concentration in **Chapter 3** and in **Chapter 4**.

2.5. Current State Of The Ocular Comfort Solution Field

The importance of comfort to the future of the ophthalmic field is expounded elsewhere in this text. However, to understand the assumptions, rationale, and impact of this work, it is necessary to understand the current state of the field. To this end, the current state of the comfort market is reviewed. All monetary values discussed in this section are in United States Dollars (*$*) and presented as found in the original cited reference. The current 2013 monetary value is immediately followed in parentheses, as calculated according to the inflation calculator provided by the U.S. Federal Bureau of Labor Statistics (*http://www.bls.gov/data/inflation_calculator.htm*).

2.5.1. Cyclosporine Solutions

The value of comfort agent solution eye drops or artificial tears was approximated at $1.9 (*$2.03*) billion in 2010. Allergan's Restasis® was introduced in 2003, as the first and currently only pharmagent-containing eye drop for the treatment of dry eye symptoms. The active ingredient in Restasis® is cyclosporine, a powerful immunosuppressant that reduces the sensations of discomfort by reducing the inflammation of the lacrimal glands. In 2010, Restasis® eye drop suspension was the most sold individual brand reached $621 (*$664*) million, approximately 30% of the sales of all dry eye relief solutions. This may be misleading as market reports typically do not track the sales for over-the-counter (*OTC*) eye drop solutions, and macromolecular comfort agents are often mixed in with pharmaceutical drops to provide comfort in addition to serving as emulsifiers or excipients

or rheology modifiers. Also, the same species of comfort agents can be formulated into numerous competing eye drop brands as shown in **Table 2.10**. For example, hyaluronic acid is the primary comfort agent in several well-known brands, whereas Restasis® is protected by patent and is the only pharmagent eye drop available on the market. However, the sales data necessary for a more complete analysis of comfort solution sales based on the primary comfort molecule is not currently available. Perhaps some relative standing and patient preference can be found by comparing between two prescription comfort molecules: cyclosporine and Hyalein, a hyaluronic acid derivative. Hyalein was developed and introduced in Japan in 1995, where it has become the majority revenue generating product for Santen Pharmaceuticals **[2.37]**. Hyalein is prescribed for treatment of 80% dry eye suffers within Japan and is the predominant majority treatment option for Eastern Asia **[2.37]**. However, acceptance and wide spread usage of Hyalein outside of the Orient has been slow, having only recently been approved for sale in areas of Europe and was recently denied for usage within the USA by the FDA **[2.37]**. **Figure 2.8** shows the annual revenue for Restasis® and Hyalein.

It is highly interesting that the annual revenue procured from Restasis® is expected to drop so dramatically in such a short time. This is potentially due to several causes. First, the propriety protection provided by the Allergan's patent on the Restasis® formulation has given Allergan monopoly profits on the pharmagent eye drop market for the past decade. Moreover, when Restasis® debuted on the market, there was high public interest and excitement, and the drops were well publicized and high initial popularity and reviews. Over time, there has been increasing consumer dissatisfaction with the drops, most often with the price, length of time necessary before any beneficial effect was noticed, and

sensations of itching and stinging upon initial application of the drop, and, most importantly, the low consumer success rate from use of Restasis®. One published report claims that the overall long term satisfaction with Restasis® is around 2% **[2.128]**. Also, Allergan reports that improvements are observed in 15% of patients that use Restasis® **[2.129]**. In addition, Restasis® is not to be used with contact lens wear. Therefore, Restasis® is best suited for long time dry eye suffers and not to relieve CLIDE symptoms or occasional/environmental discomfort. Restasis® is expected to lose patent status in 2014, unless a new patent is granted for Restasis X, a very similar formulation except with a different preservative and increased cyclosporine content (*0.1%*) **[2.37]**. Clinical trials with Restasis X have indicated increased effectiveness through patient reports that discomfort was noticeably improved 3 weeks after initiation of treatment, whereas Restasis (*0.05% cyclosporine concentration*) took an average of 4-5 weeks before any benefit was reported **[2.37]**. Also, Allergan has recently been accused of engaging in illegal and/or unethical business practices to encourage ophthalmologist and prescribing optometrists in exchange for aggressively marketing Restasis® to their patients. This is expected to shake consumer confidence in Restasis® and affect the sales.

In the past decade, more than a dozen pharmagent eye drop solutions have been submitted to the FDA for treatment of dry eye syndrome. To date, no other solution has been approved for usage. There is a very large potential market for dry eye discomfort drops and a high unmet demand. There are numerous ongoing clinical trials in the US for ocular pharmagents at various phases and are expected to apply for final approval, but it is uncertain whether any will be approved for general sale. There have been criticisms of the FDA for a perceived overly inflexible, myopic, and inaccurate model for dry eye

symptoms. Critics have cited the wide diversity of dry eye-related conditions, which make it a very difficult disease to quantify and treat particularly in a repeatable manner. In particular, critics have cited the transition from phase II to phase III studies. For this reason, there is expected to be very few pharmagent solutions introduced to the US market for the treatment of dry eye discomfort. The approval process is prohibitively difficult and requires a large investment of resources and time. Afterwards, the product would require a physician prescription, making it difficult to procure.

2.5.2. Comfort Agent Solutions

In contrast, the development and marketing of comfort agent solutions is much simpler and subject to less stringent regulations. The solutions do not require federal approval or prescription, making them available over the counter. This is because comfort agents are not pharmaceutically active molecules and can be registered as emulsifiers, excipients, or inactive ingredients, instead of therapeutic or active ingredients, while still alleviating symptoms of discomfort.

2.6. Conclusions

Chapter 2 is primarily a review and discussion of the current status and future developments within the comfort product and palliative market. Within the chapter, currently available comfort molecules and solutions are presented, discussed, reviewed, and evaluated according to sales and consumer preferences presented within the literature, research updates, corporate statements and press releases, as well as other independent market reports. To promote a greater understanding of the needs, demands, and developments within the field, it was necessary to provide a review of basic causes and medical conditions that result in sensations of ocular discomfort for both the contact lens

wearing population and for non-lens wearers, including a gross review of basic ocular anatomy and tissues, including general descriptions of the eye, the anatomical barriers to effective ocular drug delivery, and differences in the transport of certain classes of molecules within the tear film and within the ocular tissues. With this basic understanding, the behavior and properties of common comfort molecules and their respective solutions are reviewed. In addition, the most promising comfort molecules undergoing clinical and regulatory evaluation for use in commercial and medical products are presented.

In addition to the traditional review and discussion, **Chapter 2** provides a fundamental analysis and novel conclusions. For the first time within the comfort literature, **Chapter 2** attempts to provide a complete definition of ocular comfort, comfort agents, and classifications among comfort molecules, defining and distinguishing the molecules according to similarities in structure, mechanism of action, and properties (*both physical and solution properties*). One such distinction is between comfort promoters (*molecules that contribute to ocular comfort through a single, specific effect or property*), pharmagents (*pharmaceutically active comfort molecules*), and comfort agents (*molecules that contribute to ocular comfort via multiple, diverse effects or properties*). In addition, the analysis of the current trends within the field provided rationale for prediction of the future of the field.

2.7. Tables

Table 2.1. Description Of Dry Eye Syndrome And Contact Lens-Associated Discomfort

Condition	Cause(s)	Description
DES/ Keratoconjunctivitis Sicca	Loss Of Tear Volume Decreased Tear Production Increased Rate Of Tear Evaporation	• Diagnosis For Any Sensation Of Ocular Discomfort That Results From Dryness Of The Cornea And Anterior Surface Of The Eye • High Risk Are Elderly And Women • Effects Up To 10% Of The Population, Including 10% Of Post-Menopausal Women And Up To 50% Of The Elderly
Sjögren's Syndrome	Genetic Auto-Immune Disorder	• Exocrine Glands Are Attacked By The Immune System And The Rate Of Tear And Saliva Production Is Significantly Reduced • 90% Of Patients Are Women
Computer Usage	Intense Lighting Long Periods Of A Low Blink Rate	• Recognized Condition By NIH • Recommendation Include Frequent Breaks Or The "20-20-20" Rule
Age-Induced	Changes In Lipid Production Decreased Tear Production	• Women Are At High Risk
Seasonal	Changes In Humidity And Temperature, Etc Reduce Tear Volume Seasonal Allergies Cause Changes In Tear Production And Irritation, Etc	• At High Risk Are Lens Wearers. Women, And Elderly
Environmental (Office, Airplane, etc)	Lighting Causes Irritation High Air Circulation, Low Humidity, Fatigue, And Computer Usage Reduce Volume	• At High Risk Are Lens Wearers. Women, And Elderly
Surgically-Induced	Scar Tissue Changes Surface Tension	• Examples Include Burns From LASIK And Stitches From Cornea Transplant • Changes In Surface Tension Disrupts The Stability Of The Tear Film, Increasing The Rate Of Evaporation
Pharmaceutical	Pharmacological Side Effect	• Select Pharmaceutical Molecules Affect The Rate Or Protein, Lipid, And Tear Production
CLAD	Contact Lens Wear	• Table 2.2 • Figure 2.1
Computer Usage	Intense Lighting Long Periods Of A Low Blink Rate	• Recognized Condition By NIH • Recommendation Include Frequent Breaks Or The "20-20-20" Rule
Age-Induced	Changes In Lipid Production Decreased Tear Production	• Women Are At High Risk
Seasonal	Changes In Humidity And Temperature, Etc Reduce Tear Volume Seasonal Allergies Cause Changes In Tear Production And Irritation, Etc	• At High Risk Are Lens Wearers. Women, And Elderly
Environmental (Office, Airplane, etc)	Lighting Causes Irritation High Air Circulation, Low Humidity, Fatigue, And Computer Usage Reduce Volume	• At High Risk Are Lens Wearers. Women, And Elderly
Foreign Body Response	Contact Lens Wear	• Corneal Swelling, Shear Stress, Oxygen Starvation, Increases In Intraocular Pressure, And Irritation Lead To Ocular Fatigue And Exhaustion
CLIDE	Contact Lens Wear	• Contact Lens Absorbs Water From The Tear Film Or Disrupts The Film Stability • Resulting In Increased Rates Of Evaporation
Fouling Of The Lens Surface	Contact Lens Wear	• Protein, Lipids, And Other Deposits Present In The Tear Film Adhere To The Surface Of The Lens
Disruption Of The Tear Film	Contact Lens Wear	• Normal Laminar Flow Of The Tear Film Becomes Turbulent

Table 2.2. Description Of Propagators Of CLAD

Propagator	Description
Disruption Of The Tear Film	• **Normal Laminar Flow Of The Tear Film Becomes Turbulent** • **Lipid Boundary Layers Of The Tear Film Are Disrupted And Evaporation Rates Are Increased** • **Caused By The Presence Of A Lens Much Thicker Than The Tear Film Displacing Tear Fluid**
Spoiling Of The Lens Surface	• **Protein, Lipids, And Other Deposits Present In The Tear Film Adhere To The Surface Of The Lens** • **Frictional Effects And Degradation From The Blinking Action Erode The Surface** • **Makes The Lens Feel Dirty And Lowers The Ocular Tolerance Of The Lens By The Ocular Tissue**
CLIDE	• **Contact Lens Absorbs Water From The Tear Film Or Disrupts The Film Stability** • **Resulting In Increased Rates Of Evaporation**
Presence Of A Foreign Body And The Ocular Response	• **Corneal Swelling, Shear Stress, Oxygen Starvation, Increases In Intraocular Pressure, And Irritation Lead To Ocular Fatigue And Exhaustion** • **Can Cause Tissue Damage As Well As Changes In Tear And Lipid/Protein Production**
Synergistic Effects Of The Above Factors	• **Synergy Between Any Of The Above Propagators Of Discomfort Exacerbate The Effect Of Any Other Propagator**

Table 2.3. Description Of The Ocular Tissues And Features

Tissue/Ocular Feature	Description
Conjunctiva	• **Transparent Lining Of The Eyelid And Sclera** • **Helps Lubricate Eye By Producing Mucus And Tear Fluid** • **Effective Barrier To Microbes**
Cornea	• **Transparent Covering Of The Pupil And Iris** • **Lacks Vasculature Due To Clarity Demands** • **Oxygen Transport Is Completely Dependent From The Atmosphere**
Eye Lashes	• **Short Hairs Residing On The Edge Of The Eye Lids To Clear Debris From Landing On The Eye**
Eye Lids	• **Thin Fold Of Skin Folds That Covers And Protects The Eye** • **Wets The Eye, Spreads The Tear Fluid, And Refreshes The Tear Film Fluid Volume** • **Prevents The Eye From Dehydrating During Sleep**
Iris	• **Colored Part Of The Eye** • **Controls The Size And Diameter Of The Pupil**
Lacrimal Punctum	• **Drainage Point For The Tear Fluid** • **Tear Fluid Is Drained Into The Nasal Duct** • **One In Each Eye Lid**
Lens	• **Clear Crystalline Structure The Separates The Anterior And Posterior Segments** • **Changes Shape To Refract Light To The Retina** • **Changes Shape To Change The Focal Length Of The Eye To Help Focus On Distant Objects**
Meibomian Gland	• **Tarsal Glands That Excrete Lipids That Prevent Tear Evaporation** • **50 Glands In The Upper Lid** • **25 Glands In The Lower Lid**
Optic Nerve	• **Nerve That Carries The Visual Information To The Brain**
Pupil	• **Hole In The Center Of The Iris** • **Directs Light To The Retina By Expanding And Contracting** • **Diameter Can Vary From 3 mm To 15 mm**
Retina	• **Area Of Eye That Absorbs Light And Converts To Visual Information For The Brain**
Sclera	• **The White Of The Eye** • **Popularized To Have Been Told To The Soldiers At Bunker Hill To Wait Until They Saw Before They Fired** • **Tough, Fibrous, Protective Outer Layer Of The Eye**
Tear Film	• **Fluid Lining The Anterior Surface Of The Eye** • **Lubricates And Buffers The Eye From Shear Stress During Blinking** • **Removes Debris And Contaminants** • **Major Barrier To Topical Ocular Drug Delivery** • **Made Up Of 3 Distinct Layers**
Vasculature	• **Predominantly Lines The Posterior Wall Of The Eye** • **Blood-Retina Barrier Pharmacologically Isolates The Eye From The Body**
Vitreous Humor	• **Gel The Fills The Anterior Chamber** • **99% Water, But Small Amount Of Collagen Makes It A Viscous Gel**

Table 2.4. Description Of Comfort Agent Species

Species	Alternate Names	Description
HA	Hyaluronic Acid Hyaluronan Hyaluronate Hyalein	Anionic Polysaccharide With High Water Retention And Displays Shear Thinning Solution Behavior, Binds To The Endothelial Cells
HPMC	Hydroxypropyl Methylcellulose Hypromellose Methylcellulose	Nonpolar, Nonionic Polysaccharide With Mild Water Retention Behavior But Acts Primarily Via Altering Tear Fluid Viscosity
CMC	Carboxymethylcellulose Carmellose	Anionic Polysaccharide Polyelectrolyte With Mild Water Retention And Mild Solution Viscosity Properties
Dextran	Dextran Poly(Dextrose)	Nonpolar, Nonionic Simple Polysaccharide That Is Often Used With Hydroxypropyl Methylcellulose As A Dilatant
PVA	Poly(Vinyl Alcohol) Polyol	Nonionic Neutral Acrylic Comfort Agent With Mild Water Retention And Moderate Solution Viscosity Effect
PVP	Poly(Vinyl Pyrrilidone) Povidone	Nonionic Neutral Acrylic Comfort Agent With Mild Water Retention And Moderate Solution Viscosity Effect
PAA PMAA	Poly(Methacrylic Acid) Poly(Acrylic Acid) Carbomers PolyAcids	Polyelectrolyte Acrylic Comfort Agent With Mild Water Retention And Moderate Solution Viscosity Effect

Table 2.5. Comfort Molecule Definitions

Term	Description	Examples
Comfort Molecule	**Applies To Any Molecule That Results In Sensations Of Comfort, Directly Or Indirectly**	**Any Of The Below**
Comfort Agent	**(Macro)Molecule That Promotes Comfort By Augmenting The Bulk Physical Properties Of The Tear Fluid To Mitigate Sensations Of Discomfort** **Molecule Is Active Only When Residing In The Tear Film And Is Not Absorbed Into The Ocular Tissue** **Comfort Agents Can Be Incorporated Into Ocular Devices To Actively Improve Ocular Comfort Or Tolerance Of The Device Though The Comfort Agent Is Present Within The Device And Not In The Tear Film**	**HPMC** **HA** **PVA** **PVP**
Pharmaceutical Agent (*Pharmagent*)	**Pharmalogically Active Molecule That Is Absorbed Into The Ocular Tissue And Results In Relief Of Sensations Of Discomfort Via Pharmaceutical Action** **Sensations Of Comfort Are Typically Considered To Be An Indirect Result**	**Cyclosporine**
Comfort Promoter	**Molecule That Promotes Comfort By Altering A Single Characteristic Of The Tear Fluid**	**Lipid** **Surfactants**
Low Molecular Weight Comfort Agent	**MW Under 1 Kda, Effects Numerous Physical Properties Of The Tear Film But Not As Significantly As Higher Molecular Weights Due To Their Smaller Size**	**Trehalose** **Glycerol**
Lubricating Agent	**Reduce The Shear Stress Of The Eyelid Movement On The Ocular Surface**	**HA** **HPMC**
Re-Wetting Agent	**Restore Or Retain Tear Fluid Volume**	**Trehalose** **HA** **PVA**
Emulsifying Agent	**Solubilizes Proteins And Lipids And Other Deposits That Cause Irritation**	**PVA** **PVP** **Carbomers**
Demulcing Agent	**Stabilizes Fluid Film Layers Strengthening The Barrier Effect Of The Film**	**HA** **HPMC** **CMC**
Viscoelastic Agent	**Alters The Tear Fluid Viscosity To Reduce Shear Stress, Reduce Film Disruption, Drainage, Etc**	**HPMC** **Dextran** **HA**
Decongesting Agent	**Reduces Protein Concentrations**	**HA** **Carbomers**

Table 2.6. Advantage Of Incorporating Comfort Agent Into Devices And Formulations

Type	Product	Potential Advantage	Potential Disadvantage
Topical	Eye Drops/ Artificial Tears	• Retains Tear Volume • Increases/Decreases Viscosity • Lubricates The Eye • Prevents Excess Evaporation • Maintains Tear Film	• Decreased Residence Time Compared To Ointment • Applied Frequently
	Ointments		• Increased Invasiveness To Compared To Eye Drops • Reduced Vision (*Temporarily*) And Aesthetics • Increased Discomfort Due To Viscosity Or Roughness Of Coating
Devices	Contact Lenses	• Reduces Protein Adhesion • Maintains Lens Wettability • Lubricates Lens Surface • Refreshes Lens Surface • Releases Comfort Agent Into The Tear Fluid Which Leads To Same Advantages Of Eye Drops Without Disadvantages	• Must Be Optically Clear • Loading Is Constrained By Lens Thickness And Optical Clarity
	Punctual Plugs	• Increased Tolerance Of Plug Installation • Does Not Need To Be Optically Clear	• Plug Requires Professional Application • May Be Expelled Without Patient Knowledge • Limited Loading Due To Plug Volume • Limited Release Due To Decreased Surface Area And Location
	Inserts	• Releases Comfort Agent To The Tear Fluid Which Leads To Same Advantages Of Eye Drops Without Disadvantages • Does Not Need To Be Optically Clear • Versatility In Design Shape Or Thickness	• Difficult To Apply • May Be Expelled Without Patient Knowledge • Limited Release Due To Decreased Surface Area And Location

Table 2.7. Description Of Macromolecular Comfort Agent Species

Species (*CAS*)	MW (KDa) [Log P]	Charge	Functional Pendant Groups	H-Bond Acceptor Sites	H-Bond Donor Sites
HA (*9004-61-9)*	388 [-4.91]	Neutral Polar Acid Group	3 –OH 1 –COOH 1 $–OCH_2OH$ 1 –NHCOH	13	8
HA Sodium Salt (*9067-32-7)*	419 [-5]	Anionic	3 –OH 1 $–OCH_2OH$ 1 –NHCOH 1 –Sodium salt	13	7
HA Potassium Salt (*31799-91-4*)	435 [-5]	Anionic	3 –OH 1 $–OCH_2OH$ 1 –NHCOH 1 –Potassium salt	13	7
HPMC (*9004-65-3*)	410 [-0.9]	Neutral Polar Groups	1-3 –OH 1-3 $–OCH_3$ 1-3 $–OCH_2CH(OH)CH_3$	19	8
CMC (*9000-11-7*)	520 [-5.5]	Neutral Polar Groups	1-4 –OH 1-3 $–OCH_2CO_2H$ 2 $–CH_2OH$	15	8
Sodium CMC (*9002-32-4*)	502 [-5.6]	Anionic	1-4 –OH 1-3 $–OCH_2CO_2^-Na^+$ 2 $–CH_2OH$	15	6
Dextran (*9004-54-0*)	342 [-5.3]	Neutral Polar Groups	6 –OH	11	29
DSS (*9011-18-1*)	955 [-5.6]5	Anionic	6 $–SO_4^-Na^+$	8	2
PVA (*9002-89-5*)	74 [0.75]	Neutral Polar Groups	1 –OH	1	1
PVP (*9003-39-8*)	141 [2.15]	Neutral Polar Groups	1 Pyrrilidone	2	0
PAA (*9003-01-4*)	102 [0.824]	Anionic	1 –COOH or COO^-	2	1
PMAA (*25086-62-8)*	116 [1.03]	Anionic	1 –COOH or COO^-	2	1

Table 2.8. Description Of Different Classes Of Comfort Agents

Term	Description	Examples
Polyelectrolyte	Ionically Charged Macromolecule Usually In The Form Of A Metallic Salt Or Acid, And Which Dissociates In The Tear Solution	HA CMC DSS Carbomers
Neutral	Macromolecule With No Ionic Charge But Can Have High Polarity Functional Groups In The Repeat Unit	HPMC Dextran PVA PVP
Polysaccharide	High Molecular Weight Carbohydrate Macromolecules Where The Repeat Unit Is Composed Of Mono- Or Di-Saccharide Units	HA HPMC CMC Dextran
Acrylic	High Molecular Weight Vinyl Macromolecules Where The Polymeric Backbone Is Primarily Composed Of Repeating Carbon-Carbon Bonds, But May Have Diverse Pendant Functionalities	PVA PVP Carbomers

Table 2.9. Description Of Pharmagent Molecules

Species (*CAS*)	MW (Da) [Log P]	Class	H-Bond Acceptor Sites	H-Bond Donor Sites	Status
Cyclosporine (*59865-13-3*)	120 [11.33[	Immunosuppressant	23	5	Approved
Azithromycin (*83905-9-5*)	749 [2.5]	Antibiotics	14	5	Phase 4
Loteprednol Etabonate (*82034-46-6*)	467 [3.7]	Corticosteroid	7	1	Phase 4
Tacrolimus (*104987-11-3*)	804 [4.4]	Immunosuppressant	13	3	Phase 4
Bromfenac (*91714-94-2*)	334 [3.4]	NSAID	4	2	Phase 3
Dexamethasone (*50-102-2*)	392 [3.5]	Steroid	6	3	Phase 3
Dexamethasone Phosphate (*2392-39-4*)	517 [-0.5]	Steroid	6	3	Phase 3
Diquafosol Tetrasodium (*211427-08-6*)	790 [-0.5]	Receptor Antagonist	23	6	Phase 3 Approved in Japan
Ecabet Sodium (*86408-72-2*)	380 [-3.6]	Gastroprotector	5	0	Phase 3 Approved in Japan
Lifitegrast Sodium (*1119276-80-0*)	638 [-5.5]	Anti-Inflammatory	9	1	Phase 3
Sirolimus (*53123-8-8*)	914 [5.4]	Immunosuppressant	14	3	Phase 3
Ketorolac (*74103-06-3*)	255 [2.2]	NSAID	3	1	Phase 2
Rebamipide (*90098-04-7*)	371 [4.3]	Gastroprotector	5	3	Phase 2
Rimexolone (*49697-38-3*)	371 [2.7]	Anti-Inflammatory	3	1	Phase 2
Tasocitinib (*477600-75-2*)	312 [2.8]	Immunosuppressant	4	1	Phase 2
Thymosin Beta 4		Amino Acids			Phase 2
Chloroquine Diphosphate (*50-63-5*)	516 [-2]	Antibiotics	8	7	Phase 1
Pimecolimus (*137071-32-0*)	811 [5.7]	Immunosuppressant	12	2	Phase 1
Viclosporin	1215 [3.8]	Immunosuppressant	23	5	Phase 1

Table 2.10. List Of Commonly Available Over-The-Counter Comfort Agent Solutions

Species	Product	Brand	Manufacturer	% Conc
CMC	Clear Eyes	Tears	Prestige Brands Holdings	1
		Tears Liquid Gel		
	Genteal	Moderate to Severe	Alcon	0.25
	Refresh	Cellufresh	Allergan	0.5
		Dry Eye		0.5
		Optive		0.5
		Plus		0.5
		Tears		0.5
		Tears		0.5
		Celluvisc		1
		Liquigel		1
		Redness Relief		1.4
	Theratears	Original	Akorn	0.25
		Lubricant		0.25
		Contact Lens		0.5
		Contact Lens Comfort		0.5
Dextran 70	Assured	Advanced Relief	Greenbrier International	0.1
	Bion	Tears	Alcon	0.1
	CIBAVision	Aquasite	CIBAVision	0.1
	Family Wellness	Advanced Relief	Family Dollar	0.1
	Fred's	Advanced Relief	KC Pharmaceuticals	0.1
	Generic	Advanced Relief	American Sales Company	0.1
			Samchundang Pharm. Co	
			Kareway Product	
			McKesson	
		Nature's Tears	Rugby	0.4
	Leader	Dry Eye	Hanlim Pharm	0.1
	Tears	Renewed	Akorn	0.1
		Tearisol	CIBAVision	
	Tears Naturale	Forte	Alcon	0.1
		Free		
		I (Duasorb)		
		II	Alcon	0.1
	Visine	Advanced	Johnson & Johnson	0.1
HA	AQuify	AQuify Long Lasting	CIBAVision	0.1
	Blink	GelTears	Abbott Medical Optics	0.1
		Tears		0.1
		Contacts		0.15
	Boston	Rewetting	Bausch & Lomb	0.1
	DuoVisc	ProVisc	Generic	0.3
	EyeVisc	EyeVisc Plus	Generic	0.2
		EyeVisc SH	Generic	0.2
	Focus	Lens Drop	CIBA	0.2
	Generic	Healon	Santen	1
		Healon 5		
		Healon GV		
		Hyalein		
	Genteal	GelTears	Alcon	1
	Ursapharm	Hylocomod	Santen	1
HPMC	Bion	Tears	Alcon	0.3
	Boston	Rewetting	Bausch & Lomb	0.1
	Clear Eyes	7 Symptom Relief	Prestige Brands Holdings	0.2
		Complete Relief		
		Tears Plus Itchy Eye Relief		
	Clear Eyes	Tears Plus	Prestige Brands Holdings	0.8
		Tears Plus Redness Relief		
		Contact Lens Relief		0.25
	Complete	BlinkNClean	Advanced Material Optics	0.1
		BlinkNClean Lens		
		Complete Moisture Plus		
	EyeVisc	EyeVisc	Generic	0.2

Species	Product	Brand	Manufacturer	% Conc
HPMC	Generic	Nature's Tears	Rugby	0.4
	GenTeal	Moderate	Alcon	2
		Mild		0.2
		Mild to Moderate		0.3
		Severe		0.4
	GeriCare	Artificial Tears	McKesson	0.4
	Hypotears	Hypro Artific	Alcon	0.3
	Isopto	Plain	Alcon	0.3
		Tears	Alcon	0.3
	Leader	Dry Eye	Hanlim Pharm	0.3
	Medic's Choice	Lubricant Eye Drops	KC Pharmaceuticals	0.2
	Muro 128	2% Saline	Mentholatum Company	0.2
		5% Saline		
	OpconA	OpconA Itching and Redness	Bausch & Lomb	0.5
	Rohto	Ice	Mentholatum Company	0.2
		Relief		
		Hydra		0.6
		Artic Redness Relief		0.35
	Systane	Contacts	Alcon	0.1
	Tear	Tearisol	CIBAVision	0.3
	Teargen	II	Goldline Laboratories	0.4
	Tears	Renewed	Akorn	0.3
	Tears Naturale	I (Duasorb)	Alcon	0.3
		II		
		Forte		
		Free		
	Visine	Pure Tears	Johnson & Johnson	0.1
		Tears		
		Contacts		
		Original		
		Tears Dry Eye		0.2
		Tears Dry Eye Relief		
		Maximum Redness Relief		0.36
		Tears		
		Tired Eye		
		Totality		
PVA	Blink	Dakrina	Dakryon	2.7
		Dwelle		
	Boston	Rewetting	Bausch & Lomb	1.4
	Clear Eyes	Dry Eye	Prestige Brands Holdings	0.5
		Natural Tears		
		Outdoor Dry Eye Protection		
		Traveler's Eye Relief		
		Triple Action Relief		
	Comfort Tears	Tears	Sola/Barnes Hind	1.4
	Fougera	Puralube	Fougera Pharmacia	1
	Fred's	Advanced Relief	KC Pharmaceuticals	1
	Generic	Artificial Tears	McKesson	0.5
			Rugby	1.4
			KC Pharmaceuticals	
	Hypotears	Eye Drops	Alcon	1
		PF		0.6
	Liquifilm	Frte	Allergan	1.4
		Tears		1.4
	Medic's Choice	Artificial Tears	KC Pharmaceuticals	0.5
	Murine Tears	Medtech	Prestige Brands Holdings	0.5
		Original		
		Redness Relief		
	Refresh	Eye Itch	Allergan	0.2
		Classic		1.4
		Redness Relief		1.4
		Lubricant		1.6

Species	Product	Brand	Manufacturer	% Conc
PVA	Soothe	Dry Eye Lubricant	Bausch & Lomb	1.4
	Tears	Teargen	Alcon	1.4
		Tears Plus		
	Tears	AKWA Tears	Akorn	1.4
	Vismed	Tear Solution	TRB Chemedica	0.18
PVP	Alcon	Absorbotear	Alcon	1.7
	Assured	Advanced Relief	Greenbrier International, Inc	1
	Blink	Dakrina	Dakryon	2
		Dwelle		2
	Clear Eyes	Dry Eye	Prestige Brands Holdings	0.6
		Natural Tears		
		Outdoor Dry Eye Protection		
		Traveler's Eye Relief		
		Triple Action Relief		
	Family Wellness	Advanced Relief	Family Dollar	1
	Generic	Advanced Relief	American Sales Company	1
			Samchundang Pharm. Co	
			Kareway Product	
			McKesson	
		Artificial Tears	McKesson	0.6
			KC Pharmaceuticals	
	Murine Tears	Artificial Tears	Prestige Brands Holdings	0.6
		Original		
		Redness Relief		
	Refresh	Lubricant	Allergan	0.4
		Contacts		0.5
		Classic		0.6
	Visine	Advanced	Johnson & Johnson	1
	Zaditor	Allergy Relief	Alcon	0.1

2.8. Figures

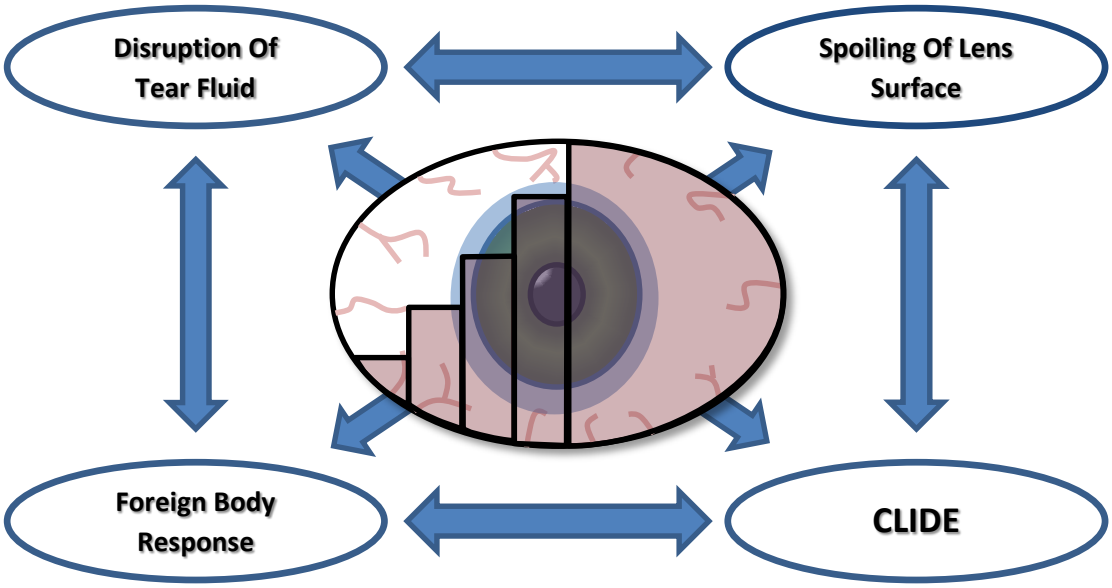


Figure 2.1. Propagators Of Ocular Discomfort In Contact Lens Wear

In general, the major propagators of discomfort can be divided into four main groups. These groups are shown above and are disruption of the tear fluid, spoiling of the lens surface, foreign body responses to the presence of the lens on the cornea, and contact lens-induced dry eye (*CLIDE*). Discomfort in lens wear arises over time through the interaction and interplay between the four groups (*represented by the arrows*). Each group can cause significant levels of discomfort independently, and most common treatments for contact lens-associated disorders (*CLAD*) tend to briefly ameliorate the discomfort derived from a single group, without addressing the other three. These groups exacerbate each other and result in significant levels of discomfort over time. These propagating groups are described in greater levels of detail in the text and in **Table 2.2**. Disruption of the tear film results from the difference in surface tension between the epithelial cells and the contact lens and

the presence of the contact lens disturbing the normal laminar flow of the tear film. This disruption can disturb the lipid boundary layer that stabilizes the tear film. Spoiling of the lens surface occurs through the adhesion of lipids and proteins to the surface of the lens, decreasing the biotolerance of the lens by the ocular tissue. In addition, the protein makes the lens feel dirty and can exacerbate the disruption of the tear film, etc. The presence of the lens on the surface tissue causes a response in the tissue, primarily in the form of swelling that causes discomfort and alters the tear fluid flow profile. The volume of the tear fluid can be severely reduced due to the presence of the lens, which can absorb water from the tear film or result in a significantly increased rate of evaporation.

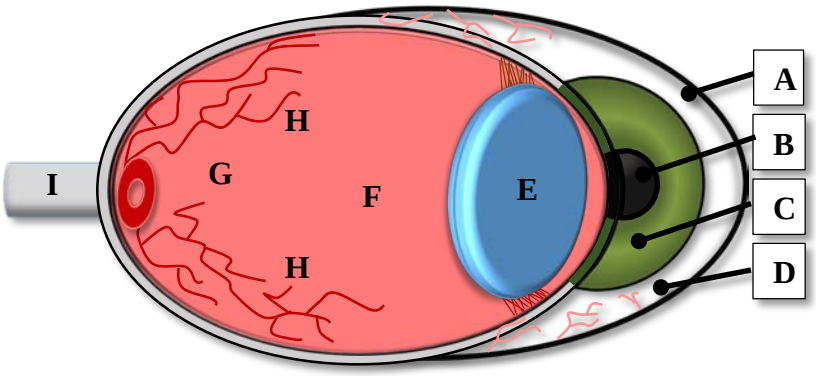
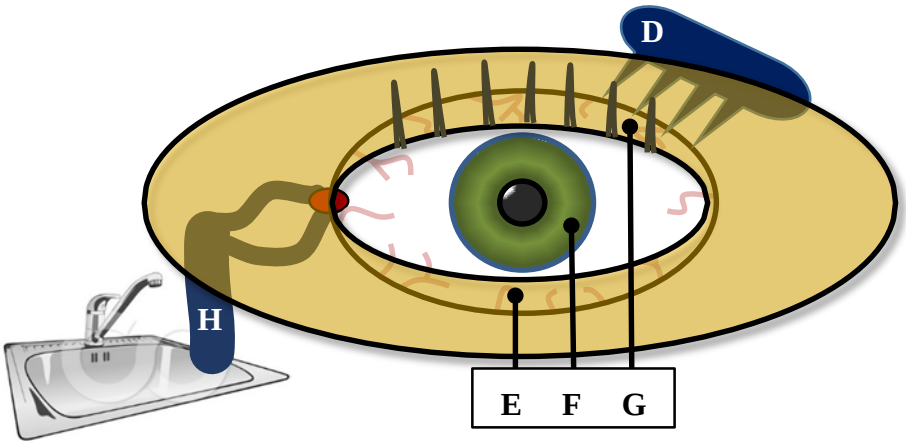


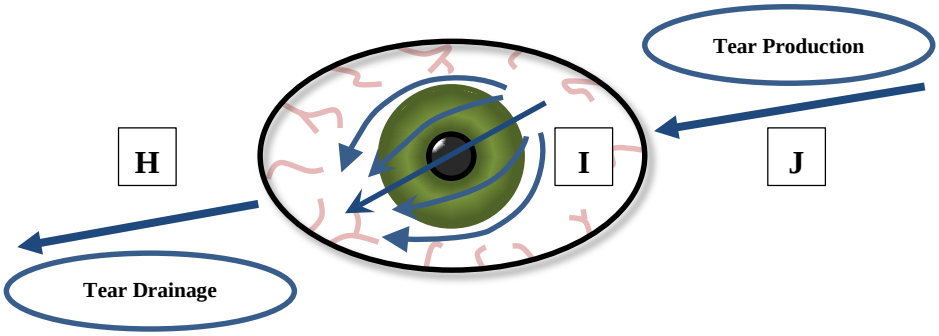
Figure 2.2. Cross-Sectional Anatomy Of The Human Eye

The anatomy of the human eye is described above. The eye can described as two distinct sections: the anterior chamber and the posterior segment. The anterior chamber is composed of the (***A***) conjunctiva, (***B***), pupil (***C***) iris, (***D***) sclera, and (***E***) the lens and accounts for the approximately 1/3 of the volume of the eye. The posterior segment is the remaining 2/3 of the ocular mass and volume. The posterior segment is made up of the (***F***) vitreous humor, (***G***) retina, (***H***) the majority of the vasculature within the eye. and (***I***) the optic nerve.

A. Tear System



B. Tear Flow



C. Tear Film

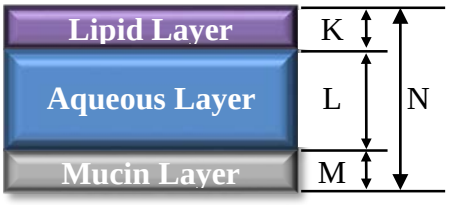
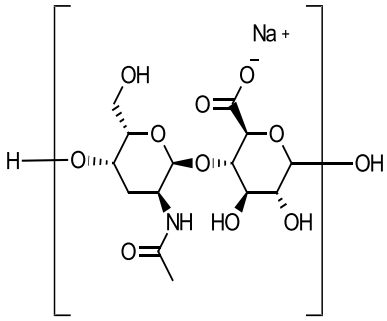


Figure 2.3. The Lacrimal System, Tear Flow, And The Tear Film

Figure 2.3A shows the overall lacrimal system. Tear fluid typically flows downward from the lacrimal gland, across the anterior surface of the eye and drains through the lacrimal ducts (***2.3B***). 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 (***2.3C***). 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.

Polyelectrolyte Polysaccharides

A.



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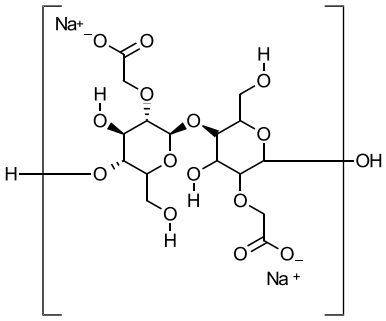

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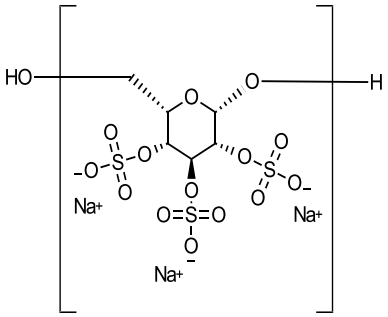
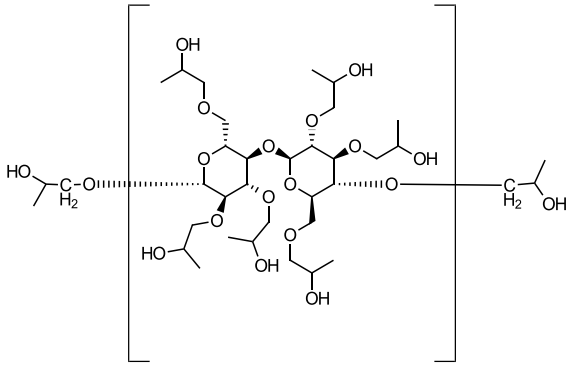
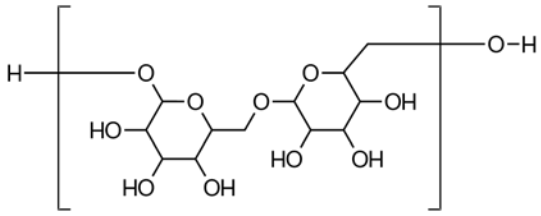


Neutral Polysaccharides

D.

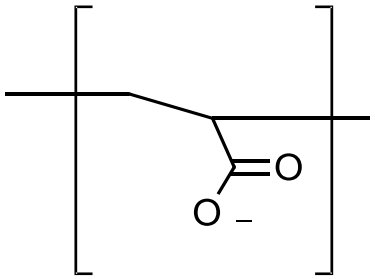


E.

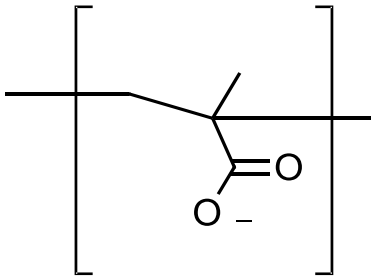


Polyelectrolyte Acrylics

F.

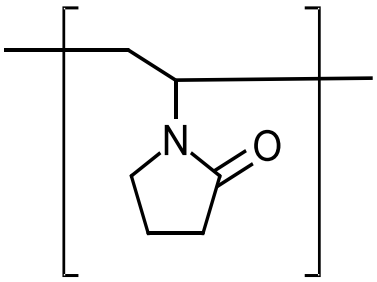


G.



Neutral Acrylics

H.



I.

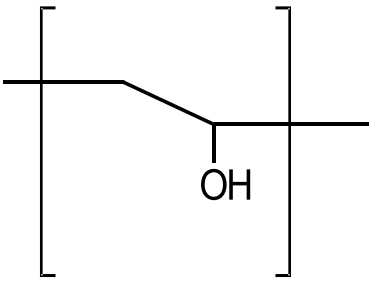


Figure 2.4. Repeating Unit Chemical Structure For Common Comfort Agents In Over-The-Counter Eye Drop Formulations

Structures represented here are common comfort agents in contact lens solutions and eye drop formulations. The comfort agents represented are divided between two categories: polysaccharide (*A-E*) and acrylic (*F-I*) molecules. Both categories can be divided according to charge. Charged or ionic molecules are polyelectrolytes (*A-C, F-G*), while those molecules are classified as neutral molecules (*D-E, H-I*). The specific molecules represented are **polyelectrolyte polysaccharides** (*A. sodium hyaluronate (HA), B. sodium carboxymethylcellulose (CMC), and C. dextran sodium sulfate (DSS)*), **neutral polysaccharides** (*D. hydroxypropyl methylcellulose (HPMC) and E. dextran (Dex)*), **polyelectrolyte acrylics** (*F. poly(acrylic acid) (PAA) and G. poly(methylacrylic acid)*

(PMAA)), and **neutral acrylics** (*H. poly(vinyl pyrrilidone) (PVP) and I. poly(vinyl alcohol)*).

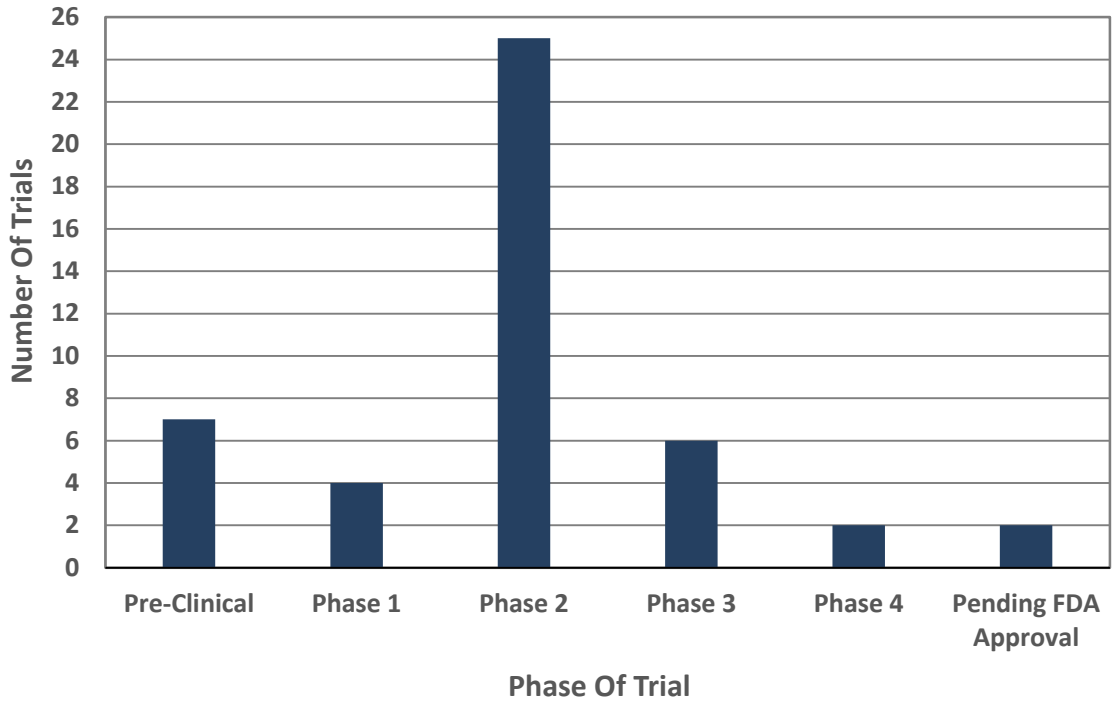
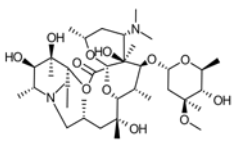


Figure 2.5. Number Of Dry Eye Drugs Undergoing Clinical Trials In The US During 2011

Number of pharmagent comfort molecules undergoing clinical investigation in the US for potential use in dry eye relief eye drops as of 2011. Only 2 were submitted to the FDA for approval, Prolacria (*denied twice previously*) and Inspire. Both were eventually denied by the FDA. No pharmagent molecule has been approved since cyclosporine in 2002. The most difficult transition is that from Phase 2 to Phase 3, as evident by the sudden drop in the number of clinical trials. The extremely low rate of approval of pharmagent solutions is due to overly strict and inflexible models of dry eye by the FDA, mostly due to the standard of repeatability between different types of dry conditions and complete clearing of the central cornea by the eye drop formulation, a requirement that has been criticized as unachievable in the ocular field.

Pharmagents Undergoing Phase 4 Clinical Trials For Treatment Of Dry Eye

A



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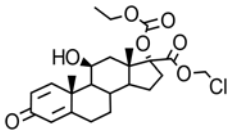

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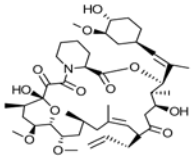

Pharmagents Undergoing Phase 3 Clinical Trials For Treatment Of Dry Eye

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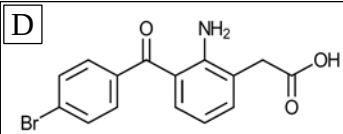

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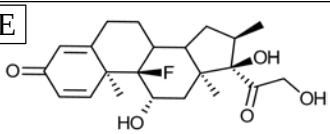

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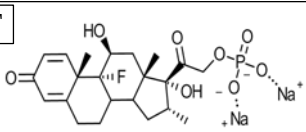

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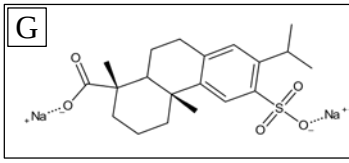

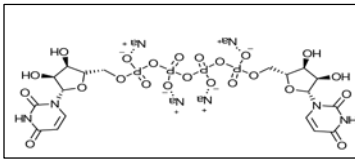

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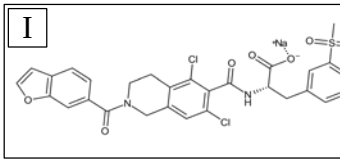

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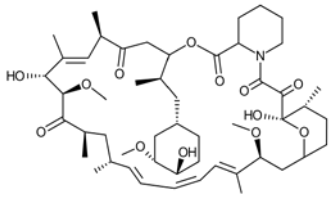

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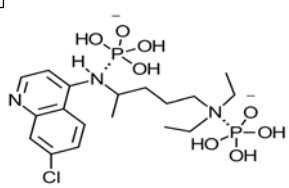

Pharmagents Undergoing Phase 2 Clinical Trials For Treatment Of Dry Eye

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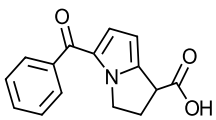

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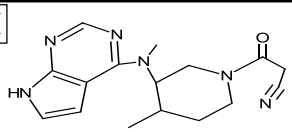

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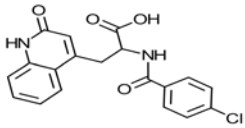

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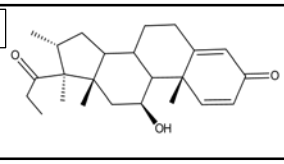

Pharmagents Undergoing Phase 1 Clinical Trials For Treatment Of Dry Eye

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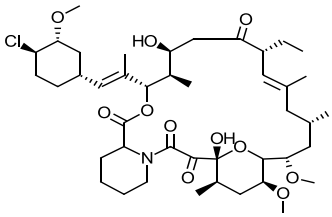

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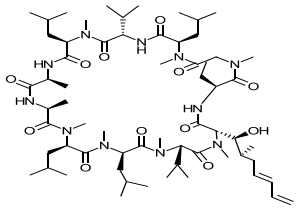

Pharmagents Currently Approved By The FDA For Treatment Of Dry Eye

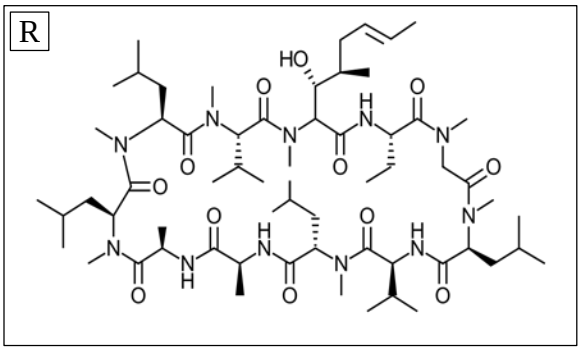

Figure 2.6. Chemical Structure Of Pharmagent Comfort Molecules Undergoing Clinical Trials For Use In The US To Treat Dry Eye Discomfort

Chemical structures for pharmaceutical molecules either approved by the FDA or currently undergoing review for use in eye drop solutions formulated to relieve dry eye symptom.ms. There are four phases of clinical trials in the review process. In the past decade or so, more than a dozen pharmagent molecules have undergone trials and have been denied by the FDA for various reasons. **Figure 2.6** depicts the chemical structure of select pharmagents molecules that have previously or presently been incorporated into clinical trials at various phases. To date, only one pharmagent solution (*Restasis, 0.05% cyclosporine*) has been approved by the FDA. It is not expected by market analysts that any new pharmagent solution will be introduced to the market with the next two years. The molecules depicted are (*A*) azithromycin, (*B*) loteprednol etabonate, (*C*) tacrolimus, (*D*) bromfenac, (*E*) dexamethasone, (*F*) dexamethasone phosphate, (*G*) ecabet sodium, (*H*) diquafosol tetrasodium, (*I*) lifitegrast sodium, (*J*) rapamycin, (*K*) chloroquine diphosphate, (*L*) keterolac, (*M*) tasocitinib, (*N*) rebamipide, (*O*) rimexolone, (*P*) pimecolimus, (*Q*) voclosporin, (*R*) cyclosporine.

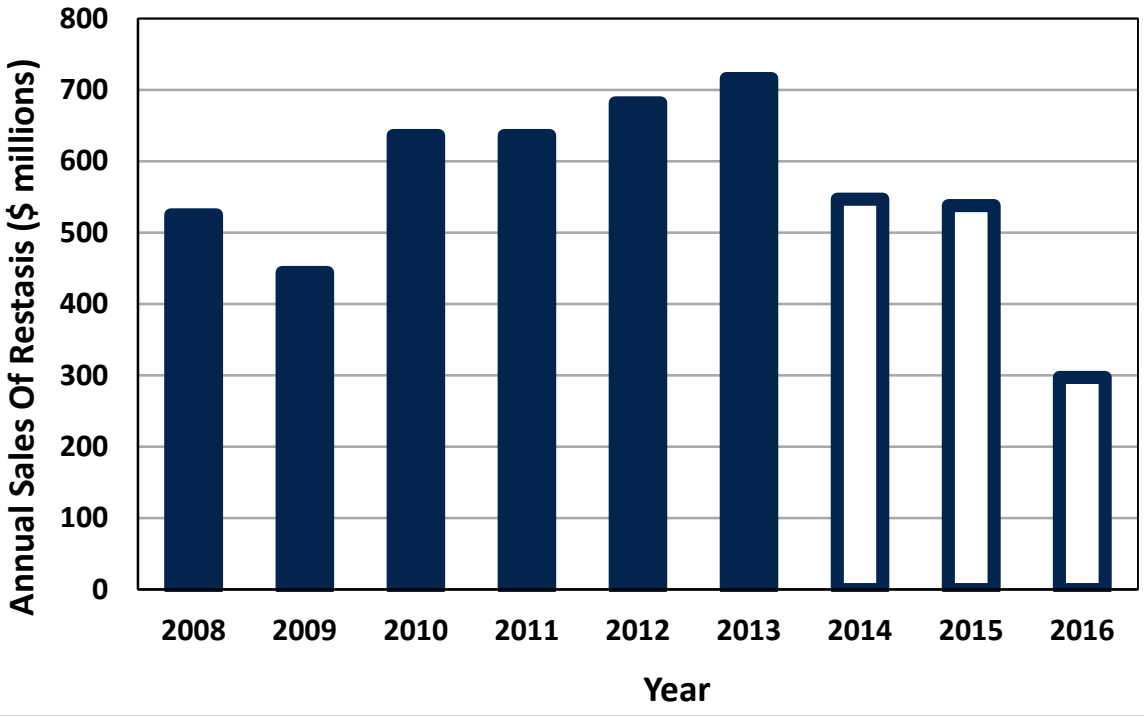

Figure 2.7. Annual Sales Revenue Of Restasis In The U.S.

The annual sales revenue (*solid*) of Allegan's Restasis in the US since 2008. In general, there has been an increasing trend, though market analyst predict that future sales (*hollow*) will decrease very quickly for several reasons, including the patient expiring for Restasis and the appearance of competitor product lines, either of another protected Restasis formulation (*Restasis X*) or from generic manufacturers. Also, Restasis has come under increasing criticism from consumers for sensations of burning and irritation upon drop application, that on average, no beneficial effect is observed before one month of treatment, a relatively low rate of observed beneficial effect in patients (*15%*) and the very low rate of long term patient satisfaction (2%). Compared to pharmagent solution, comfort agent solutions enjoy a much higher rate of patient satisfaction and fewer drawbacks.

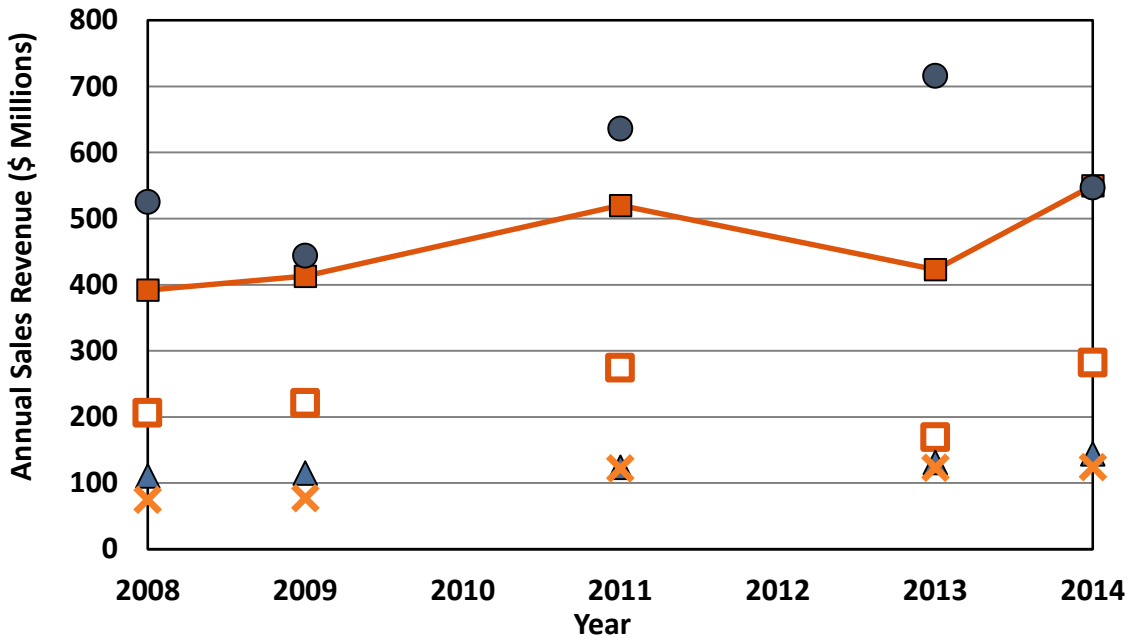

Figure 2.8. Annual Sales Revenue For Different Dry Eye Treatment Brands And Comfort Molecules

Annual sales revenue for different comfort molecule solution brands/comfort molecules, including several over-the-counter brands. The presented data includes (●) cyclosporine (*Restasis*®, *Allergan*®), (▣) hyaluronic acid (*Hyalein*, *Santen*), (▲) carboxymethylcellulose (*Celluvisc*, *Allergan*®), (✕) hydroxypropyl methylcellulose (*Tears Naturale*, *Alcon*®). Hyalein is only sold in Japan and eastern Asia and was recently denied for sale in the US. From the individual sales data, cyclosporine, and thus pharmagent solutions, appear to be highly preferred by consumers, but this can be misleading. However, when the comfort agent sales revenue are (■) combined, there is no clear distinction between consumer preference for pharmagent and comfort agent solutions. Also, this data does not include other brands or uses of comfort agents in prescription drops.

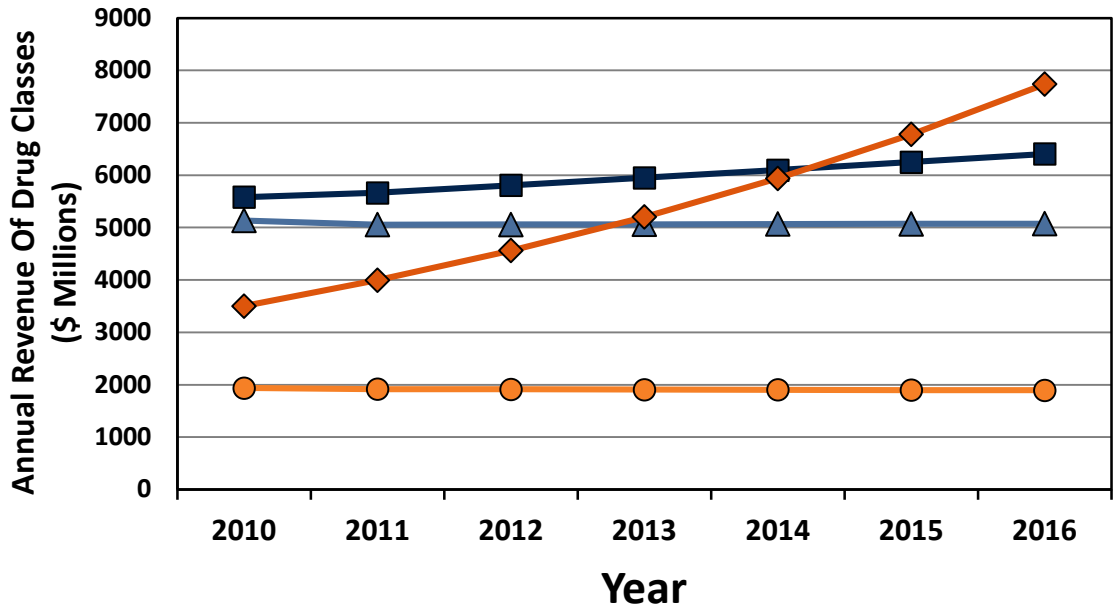

Figure 2.9. Annual Sales Of Different Classes Of Ocular Eye Drops

Annual sales of prescription grade of eye drops for various conditions including (■) glaucoma, (▲) retinal diseases, (♦) pharmagent solutions for anterior segment conditions (anti-allergy, inflammatory, etc), and (●) artificial tears. Artificial tears do not include Restasis, and are by far produce the least amount of yearly revenue in the data presented in this figure, but this can be misleading as market reports do not usually include non-prescription, over-the-counter sales reports. When including OTC sales data, there is no clear consumer preference between comfort agent solutions and pharmagent solutions as demonstrated in **Figure 2.7** and **Figure 2.8**.

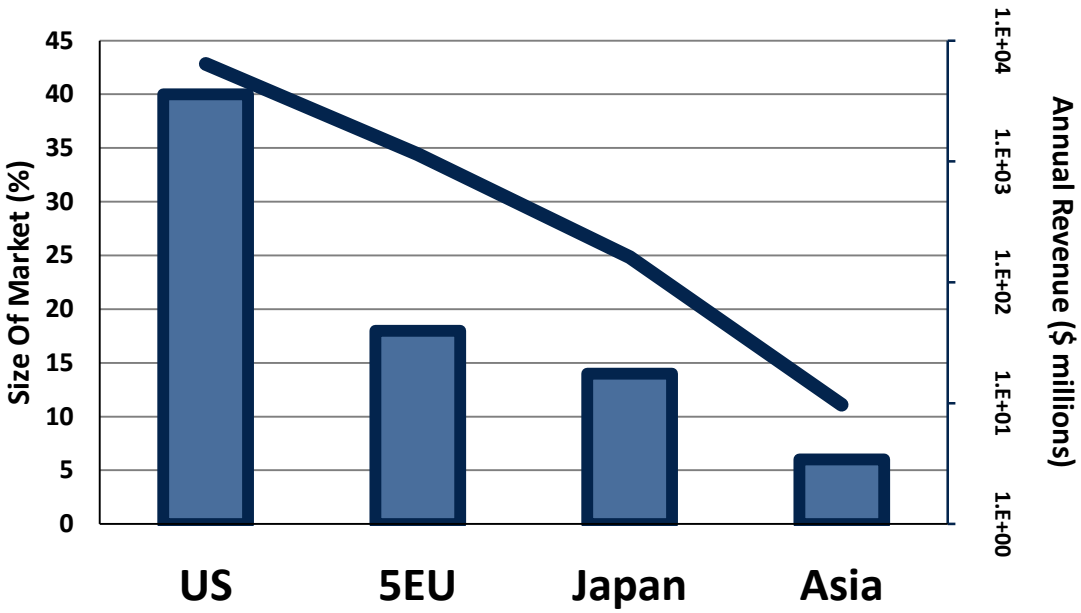

Figure 2.10. Worldwide Market For Dry Eye Relief Drops By Country/Region Presented As (*A*) Percent Of Total Market And (*B*) Millions Of Dollars

Worldwide sales revenue for dry eye relief products broken up among select markets. 5EU includes the 5 largest European markets France, Germany, UK, Italy and Spain. The primary y-axis represents the percentage of the each market represents, while the secondary y-axis and the line correspond to the total dollar value of the market in 2013 dollar values.

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CHAPTER 3

COMFORT AGENT PHYSICAL AND SOLUTION PROPERTIES – EMPIRICAL EVALUATION

3.1. Empirical Evaluation of Comfort Agent Physical And Solution Properties

Relief of ocular discomfort and the production of high comfort ocular formulations and materials and devices has become one of the greatest driving forces within the field. Comfort agents are used extensively within topical eye drop formulations **[3.1-45]**. Comfort agents promote comfort through many different mechanisms of action **[3.46-48]**, such as retaining tear volume by reducing drainage rates **[3.49]**, stabilizing the tear film **[3.50]**, changing tear film surface tension **[3.51-53]**, preventing tear evaporation **[3.48]**, and altering tear fluid viscosity **[3.51, 52, 54, 55]**. In addition, comfort agents have been incorporated into a wide variety of devices, such as contact lenses **[3.56-60]**. There is a significant need for contact lenses that have optimal material characteristics but, at the same time, possess an extended duration of comfort. Contact lens induced dry eye (*CLIDE*) and contact lens associated discomfort (*CLAD*) complaints lead to decreased contact lens use and patient dissatisfaction with contact lenses. Incorporating comfort agents into contact lenses prevents lens dehydration **[3.61-65]**, reduces protein adhesion rates **[3.66-69]**, maintains surface wettability and lubrication **[3.70]**, decreases surface friction and tension **[3.51]**, and has other effects **[3.51]**.

3.1.1. Definition And Classification Of Comfort Agents

There are many difficulties in defining and differentiating comfort agents. For instance, a number of terms are used to describe them, such as lubricating agents, re-wetting agents, demulcents, mucoprotective agents, etc. While there is no universally agreed upon definition of comfort or comfort agents within the field, comfort agents augment characteristics of the tear film (*i.e., increase stability and volume of the film*). It is important to note that "comfort agent" does not refer to drugs or molecules that relieve discomfort through pharmacological action, but from material and solution properties that act to prevent disruption of the tear film, prevent loss of tear volume, and/or reduce stress on the corneal epithelium, specifically to alleviate ocular discomfort. The strength of these properties can be highly variable among different comfort agent species, and certain comfort agents provide comfort through multiple properties while others are limited to one property and are often categorized according to the primary mechanism of action. Lubricating agents primarily reduce the shear stress of eyelid movement on the ocular surface. Re-wetting agents primarily restore or retain tear fluid volume to reduce discomfort. Demulcing agents primarily stabilize fluid films that can act as a protective barrier.

3.1.2. Distinction Between Comfort Agents And Comfort Molecules And Indirect Comfort Providers

Additionally, lipids, surfactants, decongestants, proteinases, pharmaceuticals (*anti-histamines, aesthetics, analgesics, anesthetic, antibacterials, antifungals, steroids, anti-inflammatories, anti-irritants, immunosuppressant, vasoconstrictors, etc*), proteins, and more are all used in the field to relieve signs of discomfort. Even water and saline can be

used for comfort. A distinction must be made between comfort agents and comfort molecules and indirect comfort providers. This distinction can be made difficult as there is no universally agreed upon definition of comfort agents or of comfort within the field. Comfort agents are macromolecules specifically delivered to the tear fluid to augment characteristics of the tear film (*i.e., prevent disruption of the tear film, prevent loss of tear volume, and/or reduce stress on the corneal epithelium specifically to alleviate ocular discomfort, stabilize the tear film, increase tear volume, etc*). The contributing properties are derived from the physical and solution properties of the comfort agent and not pharmacological action, such as with cyclosporine (*immunosuppressant*), ketotifen fumarate (*antihistamine*), lidocaine (*anesthetic*), naphazoline (*vasoconstrictor*), and other pharmaceuticals.

Comfort agents are not absorbed by the ocular tissues, residing only in the tear film until removed via spillage from the eye and normal drainage through the nasal cavity. The comfort agents are only active while residing in the tear fluid, ceasing to promote ocular comfort once removed from the tear fluid. Comfort molecules can promote comfort but do not act on the bulk tear film properties, such as using surfactants or emulsifiers (*increase solubility of proteins, act as antibacterials or antivirals, replace lipids*) or lipids (*prevent tear evaporation*). Comfort providers are molecules (pharmaceuticals, ions, saline or water) that relieve discomfort, such as drugs that act through pharmaceutical action within the ocular tissue or within the inner eye to relieve a specific condition/symptom that results in the cessation of discomfort almost as a side effect. **Table 3.2** demonstrates the classification of molecules according to this criteria. A brief summary of the advantages of

incorporating comfort agents into various formulations and ocular devices is provided in **Table 3.3**.

3.2.3. Classes of Comfort Agents

There are two broad classes of polymeric comfort agents: polysaccharide comfort agents and acrylic comfort agents. Polysaccharide comfort agents are macromolecules composed of one or more types of monosaccharide. Most often, polysaccharide comfort agents are typically linear, high molecular weight, and hydrophilic, though substitution along the polymer backbone is common and can affect the overall conformation of the macromolecule, particularly at high degrees of substitution. These substitutions can be branches, alkyl groups, functional groups, or even salt complexes. In solution, polysaccharides have high hydrodynamic volume and a stiff, rod-like conformation at low molecular weight and adopt a Gaussian coil conformation at higher molecular weight **[88-98]**. Solution viscosity of polysaccharide comfort agents is typically high and pseudoplastic in behavior **[99]**. However, highly diverse and varied properties can be achieved by controlling monosaccharide composition and morphology within the polysaccharide architecture. In general, polysaccharides all have high water affinity and high rheological-modifying properties. These molecules act as thickeners but demonstrate shear-thinning behavior and possess bio-adhesive properties **[99]**. These properties vary between molecular weights, concentration, and, in particular, comfort agent species. Comfort agents used in the salt form are referred to as polyelectrolytes, and charged polysaccharides are known as polyelectrolyte polysaccharides.

Acrylic comfort agents are linear chains composed of carbon-carbon backbones with regular repeat units, often including at least one functional group. Acrylic comfort

agents can be used as polyelectrolytes or in the neutral state. This category also includes polyacids, which are used less often than other agents but have slightly increased water retention properties when compared to neutral acrylic agents.

3.2.4. Clinical Trials And Comfort Agents

Various comfort agents have been tested within clinical trials and are on the market today as topical eye drop formulations. To show the prevalence and versatility of comfort agents in dry eye relief eye drops and other treatments, an incomplete list of commonly used comfort agents in over-the-counter topical eye drops is presented and described in **Table 3.4 [3.1-41]**. **Table 3.5-3.7** describes the properties of some of the more common commercial comfort agents and the respective structures are presented in **Figure 1**. Studies comparing different commercial brands often compare products by neglecting molecular weight and concentration and compare different molecular species as the only significant variable. The conclusions of clinical trials are often contradictory in the comparison of comfort agent effectiveness as polymeric properties are strongly dependent on molecular weight and solution properties vary dramatically with concentration. One example is the investigation of minimum effective concentration of hyaluronic acid (*HA*) by several independent studies. Improvements in corneal tissue staining and other measurements were seen in 24 patients after 0.1% HA eye drop solutions were applied, indicating that 0.1% HA is an effective dose **[100]**. However, an evaluation of 0, 0.1, 0.2% HA topical solutions found no effect with the 0.1% HA solution and concluded that 0.2% was the minimum effective concentration **[80]**. A more detailed study of 104 patients indicated that 0.1% HA solution was effective in relieving comfort and found that tear break-up time and consumer subjective ratings were high after 4 weeks **[79]**. Another study concluded 0.18% HA

solution was the minimum dose needed to alleviate discomfort effectively weeks **[87]**. In each respective study, each author's conclusions are statistically significant. However, there is no compelling explanation within the articles to account for the discrepancy between results, making it likely that the contradictory results may well be due to differences in HA molecular weight and concentration.

Comparisons between different comfort agent species are equally contradictory due to an underestimation of the importance of concentration and molecular weight. For instance, the conclusions of many of these studies overemphasize differences in comfort agent species and fail to investigate differences in concentration and molecular weight. In fact, most studies do not report the molecular weight of comfort agent. For example, hydroxypropyl methylcellulose (*HPMC*) was concluded to be the superior comfort agent when compared HA **[84]**. However, another study compared a commercial HPMC eye drop to another HA commercial product concluded HA was the superior comfort agent **[101]**. In both studies, the authors failed to consider that differences in concentration contributed to differences in the study and did not report comfort agent molecular weights. Another report evaluated HPMC as less effective in providing comfort than HA, but more effective than polyvinyl alcohol (*PVA*) **[70]**. While another study of HA solution compared to a PVA solution found that both solutions provided equivalent levels of comfort; however, they were at different concentrations **[79]**. It is apparent that the results may depend strongly on comfort agent concentration, though there is no molecular weight data presented within the studies. Before any confident conclusions can be made from the clinical data, correlations between molecular weight and concentration must be developed. **Table 4.8** provides additional details of clinical data.

It is therefore necessary to develop methods to understand and resolve the contradictions within the clinical data. Determining the effect of comfort agent species, molecular weight, and concentration on the dependence of comfort agent effectiveness will provide needed insight into the development of more effective comfort solutions and more comfortable devices, such as contact lenses. **Table 4.5** highlights interest and significance of recent work in the area of contact lenses.

3.3 Empirical Evaluation Of Comfort Agents And Index Value Calculation Materials And Methods

Evaluation of comfort agents focused on relating comfort agent properties measured experimentally to molecular weight, molecular species, and percent concentration. The properties chosen were water retention, apparent flow viscosity, zero shear viscosity (*extrapolated to zero comfort agent concentration*), surface tension of comfort agent concentration, and comfort agent intrinsic viscosity in DI water. Each of the selected properties have been correlated to provide or contribute to relief of ocular discomfort (***Table 4.9***). In addition, these properties offer a robust, characteristic analysis of each comfort agent species and follow similar trends, whether under *in vivo* conditions or in a laboratory setting. Another benefit of the selected properties is the ease of measurement in a laboratory setting, often with high accuracy and precision. Also, independent variables can be controlled to a high degree, whereas clinical evaluations of comfort agent effectiveness can be difficult to measure, highly invasive, or highly variable between measurements. They also offer much less control over important variables like molecular weight or concentration.

Comfort agent species (***Figure 3.1***) were selected from the most commonly used comfort agents in over-the-counter (*OTC*) eye drop formulations. Special effort was made to select diverse molecular weights between the range of 2 KDa to 5000 KDa. Molecular weights of particular interest were 10, 40, 90-120, 750, 1000-1200 KDa as multiple species of comfort agents could be procured at these molecular weights. All comfort agents were obtained in powder form, except specific dextran molecular weights that were only available in flake form. Hydroxypropyl methylcellulose (*HPMC*) (*MW = 10, 40, 86, 90, 120, 250, 420 KDa*) was purchased from Sigma-Aldrich (*Milwaukee, WI*). Additional samples of Methocel-brand HPMC (*MW = 10, 40, 86, 750, 1000, 1200 KDa*) were donated by Dow Chemical Company (*Midland, MI*). Hyaluronic acid, sodium salt or Hyaluronan (HA) was purchased from Genzyme (*Cambridge, MA*) and Sigma-Aldrich (*MW = 10, 40, 50, 75, 90, 110, 500, 750, 1050, 1200 KDa*). Carboxymethylcellulose sodium salt (*CMC*) was purchased from Sigma-Aldrich and Walocel-branded CMC was donated by Dow Chemical Company (*MW = 10, 40, 90, 250, 700, 1000, 1200, 4000 KDa*). Neutral dextran (*Dex*) was purchased from Polysciences and Sigma-Aldrich (*MW = 10, 20, 40, 105, 150, 250, 500, 750, 1050, 1200, 5000 KDa*). Dextran sodium sulfate (*DSS*) was purchased from Polysciences and Sigma-Aldrich (*MW = 10, 20, 40, 125, 250, 500, 1100, 5000 KDa*). Poly(vinyl alcohol) (*PVA*) was purchased from Sigma-Aldrich, VWR, and Polysciences (*MW = 10, 20, 40, 85, 110, 170, 950 KDa*). Poly(vinyl pyrrilidone) (*PVP*) was purchased from Sigma-Aldrich (*St. Louis, MO*), VWR (*Radnor, PA*), Fluka (*St. Louis, MO*), and Polysciences (*Warrington, PA*) (*MW = 10, 40, 350, 1000, 1200 KDa*). Poly(methacrylic acid) (*PMAA*) and poly(acrylic acid) (*PAA*) were purchased from Polysciences and Sigma-

Aldrich (*MW = 2, 10, 24, 76, 115, 550, 1100 KDa*) and (*MW = 2, 10, 30, 60, 100, 225, 450, 900, 4000 KDa*), respectively.

3.3.1. Comfort Agent Drying And Storage

All the selected comfort agents were hydroscopic and required drying before use. A known mass of comfort agent was placed in a stainless steel desiccating pan and placed in an GE electric oven at 40ºC for at least 24 hours before use. The sample was measured every 6-12 hours until no powder aggregates were observed, and the change in mass was calculated to be less than 1%. The dried powder was then stored in a desiccator at 15°C until used. The procedure was adapted from **[102-104]**.

3.3.2. Water Retention

Water retention per comfort agent repeat unit was calculated in a similar manner to ASTM D281 - 12 **[105]**, which is used in the paint and coating industry to measure the mass of oil necessary to completely wet the surface of pigment molecules. Each comfort agent was dried prior to use. A small, fixed volume of deionized water (*pH 6.7, temperature 25ºC*) was added to a measured mass of powdered or flaked comfort agent. A stainless steel spatula was then used to gently rub and fold the mixture until all the water had been absorbed by the powder, whereupon another aliquot of water was added. This step was repeated until the endpoint (*cohesive, homogeneous cake*) was achieved. All comfort agents tested were brought to the same endpoint. As the endpoint was neared, the aliquot volume was reduced to avoid overshooting. At this endpoint, the minimum volume of water is absorbed to wet each comfort agent chain with water molecules. The ratio of water molecules to the average number of molecular repeat units per comfort agent molecular repeat unit was calculated and is referred to as water retention, water binding, or bound

water. This ratio is the minimum number of water molecules required to hydrate the comfort agent chain and, when in the tear fluid, this number of water molecules will be retained within the tear fluid due to the presence of the comfort agent.

3.3.3. Apparent Flow Viscosity

The viscosity of comfort agent solutions was measured using a Cannon-Ubbelohde (*Size 50*), Cannon-Ubbelohde Dilution (*Size 50*), and Cannon Zeitfuchs Cross-Arm (*Size 1 and 2*) glass viscometer held at 25ºC. The procedure used conformed to ASTM D4450 **[3.106]**. Comfort agent was dissolved into DI water (*pH 6.7*) at high, known concentrations and kept mixed through magnetic stirring. Aliquots of the bulk solution were taken and diluted to a desired percent [*mass comfort agent/volume DI water (w/v)*] concentration. The diluted solution was pipetted into the reservoir until the fill line, a vacuum applied to the efflux tube, and the time taken for bottom of the meniscus to pass the respective fill lines was recorded with a laboratory timer. The viscosity (*milliPascal*second, mPa*sec*) was then calculated by multiplying the viscometer constant (*calibrated by Cannon*) by the efflux time and the solution density (*g/mL*). The procedure was performed a minimum of three times. Viscosity was investigated as a function of comfort agent aqueous concentrations (*w/v*). Between samples, the viscometers were cleaned, first with ethanol and, then, with DI water. The viscometer was washed with comfort agent solution, removed, and then replaced with fresh solution.

3.3.4. Zero Shear Viscosity

Zero shear viscosity was found by measuring the viscosity of comfort agent solutions at different shear rates and different concentration and then by extrapolating to zero shear and zero concentration. Shear rate (*1/sec*) was altered by changing the vacuum

volume on the pipette pump. Extrapolation to zero shear for pseudoplastic (*shear-thinning*) solutions can vary greatly due to the exponential relationship between viscosity and shear rate if inconsistent shear rates are used. Care was taken to measure viscosity at low, consistent shear rates between different comfort agent solutions.

3.3.5. Intrinsic Viscosity

Intrinsic viscosity data was either provided by the manufacturer or calculated from the Mark-Houwink equation. The Mark-Houwink equation relates intrinsic viscosity to molecular weight via empirical constants. The constants are characteristic to each comfort agent species and solvent solution and vary slightly with concentration and/or molecular weight. Literature values for the Mark-Houwink equation were taken from **[97, 98, 107]**.

3.3.6. Surface Tension

Surface tension was measured in several ways according to ASTM D7334-08 **[108]**. Aliquots (*35 μL*) of various dilutions of comfort agent solution were pipetted to a glass plate surface. A photo was then taken with a Canon Rebel T3i (*18 megapixel DSLR*) camera from a perpendicular direction. Adobe Photoshop (*Creative Suite 6*) was then used to measure both the preceding and receding contact angles. Both angles were then compared to discover any hysteresis. Secondly, a glass plate was partially submerged within a comfort agent solution and any air bubbles were removed from the surface of the plate. An Eppendorf pipette was used to place a bubble of 35 µL of air onto the glass surface. A photo was then taken in a similar method as the previous step. Surface tension was calculated through force balances as described in **[109]**.

3.3.7. Comfort Agent Index Value Calculation

The comfort agent index value was calculated as a quantitative comparison of different comfort agents and/or different molecular weights. Polymath was used to find the numerical approximation of the area under the curve (*AUC*) for each measured property (*water retention, apparent flow viscosity, zero shear viscosity, solution surface tension, and comfort agent intrinsic viscosity*) at various molecular weights up to 1200 KDa. The AUC values were then made dimensionless by dividing the calculated AUC for each property by the corresponding AUC for pure DI water. The individual AUC values were then summed together and plotted against comfort agent molecular weight. A linear regression (*passing through the origin*) was assumed, and the slope of the line was assigned as the index value for the comfort agent.

3.4. Results And Discussion

A major objective of this research was to compare the water retention of the most common comfort agents and relate this property to molecular weight. The water uptake of various molecular weight species of comfort agents are presented in **Figure 3.2**. All species exhibited increasing amounts of bound water as molecular weight was increased. At all molecular weights, polyelectrolyte polysaccharides exhibited the highest amounts of water bound per repeat unit, followed by neutral polysaccharides, polyelectrolyte acrylics, and neutral acrylics. For example, the polyelectrolyte polysaccharides [sodium hyaluronate (*HA*), sodium carboxymethylcellulose (*CMC*), and dextran sodium sulfate (*DSS*)] bound significantly more water than any other of the tested comfort agents at all molecular weights. All three demonstrated very similar water uptake values compared to the other categories of comfort agent. Polyelectrolyte polysaccharides exhibited an order of

magnitude increase in water retention compared to the worst performing class, neutral acrylics, regardless of molecular weight. At any specific molecular weight (*e.g. 90 KDa*), the lowest performing polyelectrolyte polysaccharide (*CMC, 90 KDa*) absorbed approximately 4 times more water than the best performing neutral polysaccharide (*HPMC, 90 KDa*), absorbing 85 and 22 water molecules per repeat unit, respectively. Polyelectrolyte acrylics demonstrated increased water retention properties with increasing molecular weight, approximately matching the water retention of 10 KDa HA only at molecular weights greater than 1000 KDa. Thus, to achieve the same water retention a significantly larger molecule is needed if polyelectrolyte acrylics are used. With neutral acrylics, the water retention cannot be matched except at extremely high molecular weights.

Adding comfort agents to the tear fluid decreases the surface tension of the tear fluid **[3.51, 3.110]**, and clinical studies have shown that ocular tear fluid with lower surface tension results in a more stable tear layer and longer tear breakup times **[3.46, 3.50, 3.54, 3.111]**. Published surface tension values for dilute solutions of comfort agent in deionized water show that for most dilute concentrations of comfort agent solutions, surface tension does not vary significantly with either concentration or comfort agent molecular weight **[3.52, 3.53, 3.111-114]**. However, comfort agent species matters and lowers the surface tension of the fluid by various amounts, depending on the particular agent **[3.52, 3.53, 3.113, 3.114]**. Pure deionized water has a surface tension of 72 dynes per centimeter **[3.115]**, while the ocular tear fluid surface tension has an accepted value of 42 dynes per centimeter **[3.52, 3.110]**. **Figure 3.3** shows the absolute value of the difference between the surface tension of pure water and the comfort agent solution. Of all the tested comfort

agents, HPMC was the most effective in reducing surface tension while the polyelectrolyte comfort agents (*PMAA, DSS, HA, CMC*) had the lowest effect. The neutral polysaccharides had the biggest decrease in surface tension followed by the neutral acrylics, polyelectrolyte polysaccharides, and then the polyelectrolyte acrylics. Compared to the water retention data, the polysaccharides performed best again.

The next comfort agent property investigated was the relationship between specific hydrodynamic volume per unit mass of comfort agent, or the intrinsic viscosity, to molecular weight. The greater the intrinsic viscosity, the greater the hydrodynamic volume of a comfort agent in solution, and, potentially, the more stable the resulting fluid film. The presence of the comfort agent increases the thickness of the tear film due to swelling of comfort agent; however, most of the comfort agent molecules spread across the surface of the tear film. The result is aqueous network of comfort agent molecules supporting film integrity, including the individual layers that make up the tear fluid composition. The greater the hydrodynamic volume of the comfort agent in solution, the greater surface area that the comfort agent will cover until eventually a continuous network of comfort agent molecules are spread throughout the tear fluid. The greater the surface area covered, the more uniform properties of the stabilized tear fluid and fewer local differences in film properties are observed. **Figure 3.4** shows the intrinsic viscosities versus molecular weight determined for the different comfort agents according to the Mark-Houwink parameters found in the Polymer Handbook **[3.107]** or taken from published/manufacturer data **[3.88, 3.116-121]**. The comfort agent HPMC had the highest intrinsic viscosity values as its solution conformation tends to be that of a Gaussian coil. The only distinct pattern found in the data is that polysaccharides tended to possess higher intrinsic viscosities than the

acrylic polymers at a given molecular weight. No clear trend between polyelectrolyte and neutral polymers was observed. It is hypothesized that the polysaccharide comfort agents possess higher volumes as the saccharide groups are larger and stiffer than the typical carbon-carbon backbone of acrylic polymers.

The relationship between viscosity, both zero shear and apparent flow viscosity of comfort agent solutions, and molecular weight was also investigated. Tear volume renewal is not a continuous process on the eye. Most of the tear turnover is done almost immediately after the blinking action **[3.122]**. Very quickly, the tear film returns to static conditions, where there is minimal flow and drainage. However, while the flow is minor, the volume loss due to creeping flow is not always negligible in the interval between blinks **[3.122]**. There are many cases of this creeping loss of volume, which may induce sensations of mild/severe dryness. Therefore, this rate of loss is an important factor for consideration when alleviating discomfort. Comfort agents can alleviate this effect, however, by increasing the stability of the tear volume and resisting the creeping flow. A measurable, corresponding property that resists creeping flow and reduces tear film layer disruption is zero shear viscosity. Zero shear viscosity is the viscosity of a fluid under static conditions or under no applied stress. Higher zero shear viscosity correlates to a greater resistance to jerking or instantaneous stresses and creeping flow. By reducing creeping flow the rate of drainage between blinks is reduced, and the tear volume is retained. The values measured for zero shear viscosity are presented in **Figure 3.5**. Polysaccharide comfort agents [*CMC, HA, and HPMC*] had the greatest zero shear viscosity at all molecular weights, and no statistically significant difference was observed between the three. Dextran displayed much lower viscosity than the other polysaccharides, probably due to the simpler structure

relative to HA, CMC, and HPMC. The acrylic comfort agents had significantly lower zero shear viscosities than the polysaccharides, and they demonstrated relatively similar viscosities over the tested molecular weight range. Of the tested acrylic comfort agents, PVP showed the highest viscosity, possibly due to the larger substituent (*pyrrilidone*) compared to the substituent acid and alcohol; however, the difference was minor. The PMAA, PAA, and PVA polymers behaved without any significant statistical difference.

Increasing the apparent viscosity of the tear fluid can retain tear volume by reducing the rate of drainage, increasing the barrier/buffer properties of the tear film between the ocular surface and the eyelid, maintaining the stability of the tear film layers, and increasing the residence time of the comfort agent itself (*i.e., increasing the length of time the comfort agent is actively providing comfort*). **Figure 3.6** relates apparent flow viscosity to molecular weight normalized to percent concentration and measured at a constant shear rate. The apparent viscosity of the HPMC solution is much greater than any of the other comfort agent solutions, displaying exponentially increasing behavior with respect to molecular weight. The other polysaccharide (*HA and CMC and dextran*) solutions were significantly greater in viscosity than the acrylic comfort agents, but much lower than the HPMC solution. However, no clear trend was observed between polyelectrolyte and neutral comfort agents.

Figure 3.7A shows the comfort property contribution for all the tested comfort agents at a fixed molecular weight of 1200 KDa, independent of percent concentration. The highest performing comfort agent was HA, then HPMC, then CMC, etc. Polysaccharides were better performing that the acrylic polymers due to the greater impact of the polysaccharides on the solution properties. Values for viscosity, water binding, and the

other properties were arbitrarily increased in weight to determine the sensitivity of the comfort property contribution calculation. The calculations were found to be highly robust as property values were randomly increased up to two orders of magnitude before any effect on comfort agent ranking was observed. For example, the two greatest contributing properties for HPMC were viscosity and water retention. Both these values had to be increased above 2 orders of magnitude before the comfort property contribution of HPMC was found to be equivalent to that of the next ranked comfort agent, HA. **Figure 3.7B** displays the comfort property contribution for each comfort agent when evaluated at different molecular weights. Interestingly, below 100 KDa, all comfort agents were predicted to be similar in their calculated comfort property contribution or predicted therapeutic effect. The comfort property contribution for the comfort agents was also calculated at various concentrations at a fixed molecular weight of 1200 KDa and is shown in **Figure 3.7C**. It is interesting that the magnitude of the comfort property contribution for the concentration values are much greater than the molecular weight comfort property contribution values, but the slope of the concentration curve is approximately constant as concentration increases and the slope of the comfort property versus molecular weight curve is relatively linear after 100 KDa molecular weight. To demonstrate the comfort property contribution dependence on both molecular weight and concentration, 1200 KDa HPMC was used to produce the surface pot **(*Figure 3.7D*)** and the contour plot **(*Figure 3.7E*)**. By calculating the volume under the curve for each comfort agent, the total comfort agent property contribution can be found for a given comfort agent (*in this case, HPMC*). This analysis was performed for all other comfort agents. Furthermore, an index value was developed to more easily compare different agents, which was calculated by dividing the

total comfort property contribution by molecular weight and percent concentration for each respective comfort agent. The index values for each comfort agent are shown in **Figure 3.7F**. The index value conveniently compares three conditions. First, it allows a convenient, direct comparison of comfort agent species. Different concentrations, molecular weights, and comfort agents can be easily related. For example, the index of PAA is 32, and the index of HPMC is 133 (***Table 3.10***). To achieve the same comfort property contribution or level of comfort using either solution, the product of MW of PAA and percent concentration of the PVA comfort solution would have to be approximately 4.16 times greater. If the formulations are at the same concentration, the MW of PAA would have to be increased by 4.16 times.

The rankings are interesting as the distinction among the different comfort agents is clearly seen, allowing direct comparison of comfort agents as a species. The comfort agent species HA, HPMC, and CMC are categorically demonstrated to be the most effective comfort agents at the lowest molecular weights and concentrations, and they should be given priority when selecting comfort agents. In the future with more data, a coefficient for residence time of comfort agents (*at diverse molecular weights*) measured under *in vivo* conditions could be introduced to better compare specific clinical trials and to compare comfort agent delivery methods, such as between eye drops and contact lenses (*as discussed in* ***Section 3.3***).

Analysis of our data led to substantial insight into the current clinical literature. Though current clinical studies are insufficient to determine relative effectiveness of different comfort agents with high confidence, general trends can now be determined with moderate certainty. These can include (*i*) higher concentrations of a specific comfort agent

provide greater comfort than lower concentrations of the same comfort agent, (*ii*) higher molecular weights of the same comfort agent provide greater comfort, (*iii*) sufficiently higher molecular weights of different comfort agents can provide greater comfort, (*iv*) polysaccharides comfort agents provide greater comfort than the acrylic comfort agents at similar concentrations, (*v*) sufficiently high concentrations of an inferior comfort agent can provide similar levels of comfort as low concentrations of a superior comfort agent. Though not clearly stated in the literature, our indications are that HA is the most effective comfort agent (*outside of specific concentration and molecular weight considerations*), while HPMC and CMC follow in comfort property therapeutic contribution, respectively. In addition, there are numerous implications within the field that polysaccharides outperform acrylics except when acrylics are used in much higher concentration. However, acrylics would not typically outperform polysaccharides unless there is a very large difference in MW and/or concentration. For example, comparing solutions of the same molecular weights of HA and PVA, the concentration of PVA would need to be approximately 10x greater or more than the concentration of HA. This conclusion is supported by the clinical literature where a 0.1% HA eye drop provided equivalent levels of comfort as a 1.4% PVA eye drop **[3.79]**. In the study, the cause of these results was not investigated, but now experimental justification exists to explain this conclusion.

3.5. Conclusions

There are numerous advantages for incorporating comfort agents into formulations and/or ocular devices. However, not all comfort agents are equal. Each comfort agent has unique mechanisms of action that make it difficult to compare the levels of comfort between agents. In addition, there is a strong dependence on molecular weight and comfort

agent concentration. The clinical data available is often incapable of effectively comparing different comfort agents at different concentrations and/or molecular weights and does little to contribute to the general understanding of comfort agent effectiveness. Furthermore, these studies are very poor models for the development of comfort devices. Therefore, this paper introduced a novel investigation of common ocular comfort agents. Comfort agent material and solution properties known to correlate to the reduction in ocular discomfort, such as water retention and viscosity, were selected and evaluated for dependence on concentration and molecular weight. It was found that the selected properties varied depending on molecular weight, concentration, and comfort agent species. Through experimentation, polysaccharides were found to be more effective than acrylic comfort agents. More specifically, hyaluronic acid (*HA*), hydroxypropyl methylcellulose (*HPMC*), carboxymethylcellulose (*CMC*) were the three most effective comfort agents, respectively. Though several material properties depended strongly on charge, no clear dependence on polyelectrolyte or neutral classification was apparent in the overall ranking of comfort agents. In addition, it was found that calculation of the numerical area under the curve for each property versus molecular weight and concentration resulted in a convenient index value for ranking comfort agent effectiveness at different molecular weights and concentrations. The calculated index values led to a greater understanding of general trends found within the clinical data and can be potentially used to resolve numerous contradictory published clinical trials.

3.6. Tables

Table 3.1. Basic Properties Of Comfort Agent Species

Species (*CAS*)	MW (KDa) [Log P]	Charge	Functional Pendant Groups	H-Bond Acceptor Sites	H-Bond Donor Sites
HA (*9004-61-9*)	**388 [-4.91]**	**Neutral Polar Acid Group**	**3 –OH 1 –COOH 1 –OCH_2OH 1 –NHCOH**	**13**	**8**
HA Sodium Salt (*9067-32-7*)	**419 [-5]**	**Anionic**	**3 –OH 1 –OCH_2OH 1 –NHCOH 1 –Sodium salt**	**13**	**7**
HA Potassium Salt (*31799-91-4*)	**435 [-5]**	**Anionic**	**3 –OH 1 –OCH_2OH 1 –NHCOH 1 –Potassium salt**	**13**	**7**
HPMC (*9004-65-3*)	**410 [-0.9]**	**Neutral Polar Groups**	**1-3 –OH 1-3 –OCH_3 1-3 –$OCH_2CH(OH)CH_3$**	**19**	**8**
CMC (*9000-11-7*)	**520 [-5.5]**	**Neutral Polar Groups**	**1-4 –OH 1-3 –OCH_2CO_2H 2 –CH_2OH**	**15**	**8**
Sodium CMC (*9002-32-4*)	**502 [-5.6]**	**Anionic**	**1-4 –OH 1-3 –$OCH_2CO_2^-Na^+$ 2 –CH_2OH**	**15**	**6**
Dextran (*9004-54-0*)	**342 [-5.3]**	**Neutral Polar Groups**	**6 –OH**	**11**	**29**
DSS (*9011-18-1*)	**955 [-5.6]5**	**Anionic**	**6 –$SO_4^-Na^+$**	**8**	**2**
PVA (*9002-89-5*)	**74 [0.75]**	**Neutral Polar Groups**	**1 –OH**	**1**	**1**
PVP (*9003-39-8*)	**141 [2.15]**	**Neutral Polar Groups**	**1 Pyrrilidone**	**2**	**0**
PAA (*9003-01-4*)	**102 [0.824]**	**Anionic**	**1 –COOH or COO^-**	**2**	**1**
PMAA (*25086-62-8*)	**116 [1.03]**	**Anionic**	**1 –COOH or COO^-**	**2**	**1**

Table 3.2. Review Of Comfort Agent Clinical Trials

Species	Conc	Control	Study Details	Conclusions	[Ref]
HA	0.1%	Saline	Stain, Survey 24 patients: (2 years)	HA was more effective than the saline	[72]
	0.1% 0.2%	Saline	20 patients	Minimum effective concentration of 0.2% HA	[55]
	0.1%	Saline	104 patients: (4 weeks)	Tear breakup time, consumer surveys HA rated higher than saline	[56]
	0.18%	Saline	Stain 444 patients; 3-12 drops/day (14 days)	5-10% objective improvements over saline	[62]
	0.15%	Saline	Schirmer, stain, cytology, slit lamp 44 patients: 4-8 drops/day (3 months)	HA had lower cytology	[47]
	0.1%	Saline 0.5% HPMC	Stain, tear break-up time, tear evaporation rate 30 mins	HPMC provided higher comfort	[59]
	0.1%	1.4% PVA	Osmolality, tear break-up time, staining, schirmer, cytology (8 weeks)	Neither preparation was found to be superior	[54]
HPMC	0.5%	0.1% HA Saline	Stain, Tear break up time, tear evaporation rate	HPMC provided higher comfort	[59]
	0.3%	HA/0.25% PEG	Tear meniscus volume, tomography 20 patients: 3 drops/day (1 month)	Equivalent effects	[73]
	0.3% with 0.1% dextran	0.18% HA	10 patients	HA was found to provide greater relief	[103]

Table 3.3. Contact Lenses Incorporating And Releasing Comfort Agents

Comfort Agent [MW] (*KDa*)	Method of Release	Lens Material	Mass Loaded	Release Time (*Medium/Model*)	[Ref]
HA	Diffusion (*Soaked*)	Polymacon	15 µg/ lens	6-12 hrs (*Saline at 3.8 µL/min*)	[98]
		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		
		Methafilcon A	Not Reported	Not Reported	[99]
	Molecular Imprinting	Nelfilcon A	200 µg/ lens	40 hrs (*20 mL ALS*)	[26]
HPMC [*120*]	Diffusion (*Direct Embedding*)	Silicone Hydrogel	<0.01 µg/ lens	<10 mins (*250 mL DI water*)	[100]
	Molecular Imprinting	Silicone Hydrogel	3000 µg/ lens	62 days (*250 mL DI water*)	
		Silicone Hydrogel	1000 µg/ lens	50 days (*DI water flow at 3 µL/ min*)	
	Diffusion (*Soaked*)	Silicone Hydrogel			[Thai]
PVA [*40-65*]	Diffusion (*Reptation-Direct Embedding*)	Nelfilcon A	6 µg/ lens	24 hrs (*DI water*)	[101]
				16 hrs (*in vivo human*)	[102]
PVP [*44-54*]	Diffusion (*Reptation-Direct Embedding*)	Poly(HEMA-co-EGDMA)	100 µg/ lens	30 days (*20 mL DI water*)	[43]

Table 3.4. Relating *In Vivo* Comfort Agent Property To Objective *In Vitro* Property

Discomfort Causing *In Vivo* Property	Corresponding *In Vitro* Property to Alleviate Discomfort	Relationship
Tear Break-Up Time (*TBUT*) Dry spots form in tear fluid desiccating cornea surface	Surface tension	Lower surface tension corresponds to higher TBUT
	Zero shear viscosity	Higher zero shear viscosity reduces creeping flow
Excessive Tear Drainage Detrimental loss of tear film volume due to high rate of tear drainage	Viscosity	Higher viscosity leads to reduced drainage rates
	Zero shear viscosity	Higher zero shear viscosity reduces creeping flow
Dry Eye Tear volume is reduced below 10 µL	Water binding by comfort agent	Higher water binding by comfort agent retains more water within tear fluid
Tear Evaporation Caused by disruption of lipid layer	Intrinsic viscosity	Higher hydrodynamic volumes take up more space in the tear film, stabilizing tear layers
Blink Sensitivity Caused by disruption of tear film and increased shear force on the cornea surface	Surface tension	Maintains surface lubricity to act as buffer layer
	Viscosity	Higher shear viscosity reduces stress on cornea
	Water binding by comfort agent	Water is released to the tear fluid

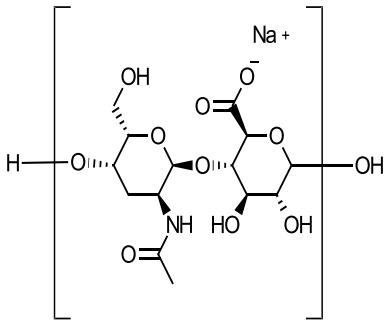
Table 3.5. Comfort Agent Index Values For Each Comfort Agent Species

Comfort Agent Species	Calculated Index Value
Hyaluronic Acid	162
Hydroxypropyl Methylcellulose	133
Carboxymethylcellulose	109
Dextran	64
Dextran Sodium Sulfate	40
Poly(Vinyl Pyrrilidone)	36
Poly(Acrylic Acid)	32
Poly(Methacrylic Acid)	31
Poly(Vinyl Alcohol)	26

3.7. Figures

Polyelectrolyte Polysaccharides

A.



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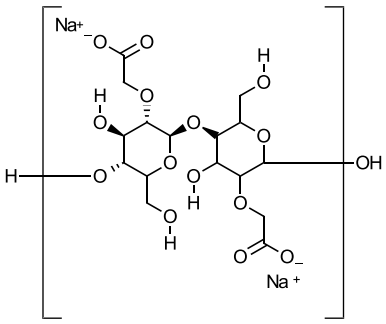

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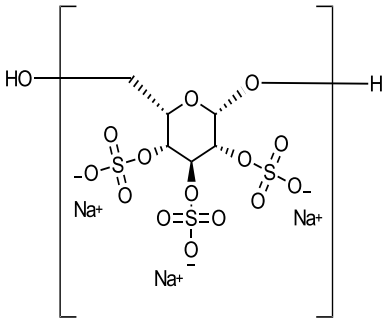

Neutral Polysaccharides

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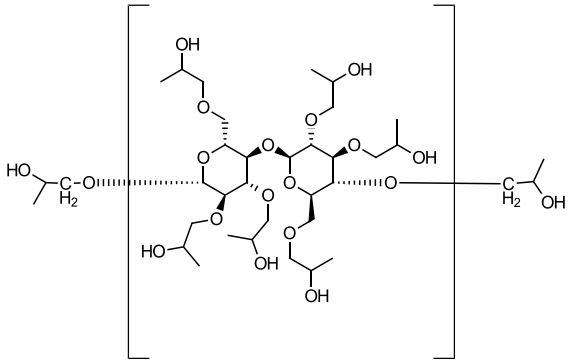

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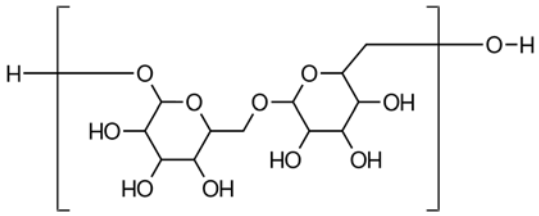

Polyelectrolyte Acrylics

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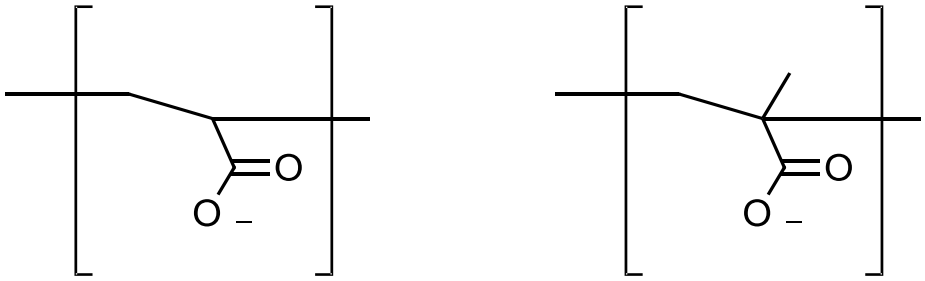


Neutral Acrylics

H. **I.**

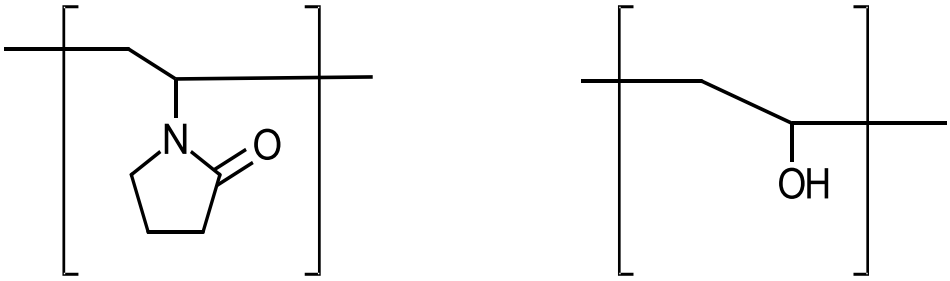


Figure 3.1. Common Comfort Agents In Over-The-Counter Eye Drop Formulations

Structures represented here are common re-wetting agents in contact lens solutions and eye drop formulations. The comfort agents represented are divided between two categories: polysaccharide (*A-E*) and acrylic (*F-I*) molecules. Both categories can be divided according to charge. Charged or ionic molecules are polyelectrolytes (*A-C, F-G*), while those molecules are classified as neutral molecules (*D-E, H-I*). The specific molecules represented are **polyelectrolyte polysaccharides** (*A. sodium hyaluronate (HA), B. sodium carboxymethylcellulose (CMC), and C. dextran sodium sulfate (DSS)*), **neutral polysaccharides** (*D. hydroxypropyl methylcellulose (HPMC) and E. dextran (Dex)*), **polyelectrolyte acrylics** (*F. poly(acrylic acid) (PAA) and G. poly(methylacrylic acid)*

(PMAA)), and **neutral acrylics** (*H. poly(vinyl pyrrilidone) (PVP) and I. poly(vinyl alcohol)*).

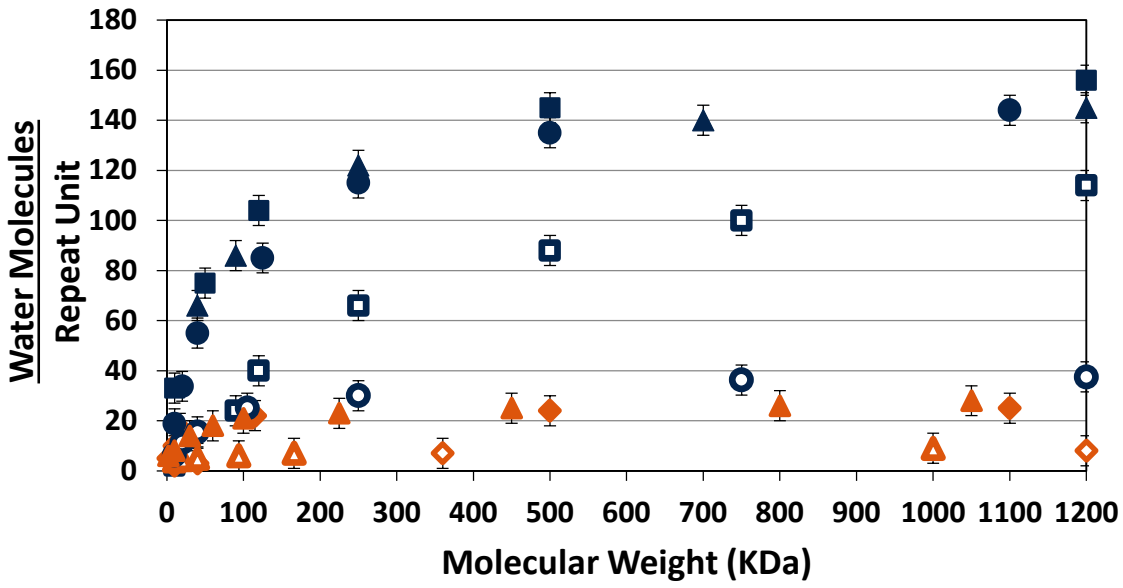


Figure 3.2. Comfort Agent Water Retention

Water retention per polymer repeat unit was measured for polyelectrolyte polysaccharides [*(■) HA, (▲) CMC, and (●) DSS*], neutral polysaccharides [*(□) HPMC and (○) Dex*], polyelectrolyte acrylics [*(◆) PAA and (▲) PMAA*], and neutral acrylics [*(◇) PVA and (△) PVP*] were shown to increase with increasing comfort agent molecular weight. Polysaccharide comfort agents (***blue***) displayed much higher water binding than the acrylic comfort agents (***orange***), even at low molecular weights. In addition, polyelectrolyte (***solid***) comfort agents displayed higher water absorption properties than similar uncharged (***hollow***) comfort agents (*e.g. CMC (**polyelectrolyte**) bound ~2x more water than HPMC (**neutral**)*). Experimental methodology was adapted from ASTM D281-12 and performed in triplicate (*T=25ºC*).

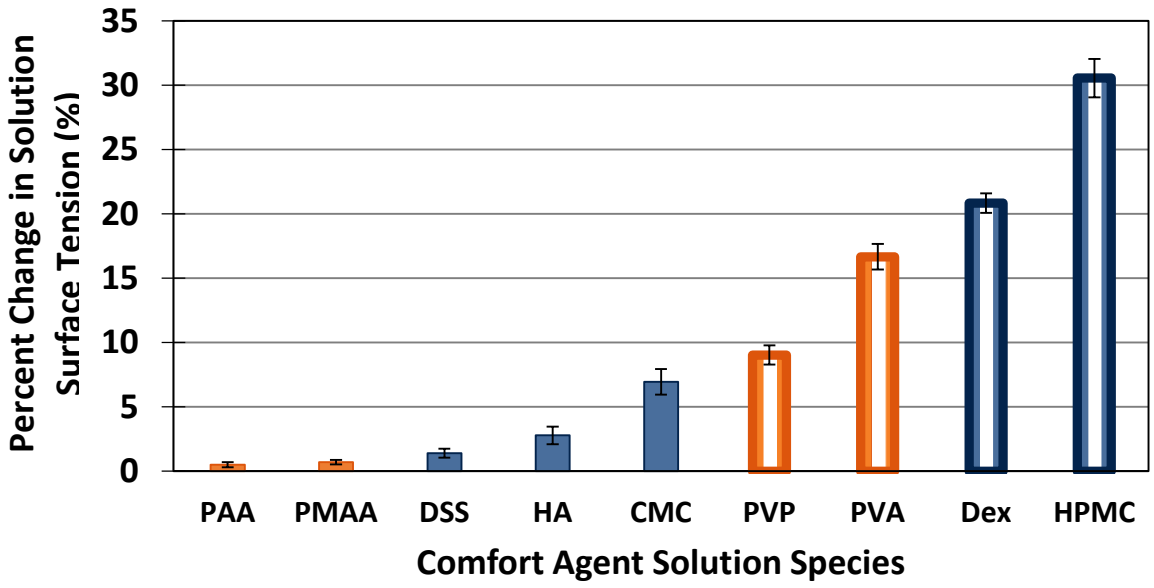


Figure 3.3. Percent Change Of Comfort Agent Solution Surface Tension Relative From DI Water Surface Tension

The surface tension of aqueous solution strongly correlates to the ability of a solution to form a continuous film and completely wet a surface. Surface tension measurements did not vary greatly with molecular weight or concentration, especially at low concentrations typical for eye drop solutions. The surface tension percent change was relative to the surface tension of DI water (*72 dynes/cm*). Neutral **(*hollow*)** comfort agents tended to lower the solution surface tension to a greater degree than polyelectrolyte (***solid***) comfort agents. Polysaccharide (***blue***) comfort agents lowered the solution surface tension more similarly charged acrylic (***orange***) comfort agents.

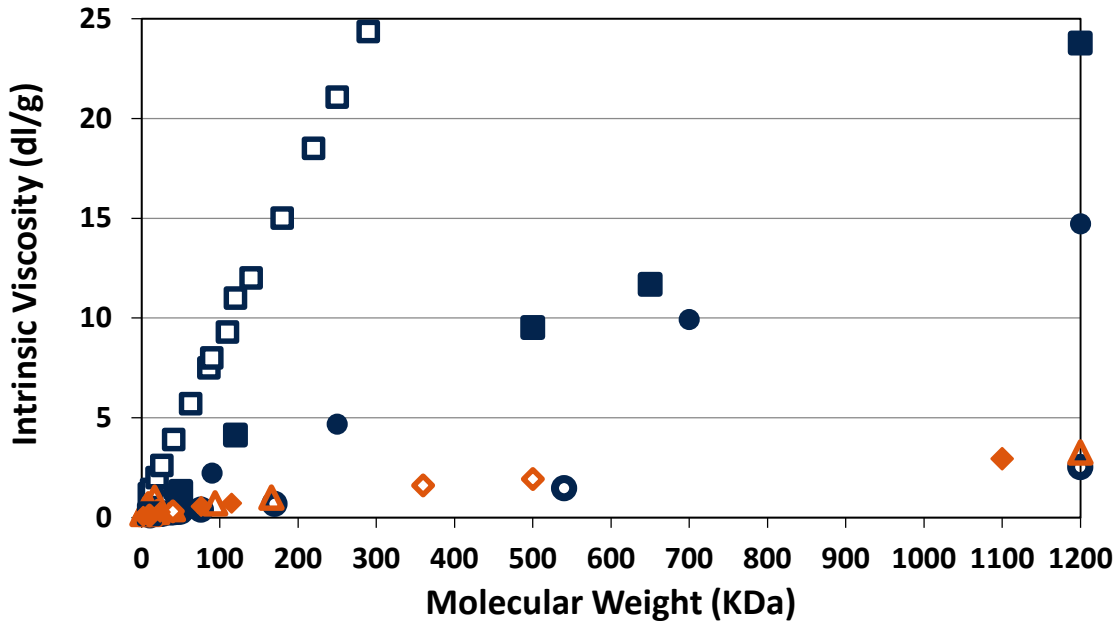


Figure 3.4. Comfort Agent Intrinsic Viscosity As A Function Of Molecular Weight

The intrinsic viscosity of common comfort agents for polyelectrolyte polysaccharides [(■) HA, (▲) CMC, and (●) DSS], neutral polysaccharides [(□) HPMC and (○) Dex], polyelectrolyte acrylics [(◆) PAA and (▲) PMAA], and neutral acrylics [(◇) PVA and (△) PVP] were provided by the manufacturer or were calculated according to the Mark-Houwink Equation. Higher intrinsic viscosities (*higher hydrodynamic volumes*) stabilize the tear fluid film. Polysaccharide comfort agents (***blue***) typically have much higher intrinsic viscosities than acrylic (***orange***) comfort agents, probably due to the greater size and stiffness of the polysaccharide repeat unit. No trend is apparent between polyelectrolyte (***solid***) or neutral comfort agents (***hollow***).

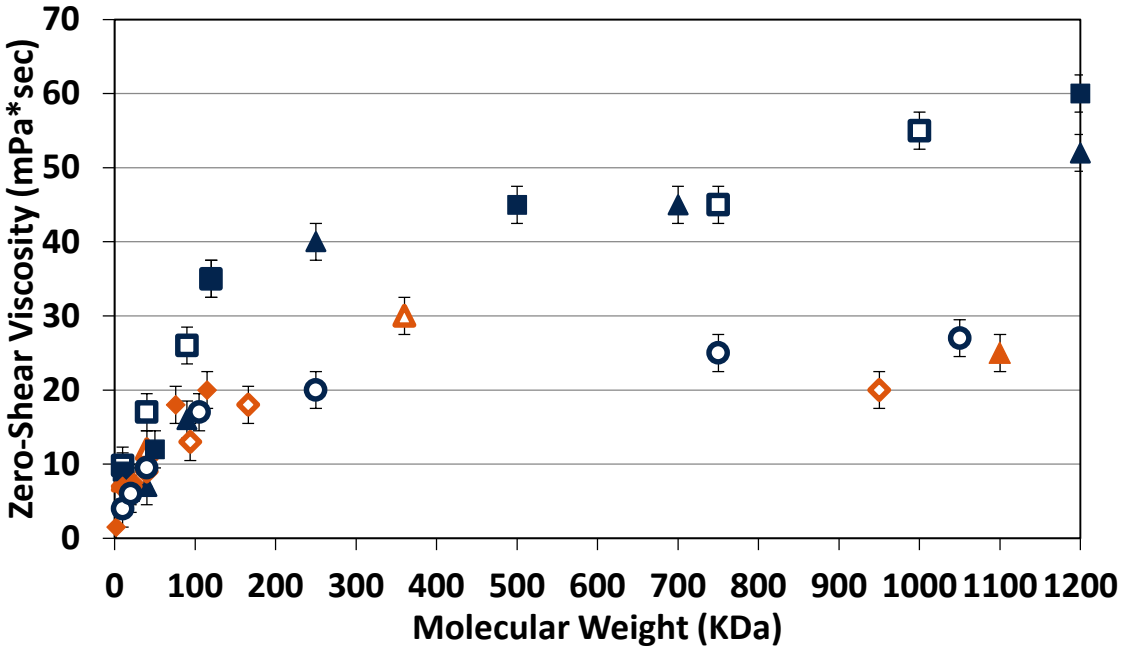


Figure 3.5. Zero-Shear Viscosity of Comfort Agent Solution Extrapolated to Zero Concentration

The viscosity at different shear rates was measured for various dilutions of diverse molecular weights of polyelectrolyte polysaccharides [(■) HA, (▲) CMC, and (●) DSS], neutral polysaccharides [(□) HPMC and (○) Dex], polyelectrolyte acrylics [(◆) PAA and (▲) PMAA], and neutral acrylics [(◇) PVA and (△) PVP]. Polysaccharide (***blue***) comfort agent solutions had greater zero shear viscosity than acrylic (***orange***) comfort agent solutions. With the exception of the polysaccharide dextran, there was no statistical difference between the polyelectrolyte (***solid***) and neutral (***hollow***) comfort agents.

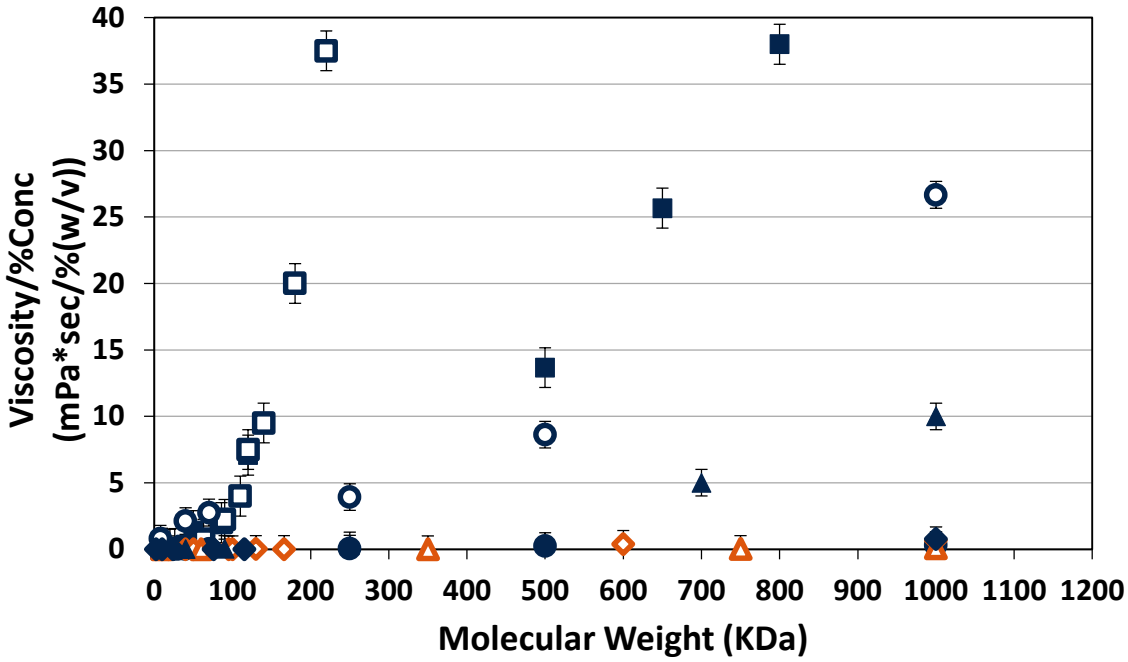
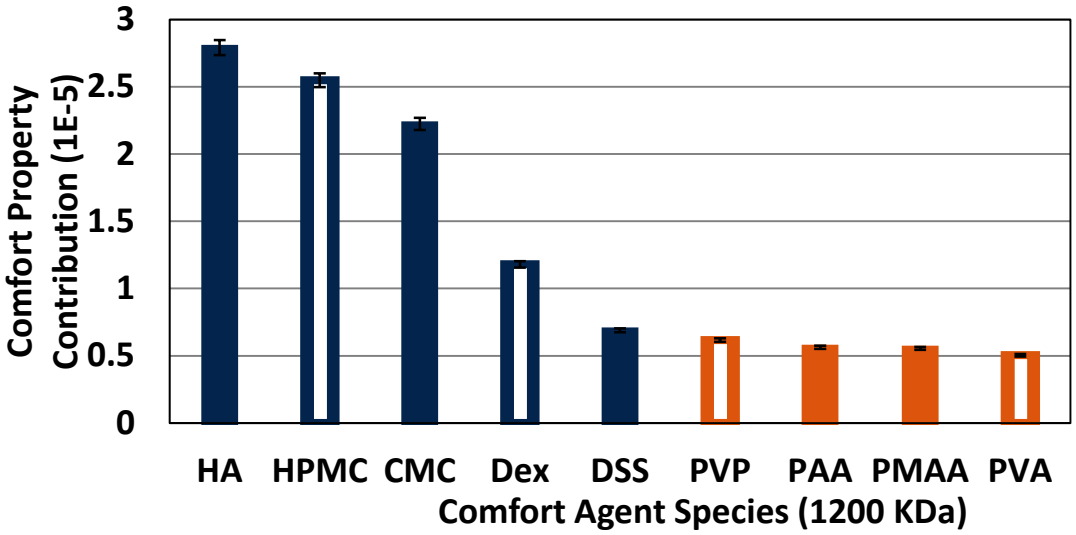


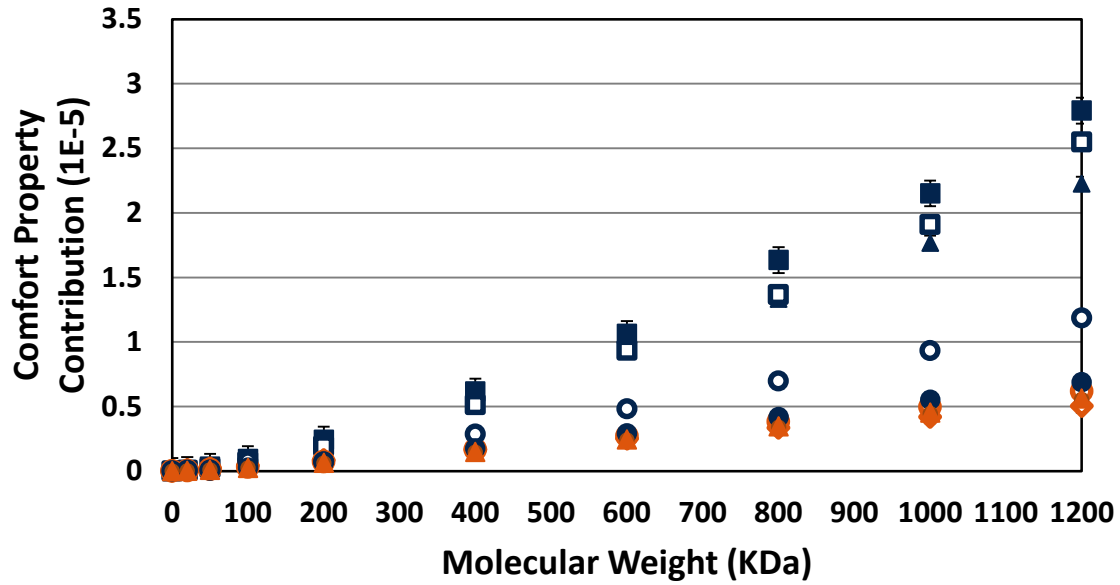
Figure 3.6. Apparent Flow Viscosity of Aqueous Comfort Agent Solutions

Apparent flow viscosity of polyelectrolyte polysaccharides [(■) HA, (▲) CMC, and (●) DSS], neutral polysaccharides [(□) HPMC and (○) Dex], polyelectrolyte acrylics [(◆) PAA and (▲) PMAA], and neutral acrylics [(◇) PVA and (△) PVP] in DI water. Polysaccharide solutions (HPMC, HA, and CMC, specifically) had the greatest apparent viscosity, increasing exponentially with molecular weight. The same order is demonstrated in **Figure 3.3**, where HPMC, HA, and CMC intrinsic viscosity increases in a similar manner. The increase in viscosity observed in polysaccharide solutions is probably due to the increasing intrinsic viscosity and an increasing number of entanglements between the chains in solution. The more linear acrylic chains (***orange***) display negligible increases in apparent flow viscosity with molecular weight relative to the polysaccharide (***blue***) solutions. No relationship between apparent flow viscosity and classification as polyelectrolyte/neutral is demonstrated.

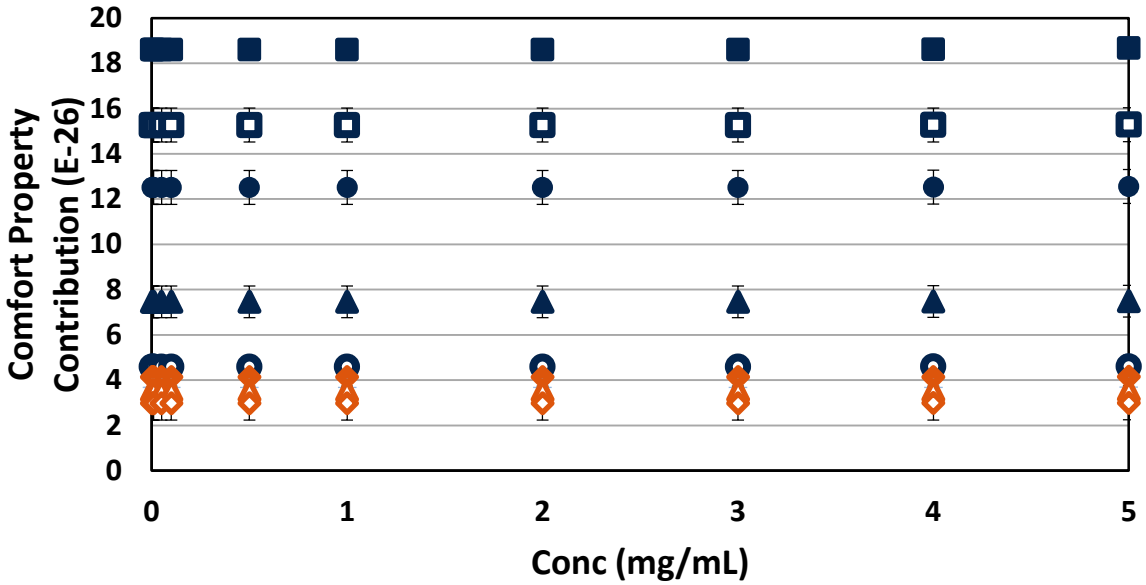
A. Comfort Property Contribution Of Comfort Agents At 1200 KDa



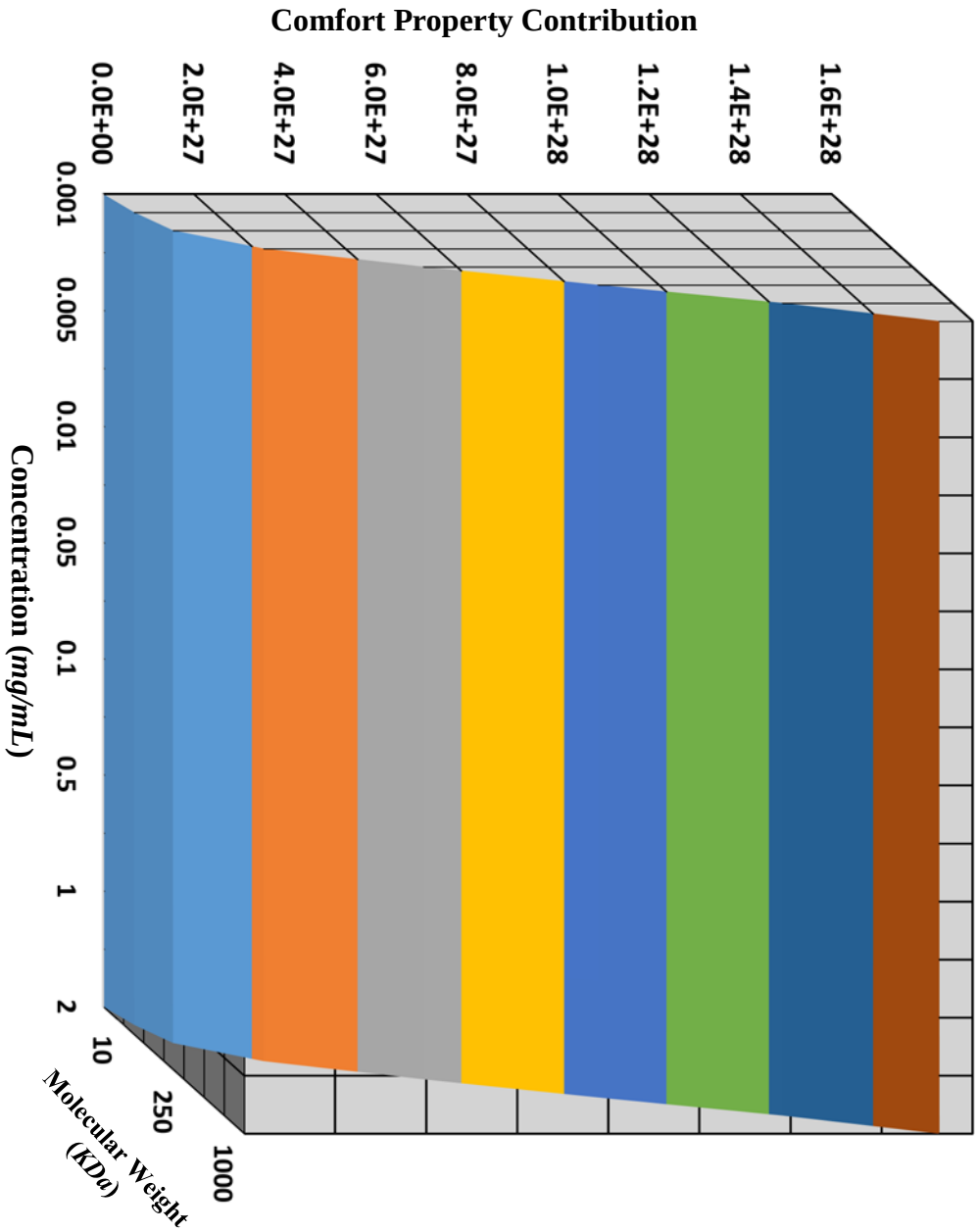
B. Comfort Property Contribution Of Comfort Agents At Diverse Molecular Weights



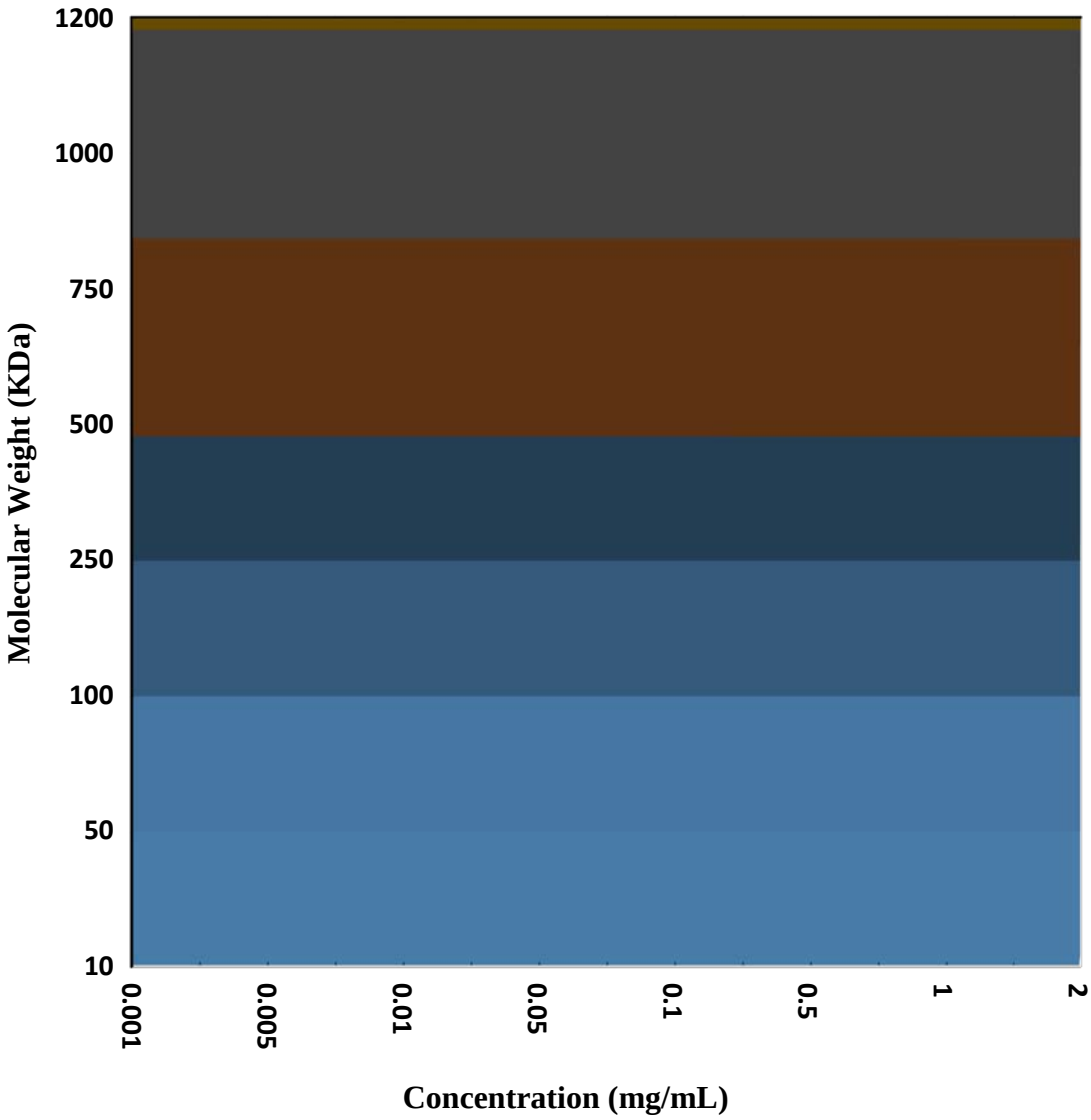
C. Comfort Property Contribution Of Comfort Agents At Diverse Solution Concentrations



D. Comfort Property Contribution Of HPMC At Diverse Molecular Weights And Concentrations – Surface Plot



E. Comfort Property Contribution Of HPMC At Diverse Molecular Weights And Concentrations – Contour Plot



F. Index Values For Different Comfort Agents

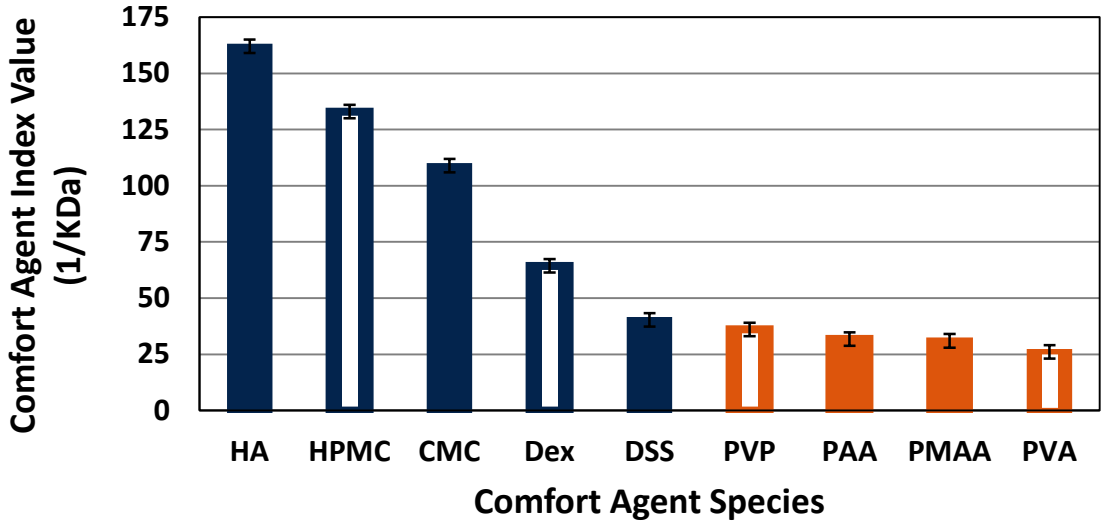


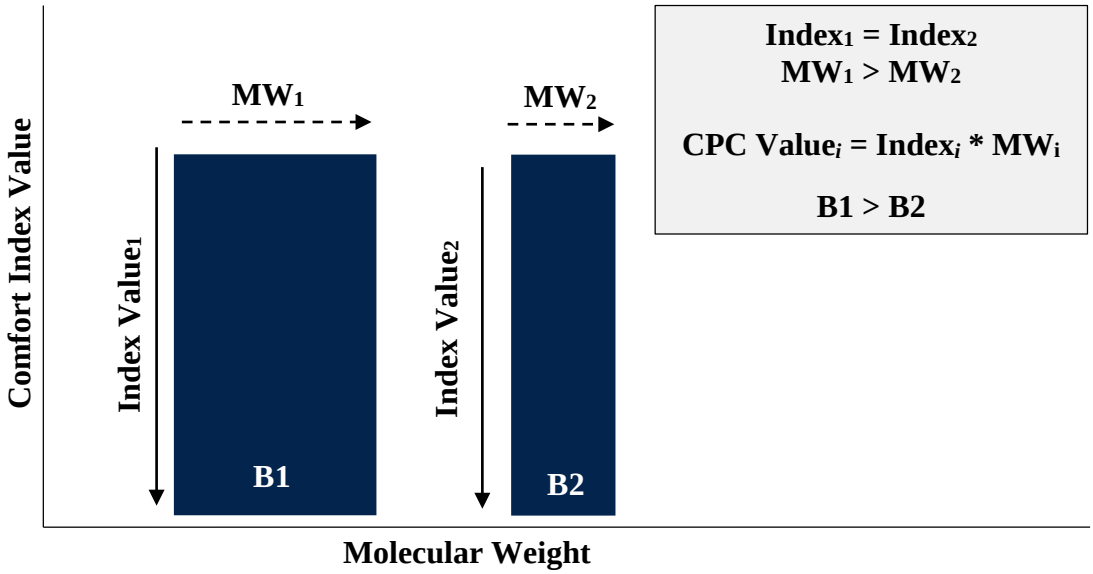
Figure 3.7. Comfort Property Contribution And Agent Index Values At Various Molecular Weights And Concentrations

The measured properties area under the curve (*AUC*) for each comfort agent at 1200 KDa was totaled (**6A**). In general, polysaccharide comfort agents (***blue***) [(■) HA, (□) HPMC, (▲) CMC, (●) DSS (○) Dex] had much higher values the other or acrylic comfort agents (***orange***) [(◆) PAA, (▲) PMAA, (◇) PVA and (△) PVP], though no apparent trend between polyelectrolyte/neutral comfort agent (***solid/hollow***, *respectively*) is evident. Polysaccharide comfort agents [*HA, HPMC, and CMC*] were shown to have the highest comfort property contribution over the molecular weight interval (***6B***) demonstrates the molecular weight dependence for each comfort agent. The comfort agent contribution as a function of concentration is shown in **6C**. By varying both the concentration and molecular weight contribution for 1200 KDa HPMC, **6D** and **6E** demonstrates that equivalent comfort can be achieved at high concentrations of low molecular weight comfort agent or with low concentrations of high molecular weight comfort agent. Index values (***6F***) were derived to

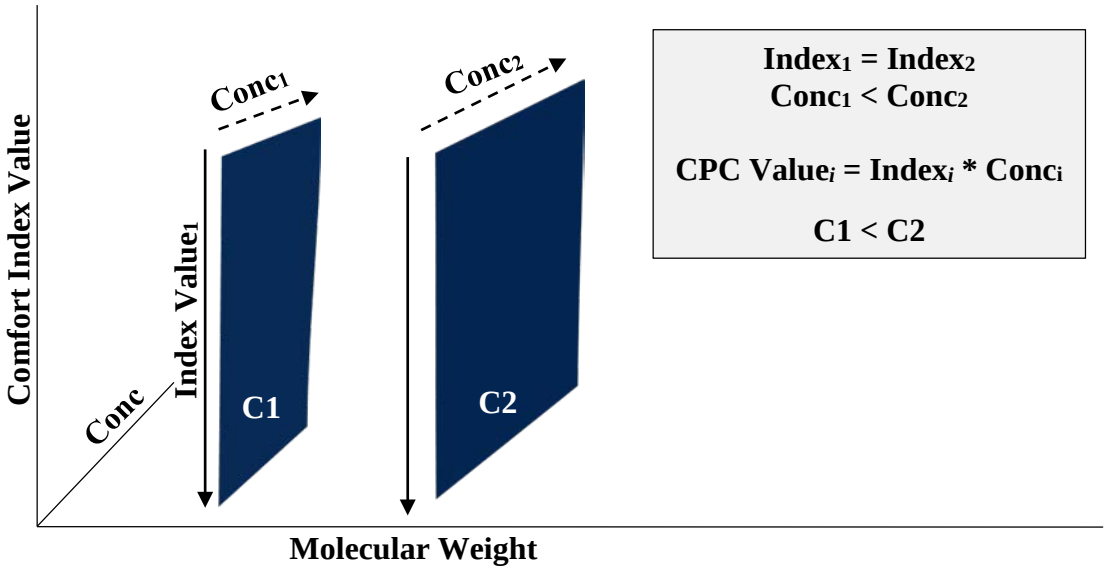
easily calculate volumes at depending on comfort agent species, molecular weight, and concentration.

A) Using The Comfort Agent Index Values To Compare Between Different Comfort Agent Species

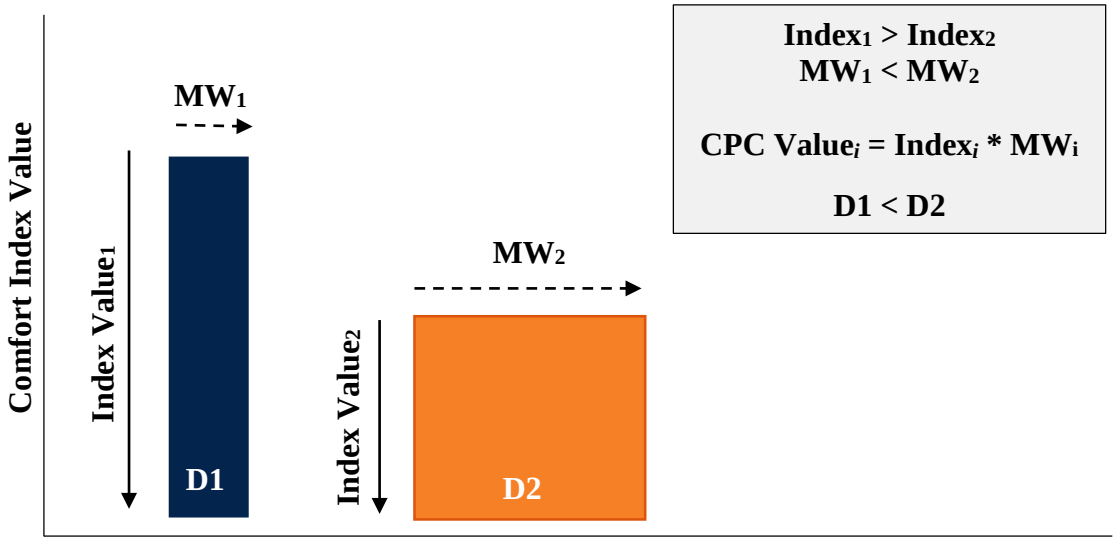
B) Using The Comfort Agent Index Values To Compare Between The Same Comfort Agent Species At Different Molecular Weights



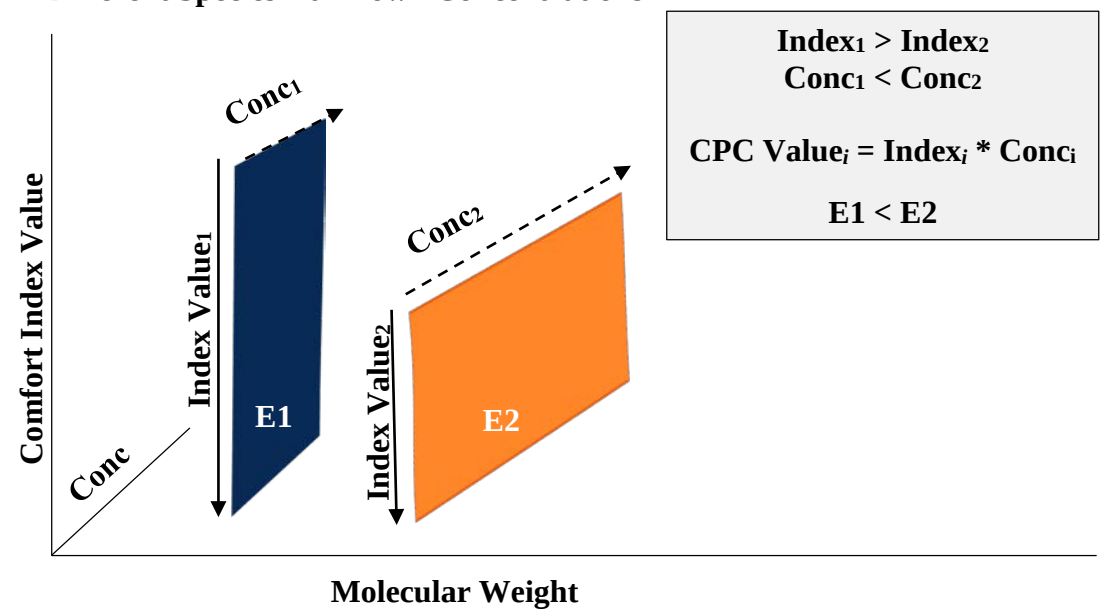
C) Using The Comfort Agent Index Values To Compare Between The Same Comfort Species At Different Concentrations



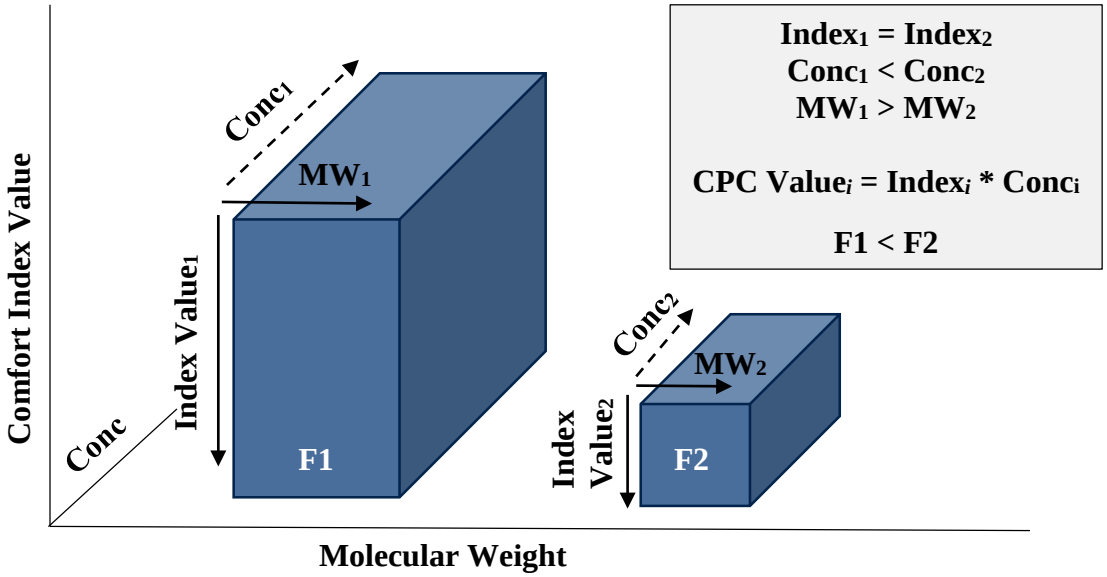
D) Using The Comfort Agent Index Values To Compare Between Different Comfort Species At Known Molecular Weights



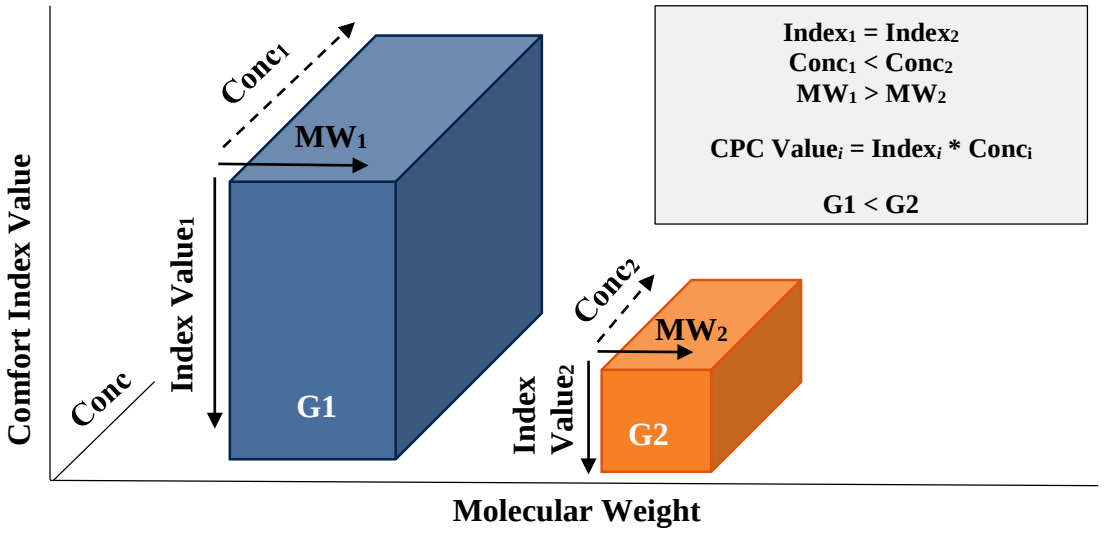
E) Using The Comfort Agent Index Values To Compare Between Different Species At Known Concentrations



F) Using The Comfort Agent Index Values To Compare Between The Same Species At Different Concentrations And Different Molecular Weights



G) Using The Comfort Agent Index Values To Compare Different Species At Different Concentrations And Different Molecular Weights



H) Using The Comfort Agent Index Values To Match CPC Between Different Comfort Agent Species Formulations

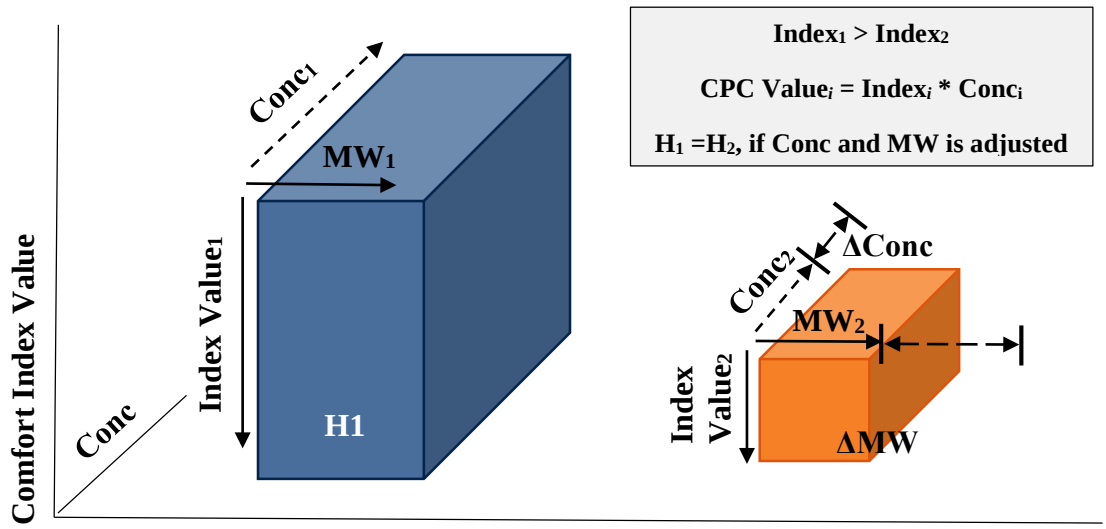


Figure 3.8. Using The Comfort Agent Index Values To Compare Between Comfort Solutions

Comfort agent index values were derived in **Section 3.4**. These values have high potential value for comparing among comfort agent solutions, which has not been possible with any confidence before. The basis of comparison is between comfort agent species, comfort agent molecular weight, and comfort agent solution concentration. Various potential comparison scenarios are presented in **Figure 3.8** to demonstrate the value of these indices. Different species can be directly compared as shown by **3.8A**. In addition, the same comfort agent species can be compared at different molecular weights or at different concentrations (***3.8B-3.8C****, respectively*). The same comparison can be made between different comfort agent species (***3.8D-3.8E***). Comparisons between different solutions composed of either the same comfort agent species or of different comfort agent species with differences in both molecular weight and solution concentration are shown in **3.8F-3.8G**. Using the comfort agent index values, it is possible to match the comfort property contribution of different comfort agent solutions by adjusting concentration or molecular weight to compensate for differences in the index value.

3.8. References

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[6] Alcon. Genteal Lubricant Eye Drops Mild Dry Eye Relief Package Insert. *Package Insert.*

[7] Alcon. Genteal Lubricant Eye Drops Package Insert. *Package Insert.*

[8] Alcon. Genteal Severe Dry Eye Relief Lubricant Eye Gel Package Insert. *Package Insert.*

[9] Alcon. Genteal Lubricant Eye Drops Moderate to Severe Dry Eye Relief Package Insert. *Package Insert.*

[10] Optics AM. Blink Contacts Complete Eye Drops Package Insert. *Package Insert.*

[11] Alcon. Blink Gel Tears Lubricating Eye Drops Moderate-Severe Dry Eye Package Insert. *Package Insert.*

[12] CIBAVision. Aquify Long Lasting Comfort Eye Drop Package Insert. *Package Insert.*

[13] Allergan. Refresh Optive Lubricant Eye Drops. *Package Insert.*

[14] Novartis. Hypotears Lubricant Eye Drops Package Insert. *Package Insert.*

[15] Zone DE. Nutratear Lubricant Eye Drop Package Insert. *Package Insert.*

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[17] Alcon. Opti-Free Express Rewetting Drops Package Insert. *Package Insert.*

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[24] Refresh Classic Lubricating and Rewetting Eye Drops Package Insert. *Package Insert.*

[25] Refresh Liquigel Lubricating and Rewetting Eye Drops Package Insert. *Package Insert.*

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CHAPTER 4

COMFORT AGENT META-ANALYSIS OF THE LITERATURE

4.1. Ocular Comfort Agents And Precorneal Residence Time – Meta-Analysis Of The Literature

The large number of conflicting clinical reports within the literature were discussed briefly in **Section 3.2**. It was suggested that the previously unexplored relationship between ocular comfort property contribution (*CPC*), comfort agent molecular weight, and solution concentration can partially explain and resolve these conflicts. In addition, this relationship was used to develop novel index values to compare between different comfort agent species, concentrations, and molecular weights in various ways. Various potential uses of the index values to compare between comfort agents and comfort agent solutions are shown in **Chapter 3** (***Figure 3.8***). The index values developed in **Chapter 3** are potentially very useful to compare between comfort agent species and comfort agent solutions. However, during the course of this work, there has been need to compare between more complicated scenarios where comfort agent solution concentration varies with time, such as comparing the level of comfort from comfort agents delivered from different vehicles, such as eye drop solutions and contact lenses.

However, empirical evaluation of the precorneal contact time of comfort agents or the residence time of the comfort agent in the ocular tear film is rare and not usually available for diverse comfort agents or for comfort agent molecular weights or comfort

agent solution concentration. Partially, this scarcity of published measurements is due to the difficulty of the measurement of the comfort agent solution concentration the tear film. Rather than direct measurement of the comfort agent solution concentration, the large majority of studies will attempt to correlate the comfort agent ocular residence time with a separate and easily measured property. However, the easily measured property seldomly demonstrates a direct or objective empirical correlation to the precorneal contact time of the comfort agent and cannot be used to estimate the ocular residence time within the tear fluid. Of the available published clinical studies, very few articles properly explore the effects of comfort agent molecular weight or instilled solution concentration on the residence time within the tear fluid in a robust and statistical manner.

4.2. Motivation For Analysis

The index values developed in **Chapter 3** (***Table 3.5***) are representative only of static solution concentrations and not applicable to dynamic flow conditions experienced under *in vivo* ocular conditions, as the comfort agent effectiveness depends strongly on both the comfort agent solution concentration and of the precorneal contact time between the comfort agent and the ocular surface/tear fluid. The development of the index values was based on the rheological and physical behavior of static comfort agent solution concentrations and did not account for the gradual loss of concentration with time due to the natural flow of tears. Thus, while the novel index values provided high value in the comparison between diverse comfort agent eye drop solutions and allowed the resolution of many discrepancies in the clinical literature, the values are not useful in the prediction of the comfort contribution of comfort agents delivered via contact lenses. To properly model the comfort contribution of contact lenses, further analysis is needed that accounts

for the dynamic changes in the solution concentration of comfort agents under in vivo conditions as both the input and removal of comfort agent from the ocular tear film can vary with time (*behavior shown in* ***Figure 4.1***).

As shown in **Figure 4.1**, when a drop is applied to the ocular surface, a maxima in tear fluid concentration is instantaneously achieved and immediately begins to wane due to natural tear flow, tear drainage, and spillage of the tear fluid over the eye lids. However, controlled release of comfort agents from contact lenses can potentially provide a sustained and constant concentration within the tear film. Presently, the difference in comfort contribution resulting from a pulsatile and intermediate comfort agent solution concentration compared to a sustained concentration is unknown for any comfort agent, let alone between diverse comfort agent species, comfort agent molecular weight, and solution concentration. In the development of high comfort ocular materials and formulations, this is a vital unanswered question within the field. To date, there has not been a convenient model or method for comparing between these two devices. The concentration profiles of the comfort agent concentrations residing within the tear fluid when delivered by either of these devices are very different and cannot be easily related.

By accurately modeling the comfort agent concentration profile within the ocular tear film, it is hypothesized that the comfort contribution can be found and compared among any delivery vehicle with high degree of confidence by comparing the product of the specific comfort index value in **Table 3.5** for a specific comfort agent/solution in and the calculated area under the comfort agent concentration profile. This method will allow the consideration of both the physical/solution properties of comfort agents/solutions and the duration of the residence time within the ocular tear film in the determination of the

comfort contribution. To develop this model, it is necessary to perform a novel meta-analysis of the comfort agent clinical literature to determine the precorneal residence time of comfort agents at various comfort agent molecular weight intervals and various instilled concentrations.

4.3. Meta-Analysis Materials And Methods

It is important to note that this is a meta-analysis and not simply a literature review. Clinical investigations and published peer reviewed papers measuring the residence time of comfort agents *in vivo* are discussed and reviewed in **Section 4.4**. The data necessary for the development of the respective models was extracted from these references including the half-life of the instilled comfort agent concentration, the comfort agent molecular weight, etc. However, the half-life is not always calculated within the cited references and had to be determined under certain assumptions and is occasionally incorrectly reported by the authors within the work due to poor conceptual understanding of the experimental concepts or poor experimental methodology and had to be recalculated for use in the meta-analysis. Additionally, the instilled comfort agent solution concentration is often not provided and has to be found from other sources including product descriptions, regulatory agencies, patents, or other research articles. The comfort agent molecular weight is rarely given within the clinical literature and had be extracted from product descriptions, other reports, or patents. Typically though, the molecular weight of the comfort agent had to be calculated from the comfort agent solution concentration and the solution viscosity using different relationships from polymer dilute solution viscosity equations or correlations from manufacturers of the comfort agent.

As such, the data extracted from the papers in this analysis is not always the same as the reported values or even representative of the conclusions presented within the original article. As such, the conclusions presented within **Section 4.3.4** are often well beyond the scope of the original cited reference and includes significant outside information from other sources. In addition, novel correlations between healthy and dry human eyes as well as between animal and human eyes were determined to include a greater amount of empirical clinical data within the meta-analysis. The extracted meta-data was used in a novel statistical analysis, qualifying it as a novel meta-analysis instead of a review of the literature.

4.3.1. Selection Of Clinical Evaluations For Use In The Meta-Analysis

Analysis of the clinical data was performed on studies of hydroxylpropyl methylcellulose (*HPMC*), sodium hyaluronic acid (*HA*), sodium carboxymethylcellulose (*CMC*), polyvinyl alcohol (*PVA*), dextran (*Dex*), and other comfort agents formulated into solutions or drops and instilled in either human or lupine eyes. Also investigated were fluorescein tagged isocyanate (*FTIC*) derivatives of hyaluronic acid and dextran (*FTIC-HA and FTIC-Dex, respectively*).

As mentioned in **Section 4.3**, the number of clinical evaluations measuring the residence time of comfort agents are very few. Since the late 1950's, no published work has directly measured the comfort agent concentration *in vivo*. The two most common methods used in the clinical literature to evaluate the ocular contact time of the comfort agents were either patient surveys (*which are highly inconsistent and unreliable*) or through the residence of a secondary tracer molecule. In this meta-analysis, it was decided that only references that correlated residence time with a secondary tracer molecule would

be considered. This sharply limited the number of clinical studies available and forced the use of dated references, though the data was consistent with contemporary studies, in some cases dating back to 1958. This resulted in the selection of approximately 40 citations published over 6 decades as is shown in **Figure 4.2**. The selected studies incorporated diverse comfort agents species, and the totals are shown in **Figure 4.3**. Details of the clinical studies used in this analysis are given in **Table 4.1**. The structures of the small molecule tracers and of the fluorescent comfort agents used as tracers in some of the cited references are shown in **Figure 4.4** and **Figure 4.5**, respectively. Properties of the tracers are provided in **Table 4.2, 4.3, 4.4, and 4.5**.

Selection of the studies gave priority to those trials conducted on healthy, human eyes. However, due to the rarity of the published accounts measuring comfort agent residence time *in vivo*, it was necessary to incorporate studies involving subjects with dry eyes and rabbit models. **Figure 4.6** shows the number of studies performed with each of the 3 models. **Table 4.6** briefly describes the major differences between the different models. In the analysis, novel correlations were developed to extrapolate normal comfort agent residence time values for healthy human eyes from data found in evaluations in rabbit or dry eye models for polysaccharide comfort agents (***Tables 4.7*** *and* ***Table 4.8***) and for acrylic comfort agents (***Table 4.9*** *and* ***Table 4.10***) within the various models. Also, this analysis did not incorporate data using results from studies correlating comfort agent residence time to pharmacodynamic activity.

4.3.2. Extraction Or Independent Calculation Of Comfort Agent Solution Concentration and Comfort Agent Molecular Weight From Clinical Evaluation

The rheology of the comfort agent solution was used to the approximate the molecular weight of the comfort agent from manufacturer data. This assumes the comfort agent is the viscosity determining ingredient in the eye drop formulation. Concentration and other data about commercially available comfort agent eye drop solutions were gathered and can be seen in some detail in **Table 4.1**.

4.3.3. Extraction Or Independent Calculation Of Comfort Agent Precorneal Residence Time From Clinical Evaluations

The most common method of *in vivo* measurement is the use of a fluorescent or radioactive molecule. The radioactive/fluorescent tracer is added to a comfort agent solution and delivered to the eye with the comfort agent solution. The precorneal activity/contact time of the tracer is measured. The underlying assumption is that the residence time of the tracer is the same or similar to the contact time of the comfort agent. This claim is very much debatable. The presence of comfort agent in the tear fluid increases the viscosity of the tear fluid and can increase the residence time of both the comfort agent and small molecules in the tear film, at least, some extent. Due to their high molecular weight, comfort agents are not usually absorbed into the ocular tissue, though some comfort agents, particularly hyaluronic acid, have been shown to possess strong muco-adhesive properties, which cause the comfort agent to temporarily and reversibly adhere to the lipophilic corneal epithelial cells. However, small molecules, particularly hydrophobic molecules, are more susceptible to uptake by the ocular tissue.

For instance, several articles measuring the residence time of hyaluronic acid use fluorescein as the tracer molecule. Other articles have shown that including fluorescein in hyaluronic acid solutions indeed increases the pre-corneal contact time of the fluorescein but will also increase the uptake of fluorescein into the cornea and sclera and other ocular tissues due to the increased residence time. This unfortunate effect makes accurate determination of drainage kinetics difficult to determine, particularly the 100% drainage point. This results in the observation of false drainage kinetics unless great care is taken.

As one author points out, it is impossible to tell if the extension of fluorescence is due to the presence of hyaluronic acid in the tear fluid, high hyaluronic acid adhering to the surface of the ocular kit tissue, or fluorescein having been absorbed into the tissue. This effect and the resulting demonstration of false drainage kinetics is shown conceptually in **Figure 4.7**. This error was minimized by determining the tracer half-life (*the point where half of the administered comfort agent concentration has been removed from the tear fluid*) instead of the 100% drainage point,.

The half point is much more easily and accurately determined. In addition, drainage constants can be approximated from the half-life equations (*zero, first, second, and Nth order half-life equations and corresponding characteristic release profiles are shown in* ***Table 4.11*** *and* ***Figure 4.8****, respectively*). The residence time or drainage constants can then be used to predict the *in vivo* concentration of comfort agent in the tear fluid. In the meta-analysis, the behavior of the comfort agent drainage profiles were found to more closely resemble first order kinetics. First order drainage kinetics were assumed for all comfort agent drainage profiles and used to estimate the half-life. The half-life (*in minutes*) for polysaccharide and acrylic comfort agents at various instilled concentrations and

molecular weights were found/modelled and are presented in **Table 4.12** and **Table 4.13**, respectively. It is important to note that in **Tables 4.12** and **Table 4.13,** the darkly shaded squares correspond to empirical values measured in the clinical literature while the other values are modeled according to the standard first order decay field equations. The residence constant (k) was calculated from after the half life ($t_{1/2}$) time was found from the corresponding half life equation and are shown for polysaccharide comfort agents (***Table 4.14***) and acrylic comfort agents (***Table 4.15***).

4.3.4. Statistical Analysis Of The Gathered Meta-Data

The half-life of the drop was calculated if it was not given within the original cited reference as described in **Section 4.3.3**. MATLAB® and Polymath® mathematical softwares were used to find a nonlinear regression and produce a surface fit for the data over a standard interval range. Three dimensional surface plots for polysaccharide and acrylic comfort agents (***Figures 4.9*** *and* ***4.10****, respectively*) were created in Microsoft® Excel 2013®. A proportionality constant for each of the 3D plots was also calculated by regression in Polymath® and Microsoft® Excel 2013®. The proportionality equation and the calculated constants used to model the 3D plot surface are shown in **Table 4.16**. Any other assumptions necessary to produce the 3D surface plots are provided in **Table 4.17**.

4.4. Discussion Of Selected Clinical Evaluations Used In The Meta-Analysis

The first analyzed study measuring the residence time of ocular comfort agents (*published in 1968*) **[4.1]** attempted to correlate the residence time of methylcellulose added to eye drop formulations increased the apparent residence time and bioavailability of different ocular pharmaceuticals **[4.2-4]**. The increased bioavailability of small molecule pharmaceuticals when used in conjunction with comfort agents in eye drop formulations is

an interesting and potentially valuable benefit of incorporating comfort agents into drug-eluting ocular devices/formulations. This effect has been investigated by many authors over the years and will be discussed in much greater detail in **Section 4.8**. A HPMC solution were diluted until different viscosities were achieved **[4.1]**. All solutions therefore incorporated the same grade of HPMC and can be assumed to be of the same or very similar molecular weight. A second comfort agent solution (*1.4% PVA*) was used as a comparative solution. A small amount of fluorescein was added to each solution, and the drops were placed into the eyes of 20 student volunteer (*healthy*) subjects **[4.1]**. A cotton swab was inserted into the nasal cavity via a long thin wire and remained until the first leading-edge was observed to be stained by the tracer. The time between installation of the drops and the detection of the tracer on the cotton swab was determined to be the contact time or residence time of the fluorescein and therefore the comfort agent. It was found that HPMC had a much longer residence time that PVA. This method used in the study was relatively invasive and therefore potentially less accurate due to the increased or decreased lacrimation and tear volume cause by the presence of the cotton swab. To date, this is the only study to date to measure residence time in such a fashion. In addition, this method did not allow for the development of a concentration profile (*tear concentration as a function of time*) as later studies that used different methodology, such as, slit-lamp fluorometers.

Slit-lamp fluorometers measure the total fluorescence and are not specific to fluorescein present in particular tissues in the eye unless this is specifically accounted for. Unless great care is taken, a falsely extended residence time for fluorescein in the tear fluid can be determined because fluorescein can adhere to the surface of the ocular tissue or be absorbed into the inner ocular tissues and cavities, where they remain even after the

comfort agent has been removed. The authors report that the penetration time for transit time for the dye to make contact with the cotton swab increased with increasing viscosity **[4.1]**. It should be noted here that as all the sample comfort agent was of the same molecular weight and any increases in viscosity were due to increases in HPMC concentration, alone.

A later study (*1972*) used the same molecular weight and concentration of HPMC as the 1968 paper, but instead of using fluorescein as tracer, used a silver-based dye (*Argyrol*) to measure the presence of the dye in the tear film **[4.5]**. The study found that the calculated HPMC half-life (***Table 4.12***) was very similar to the 1968 study calculation **[4.1]**. No statistically significant difference in the half-life calculation was found, adding strength to the conclusions of both papers. The studies were remarkably similar, and the 1972 study adds little novelty to the field, except that it demonstrated the use of argyrol silver tracer and provided additional details measured in the study, such as the average number of subject's blinks and the results of the Schirmer test, which the first study either did not perform or did not report. However, this study is consistent with the first and later reports, making it valuable.

Both of the previously discussed studies concluded that the HPMC possessed increased residence time when compared to PVA in healthy humans by using a fluorescent tracer molecule. In 1975, lacrimal microscintigraphy was demonstrated as an effective method to measure comfort agent residence time *in vivo* **[4.6]**. Lacrimal microscintigraphy works through the introduction of radioactive isotopes (*radiotopes*) as tracers into ocular formulations and provide several advantages. These benefits include the ability to determine a radiotope concentration profile in the ocular tear fluid/tissue and accurate measurements of the radiotope location, even behind the eyelids within the puncta or nasal

cavities, or any area where visual dyes cannot be directly observed except through invasive techniques. There are, however, potential disadvantages with the use of specific radiotopes that must be discussed. The radiotope used in the 1975 study was technetium 99m, which was mixed into the comfort agent solution but was not chemically or covalently bonded to the comfort agent.

The 1972 study evaluated two different commercial formulations (*containing HPMC and PVA, respectively*) and concluded instead that HPMC possessed a superior residence time compared to the residence time of PVA **[4.5]**. In the 1975 article, the authors used similar eye drop formulations, but used the radiotope to find the residence time and measured the percent radioactivity 90 seconds after the drop was instilled **[4.6]**. In this study, PVA was reported to be the comfort agent with the superior residence time when compared to HPMC contradicting the earlier reports **[4.6]**. As discussed in **Section 4.2.,** this conflict is common in the clinical data, but is seldom understood. No hypothesis was suggested for this conflicting report by the authors, though it was noted by the authors that this result was inconsistent with the previously cited reports. A meta-analysis investigation of this and other conflicting reports is presented in **Section 4.3.4**. Again, no investigation into the cause of the disparity with other studies was discussed.

Overall, relatively little detail was provided by the previously described studies. Different methods and tracers were used. No concentration profiles were calculated that might help correlate between conflicting studies. Without additional information, the conflicting reports would be very difficult to reconcile. Fortunately, later studies provided greater amounts of detail. More importantly, the findings were consistent with the above studies and allowed for confident assumptions to be made in the meta-analysis. Most of

the aforementioned studies have focused on comfort agent residence times in healthy human eyes. A thorough and highly detailed 1974 study used microscintigraphy techniques in rabbit eyes to measure the residence time of comfort agent formulations (HPMC and PVA) with highly diverse viscosities (*ranging from approximately 1 cP to approximately 100 cP*) **[4.7]**. Furthermore, the study attempted to use a pharmaceutical dilator to correlate with comfort agent residence time. While other reports have also attempted to develop the relationship between the magnitude and duration of dilation and comfort agent residence time, the pharmaceutical effect can vary significantly. The data determined through pharmaceutical or chemical correlation will be discussed in greater detail in **Section 4.8**, where it will be shown that including comfort agents as excipients, emulsifiers, and wetting agents, etc in drug solutions increases the efficacy and efficiency of drug solutions by increasing the ocular uptake of drug into the ocular tissue.

This is a very interesting study for several reasons. A high level of detail was provided by the authors. In addition, this is the first demonstration of the use of a rabbit model to investigate and the wide number of concentrations used in the study. This paper is the first to demonstrate the increased absorption of the tracer molecule into the ocular tissue and that this absorbed mass increases with HPMC concentration **[4.7]**. In addition, it is relatively easy to distinguish between the concentrations of tracer residing within the tear fluid versus the tracer absorbed by the ocular tissue. **Figure 4.7** demonstrates this to greater clarity.

Shortly afterward several more studies were published using fluorescein as the tracer for polyvinyl alcohol and methylcellulose comfort agents and are described in **Table 4.1**. A particularly detailed study demonstrated that the presence of HPMC increased in the

volume of the tear fluid and decreased the rate of tear drainage **[4.8]**. This paper was one of the first to conclusively show that the rate of tear drainage rate is proportional to the tear volume. The authors also showed that presence of the comfort agent polymers in the tear fluid increases the thickness of the tear. The 1975 study also attempted to resolve discrepancies in the reported residence times of HPMC and PVA solutions by measuring the residence time of the different comfort agents in solutions with the same viscosity **[4.9]**. In the paper, the authors claim that comparisons between different comfort agent drops (*for example, comparing hydroxypropyl methylcellulose-containing drops to poly(vinyl alcohol)-containing drops*) should only be made between formulations of similar viscosities rather than those of similar concentrations. The effect of methylcellulose on the solution viscosity is much greater than the effect of acrylic polymers (*up to two orders of magnitude greater than that of the acrylic comfort agent*). This effect was discussed previously in **Section 4.2**. Solutions of HPMC and PVA were formulated to similar viscosities and placed into healthy human eyes. Five additional commercial eye drop formulations were tested as well (***Table 4.1***). It was shown that HPMC had a much greater residence time than the acrylic comfort agents. The authors state that the HPMC solutions prolonged the residence of fluorescein while PVA did not. This is one of the first attempts to resolve the many discrepancies in the clinical literature. However, viscosity is a function of both molecular weight and concentration. The authors failed to investigate molecular weight as a variable.

The effect of blinking on the residence time of HPMC and PVA were briefly described in a 1975 study where 1.4% PVA was shown to reside in the tear fluid longer than 1% HPMC solution in 4 healthy human eyes **[4.10]**. The study has few details,

however. When the test was repeated with closed eyes, both comfort agents demonstrated increased residence time, though HPMC was superior under closed high conditions. The authors did not manage to explain this, but discussion of the zero shear viscosity in **Section 4.2.** could easily explain this observation.

HPMC and PVA were again used in an 1986 study that compared the rate of drainage of a wide variety of concentrations **[4.11]**. The viscosities of the solutions were varied between 1 and 102 mPas. It was found that the rate of comfort agent drainage was much faster in humans compared to rabbits. The authors report that the residence time of the different comfort agents were extended only at high concentration (*1% HPMC and 6% PVA*). The study used scintigraphy to evaluate the residence time of the comfort agents.

In an interesting series of articles published between 1985-1992, Ludwig et al attempted to correlate the ocular residence time of comfort agents with various *in vivo* properties of the tear fluid, including tear osmolality **[4.12]**, tear surface tension **[4.13]**, tear viscosity **[4.14, 15]**, the relationship between tear surface tension and viscosity **[4.16]**, and tear composition **[4.17]** as well as to the drop size/tear volume **[4.18]**. These series of papers are interesting, but do little to provide conceptual understanding and alleviate the conflicts that fracture the clinical data.

The previous work in the field focused exclusively on hydroxypropyl methylcellulose and poly(vinyl alcohol) comfort agent solutions. It is interesting that both these comfort agents are neutral chains. It was not until the early 1990's that polyelectrolyte comfort agents, notably hyaluronic acid, were introduced into the literature. Most notable of these works are those of Snibson **[4.19, 20]**, Gurny **[4.21]**, and Greaves **[4.22-25]**. The ocular residence time of hyaluronic acid determined in these works was evaluated via

scintigraphy. One of the only papers to consider molecular weight in the evaluation was published in 1995 **[4.26]**.

One of the most recent developments in the field is the development of a new tracer that potentially can be used to measure the residence time without the errors inherent in the use of traditional small molecule radiotopes. Medium molecular weight dextran or hyaluronic acid is commonly tagged with fluorescein isocyanate (*FITC*) and can be used to measure the residence time without being absorbed into the ocular tissue due to its high molecular weight as discussed in further detail in **Table 4.5**. The most significant of this work has been done by Paugh et al **[4.27-32]**.

4.5. Results And Discussion

A large sections of **Chapter 3** were dedicated to the development and discussion of a novel method of analysis and characterization of ocular comfort beyond the traditional model where comparison was primarily between different species of comfort agent and any differences between comfort agent molecular weight and comfort agent solution concentration were either neglected or not explored. This resulted in numerous conflicts and confusion and prevented significant understanding of ocular comfort for 6 decades within the clinical data. The novel model stringently explored the relationship between molecular weight, solution concentration, comfort agent species and the physical and solution properties of comfort agents and/or their corresponding dilute aqueous solutions. The work in **Chapter 3** was the first comprehensive analysis of comfort agents and comfort agent solution properties to demonstrate variation in the contribution of different solution to ocular comfort properties. In addition, the determined relationship strongly correlated to trends within the published clinical data. Furthermore, the same relationship was used to

empirically resolve previously conflicting reports demonstrating the importance and high value of including the effects between comfort agent species, comfort agent molecular weight, and comfort agent solution concentration in the evaluation and consideration of ocular comfort solutions to alleviate pain and irritation for the subject.

The conclusions of **Chapter 3** focused on the analysis of static solutions and comfort agent species. The value of this analysis is highly valuable for the conceptual understanding of ocular comfort. The analysis of **Chapter 4** focused instead on the dynamic solution concentration and ocular contact of the comfort agent experiencing *in vivo* clinical conditions. This analysis was developed partially to provide a greater understanding of the contribution of these solutions to comfort, but was primarily concerned with the development of a model capable of comparing the comfort contribution provided by different delivery methods such as a static solution or the dynamic release of comfort agents from contact lenses, where the ocular concentration profile can be drastically different and even incomparable between delivery devices. This was achieved by performing a meta-analysis on the clinical literature where the average precorneal contact time of the diverse comfort agent specimen was measured under physiological conditions.

The collected data allowed for a novel statistical analysis and survey of the sample data where a multidimensional regression allowed the production of complete surface plot of the ocular half-life of an instilled concentration of comfort agent according the same design variables as used in **Chapter 3**, specifically comfort agent species, comfort agent molecular weight, and comfort agent solution concentration. The derived statistical model was unique to each species of comfort agent and the characteristic behavior of each sample

with respect to changes in value of either comfort agent molecular weight or the instilled concentration of comfort agent solution.

4.5.1. Significance Of Analysis And The Value Of The Novel Results

Determination of ocular residence time values of various comfort agent species was vital for the production of a model capable of serving as a method to compare between different methods of comfort agent delivery. Before this study was undertaken, there was no model that would predict the release of comfort agents from a contact lens under in vivo wear conditions as a function or predict the precorneal concentration mass profile of the comfort agent. Therefore, there was no method to compare the comfort property contribution between devices; the most common comparison was the delivery of comfort agent via ocular eye drops, though this was universally acknowledged as both a terrible model for release devices and as being highly inaccurate when used as the concentration mass profiles for comfort agents delivered from a drop solution than the mass profile for comfort agents eluting from an ocular device.

As discussed previously, **Chapter 3** was primarily interested in the development of a simple relationship to allow comparison between specific comfort agents and respective aqueous solution concentrations. A simple expression for the comfort property contribution was developed by taking product of the comfort agent molecular weight and solution concentration (*if applicable*) with a proportionality constant specific for each comfort agent developed from empirical evaluation of comfort agent physical and solution properties. This relationship was used later in **Chapter 3** (***Section 3.5***) to evaluate solutions with static concentrations. In **Chapter 4**, the expression was expanded to evaluate the comfort property contribution of dynamic systems (*conditions where the comfort agent*

concentration is changing with time such as in vivo ocular conditions). To account for differences in the mass profiles, it was decided that calculating the area under the curve (*AUC*) of the precorneal mass profiles found for the comfort agent in the tear film over a specified time period would be a simple and convenient method to accurately compare between different profile resulting from different methods of delivery. In a similar manner, the AUC under the *in vivo* mass profile of pharmaceuticals delivered from eye drop solutions is proportional to the bioavailability of the drug and, thus, the pharmaceutical efficiency of the drug in reaching the ocular tissue.

If the AUC is representative of the bioavailability and molecular efficiency and if the comfort property contribution index values correlate to sensations of comfort, then the product of the two values can be used to evaluate the comfort contribution for dynamic systems. This is the primary fundamental contribution of **Chapter 4**. The development of the comfort contribution expression for dynamic systems required the performance of a meta-analysis of the clinical literature to obtain a relationship to estimate the precorneal ocular residence time of different comfort agents and the two investigated variables – comfort agent molecular weight and comfort agent instilled concentration. The meta-analysis was necessary as reports measuring the precorneal residence time of the comfort agents by direct measurement are rare and do not represent a diverse subset of the comfort agents used in commercial products. A statistical analysis was performed incorporating the empirical data resulted in the development of novel expressions for the precorneal tear film contact time for the selected comfort agents at any desired molecular weight or instilled concentration instead of the limited number of samples tested in the clinical data. Another contribution presented within **Chapter 4** was the analysis and discussion of the different

methods of evaluating ocular contact time of the comfort agents. It was found through the statistical analysis that the data collected from the various models and through different methods are consistent with each other once the proper assumption and corrections for comparison were made. This was the first demonstration of such an analysis

Most clinical studies of comfort agents use patient satisfaction surveys or measure the changes in corneal staining or tear break-up time, etc. These are important measurements but do not always correlate to residence time, *in vivo* comfort, or accurate comparison between comfort agent solutions. The popularity `of these measurements is that they are relatively easily measured, relatively non-invasive, and more comfortable for the subject. By and large, direct measurement of comfort agents in tear fluid is difficult. Most are sugar or saccharide-based, which make most spectroscopy methods unavailable, and commonly used assays for comfort agents are often unreliable when used to detect comfort agent concentration in lacrimal, as the chemistry necessary to the assay is typically nonspecific to comfort agents, and the concentrations are often too low for confident measurement.

4.5.2. Novel Models For Ocular Comfort Agents And Precorneal Residence Time At Various Comfort Agent Molecular Weight And Solution Concentration Ranges

Our analysis resulted in three dimensional plots of comfort agent half-life in relation to molecular weight and percent concentration of comfort agent in solution. The plots were constructed by regression of clinical trial measurements by assuming the half-life relationship is equal to A + B * MW + C * %Conc and that the residence time is proportional to comfort agent molecular weight and comfort agent solution percent concentration (***Table 4.16***). Polymath and MATLAB mathematical softwares were used to

extrapolate the plot surface, according to decay field equations. A proportionality constant was calculated from the experimental data to a high confidence level, with R^2 values >0.9. This was done so that a comparison could be made over uniform ranges. The calculated half-life for the various comfort agents are presented in graphical form in **Figures 4.9-4.10** and in tabular form for select molecular weights and concentrations in **Tables 4.12-4.13**. In addition, the drainage constant for first order kinetics were calculated for certain molecular weights and concentrations and are presented in **Tables 4.14-4.15**.

4.5.3. Behavior Of Specific Comfort Agents And Classes Of Comfort Agents

Figures 4.9-4.10 demonstrate the results of the meta-analysis for the various polysaccharide comfort agents. Unexpectedly, it was found that the neutral polysaccharides, FITC dextran and HPMC, possessed the greatest residence times, longer than the two polyelectrolyte polysaccharides (*CMC and HA*). CMC and HA possessed very similar residence time values. Though unexpected, this trend is at least consistent with the results of **Section 4.2**, which demonstrated a similar correlations between polyelectrolyte behavior and neutral polysaccharide behavior. In addition, it must be noted that data was not available for true dextran and DSS, and that the data available for HA was almost uniformly at very high molecular weight and low concentration, whereas the data CMC and HPMC was evaluated at a greater diversity of concentration and molecular weight. It would be very interesting to see if the polyelectrolyte and neutral polysaccharide behavior was confirmed by investigation of neutral dextran and DSS and greater diversity of molecular weight and concentration for FITC dextran. Furthermore, the addition of fluorescein to the dextran structure could potentially alter the residence time of the dextran chain itself. Also, clinical trials observing the residence time of hyaluronic acid at low

molecular weight and of high molecular weight hyaluronic acid at high concentration would result in a greater understanding of the residence time.

The results, however, were initially surprising. Trends in the clinical data including comfort agent evaluation, the results of **Section 4.2**, etc. seem to indicate that hyaluronic acid is the superior comfort agent currently available on the market due to its high muco-adhesive properties, it's high comfort property contribution, and popularity among consumers. In addition, it is commonly seen among various *in vivo* testing that the beneficial effect of hyaluronic acid is much longer than other comfort agents. It was expected that hyaluronic acid would possess the longest residence time of the polysaccharide comfort agents; this, however, was not the case.

4.5.4. Using The Novel Models For The Comfort Agent Precorneal Residence Time To Predict The Comfort Contribution Of Eye Drop Solutions

The results of the meta-analysis produced novel expressions for the concentration mass profiles in the ocular tear fluid for common comfort agents. Like the analysis in **Chapter 3**, a strong dependence on comfort agent molecular weight and solution concentration is demonstrated for residence times of the comfort agent in the precorneal tear fluid. The results indicate that there is a more significant or greater degree of dependence upon the instilled comfort agent solution concentration, but the dependence is non-linear with instilled solution concentration, but the degree of dependence seems to increase exponentially across the solution concentrations analyzed. In contrast, the dependence of the residence time expression on molecular weight is not as significant as the dependence on instilled concentration, but remains approximately constant as the molecular weight increases across the range evaluated in the selected references. Using the

data to perform a surface multi-variable regression, the predicted *in vivo* concentration were calculated for each comfort agent of various molecular weights and at an eye drop solution concentrations of 0.05, 0.5, and 5 (*wt*)% by assuming the comfort agent was delivered in an eye drop volume of 35 μL. The mass profiles can be seen in **Figure 4.11**.

According to the predicted concentration profiles, the polysaccharide comfort agents reside within the tear fluid for much longer periods of time than the acrylic comfort agents at all comfort agents at all molecular weights and solution concentrations. Of the comfort agent evaluated, polysaccharide comfort agents possessed the greatest residence times by far, much longer than acrylic comfort agents. The specific species of comfort agent predicted to possess the longest residence time in the precorneal tear film is HPMC. This corresponds well with the proposed mechanism of comfort for HPMC, which is that HPMC increases the tear fluid viscosity and prevents the drainage and loss of the tear film volume. The polyelectrolyte polysaccharide comfort agents, HA and CMC, had very similar residence profiles to each other. In comparison, the length of time that the acrylic comfort agents are in contact with the corneal surface are minor and uniform compared to the polysaccharide comfort agents.

The AUC for each of the comfort agent residence curves were calculated with Polymath statistical software and are presented in **Table 4.18**. In order to calculate the comfort contribution of the dynamic concentration profile, the AUC values are multiplied by the comfort index values in developed in **Chapter 3**. For example, the review portion of **Chapter 3** discussed that HA seemed to be the most effective comfort agent, which was supported by the developed comfort index values. However, the clinical evaluations also assumed that the because HA provided greater levels of comfort that the residence time of

HA had to be greater than the other comfort agents. This turns out to be incorrect. Comparing between eye drop solutions show a greater distinction between the comfort property contribution for analysis of the comfort agent drop solutions. For example, the AUC calculated for the comfort contribution of a 0.5% drop of 100 KDa HA is 4.2. Multiplication by the comfort index value of 162 results in a total contribution of 680. A similar calculation for 0.5% concentration of 100 KDa HPMC results in a total contribution of 578.5. The ratio of the contributions is much greater after considering the precorneal residence time effect. Multiple drops of the comfort agent solutions follow the same concentration profile, making the comfort contribution a multiple the contribution of the single drop.

4.5.5. Using The Novel Models For The Comfort Agent Precorneal Residence Time To Predict The Comfort Contribution Of Contact Lenses Releasing Comfort Agents

By comparison to predicting the concentration profile of comfort agent in the tear film when delivered from eye drops, determining the comfort agent concentration profile of comfort agents delivered from contact lenses is much more difficult as there is both a comfort agent input and output from the eye. For an eye drop, there is an instantaneous pulse of comfort agent delivered to the tear fluid, and the concentration immediately begins to decay according to first order decay kinetics. With contact lens comfort agent delivery, there is a steady input of comfort agent mass in addition to the drainage of comfort agent mass proportional the instantaneous comfort agent concentration within the tear fluid. This input provides the difficulty of predicting the *in vivo* comfort agent concentration. The release rate from contact lenses have been shown *in vitro* to be proportional to the flow rate

and release media volume. However, the comfort agent release from lenses has never been demonstrated *in vivo*.

For this reason, the Byrne Lab has pioneered the use of microfluidic devices to measure the release rate of molecules from contact lenses under small volume, continuous flow sinks that mimic the physiological conditions of the ocular environment. Performing the release of 120 KDa HPMC from the imprinted lenses showed a release rate of 16 μg HPMC/hr. This release rate can be taken to be the input value for the mass balance performed for the eye, while the output rate can be determined from the half-life regression values determined in **Section 4.5**. Performing a mass balance to determine the in vivo release profile for the imprinted contact lens, it was found that the input and output of comfort agent resulted in a steady state concentration of comfort agent within the tear film in a short amount of time. The AUC at 24 hours of comfort agent release from contact lenses was found for 24 hours to be 48. The one day CPC value was calculated from the product of AUC and the comfort index value to be 6384, while the CPC value for the full 60 days demonstrated for release from the microfluidic device was calculated to be 383040.

4.5.6. Comparison Between The Comfort Contribution Of Comfort Agents Delivered Via Eye Drop Solutions And Release From Contact Lenses

The comfort contribution of a single drop of a 1 wt% 120 KDa HPMC eye drop solution was found to be 19.4. By comparison, the comfort property contribution of the contact lens releasing 120 KDa HPMC for 60 days was found to be 383040. By matching the AUC, it is possible to directly compare the comfort provided from the eye drop solution and the contact lens. It was found that the daily comfort contribution of the contact lens was equivalent to the contribution of 150 eye drops/day.

4.6. Conclusions Of The Meta-Analysis

Chapter 4 resulted in valuable contributions to the field by analyzing the comfort contribution of comfort agent solutions delivered to the ocular tear film. The index values developed from the comfort agent physical and solution properties of static solutions in **Chapter 3** were expanded to predict the *in vivo* tear fluid concentration. The analysis required the review of the clinical literature to determine novel correlations between ocular residence time of comfort agents and the two independent variables comfort agent molecular weight and solution concentration. These expressions allowed for the prediction of contact time of comfort agents with the precorneal tear film. Overall, the polysaccharide comfort agents had a much longer residence time than the acrylic molecules, providing further explanation as to the difference in performance between the two classes of comfort agents.

4.7. Tables

Table 4.1. Measured Ocular Residence Time Of Comfort Agents Delivered Via Eye Drops

Species	MW (KDa)	Brand	Study Details	Concentration (%)	$t_{1/2}$ (min)	[Ref]
CMC	25	Refresh Tears Eye Drop	Fluorometry 16 patients (DE)	0.5	4.6	[4.32]
	90	Aqualon Cellulose Gum	Fluorometry FITC Dextran 70 18 patients	3.5 5 6.21	3.5 10 18	[4.30]
	400	Refresh Liquigel Eye Drop	Fluorometry 16 patients (DE)	1	8.3	[4.32]
	400	Refresh Liquigel Eye Drop	Fluorometry 60 patients	1	4	[4.33]
	700	Aqualon Cellulose Gum	Fluorometry FITC Dextran 70	0.4 0.57 0.8	5 10 22	[4.30]
FITC Dextran	70	Sigma-Aldrich	Fluorometry 16 patients (DE)	0.1	8.3	[4.32]
	72	Sigma-Aldrich	Fluorometry 18 patients	0.1	4	[4.34]
FITC-HA	800	Sigma-Aldrich	Fluorometry 30 patients	0.1	6	[4.35]
HA	134 400	Healon	Scintigraphy 5 rabbits	0.2 0.2	1.2 1.7	[4.26]
	800	Sigma-Aldrich	Fluorometry 10 patients	0.1	2.3	[4.35]
	2200	Healon	Scintigraphy 5 rabbits	0.2	11.2	[4.26]
	3000	Healon	Scintigraphy 12 patients (DE)	0.2 0.3	11.11 23.5	[4.19]
	3000	Healon	Scintigraphy 6 patients	0.2 0.3	5 13	[4.19]
	3000	Pharmicia-Leo	Scintigraphy 7 patients	0.25 0.125	5.35 0.733	[4.21]
	4000	Hylorin	Scintigraphy 6 patients (DE)	0.2	11.7	[4.20]

Species	MW (KDa)	Brand	Study Details	Concentration (%)	$t_{1/2}$ (min)	[Ref]
HPMC	2	Presert Eye Drop	Scintigraphy 15 patients	0.3	0.15	[4.8]
	4	HPMC 4000	Scintigraphy 5 patients	0.3	0.35	[4.24]
	10	Isopto Tears Eye Drop	Scintigraphy 18 patients	0.5	0.43	[4.6]
	10	Adapt Eye Drop	Fluorometry 16 patients	1	1	[4.8]
	10	Dow Chemical Methocel	Scintigraphy 16 patients	0.41 0.63 0.77 0.90	0.24 0.41 0.46 0.665	[4.11]
	10	Dow Chemical Methocel	Scintigraphy 12 rabbits	0.41 0.63 0.77 0.90	1.2 1.3 1.4 1.5	[4.11]
	15	Not Reported	Scintigraphy 6 patients	0.3	0.95	[4.20]
	20	Lacril Eye Drop	Scintigraphy 16 patients	0.5	1	[4.8]
	80	Barnes-Hinds Eye Drop	Scintigraphy 16 patients	0.5	1.5	[4.8]
	86	Alcon	Argyrol 15 patients	0.5	1.5	[4.5]
	86	Alcon	Fluorescein dye and a cotton swab 20 patients	0.25 0.5 1 2.5	1.5 2.3 3.5 4.25	[4.1]
	94	GenTeal Moderate Eye Drop	Fluorometry 16 patients (DE)	0.3	5	[4.32]
	100	Methocel GS HG 4000	Scintigraphy 6 patients	0.5 1 2 5	3 3.5 4 10	[4.8]
	120	Not Reported	Scintigraphy 17 patients	1	4.2	[4.10]
	120	Visculose Eye Drop	Scintigraphy 6 patients (DE)	0.5 1	3 10	[4.8]
	120	Not Reported	Scintigraphy 6 rabbits	1	10	[4.10]
PVA	100	Liquifilm Eye Drop	Fluorescein dye and a cotton swab 20 patients	1.4	1.2	[4.1]
	75	Polyviol Grade W40/140	Scintigraphy 16 patients	2.7 4.5 5.4 5.9	0.26 0.34 0.48 0.54	[4.11]

Species	MW (KDa)	Brand	Study Details	Concentration (%)	$t_{1/2}$ (min)	[Ref]
	75	Polyviol Grade W40/140	Scintigraphy 12 rabbits	2.7 4.5 5.4 5.9	0.63 1 1.13 2.5	[4.11]
	100	Liquifilm Eye Drop	Fluorescein dye and a cotton swab 20 patients	1.4	1.2	[4.1]
	100	Liquifilm Eye Drop	Scintigraphy 18 patients	1.4	0.278	[4.6]
	78	Polysciences	Fluorometry 16 patients	3.2 19.2	0.3 2	[4.8]
	100	Liquifilm Eye Drop	Scintigraphy 17 patients	1.4	0.75	[4.10]
	75	Polyviol Grade W40/140	Scintigraphy 16 patients	2.7 4.5 5.4 5.9	0.26 0.34 0.48 0.54	[4.11]
	75	Polyviol Grade W40/140	Scintigraphy 12 rabbits	2.7 4.5 5.4 5.9	0.63 1 1.13 2.5	[4.11]
	100	Liquifilm Eye Drop	Argyrol Dye 15 patients	1.4	0.8	[4.5]
	97	Allergan 20-90 Grade	Scintigraphy Unreported number of rabbits	0.5 1.1 1.9 2.25 3.5 5	2.17 2.77 2.77 2.24 8.66 4.95	[4.36]
	100	Liquifilm Eye Drop	Scintigraphy 6 patients	1.4	0.65	[4.20]

Table 4.2. Basic FITC-Functionalized Comfort Agent Properties

Properties	FITC HA	FITC Dextran
Root Comfort Agent	HA	Dextran
Repeat Unit MW	777	557
Log P	-0.256	-0.618
Charge	None	None
H-Bond Acceptors	19	17
H-Bond Donors	10	10

Table 4.3. Differences Between FITC-Comfort Agents And Unmodified Comfort Agent

Species	Na HA	HA	FITC-HA	FITC-Dextran	Dextran	DSS
Repeat unit MW	419	388	777	732	342	955
CAS	9067-32-7	9004-61-9	-	-	9004-54-0	9011-18-1
Functionality	Sodium Salt	-COOH	Pendant fluorescein group	Pendant fluorescein group	hydroxyl	6 pendant sulfate groups 6 sodium salts
Log P	-5	-4.91	-0.256	-0.618	-5.3	-5.65
H-Bond Acceptor	13	13	19	17	11	29
H-Bond Donor	7	8	10	10	8	2

Table 4.4. FITC-Based Repeat Units

Comfort Agent Species	HA	FTIC-HA	Dextran	FTIC-Dextran
Repeat Unit MW (Da)	388	777	342	731
Chain MW (KDa)	**Number Of Repeating Units**			
10	26	13	29	14
15	39	19	44	21
20	52	26	58	27
25	64	32	73	34
30	77	39	88	41
40	103	51	117	55
50	129	64	146	68
60	155	77	175	82
70	180	90	205	96
75	193	97	219	103
80	206	103	234	109
90	232	116	263	123
100	258	129	292	137
110	284	142	322	150
120	309	154	351	164
130	335	167	380	178
140	361	180	409	192
150	387	193	439	205
175	451	225	512	239
250	644	322	731	342
300	773	386	877	410
400	1031	515	1170	547
500	1289	644	1462	684
600	1546	772	1754	821
700	1804	901	2047	958
750	1933	965	2193	1026
800	2062	1030	2339	1094
900	2320	1158	2632	1231
1000	2577	1287	2924	1368
1100	2835	1416	3216	1505
1200	3093	1544	3509	1642

Table 4.4. Comparison Of Polysaccharide Comfort Agent Half Life In Healthy Eyes And Dry Eyes

Species	MW (KDa)	Conc (%)	Dry Human Eye $t_{1/2}$ (min)	Healthy Human Eye $t_{1/2}$ (min)	Dry/Healthy Ratio
CMC	10-100	0.5	4.6	1.5	3
	400	1	8.3	2.37	3
HA	2000-3000	0.2	5	11.11	2.22
	3000	0.3	13	23.5	1.8
HPMC	80-95	0.3	2.46	5	2.03
	120	1	10	4.2	2.4
FITC-Dex	70	0.1	8.3	4	2

Table 4.5. Advantages Of Using Fluorescein Isothiocyanate-Functionalized Comfort Agents

Use Of Fluorescein Isothiocyanate-Functionalized Comfort Agents To Measure Ocular Residence Time Of Comfort Agents	
Advantages	• Potentially Better Approximation Of Comfort Agent Ocular Residence Time • No Tissue Absorption • Diverse Molecular Weights Are Available Of Various Comfort Agent Species To Better Approximate The Comfort Agents
Disadvantages	• Not Exact Approximation • The Fluorescein Pendants Alters The Macromolecular Conformation Extending Non-Functionalized Comfort Agent • Pendant Fluorescein Group Alters Comfort Agent Properties

Table 4.6. Steady Conditions For The Normal Human Eye, The Rabbit Eye, The Human Dry Eye, And The Lens Wearing Eye

Property	Normal Eye	Rabbit Eye	Dry Human Eye	Lens Wearing Human Eye
Tear Volume	30	15	<25	
Blinks/min	5		Variable	
TBUT	~15-20 sec		<10 sec	
Tear Flow	1.5	1.5		3
Average Tear Turnover Time				

Table 4.7. Comparison Of Polysaccharide Comfort Agent Half Life In Healthy Eyes And Rabbit Eyes

Species	MW (KDa)	Conc (%)	Healthy Human Eye $t_{1/2}$ (min)	Rabbit Eye $t_{1/2}$ (min)	Healthy Human/ Rabbit Ratio
HA	2000	0.2	5	11.7	2.34
HPMC	10	0.5	0.43	1.24	2.88
	10	1	1	1.6	1.6
	120	1	4.2	10	2.4

Table 4.8. Comparison Of Polysaccharide Comfort Agent Half Life In Dry Eyes And Rabbit Eyes

Species	MW (KDa)	Conc (%)	Dry Human Eye $t_{1/2}$ (min)	Healthy Human Eye $t_{1/2}$ (min)	Dry/Healthy Ratio
HA	2000	0.2	11.11	11.7	0.99
HPMC	120	1	10	10	1

Table 4.9. Comparison Of Acrylic Comfort Agent Half Life In Healthy Eyes And Rabbit Eyes

Species	MW (KDa)	Conc (%)	Dry Human Eye $t_{1/2}$ (min)	Rabbit Eye $t_{1/2}$ (min)	Dry Eye/Rabbit Ratio
PVA	90-100	1.4	1.2	2.77	2.3

Table 4.10. Comparison Of Acrylic Comfort Agent Half Life In Healthy Eyes And Rabbit Eyes

Species	MW (KDa)	Conc (%)	Healthy Human Eye $t_{1/2}$ (min)	Rabbit Eye $t_{1/2}$ (min)	Healthy Human/ Rabbit Ratio
HA	2000	0.2	5	11.7	2.34
HPMC	120	1	4.2	10	2.4
PVA	90-100	1.4	1.2	2.77	2.3

Table 4.11. Half-Life Equations

Order Of Equation	Rate equation r_a =	Integrated Equation A =	Half Life Equation $t_{½}$ =	Residence Constant k =
Zero	**k**	**k * t**	$\frac{A_o}{2 * k}$	$\frac{A_o}{2 * t_{½}}$
First	**k*A**	**A_o*exp(k*t)**	$\frac{0.693}{k}$	$\frac{0.693}{t_{½}}$
Second	**$k*A^2$**	$\left(\frac{1}{A_o} + k * t\right)^{-1}$	$\frac{1}{k * A_o}$	$\frac{1}{t_{½} * A_o}$
Nth	**$k*A^N$**	$\left(\frac{1}{{A_o}^{n+1}} + (n+1) * k * t\right)^{\frac{1}{n-1}}$	$\frac{2^{n-1} - 1}{(n-1) * k * {A_o}^{n-1}}$	$\frac{2^{n-1} - 1}{(n-1) * t_{½} * {A_o}^{n-1}}$

Table 4.12. Half-Life Of Polysaccharide Comfort Agents At Selected Molecular Weights And Percent Concentrations

A. Hyaluronic Acid, Sodium Salt

HA MW (KDa)	Hyaluronic Acid Solution Percent Concentration								
	0.05	0.1	0.25	0.5	1	2	3	4	5
5	0.12	0.24	1.02	2.5	4	4.33	4.67	5.33	5.48
10	0.12	0.26	1.03	2.63	4.20	4.55	4.90	5.60	5.75
25	0.13	0.27	1.05	2.76	4.41	4.78	5.15	5.88	6.04
50	0.175	0.365	1.08	3.75	6.00	6.50	7.00	8.00	8.22
75	0.204	0.426	1.11	4.38	7.00	7.58	8.17	9.33	9.59
100	0.23	0.49	1.14	5.00	8.00	8.67	9.33	10.67	10.96
125	0.28	0.59	1.2	6.05	9.68	10.49	11.29	12.91	13.26
250	0.29	0.61	1.43	6.25	10.00	10.83	11.67	13.33	13.70
500	0.31	0.64	1.7	6.56	10.50	11.38	12.25	14.00	14.38
750	0.32	0.67	2.3	6.89	11.03	11.94	12.86	14.70	15.10
1000	0.35	0.73	3.8	7.5	12	13	14	16	18

B. Hydroxypropyl Methylcellulose

HPMC MW (KDa)	Hydroxypropyl Methylcellulose Solution Percent Concentration								
	0.05	0.1	0.25	0.5	1	2	3	4	5
5	0.14	0.15	0.15	0.20	0.23	0.34	0.44	0.54	0.64
10	0.20	0.25	0.30	0.43	0.50	1.38	1.89	2.26	2.60
25	0.59	0.61	0.95	1.00	2.12	3.12	4.18	5.06	6.32
50	1.31	1.35	1.20	1.50	3.13	4.44	5.91	7.17	9.13
75	1.85	1.92	1.50	2.30	3.50	5.21	6.92	8.41	10.78
100	2.16	2.24	2.50	3.00	3.90	5.24	7.00	9.20	10.00
125	2.33	2.42	2.76	3.25	4.47	6.19	8.20	9.96	12.85
250	2.91	3.02	3.47	3.50	5.48	7.50	9.93	12.08	15.67
500	3.49	3.61	4.17	4.11	6.50	8.82	11.67	14.19	18.48
750	3.82	3.96	4.59	5.26	7.09	9.59	12.68	15.43	20.13
1000	4.33	4.49	4.88	6.48	7.80	10.49	14.00	18.40	22.40

C. Carboxymethylcellulose, Sodium Salt

CMC MW (KDa)	Carboxymethylcellulose Sodium Solution Percent Concentration								
	0.05	0.1	0.25	0.5	1	2	3	4	5
5	0.12	0.16	0.2	0.43	1.5	1.58	1.63	2.1	3.3
10	0.121	0.22	0.25	2.15	2.1	2.22	2.5	3.3	4.2
25	0.15	0.32	0.34	2.31	2.4	2.5	2.64	3.8	4.9
50	0.19	0.36	0.47	2.5	2.7	2.9	3.1	4.4	5.6
75	0.22	0.41	0.55	2.7	2.8	3.2	3.3	4.8	7.2
100	0.27	0.48	0.63	2.9	3.0	3.25	3.5	5.2	10
125	0.33	0.61	0.74	3.0	3.1	3.5	3.9	7.3	12
250	0.46	0.64	0.88	3.2	3.6	4.1	4.5	8.8	13
500	0.52	0.71	0.91	3.8	4	6.5	8.9	10.4	14
750	0.64	0.90	1.12	5	10	11.4	13.3	12	15
1000	0.74	1.1	1.48	10	12	13.9	15.1	16.4	17

D. Dextran

Dextran MW (KDa)	Dextran Solution Percent Concentration								
	0.05	0.1	0.25	0.5	1	2	3	4	5
5	0.4	1.1	1.3	1.6	2.2	3.5	4.7	6.0	7.3
10	0.4	1.2	1.4	1.8	2.5	3.8	5.2	6.6	8.0
25	0.5	1.3	1.6	1.9	2.7	4.2	5.7	7.3	8.8
50	0.5	1.4	1.7	2.1	3.0	4.6	6.3	8.0	9.7
75	0.6	2.4	2.5	2.6	3.3	5.1	7.0	8.8	10.6
100	0.6	2.6	2.7	2.9	3.6	5.6	7.6	9.7	11.7
125	0.7	2.8	3.0	3.2	4.0	6.2	8.4	10.6	12.9
250	1.1	3.1	3.3	3.5	4.4	6.8	9.3	11.7	14.1
500	1.2	3.4	3.6	3.9	4.8	7.5	10.2	12.9	15.6
750	1.7	3.8	4.0	4.3	5.3	8.2	11.2	14.2	17.1
1000	2.0	4.2	4.4	4.7	5.8	9.0	12.3	15.6	18.8

E. Dextran Sodium Sulfate

Dextran MW (KDa)	FITC-Dextran Solution Percent Concentration								
	0.05	0.1	0.25	0.5	1	2	3	4	5
5	0.2	0.5	0.6	0.8	1.1	1.7	2.4	3.0	3.6
10	0.2	0.6	0.7	0.9	1.2	1.9	2.6	3.3	4.0
25	0.2	0.6	0.8	1.0	1.4	2.1	2.9	3.6	4.4
50	0.3	0.7	0.9	1.1	1.5	2.3	3.2	4.0	4.8
75	0.3	1.2	1.2	1.3	1.6	2.6	3.5	4.4	5.3
100	0.3	1.3	1.4	1.5	1.8	2.8	3.8	4.8	5.8
125	0.4	1.4	1.5	1.6	2.0	3.1	4.2	5.3	6.4
250	0.6	1.6	1.6	1.8	2.2	3.4	4.6	5.9	7.1
500	0.6	1.7	1.8	1.9	2.4	3.7	5.1	6.4	7.8
750	0.9	1.9	2.0	2.1	2.6	4.1	5.6	7.1	8.6
1000	1.0	2.1	2.2	2.3	2.9	4.5	6.2	7.8	9.4

F. FITC-Dextran

Dextran MW (KDa)	FITC-Dextran Solution Percent Concentration								
	0.05	0.1	0.25	0.5	1	2	3	4	5
5	0.7	1.8	2.2	2.7	3.8	5.9	8.1	10.2	12.3
10	0.7	2.0	2.4	3.0	4.2	6.5	8.9	11.2	13.6
25	0.8	2.2	2.7	3.3	4.6	7.2	9.8	12.4	14.9
50	0.9	2.4	2.9	3.6	5.1	7.9	10.7	13.6	16.4
75	1.0	4.0	4.2	4.5	5.6	8.7	11.8	14.9	18.1
100	1.0	4.4	4.6	5.0	6.1	9.6	13.0	16.4	19.9
125	1.2	4.8	5.1	5.4	6.7	10.5	14.3	18.1	21.9
250	1.9	5.3	5.6	6.0	7.4	11.6	15.7	19.9	24.0
500	2.1	5.9	6.2	6.6	8.1	12.7	17.3	21.9	26.5
750	2.9	6.4	6.8	7.2	9.0	14.0	19.0	24.1	29.1
1000	3.4	7.1	7.5	8.0	9.9	15.4	20.9	26.5	32.0

G. FITC-Hyaluronic Acid

FITC HA MW (KDa)	FITC-Hyaluronic Acid Solution Percent Concentration								
	0.05	0.1	0.25	0.5	1	2	3	4	5
5	0.25	0.27	0.27	0.36	0.41	0.61	0.79	0.97	1.15
10	0.36	0.45	0.54	0.77	0.90	2.48	3.40	4.07	4.68
25	1.06	1.10	1.71	1.80	3.82	5.62	7.52	9.11	11.38
50	2.36	2.43	2.16	2.70	5.63	7.99	10.64	12.91	16.43
75	3.33	3.46	2.70	4.14	6.30	9.38	12.46	15.14	19.40
100	3.89	4.03	4.50	5.40	7.02	9.43	12.60	16.56	18.00
125	4.19	4.36	4.97	5.85	8.05	11.14	14.76	17.93	23.13
250	5.24	5.44	6.25	6.30	9.86	13.50	17.87	21.74	28.21
500	6.28	6.50	7.51	7.40	11.70	15.88	21.01	25.54	33.26
750	6.88	7.13	8.26	9.47	12.76	17.26	22.82	27.77	36.23
1000	7.79	8.08	8.78	11.66	14.04	18.88	25.20	33.12	40.32

Table 4.13. Half-Life Of Acrylic Comfort Agents At Selected Molecular Weights And Percent Concentrations

A. Polyvinyl Alcohol

PVA MW (KDa)	PVA Solution Percent Concentration								
	0.05	0.1	0.25	0.5	1	2	3	4	5
5	0.0365	0.0465	0.076	0.1245	0.2225	0.418	0.6135	0.809	1.0045
10	0.051	0.061	0.09	0.139	0.237	0.4325	0.628	0.8235	1.019
25	0.094	0.104	0.133	0.182	0.28	0.4755	0.671	0.8665	1.062
50	0.166	0.1755	0.205	0.254	0.3515	0.547	0.7425	0.938	1.1335
75	0.2375	0.2475	0.2765	0.3255	0.4235	0.619	0.8145	1.01	1.2055
100	0.3095	0.319	0.3485	0.3975	0.495	0.6905	0.886	1.0815	1.277
125	0.381	0.391	0.42	0.469	0.567	0.7625	0.958	1.1535	1.349
250	0.74	0.7495	0.779	0.828	0.9255	1.121	1.3165	1.512	1.7075
500	1.4575	1.467	1.4965	1.5455	1.643	1.8385	2.034	2.2295	2.425
750	2.175	2.1845	2.214	2.263	2.3605	2.556	2.751	2.947	3.142
1000	2.8925	2.902	2.9315	2.9805	3.078	3.273	3.469	3.6645	3.86

B. Polyvinyl Pyrrilidone

PVP MW (KDa)	PVP Solution Percent Concentration								
	0.05	0.1	0.25	0.5	1	2	3	4	5
5	0.03	0.04	0.06	0.11	0.19	0.36	0.52	0.69	0.85
10	0.04	0.05	0.08	0.12	0.20	0.37	0.53	0.70	0.87
25	0.08	0.09	0.11	0.15	0.24	0.40	0.57	0.74	0.90
50	0.14	0.15	0.17	0.22	0.30	0.46	0.63	0.80	0.96
75	0.20	0.21	0.24	0.28	0.36	0.53	0.69	0.86	1.02
100	0.26	0.27	0.30	0.34	0.42	0.59	0.75	0.92	1.09
125	0.32	0.33	0.36	0.40	0.48	0.65	0.81	0.98	1.15
250	0.63	0.64	0.66	0.70	0.79	0.95	1.12	1.29	1.45
500	1.24	1.25	1.27	1.31	1.40	1.56	1.73	1.90	2.06
750	1.85	1.86	1.88	1.92	2.01	2.17	2.34	2.50	2.67
1000	2.46	2.47	2.49	2.53	2.62	2.78	2.95	3.11	3.28

C. Poly(Acid)

Poly(Acid) MW (KDa)	Poly(Acid) Solution Percent Concentration								
	0.05	0.1	0.25	0.5	1	2	3	4	5
5	0.03	0.04	0.06	0.10	0.17	0.33	0.48	0.63	0.78
10	0.04	0.05	0.07	0.11	0.18	0.34	0.49	0.64	0.79
25	0.07	0.08	0.10	0.14	0.22	0.37	0.52	0.68	0.83
50	0.13	0.14	0.16	0.20	0.27	0.43	0.58	0.73	0.88
75	0.19	0.19	0.22	0.25	0.33	0.48	0.64	0.79	0.94
100	0.24	0.25	0.27	0.31	0.39	0.54	0.69	0.84	1.00
125	0.30	0.30	0.33	0.37	0.44	0.59	0.75	0.90	1.05
250	0.58	0.58	0.61	0.65	0.72	0.87	1.03	1.18	1.33
500	1.14	1.14	1.17	1.21	1.28	1.43	1.59	1.74	1.89
750	1.70	1.70	1.73	1.77	1.84	1.99	2.15	2.30	2.45
1000	2.26	2.26	2.29	2.32	2.40	2.55	2.71	2.86	3.01

Table 4.14. Table Of Polysaccharide Residence Constants

A. Hyaluronic Acid, Sodium Salt

HA MW (KDa)	Hyaluronic Acid, Sodium Salt Solution Percent Concentration								
	0.05	0.1	0.25	0.5	1	2	3	4	5
5	5.78	2.89	0.68	0.28	0.17	0.16	0.15	0.13	0.13
10	5.78	2.67	0.67	0.26	0.17	0.15	0.14	0.12	0.12
25	5.33	2.57	0.66	0.25	0.16	0.15	0.13	0.12	0.11
50	3.96	1.90	0.64	0.18	0.12	0.11	0.099	0.087	0.084
75	3.40	1.63	0.62	0.16	0.10	0.09	0.085	0.074	0.072
100	3.01	1.41	0.61	0.14	0.087	0.080	0.074	0.065	0.063
125	2.48	1.17	0.58	0.11	0.072	0.066	0.061	0.054	0.052
250	2.39	1.14	0.48	0.11	0.069	0.064	0.059	0.052	0.051
500	2.24	1.08	0.41	0.11	0.066	0.061	0.057	0.050	0.048
750	2.17	1.03	0.30	0.10	0.063	0.058	0.054	0.047	0.046
1000	1.98	0.95	0.18	0.092	0.058	0.053	0.050	0.043	0.039

B. Hydroxypropyl Methylcellulose

HPMC MW (KDa)	Hydroxypropyl Methylcellulose Solution Percent Concentration								
	0.05	0.1	0.25	0.5	1	2	3	4	5
5	4.95	4.62	4.62	3.47	3.01	2.04	1.58	1.28	1.08
10	3.47	2.77	2.31	1.61	1.39	0.50	0.37	0.31	0.27
25	1.17	1.14	0.73	0.69	0.33	0.22	0.17	0.14	0.11
50	0.53	0.51	0.58	0.46	0.22	0.16	0.12	0.10	0.08
75	0.37	0.36	0.46	0.30	0.20	0.13	0.10	0.08	0.07
100	0.32	0.31	0.28	0.23	0.18	0.13	0.10	0.08	0.07
125	0.30	0.29	0.25	0.21	0.16	0.11	0.08	0.07	0.05
250	0.24	0.23	0.20	0.20	0.13	0.09	0.07	0.06	0.04
500	0.20	0.19	0.17	0.17	0.11	0.08	0.06	0.05	0.04
750	0.18	0.18	0.15	0.13	0.10	0.07	0.05	0.04	0.03
1000	0.16	0.15	0.14	0.11	0.09	0.07	0.05	0.04	0.03

C. Carboxymethylcellulose, Sodium Salt

CMC MW (KDa)	Carboxymethylcellulose Solution Percent Concentration								
	0.05	0.1	0.25	0.5	1	2	3	4	5
5	5.78	4.33	3.47	1.61	0.46	0.44	0.43	0.33	0.21
10	5.73	3.15	2.77	0.32	0.33	0.31	0.28	0.21	0.17
25	4.62	2.17	2.04	0.30	0.29	0.28	0.26	0.18	0.14
50	3.65	1.93	1.47	0.28	0.26	0.24	0.224	0.158	0.124
75	3.15	1.69	1.26	0.26	0.25	0.22	0.210	0.144	0.096
100	2.57	1.44	1.10	0.24	0.231	0.213	0.198	0.133	0.069
125	2.10	1.14	0.94	0.23	0.224	0.198	0.178	0.095	0.058
250	1.51	1.08	0.79	0.22	0.193	0.169	0.154	0.079	0.053
500	1.33	0.98	0.76	0.18	0.173	0.107	0.078	0.067	0.050
750	1.08	0.77	0.62	0.14	0.069	0.061	0.052	0.058	0.046
1000	0.94	0.63	0.47	0.069	0.058	0.050	0.046	0.042	0.041

D. Dextran

Dextran MW (KDa)	Dextran Solution Percent Concentration								
	0.05	0.1	0.25	0.5	1	2	3	4	5
5	9.90	7.70	4.62	2.77	1.54	0.83	0.56	0.43	0.34
10	6.93	5.78	3.85	2.48	1.47	0.80	0.55	0.42	0.34
25	3.65	3.30	2.57	1.93	1.24	0.73	0.52	0.40	0.33
50	2.10	1.98	1.69	1.36	0.99	0.64	0.47	0.37	0.31
75	1.44	1.39	1.26	1.07	0.82	0.56	0.43	0.34	0.29
100	1.12	1.08	0.99	0.87	0.70	0.50	0.39	0.32	0.27
125	0.91	0.89	0.83	0.74	0.61	0.45	0.36	0.30	0.26
250	0.47	0.46	0.44	0.42	0.37	0.31	0.26	0.23	0.20
500	0.24	0.24	0.23	0.22	0.21	0.19	0.17	0.16	0.14
750	0.16	0.16	0.16	0.15	0.15	0.14	0.13	0.12	0.11
1000	0.12	0.12	0.12	0.12	0.11	0.11	0.10	0.09	0.09

E. Dextran Sodium Sulfate

Dextran MW (KDa)	Dextran Solution Percent Concentration								
	0.05	0.1	0.25	0.5	1	2	3	4	5
5	3.4	1.3	1.1	0.9	0.6	0.4	0.3	0.2	0.2
10	3.4	1.2	1.0	0.8	0.6	0.4	0.3	0.2	0.2
25	2.9	1.1	0.9	0.7	0.5	0.3	0.2	0.2	0.2
50	2.6	1.0	0.8	0.6	0.5	0.3	0.2	0.2	0.1
75	2.4	0.6	0.6	0.5	0.4	0.3	0.2	0.2	0.1
100	2.4	0.5	0.5	0.5	0.4	0.2	0.2	0.1	0.1
125	2.0	0.5	0.5	0.4	0.4	0.2	0.2	0.1	0.1
250	1.2	0.4	0.4	0.4	0.3	0.2	0.1	0.1	0.1
500	1.1	0.4	0.4	0.4	0.3	0.2	0.1	0.1	0.1
750	0.8	0.4	0.3	0.3	0.3	0.2	0.1	0.1	0.1
1000	0.7	0.3	0.3	0.3	0.2	0.2	0.1	0.1	0.1

F. FITC-Dextran

Dex MW (KDa)	FITC Dextran Solution Percent Concentration									
	0.01	0.05	0.1	0.25	0.5	1	2	3	4	5
5	0.950	0.745	0.456	0.278	0.156	0.083	0.056	0.043	0.035	0.950
10	0.680	0.568	0.385	0.249	0.146	0.080	0.055	0.042	0.034	0.680
25	0.369	0.333	0.261	0.190	0.124	0.073	0.052	0.040	0.033	0.369
50	0.209	0.197	0.169	0.136	0.099	0.063	0.047	0.037	0.031	0.209
75	0.146	0.140	0.125	0.106	0.082	0.056	0.043	0.034	0.029	0.146
100	0.112	0.109	0.099	0.087	0.070	0.050	0.039	0.032	0.027	0.112
125	0.091	0.089	0.083	0.074	0.061	0.045	0.036	0.030	0.026	0.091
250	0.047	0.046	0.044	0.042	0.037	0.031	0.026	0.023	0.020	0.047
500	0.024	0.024	0.023	0.022	0.021	0.019	0.017	0.016	0.014	0.024
750	0.016	0.016	0.016	0.015	0.015	0.014	0.013	0.012	0.011	0.016
1000	0.012	0.012	0.012	0.012	0.011	0.011	0.010	0.009	0.009	0.012

G. FITC Hyaluronic Acid

FITC-HA MW (KDa)	FITC-HA Solution Percent Concentration									
	0.01	0.05	0.1	0.25	0.5	1	2	3	4	5
5	2.04	2.04	1.36	0.82	0.48	0.26	0.18	0.14	0.11	2.04
10	1.16	1.16	0.90	0.62	0.41	0.24	0.17	0.13	0.11	1.16
25	0.54	0.51	0.45	0.37	0.28	0.19	0.14	0.11	0.10	0.54
50	0.27	0.27	0.25	0.23	0.19	0.14	0.11	0.10	0.08	0.27
75	0.19	0.18	0.17	0.16	0.14	0.11	0.09	0.08	0.07	0.19
100	0.14	0.14	0.13	0.13	0.11	0.09	0.08	0.07	0.06	0.14
125	0.11	0.11	0.11	0.10	0.09	0.08	0.07	0.06	0.06	0.11
250	0.06	0.06	0.05	0.05	0.05	0.05	0.04	0.04	0.04	0.06
500	0.03	0.03	0.03	0.03	0.03	0.03	0.02	0.02	0.02	0.03
750	0.02	0.02	0.02	0.02	0.02	0.02	0.02	0.02	0.02	0.02
1000	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01

Table 4.15. Table Of Acrylic Residence Constants

A. Polyvinyl Alcohol

PVA MW (KDa)	PVA Solution Percent Concentration								
	0.05	0.1	0.25	0.5	1	2	3	4	5
5	18.99	14.91	9.12	5.57	3.12	1.66	1.13	0.86	0.69
10	13.59	11.36	7.70	4.99	2.92	1.60	1.10	0.84	0.68
25	7.37	6.66	5.21	3.81	2.48	1.46	1.03	0.80	0.65
50	4.18	3.95	3.38	2.73	1.97	1.27	0.93	0.74	0.61
75	2.92	2.80	2.51	2.13	1.64	1.12	0.85	0.69	0.57
100	2.24	2.17	1.99	1.74	1.40	1.00	0.78	0.64	0.54
125	1.82	1.77	1.65	1.48	1.22	0.91	0.72	0.60	0.51
250	0.94	0.92	0.89	0.84	0.75	0.62	0.53	0.46	0.41
500	0.48	0.47	0.46	0.45	0.42	0.38	0.34	0.31	0.29
750	0.32	0.32	0.31	0.31	0.29	0.27	0.25	0.24	0.22
1000	0.24	0.24	0.24	0.23	0.23	0.21	0.20	0.19	0.18

B. Polyvinyl Pyrrilidone

PVP MW (KDa)	PVP Solution Percent Concentration								
	0.05	0.1	0.25	0.5	1	2	3	4	5
5	23.10	17.33	11.55	6.30	3.65	1.93	1.33	1.00	0.82
10	17.33	13.86	8.66	5.78	3.47	1.87	1.31	0.99	0.80
25	8.66	7.70	6.30	4.62	2.89	1.73	1.22	0.94	0.77
50	4.95	4.62	4.08	3.15	2.31	1.51	1.10	0.87	0.72
75	3.47	3.30	2.89	2.48	1.93	1.31	1.00	0.81	0.68
100	2.67	2.57	2.31	2.04	1.65	1.17	0.92	0.75	0.64
125	2.17	2.10	1.93	1.73	1.44	1.07	0.86	0.71	0.60
250	1.10	1.08	1.05	0.99	0.88	0.73	0.62	0.54	0.48
500	0.56	0.55	0.55	0.53	0.50	0.44	0.40	0.36	0.34
750	0.37	0.37	0.37	0.36	0.34	0.32	0.30	0.28	0.26
1000	0.28	0.28	0.28	0.27	0.26	0.25	0.23	0.22	0.21

C. Poly(Acid)

Poly(Acid) MW (KDa)	Poly(Acid) Solution Percent Concentration								
	0.05	0.1	0.25	0.5	1	2	3	4	5
5	23.10	17.33	11.55	6.93	4.08	2.10	1.44	1.10	0.89
10	17.33	13.86	9.90	6.30	3.85	2.04	1.41	1.08	0.88
25	9.90	8.66	6.93	4.95	3.15	1.87	1.33	1.02	0.84
50	5.33	4.95	4.33	3.47	2.57	1.61	1.20	0.95	0.79
75	3.65	3.65	3.15	2.77	2.10	1.44	1.08	0.88	0.74
100	2.89	2.77	2.57	2.24	1.78	1.28	1.00	0.83	0.69
125	2.31	2.31	2.10	1.87	1.58	1.17	0.92	0.77	0.66
250	1.20	1.20	1.14	1.07	0.96	0.80	0.67	0.59	0.52
500	0.61	0.61	0.59	0.57	0.54	0.48	0.44	0.40	0.37
750	0.41	0.41	0.40	0.39	0.38	0.35	0.32	0.30	0.28
1000	0.31	0.31	0.30	0.30	0.29	0.27	0.26	0.24	0.23

Table 4.16. Proportionality Constant For Residence Constant Calculation

Comfort Agent	Proportionality Constant
HA	0.11
HPMC	0.15
CMC	0.091
Dextran	0.088
DSS	0.026
FITC Dex	1.8
FITC-HA	1.1
PVA	0.066
PVP	0.054
PolyAcid	0.043

Residence drainage coefficient was calculated according to the following relationship:

$$k = \frac{1}{Coefficient * \%Conc^{0.75} * MW^{0.45}}$$

Table 4.17. Table Of Assumptions Used For 3D Plots

Species	Assumptions
All Molecules	Rheology is proportional to comfort agent molecular weight Each comfort agent obeys similar decay kinetics (first order)
HA	Extrapolations were made to low molecular weights and to high concentrations
HPMC	First order drainage kinetics
CMC	Extrapolations were made to low molecular weights and to high concentrations
Dextran	Residence time was 1/3 of FITC-Dextran residence time
DSS	Polyelectrolyte form of dextran Residence time corresponds to ½ neutral dextran
FITC-Dextran	Residence time corresponded to residence time of dextran in a similar manner as FITC-HA did to HA Residence time follows same decay equation as FITC-HA
FITC-HA	Residence time was a factor of 3 greater than the corresponding HA residence time
PVA	First order drainage kinetics
PVP	Residence time followed same decay field equation as PVA
Carbomers	First order drainage kinetics

Table 4.18. Calculated AUC And CPC Of Various Eye Drop Formulations

A. Hyaluronic Acid, Sodium Salt

HA MW (KDa)	Hyaluronic Acid Solution Percent Concentration								
	0.05	0.1	0.25	0.5	1	2	3	4	5
5	1	2	3	4	5	6	7	8	9
10	2	3	4	5	6	7	8	9	10
25	3	4	5	6	7	8	9	10	11
50	4	5	6	7	8	9	10	11	12
75	5	6	7	8	9	10	11	12	13
100	6	7	8	9	10	11	12	13	14
120	7	8	9	10	11	12	13	14	15
250	8	9	10	11	12	13	14	15	16
500	9	10	11	12	13	14	15	16	17
750	10	11	12	13	14	15	16	17	18
1000	11	12	13	14	15	16	17	18	19

B. Hydroxypropyl Methylcellulose

HPMC MW (KDa)	Hydroxypropyl Methylcellulose Solution Percent Concentration								
	0.05	0.1	0.25	0.5	1	2	3	4	5
5	1	2	3	4	5	6	7	8	9
10	2	3	4	5	6	7	8	9	10
25	3	4	5	6	7	8	9	10	11
50	4	5	6	7	8	9	10	11	12
75	5	6	7	8	9	10	11	12	13
100	6	7	8	9	10	11	12	13	14
120	7	8	9	10	11	12	13	14	15
250	8	9	10	11	12	13	14	15	16
500	9	10	11	12	13	14	15	16	17
750	10	11	12	13	14	15	16	17	18
1000	11	12	13	14	15	16	17	18	19

C. Dextran

Dex MW (KDa)	Dextran Solution Percent Concentration								
	0.05	0.1	0.25	0.5	1	2	3	4	5
5	1	2	3	4	5	6	7	8	9
10	2	3	4	5	6	7	8	9	10
25	3	4	5	6	7	8	9	10	11
50	4	5	6	7	8	9	10	11	12
75	5	6	7	8	9	10	11	12	13
100	6	7	8	9	10	11	12	13	14
120	7	8	9	10	11	12	13	14	15
250	8	9	10	11	12	13	14	15	16
500	9	10	11	12	13	14	15	16	17
750	10	11	12	13	14	15	16	17	18
1000	11	12	13	14	15	16	17	18	19

D. Polyvinyl Alcohol

PVA MW (KDa)	Polyvinyl Alcohol Solution Percent Concentration								
	0.05	0.1	0.25	0.5	1	2	3	4	5
5	1	2	3	4	5	6	7	8	9
10	2	3	4	5	6	7	8	9	10
25	3	4	5	6	7	8	9	10	11
50	4	5	6	7	8	9	10	11	12
75	5	6	7	8	9	10	11	12	13
100	6	7	8	9	10	11	12	13	14
120	7	8	9	10	11	12	13	14	15
250	8	9	10	11	12	13	14	15	16
500	9	10	11	12	13	14	15	16	17
750	10	11	12	13	14	15	16	17	18
1000	11	12	13	14	15	16	17	18	19

E. Polyvinyl Pyrrilidone

PVP MW (KDa)	Polyvinyl Pyrrilidone Solution Percent Concentration								
	0.05	0.1	0.25	0.5	1	2	3	4	5
5	1	2	3	4	5	6	7	8	9
10	2	3	4	5	6	7	8	9	10
25	3	4	5	6	7	8	9	10	11
50	4	5	6	7	8	9	10	11	12
75	5	6	7	8	9	10	11	12	13
100	6	7	8	9	10	11	12	13	14
120	7	8	9	10	11	12	13	14	15
250	8	9	10	11	12	13	14	15	16
500	9	10	11	12	13	14	15	16	17
750	10	11	12	13	14	15	16	17	18
1000	11	12	13	14	15	16	17	18	19

F. PolyAcids

PolyAcid MW (KDa)	PolyAcid Solution Percent Concentration								
	0.05	0.1	0.25	0.5	1	2	3	4	5
5	1	2	3	4	5	6	7	8	9
10	2	3	4	5	6	7	8	9	10
25	3	4	5	6	7	8	9	10	11
50	4	5	6	7	8	9	10	11	12
75	5	6	7	8	9	10	11	12	13
100	6	7	8	9	10	11	12	13	14
120	7	8	9	10	11	12	13	14	15
250	8	9	10	11	12	13	14	15	16
500	9	10	11	12	13	14	15	16	17
750	10	11	12	13	14	15	16	17	18
1000	11	12	13	14	15	16	17	18	19

4.8. Figures

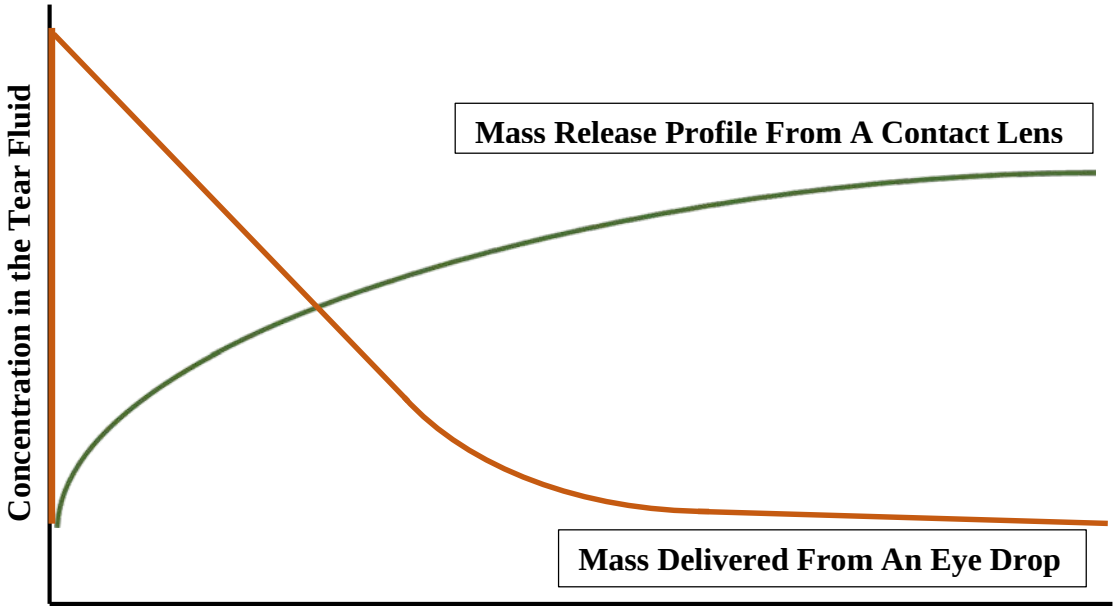


Figure 4.1. Ocular Tear Film Comfort Agent Concentration Profile

Comfort agents delivered by eye drop solutions achieve a maxima concentration instantaneously and decreases steadily. For most commercially available formulations, the comfort agent is removed from the ocular surface very quickly, within 6-10 mins. The mass concentration profile for contact lenses gradually reaches a sustained concentration for the duration of release.

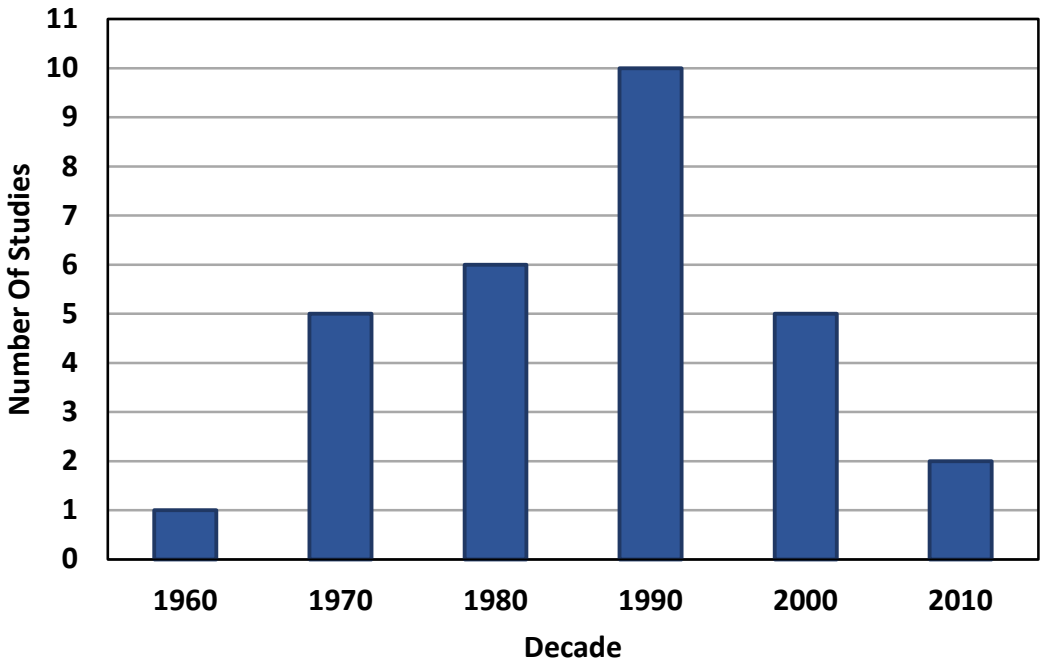
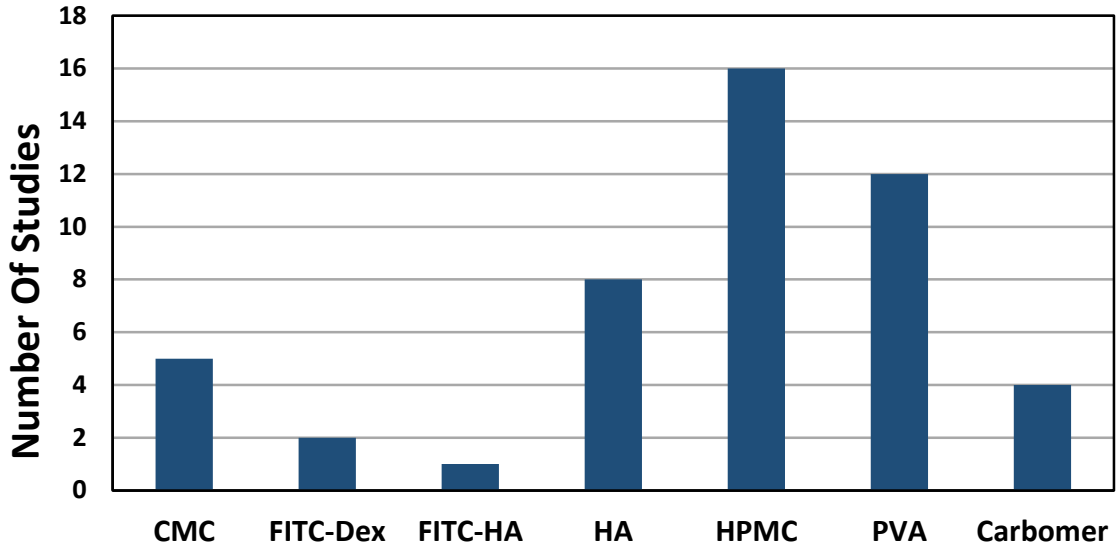


Figure 4.2. Residence Time Studies Per Year

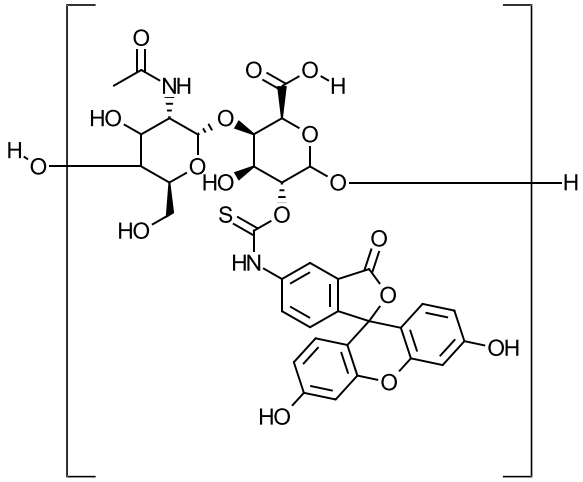
Relatively few residence times studies of comfort agents have been published over the past 5 decades. This has necessitated the use of a statistical meta-analysis to model the in vivo behavior of comfort agents instead of using values form the clinical data.



Figures 4.3. Residence Time Studies Per Species

The available clinical studies describing the residence time measured for specific species or of individual classes of comfort agents.

A. Fluorescein Isothiocyanate Hyaluronic Acid



B. Fluorescein Isothiocyanate Dextran

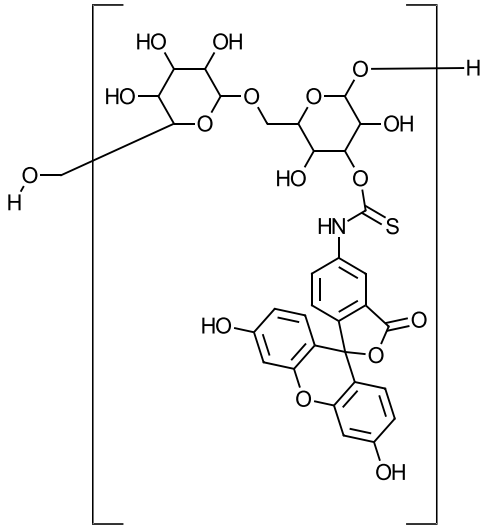
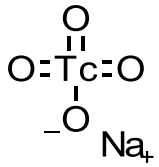


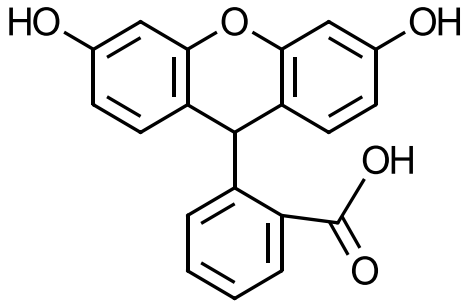
Figure 4.4. Fluorescent Hyaluronic Acid And Fluorescent Dextran

Fluorescein isothiocyanate was added in a statistically random manner to neutral hyaluronic acid and neutral dextran for use as a fluorescent tracer molecule in comfort agent resident time evaluations.

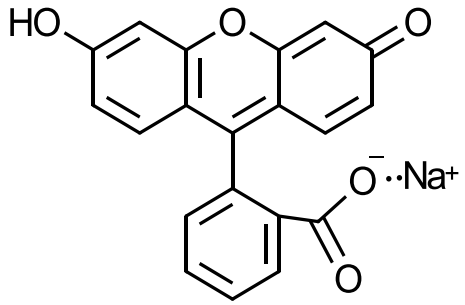
Sodium Pertechenate



Fluorescein



Sodium Fluorescein



Disodium Fluorescein

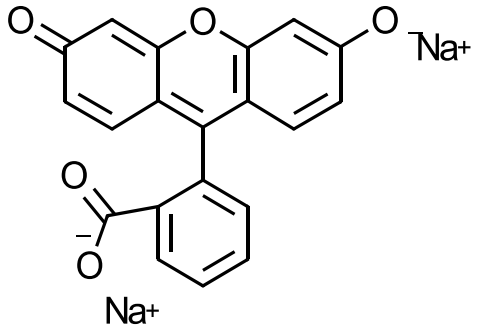


Figure 4.5. Tracer Molecule Chemical Structures Of Tracer Molecules Used In The Clinical Literature To Evaluate Comfort Agent Residence Time

The chemical structures for small molecule tracer molecules are presented. The tracers are similar in that they are radio or photoactive at various intensities, wavelengths, or at various degrees. It was assumed that by mixing the tracer into dilute comfort agent solutions, the tracers would demonstrate equivalent residence times as the comfort agent in the tear film. As discussed in the text, this is not an unreasonable approximation, but for various reasons discussed in **Chapter 4**, this claim is very much debatable and potentially inaccurate.

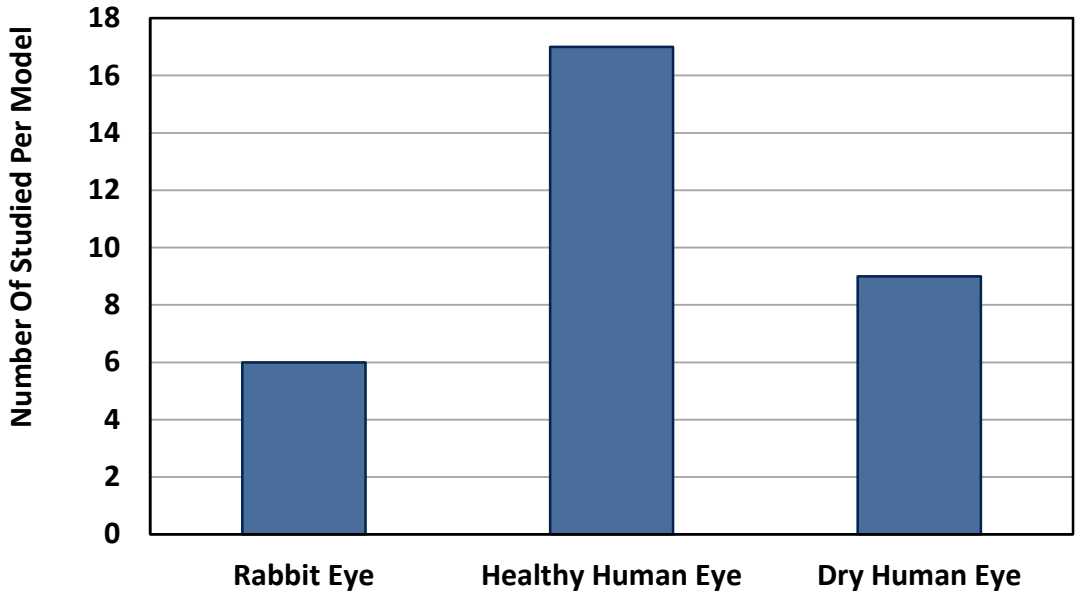


Figure 4.6. Residence Time Studies Per Model

Of the few resident time published studies, only a fraction of the studies were performed in healthy human eyes. In the meta-analysis, novel correlations were developed to incorporate as much clinical data as possible into the statistical analysis to produce the most accurate models as possible.

% Fluorescence
Time
Tracer residing in the tear fluid
B
Magnitude corresponds to solution concentration
A
Tracer adsorbed into the ocular tissue

Figure 4.7. Tracer Concentration Profile

A common error in fluorometric evaluation of ocular contact times is that low molecular weight tracers can be absorbed into the ocular tissue and detected for much longer intervals than the period the tracer and comfort agent are residing in the tear fluid. This effect can be commonly seen in the clinical literature and is particularly demonstrated in ref [**4.11**]. The magnitude of the profile curve (*as shown at point A*) correlates in a linear fashion to the concentration of the tracer in solution, (*i.e., the greater the tracer solution concentration, the greater the magnitude of the curve*). The analysis in **Section 4.3** is concerned with the tracer residing in the tear film. From the analysis of the literature, it was observed that the drainage kinetics of the tracer most closely follow first order kinetics. Therefore, the most accurate determination of the tracer half-life is found by extrapolating first order drainage until no tracer remains in the tear fluid (*point B*). Error in the determined half-life by the cited authors is largely due to this effect and is difficult to overcome unless care to establish a proper baseline or perform a multi-angle measurement is taken.

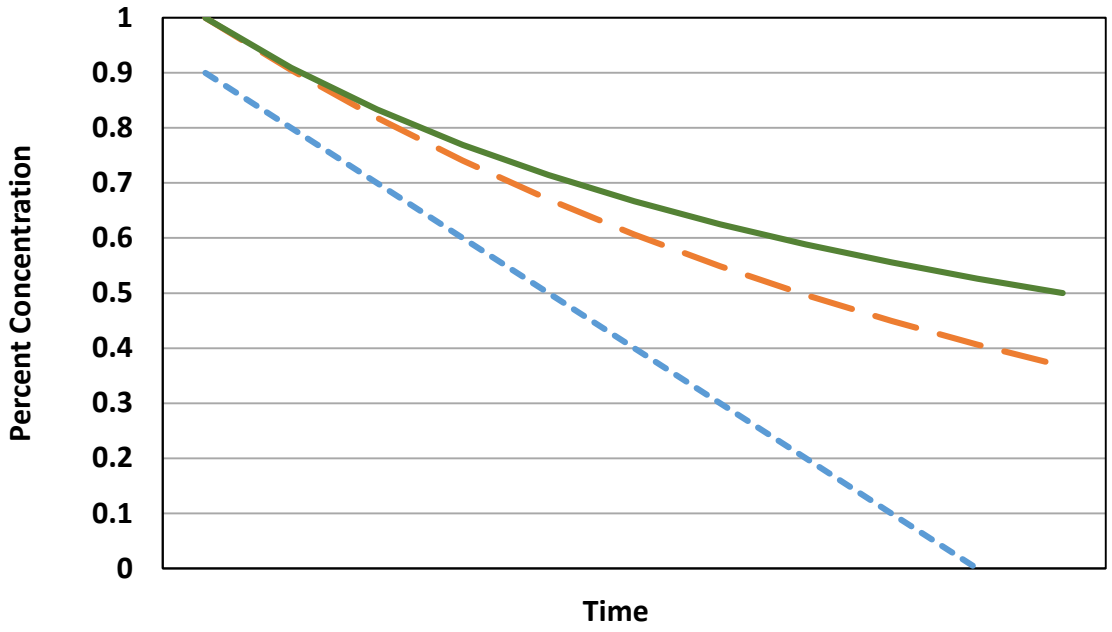
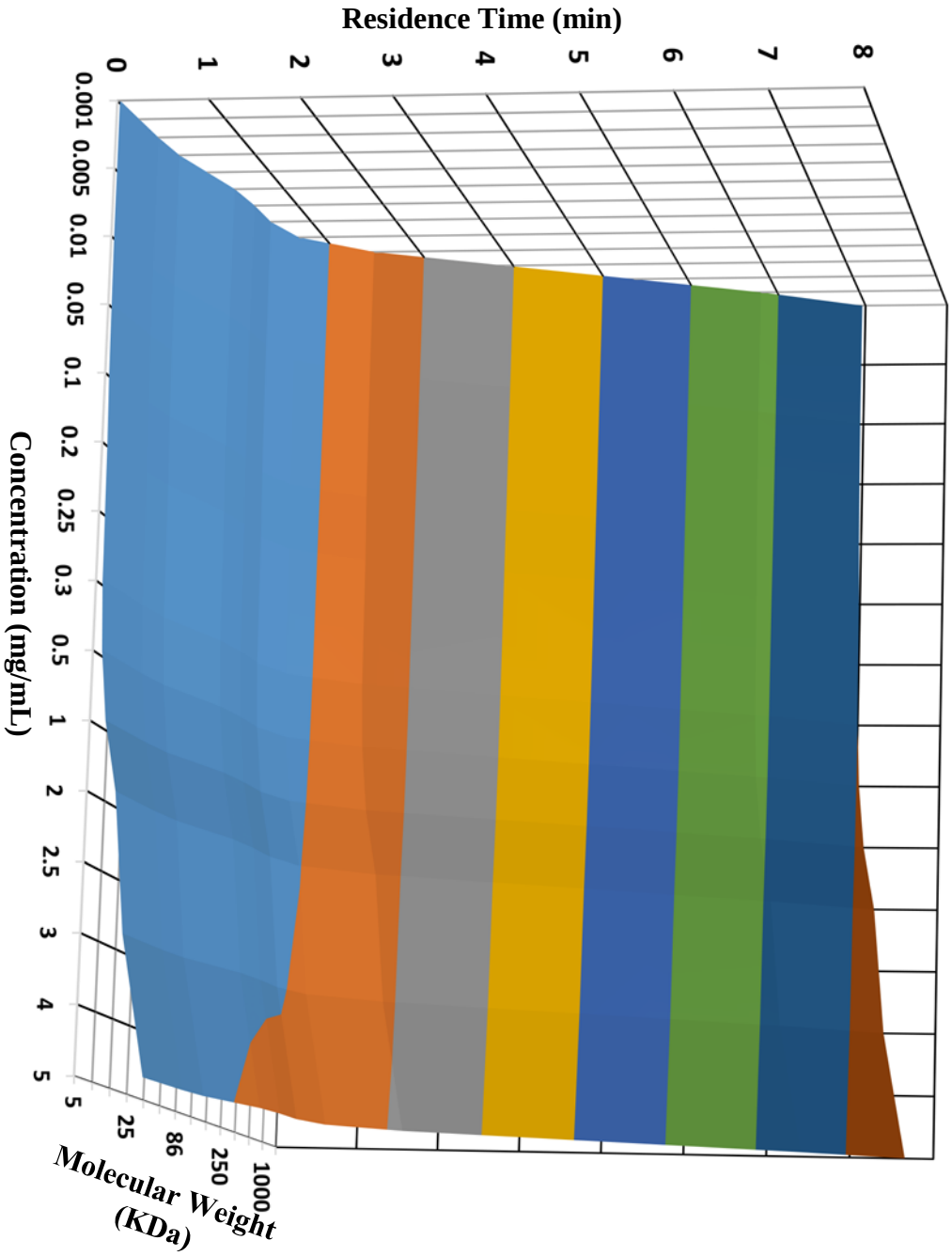


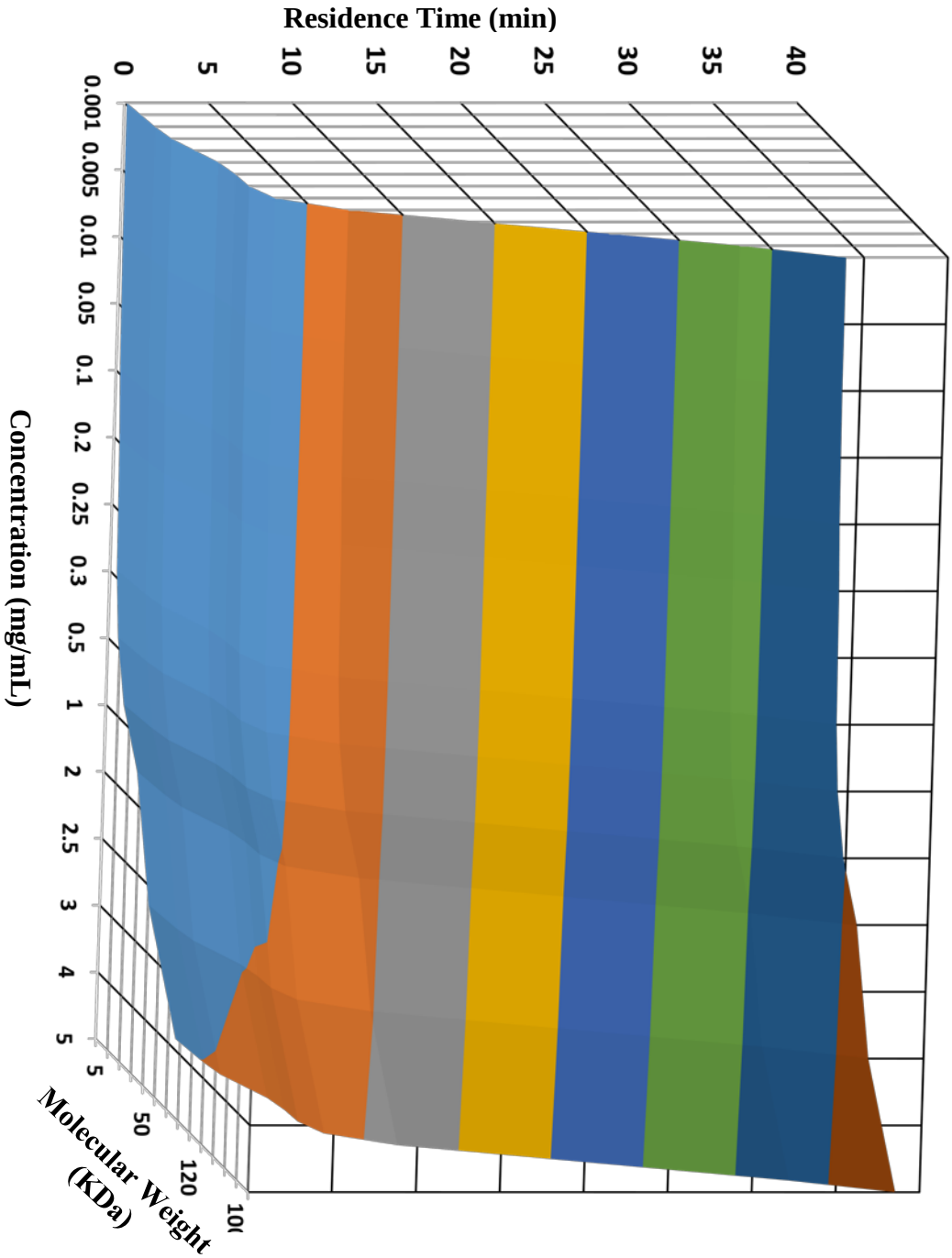
Figure 4.8. Tear Drainage Profiles At Various Orders

Fluid drainage kinetics vary with solutions, viscosity, concentration, etc. In the residence time analysis in **Section 4.3**, special care was taken to identify the order of drainage kinetics to better approximate the resident constant of the comfort agent solution. Typical drainage profiles for 0-order (**blue dash**), 1st-order (**orange long dash**), and 2nd-order (**green solid**) drainage kinetics are shown.

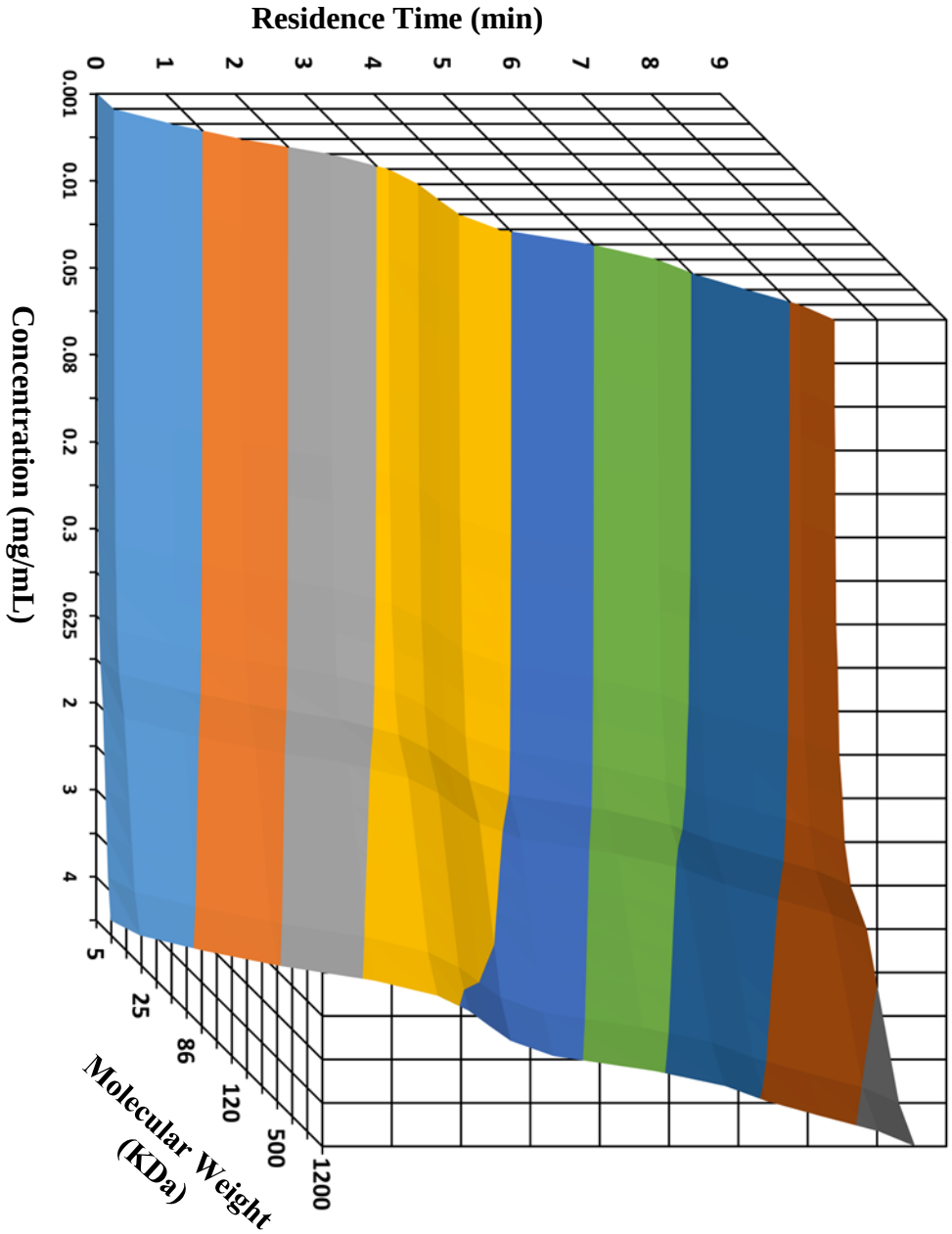
A. Ocular Residence Time Of Sodium Hyaluronic Acid



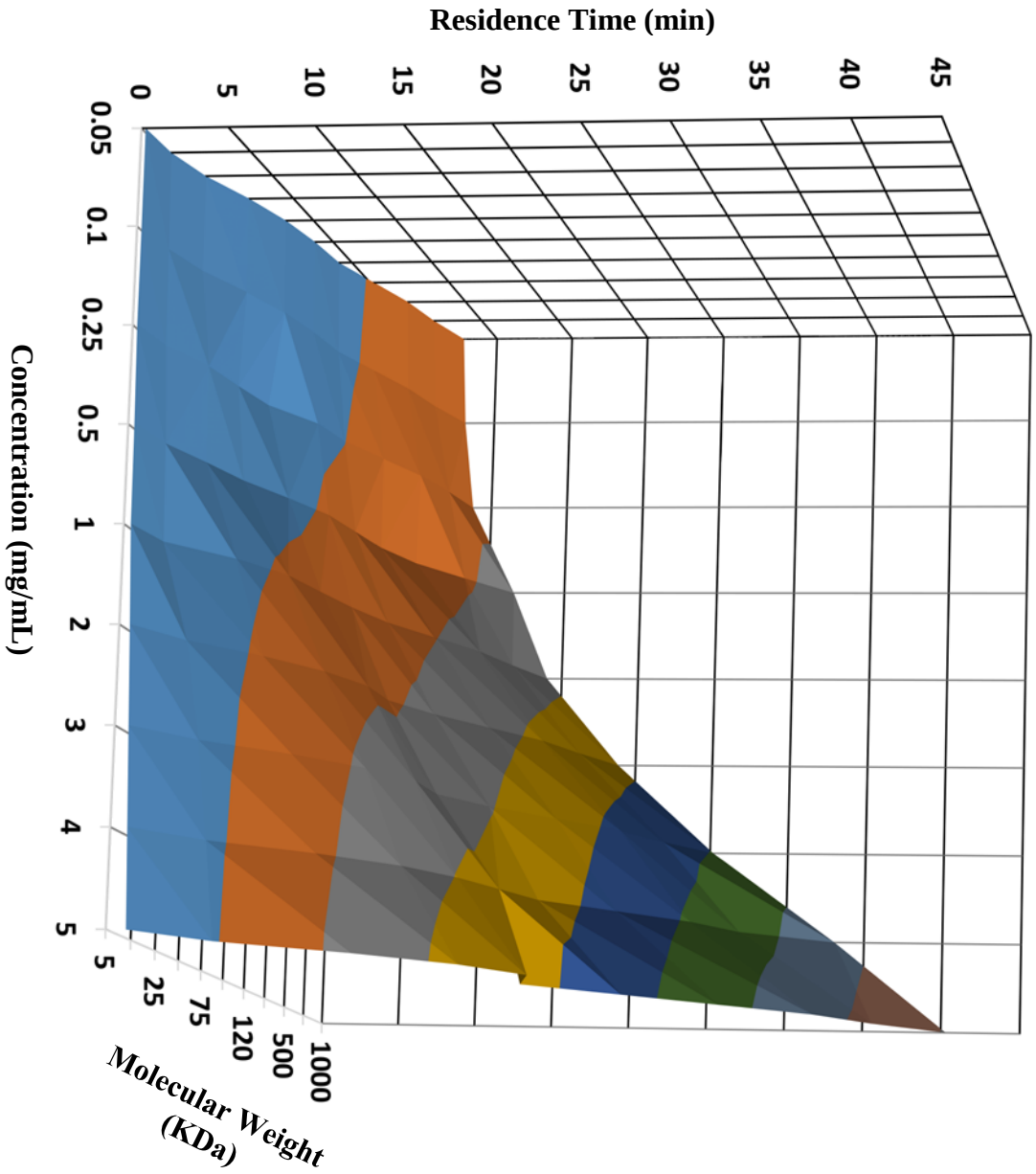
B. Ocular Residence Time Of Hydroxypropyl Methylcellulose



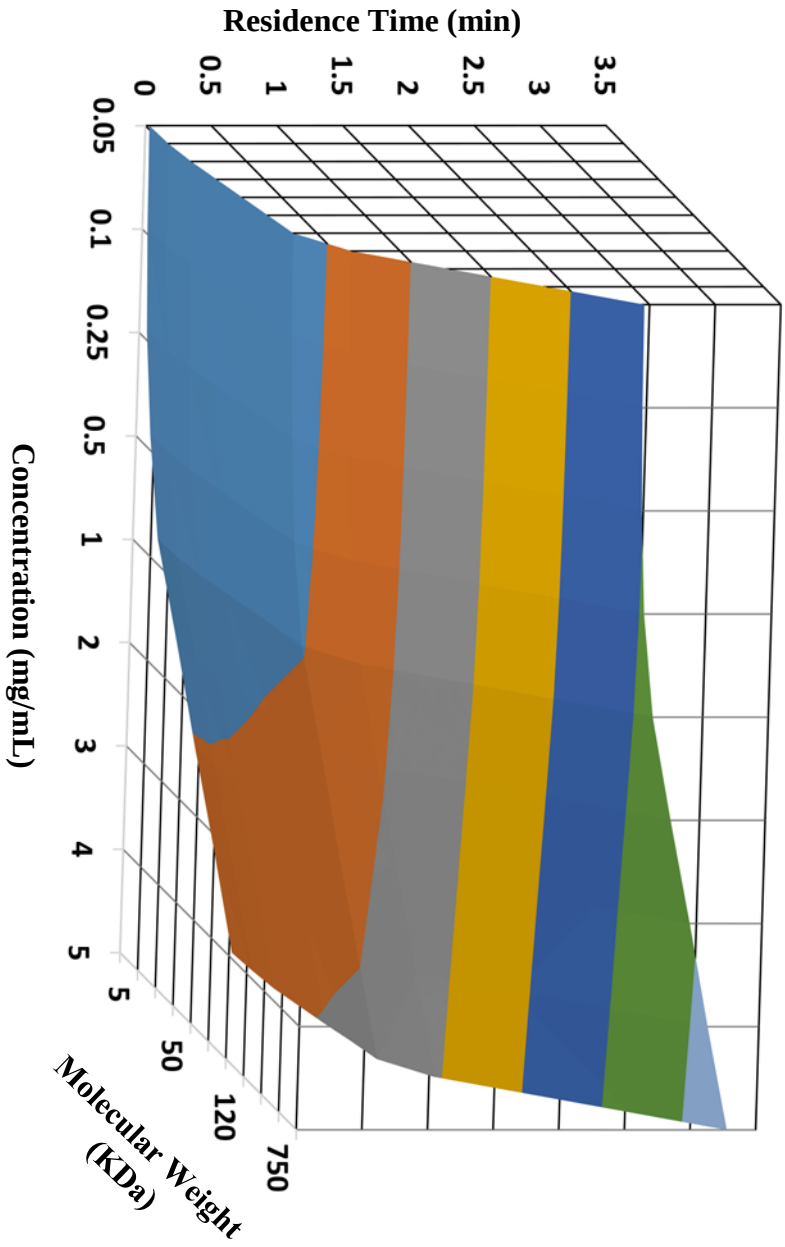
C. Ocular Residence Time Of Sodium Carboxymethylcellulose



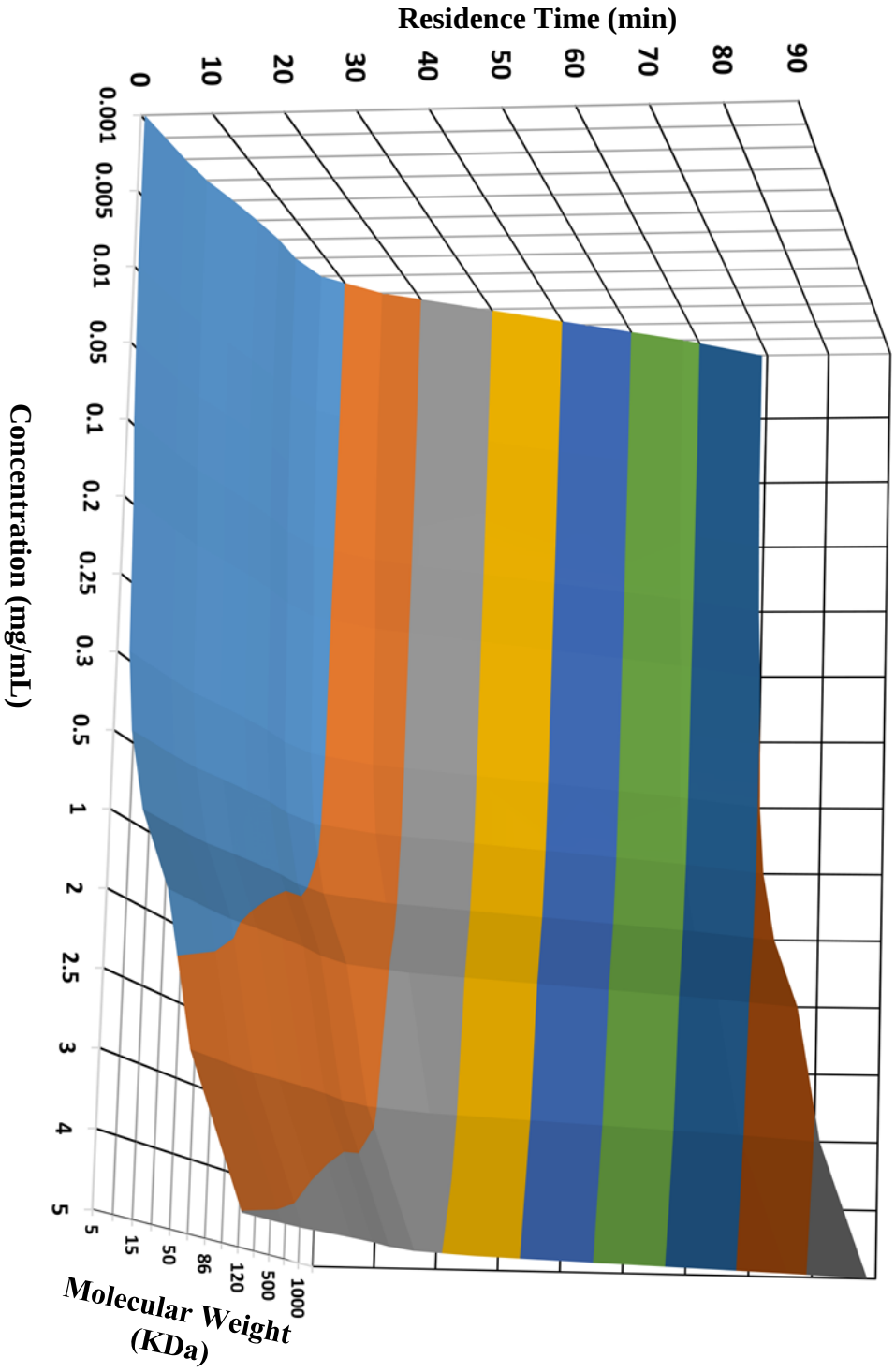
D. Ocular Residence Time Of Dextran



E. Ocular Residence Time Of Dextran Sodium Sulfate



F. Ocular Residence Time Of FITC-Dextran



G. Ocular Residence Time Of FITC-Hyaluronic Acid

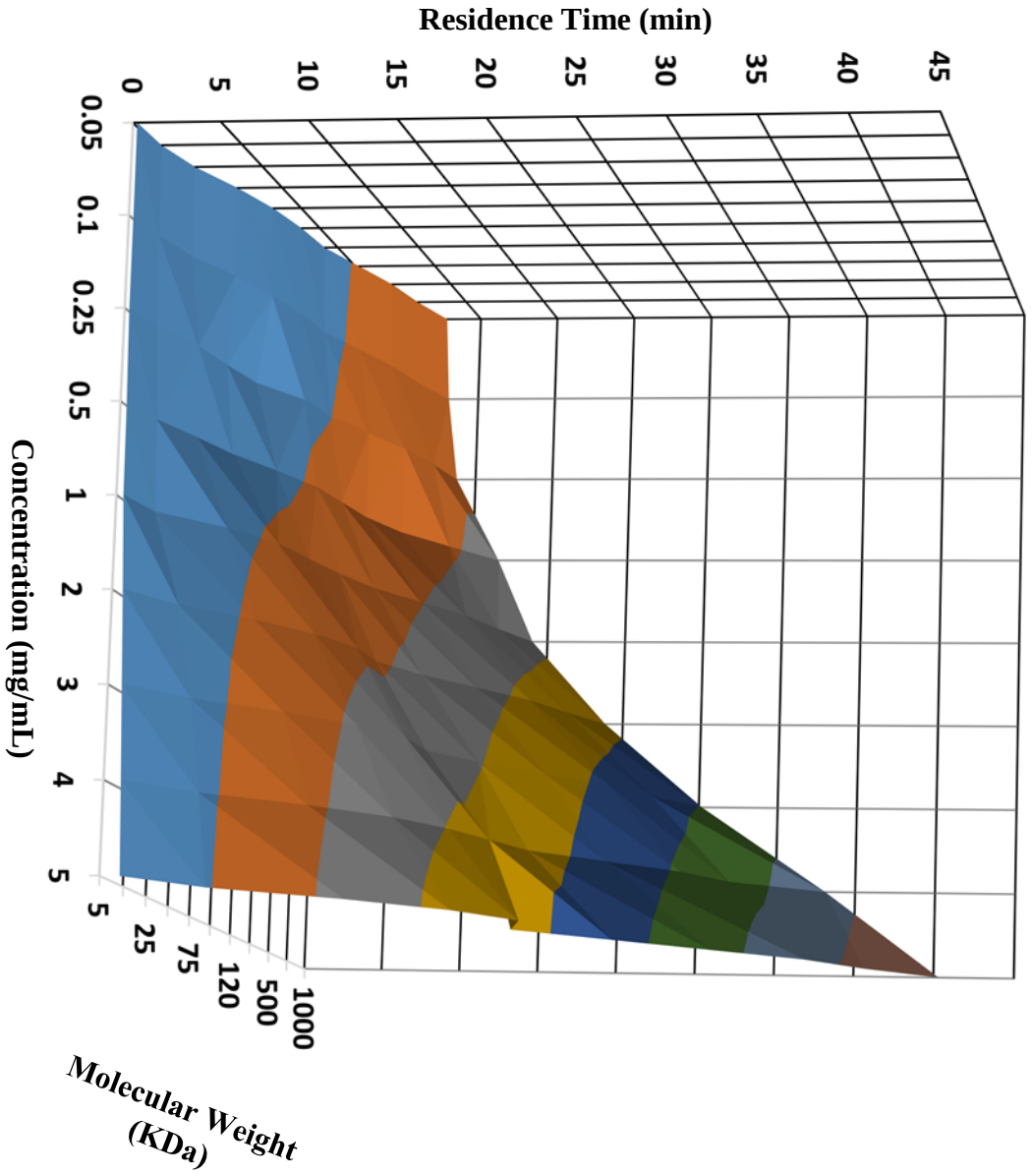
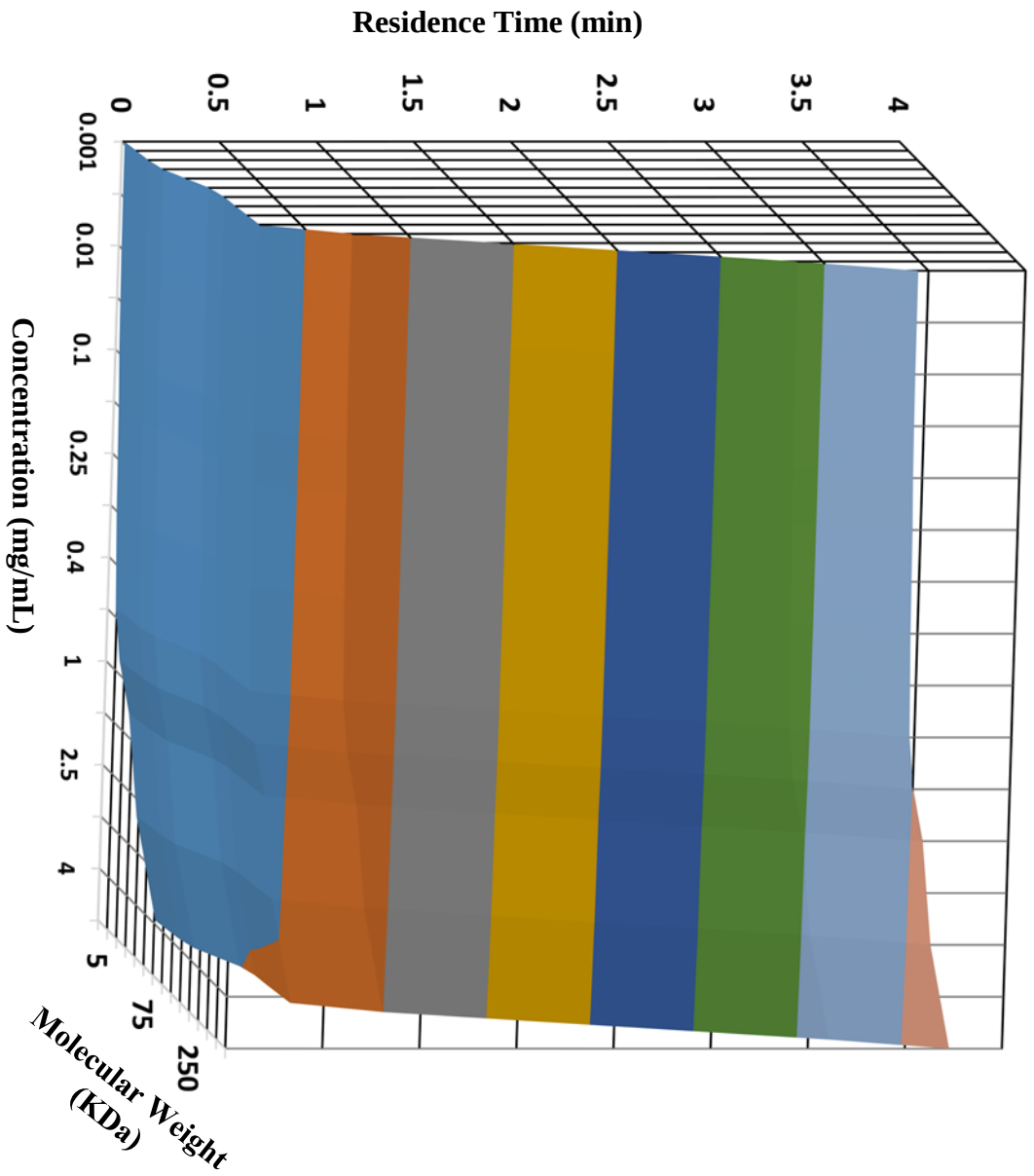


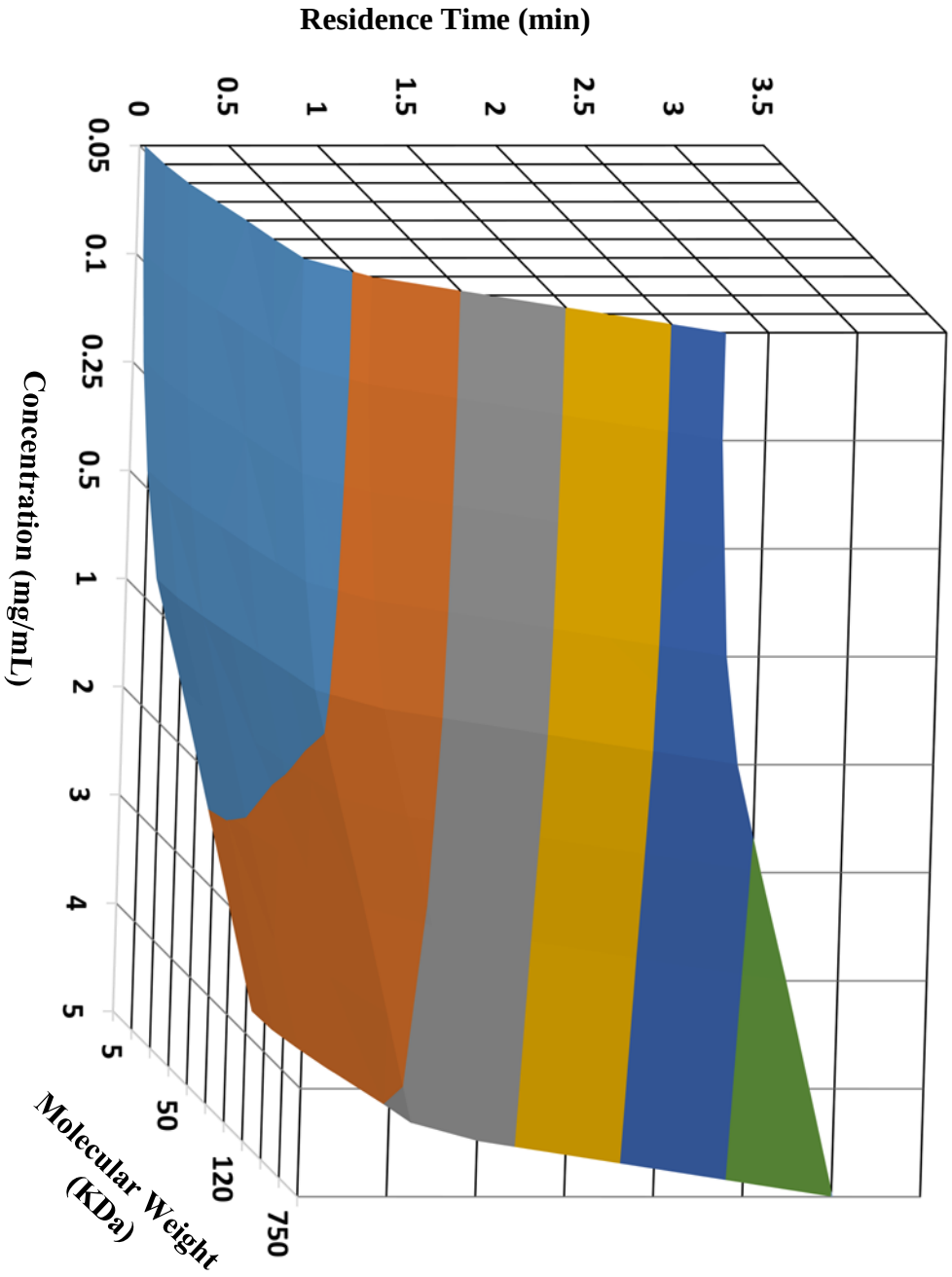
Figure 4.9. A-D. Polysaccharide 3D Plot With % Concentration

The residence times of (***A***) sodium hyaluronate, (***B***) hydroxypropyl methylcellulose, (***C***) sodium carboxymethylcellulose, (***D***) fluorescein isothiocyanate dextran (*FITC-Dex*), (***E***) dextran, (***F***) dextran sodium sulfate, and (***G***) fluorescein isothiocyanate hyaluronic acid (*FITC-HA*) comfort agent solutions are presented as a function of comfort agent molecular weight (*KDa*) and comfort agent solution concentration (*mg/mL*).

A. Ocular Residence Time of Polyvinyl Alcohol



B. Ocular Residence Time of Polyvinyl Pyrrilidone



C. Ocular Residence Time of PolyAcids

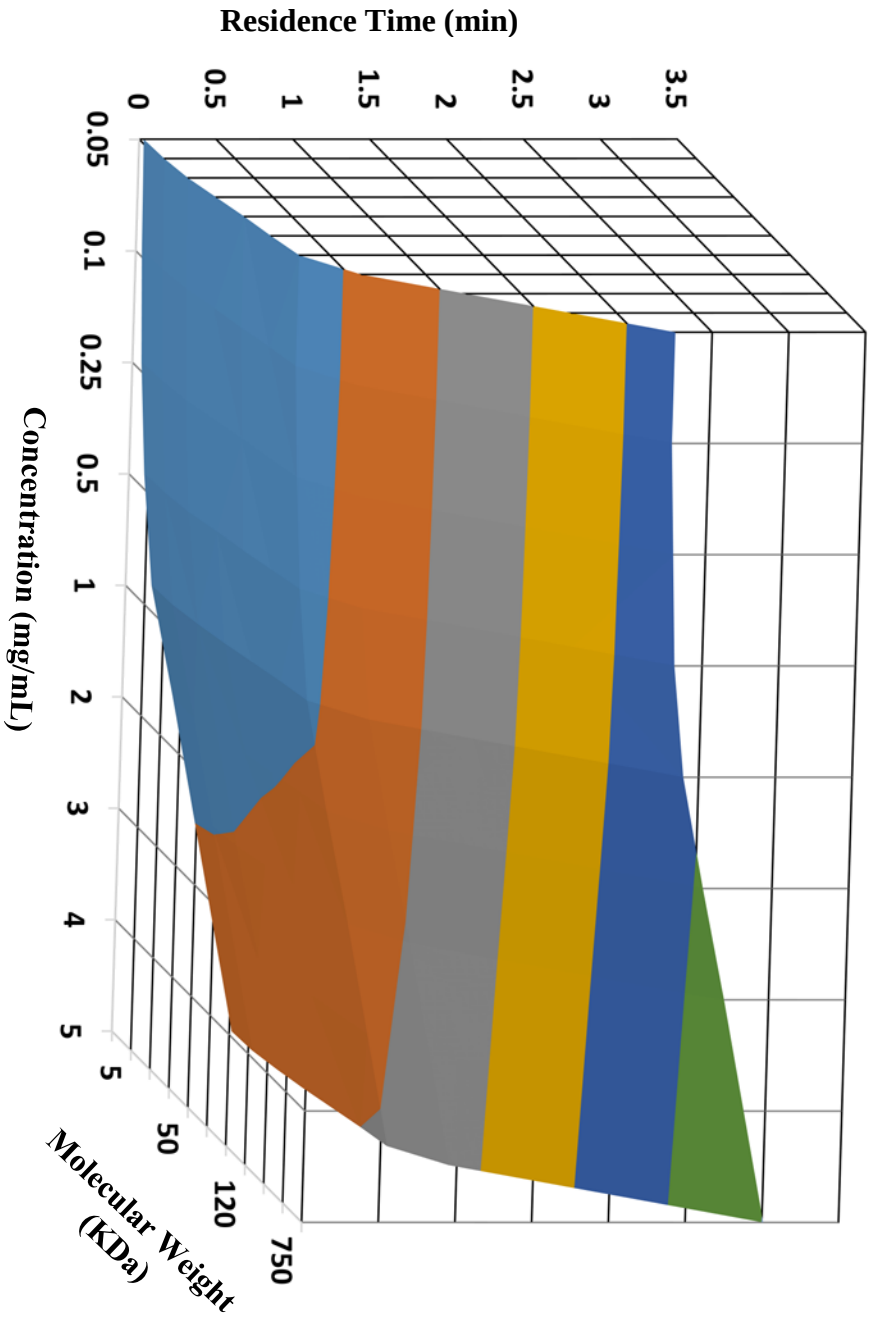
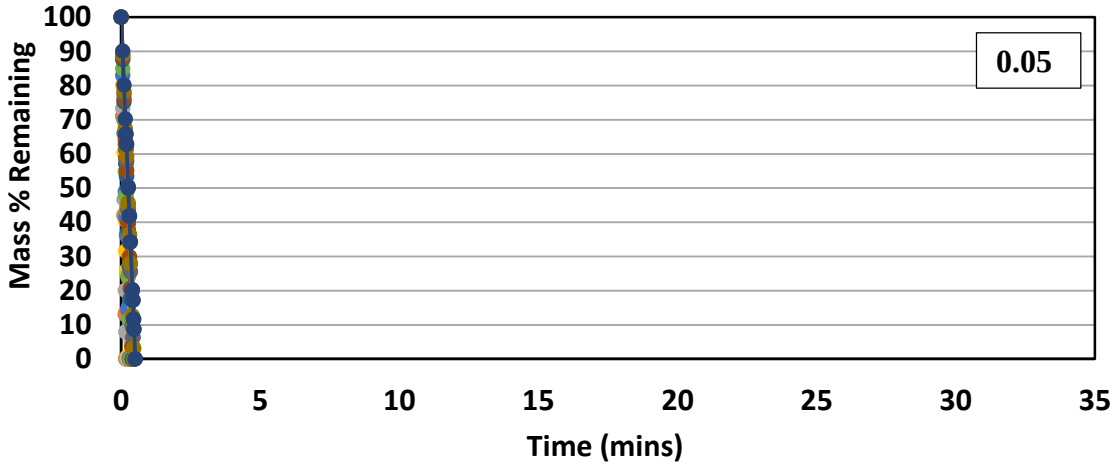
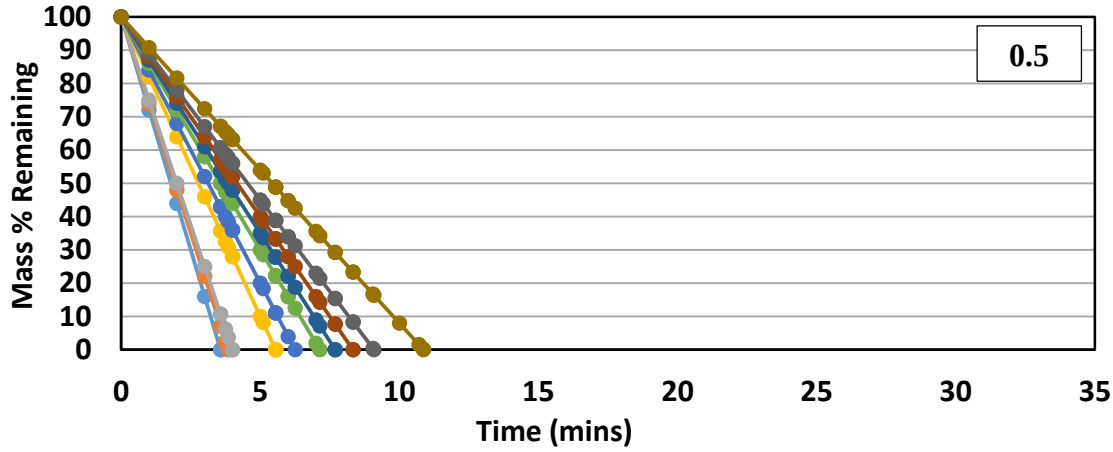


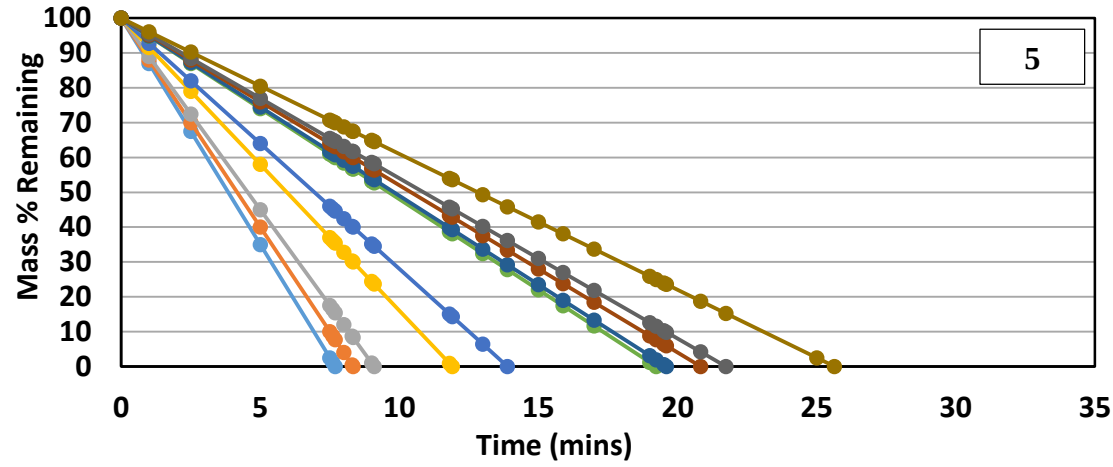
Figure 4.10. Acrylic 3D Plot with % Concentration

The residence times of (***A***) polyvinyl alcohol, (***B***) polyvinyl pyrrilidone, (***C***) polyacids, comfort agent solutions are presented as a function of comfort agent molecular weight (*KDa*) and comfort agent solution concentration (*mg/mL*). The contour plot is provided for clear demonstration of the relation between ocular comfort agent residence times and comfort agent molecular weight and comfort agent solution concentration.

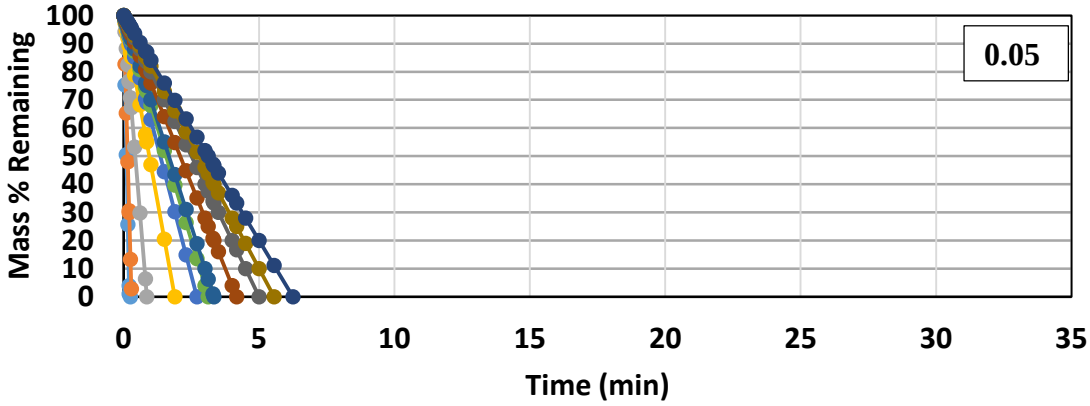
A. HA at 0.05, 0.5, and 5% Concentration

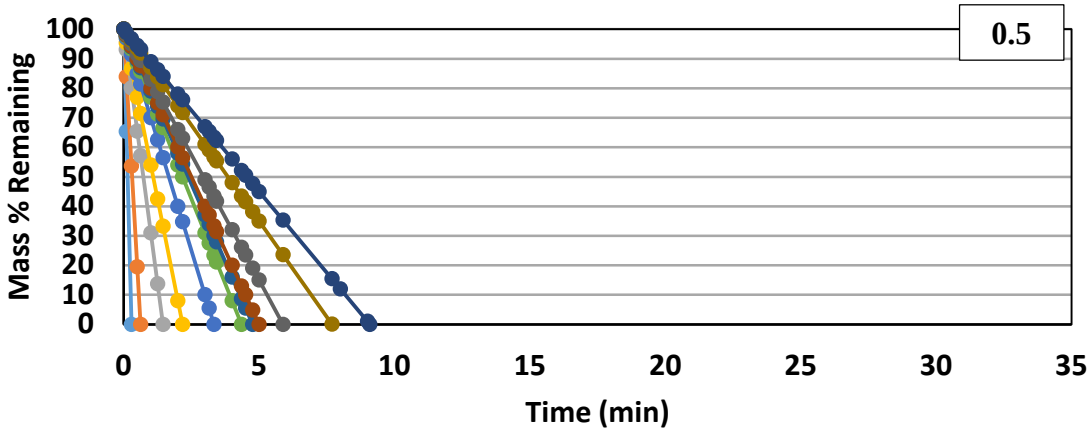


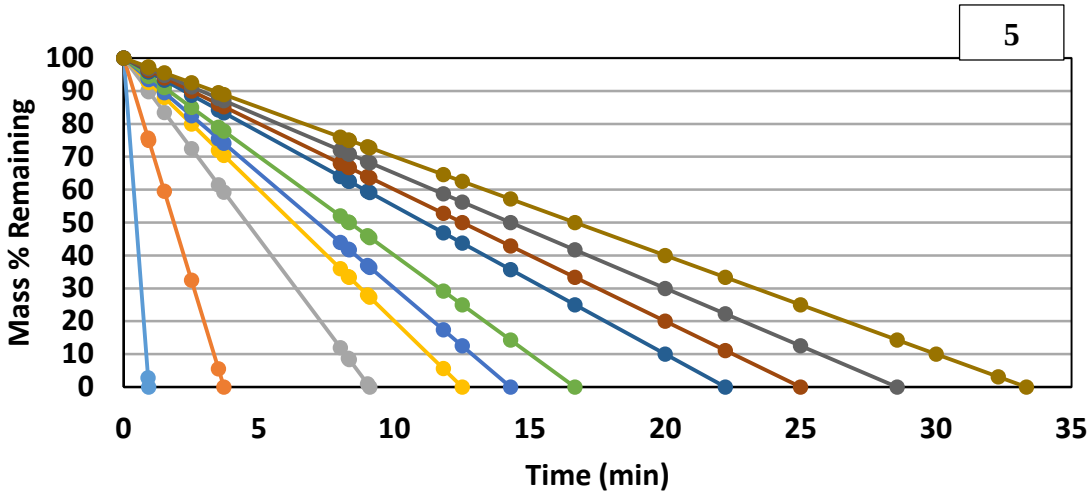




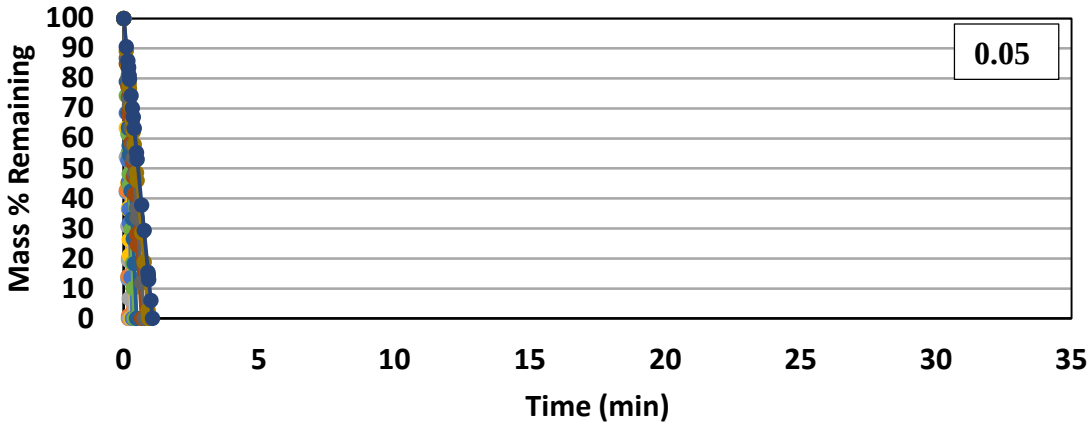
B. HPMC at 0.05, 0.5, and 5% Concentration

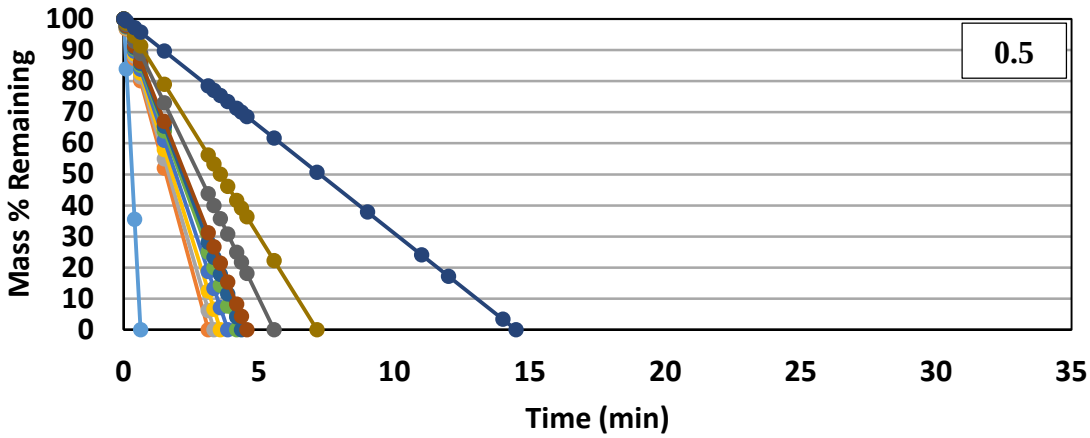


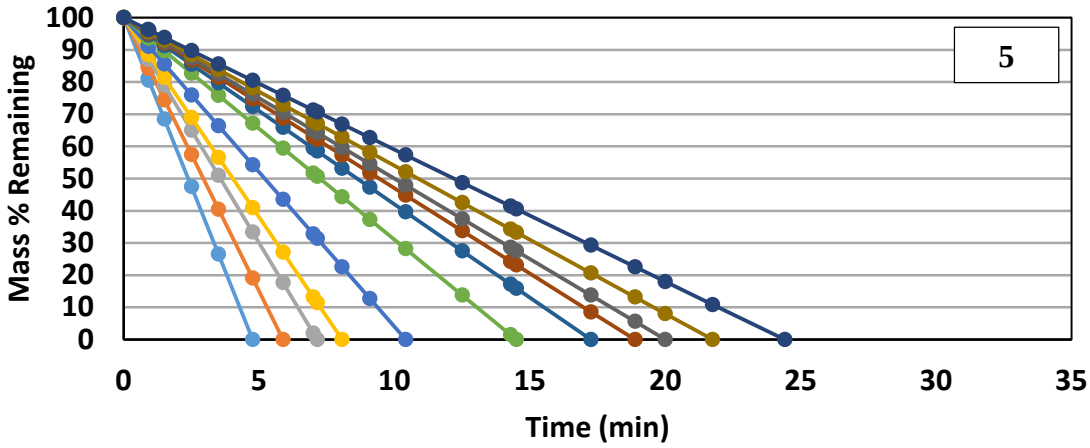




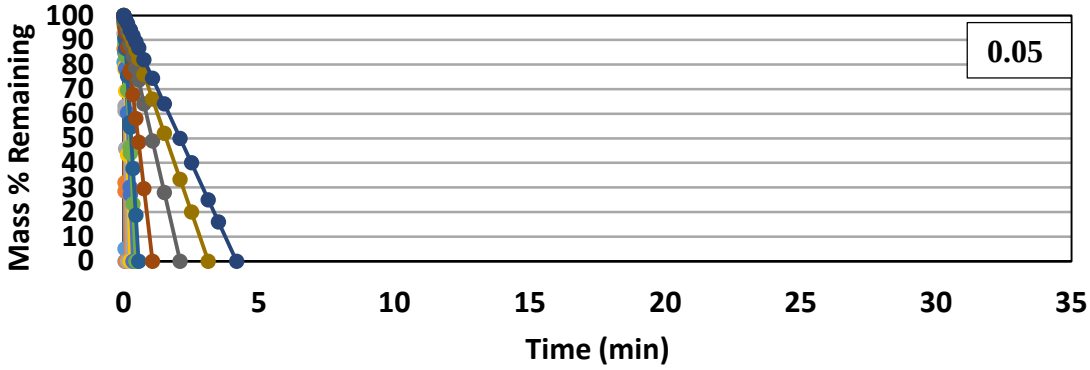
C. CMC at 0.05, 0.5, and 5% Concentration

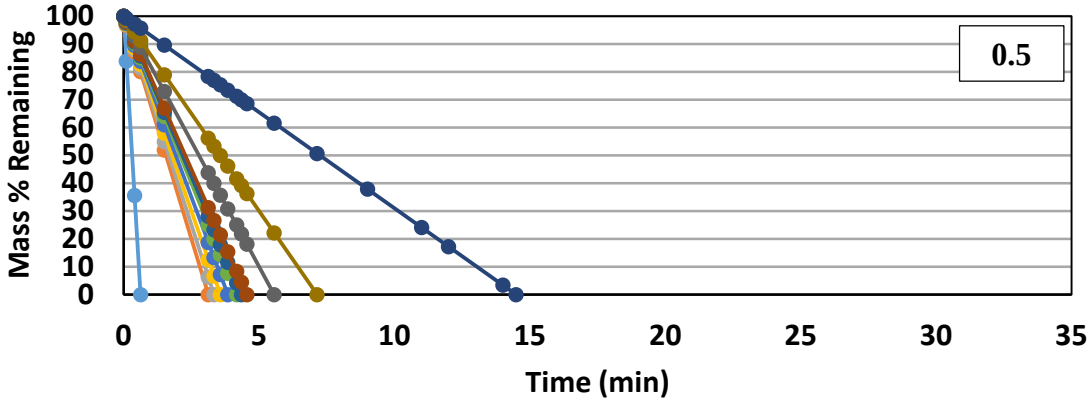


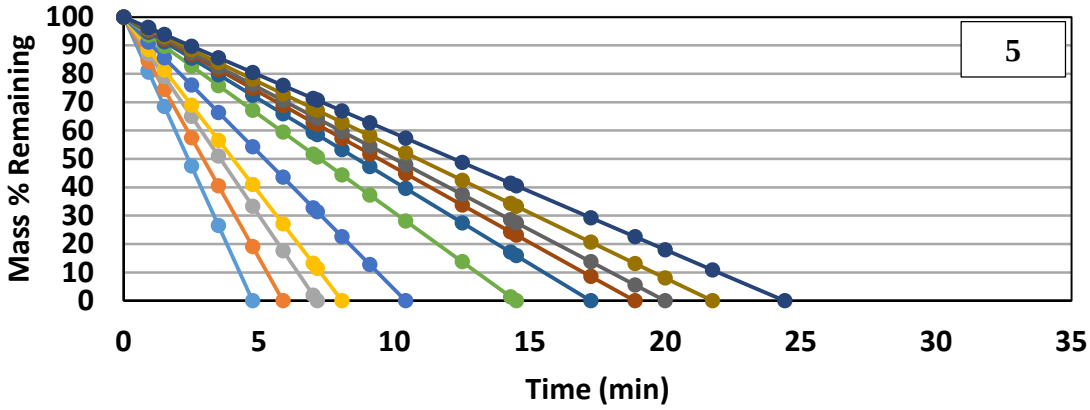




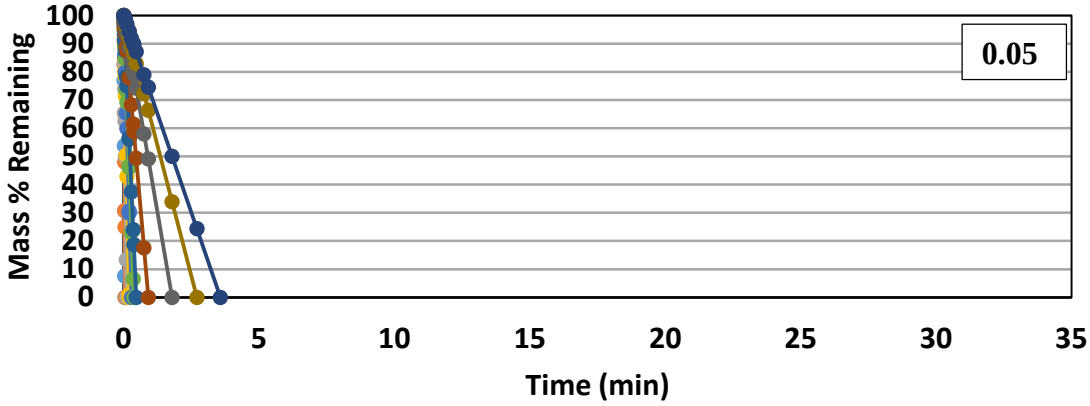
D. PVA at 0.05, 0.5, and 5% Concentration

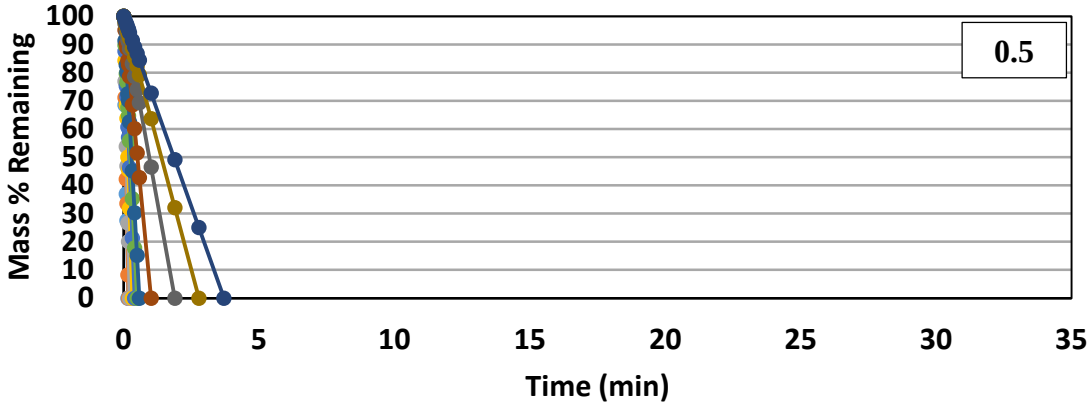


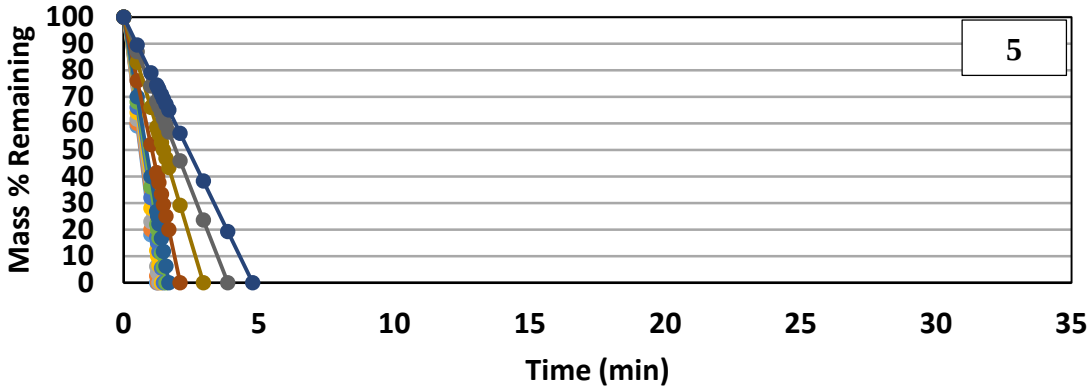




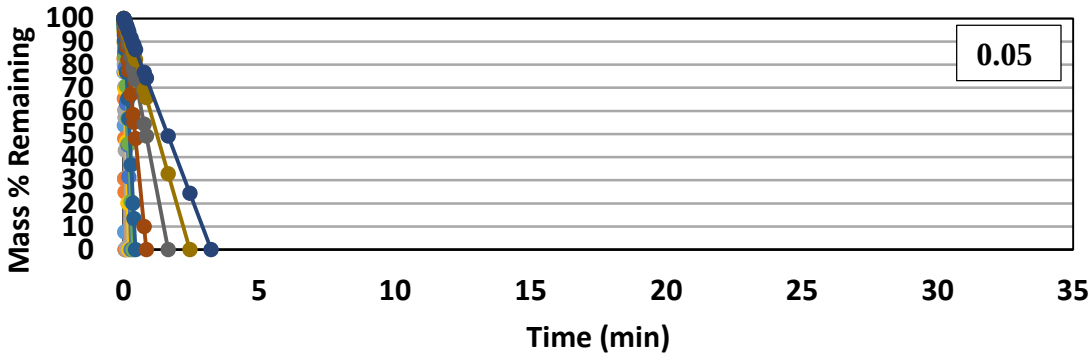
E. PVP at 0.05, 0.5, and 5% Concentration

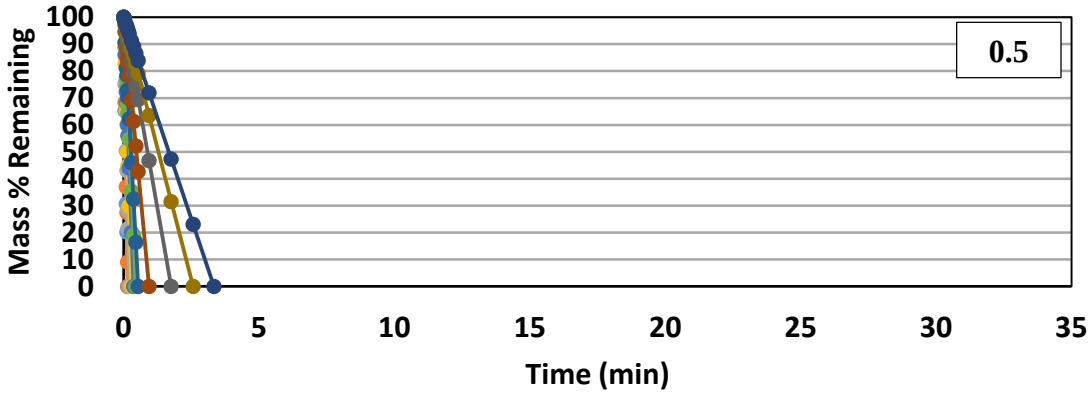






F. PAcids at 0.05, 0.5, and 5% Concentration





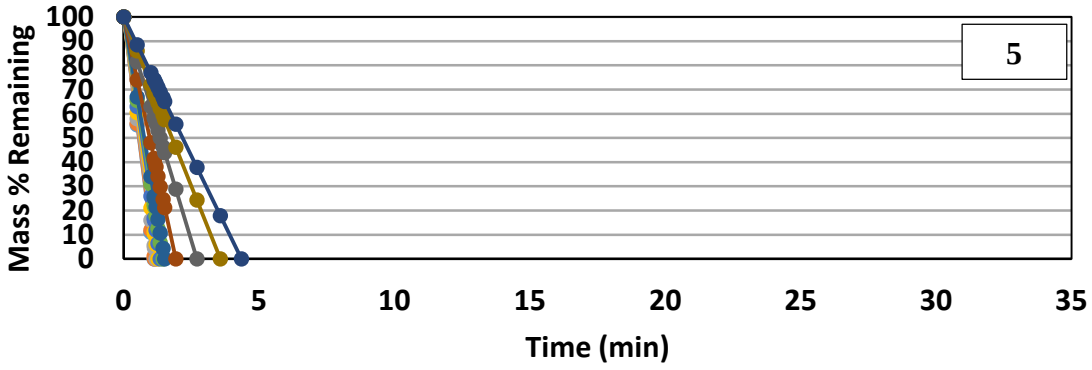


Figure 4.11. Predicted *In Vivo* Mass Profiles For Various Concentrations And Molecular Weight Comfort Agent Solutions

Using the data to perform a surface multi-variable regression, the predicted *in vivo* concentration were calculated for each comfort agent of various molecular weights and at an eye drop solution concentrations of 0.05, 0.5, and 5 (*wt*)% by assuming the comfort agent was delivered in an eye drop volume of 35 μL.

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CHAPTER 5

REVIEW OF CONTACT LENSES

5.1. Review Of 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 are gas permeable (GP) lenses (*both rigid and flexible*), which 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.

In the past two decades, the number of lenses in the United States has steadily increased as the number of lens wearers has increased. **Figure 5.1** demonstrates the trend for number of lenses available in the US and the growth of silicone hydrogel lenses. The figure was created from data compiled from references **[5.1-14]** based on approved lens wear times with some brands represented more than once as they are approved for multiple wear times. At least since 1990, the type of lenses produced in the greatest number of

brands by lens manufacturers has been hydrophilic hydrogels, but in recent years, the number of brands of silicone contact lenses has grown in popularity. 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 5.2***) **[5.1, 10]**. Silicone hydrogels lenses first debuted on the market in 1999 with 1 brand and have increased to 26 brands (*6% of US brands*) by 2010 **[5.10, 15, 16]**. Considering the large growth of the silicone hydrogel products and that ~5% of the brands make up 60% of all the fittings in the US in 2009, 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 **[5.15]**. However, each new macromer used in lenses for sale in the US must be approved by the FDA.

5.2. Discussion Of The Popularity Of Silicone Hydrogels

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. 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. 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. **Chapter 5** reviews the progress within the field of drug releasing contact lenses since 1965. It highlights the enormous potential of controlled release mechanisms and offers a comprehensive, comparative review of lenses, drugs, methods, drug loading, drug delivery rate, and release duration. Methods have included molecular imprinting as well various forms of mediated release via carriers, surfactants, inclusion complexes, and molecular barriers. Drug-soaked lens were the earliest releasing lenses, but they offer very little control over the release profile with low drug loading, are characterized by a decaying, Fickian release rates, and typically reach completion in a very short amount of time. Molecular imprinting is consistently one of the most promising and versatile methods of enhanced drug loading and extended release with tailorable control over release rate when factors are balanced such as lens thickness, material, and release media and conditions.

5.3. Drug-Eluting Contact Lenses

Hydrogel contact lenses were first developed by Otto Wichterle in 1965 **[5.17, 18]**. In his patent, he briefly discussed the potential for soft contact lenses to act as drug delivery platforms through diffusion mechanisms. This essentially involved the transport barriers of the chains within the crosslinked networks limiting the transport of the drug molecule. In the same year, Sedlacek used hydrogel lenses to load and release homatrope, an ocular

paralytic, in human eyes **[5.19]**. The lenses were soaked in a low concentration homatrope solution, and release from the lenses induced complete dilation in patients for approximately 1-2 hrs longer than achieved from eye drops alone. This was the earliest published account of drug releasing contact lenses, and it was a clear indication that drug release from contact lenses could potentially be more effective than topical eye drop administration. However, drug-soaked lenses only demonstrated improvement over eye drops for a short amount of time, and multiple administrations would still be needed as with topical eye drops. To this day, eye drop formulations have remained the dominant form of ocular drug delivery.

Since 1965, there has been much interest in drug delivery from contact lenses. Most of the published work has involved drug release from drug-soaked contact lenses, or lenses soaked in a concentrated drug solution. Many different drugs have been loaded into lenses and released; however, after 46 years, no commercial drug releasing lens products have been produced from drug-soaked lenses. For drug-soaked lenses, almost regardless of lens material and drug, the lenses are characterized by very quick elution times, most less than 30 minutes, and low loadings. Controlled release technologies have been shown to increase drug loading within lenses and significantly prolong release times. These methods have included molecular imprinting as well various forms of mediated release via carriers, surfactants, inclusion complexes, and molecular barriers. The development of daily wear lenses, daily disposable lenses, and newer extended, continuous wear lenses has increased interest in controlled delivery, particularly for release durations relating to the duration of wear.

This review highlights the development of drug releasing contact lenses since the field's inception in 1965. As the focus of this article is the release of drugs from contact lenses, other technology that sequesters drugs within the lens or drug covalently attached to the lens are not reviewed. Release from films is included where it is specifically described as potential mechanisms to deliver drug from lenses since 1965 is presented also. An exhaustive list of lenses, drugs, and methods are presented within this article and the advantages and disadvantages of each method are discussed (***Table 5.1, Figure 5.1***). The development of contact lens controlled drug delivery strategies has allowed unprecedented control over drug loading and release demonstrating high potential to lead to enhanced efficacy and efficiency.

5.4. Drug-Soaked Lenses And Diffusion Controlled Release Strategies

The most common type of diffusion controlled release methods in the literature are those involving drug-soaked lenses. Typically, diffusion controlled lenses have high initial rates of release and short delivery times, typically much less than 12 hours with complete release within 1 hour. Drug diffusion occurs with only minor control over release rates and loading, and thus, it is considered to be a passive method of controlling release. Diffusion release methods do not typically give tailorable control over release rates beyond drug solubility and Fickian (*i.e. concentration gradient driven*) kinetics. Different lens materials often yield different drug release rates due to drug solubility within the polymer lens, lens water content relating to free volume with the polymer structure, and network crosslink density. Water content is high to predominantly increase oxygen permeability and increase comfort. As water content increases, the transport of drugs through the free volume within the lens begins to mimic diffusion through water. Using passive diffusion methods of

release, such as those used by drug-soaked lenses, have remained popular in the literature despite these inadequacies.

Drug-soaked lenses are the majority of drug releasing lenses within the literature to date. It is worth noting, however, that while diffusion controlled lens delivery has been unsuccessful in producing commercially viable lenses, the variety of drugs demonstrated to load into lenses highlights the potential for growth in the field by formulating lenses with more sophisticated methods to control delivery. 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 within ocular tissues and the tear film when drugs are delivered from contact lenses when compared to eye drops. Repeated efforts have been made to make drug-soaked lenses more successful, including soaking in solutions up to a week, dehydrating the lens before soaking to increase loading, using supercritical solvents to increase loading, selecting drugs of different solubility, using large molecules as diffusion barriers. However, the time needed to saturate drug-soaked lenses is usually much greater than the increased elution time compared to eye drops, making eye drops the more practical and convenient product.

In 1965, the first account of drug release from hydrogel contact lenses was published, and it involved the replacement of water used as solvent in the lens pre-polymer with 50 mg of a 1% homatrope aqueous solution **[5.19]**. Homatrope is used for nerve paralysis and pupil dilation in ocular procedures. Testing on 25 patient eyes showed complete pupil dilation for about 10 hours while wearing the lens; however, comparisons to eye drops were not made. In addition, the first indication of increased effectiveness and bioavailability 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 **[5.19]**.

Shortly after the Sedlacek publication, other researchers investigated pilocarpine release from drug-soaked contact lenses **[5.20-28]**. Pilocarpine had been used for many years in eye drop formulations to treat glaucoma by reducing intraocular pressure (*IOP*) and is one of the drugs most studied for release from contact lenses. However, use of pilocarpine to control IOP has been largely replaced by later generations of drugs. The data is still valuable, however, as the number of published articles indicate the interest in drug eluting lenses and difficulties in producing a practical drug-soaked lens. Also, the studies reinforce that drug bioavailability in ocular tissues is greater when drugs are delivered by contact lenses.

Pilocarpine was loaded into Sauflon (*vinyl pyrrolidone and acrylic copolymer*) lenses by soaking in 1% pilocarpine solution for at least 3 days **[5.20]**. Intraocular pressure was observed to drop an average of 36% within 30 minutes 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 a 50% drop in IOP in patients treated with 4% pilocarpine eye drops **[5.20]**. It is important to note that similar IOP levels were achieved even though the lens was loaded with approximately a quarter of the concentration in eye drops, indicating increased bioavailability from lenses. The lenses were found to contain 400-500 μg pilocarpine after soaking for 24 hours and released for 2 hours **[5.20]**. To enhance loading, the lenses were dried and rehydrated in various pilocarpine solutions. Further testing demonstrated similar results (*i.e. release time of 2 hours and loading of 700 μg pilocarpine/ lens*) where release strongly correlated to water content. Sauflon lenses, which are 70-90% water, delivered

more pilocarpine to the eye and loaded in 3 to 12 hours after being dried, but release duration was not affected **[5.21]**.

Similar results were obtained from Bionite™ (*poly(hydroxyethylmethacrylate) or PHEMA*) lenses 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*, human studies **[5.22]**. PHEMA lenses were shown to deliver less pilocarpine and require longer soak times to saturate with pilocarpine compared to Sauflon lenses **[5.28]**. Attempts to prolong pilocarpine residence time by applying 1% pilocarpine drops while wearing the lenses reduced IOP for up to 24 hrs **[5.24]**. This technology was a variation on the drug-soaked lens concept. In drug-soaked lenses, the lens absorbs pilocarpine from a storage solution and then be placed in the eye, releasing the drug for the duration of lens wear. This article described an attempt to reload the lens while the patient wore the lens, significantly decreasing the time needed to load lenses and increase bioavailability. This method is not ideal as it would still require the frequent application of eye drops. The lens would preferentially absorb pilocarpine from the tear fluid, and release it later. However, the results were variable and were difficult to reproduce. Although pilocarpine release from lenses was heavily investigated, low release times, uncertainty as to toxic concentrations, and the development of more effective anti-glaucoma therapeutics rendered these devices uninteresting from a treatment perspective. However, the published data clearly shows that bioavailability increased when lower concentrations of pilocarpine were delivered from contact lenses than higher concentrations of pilocarpine delivered via eye drops. Other work with pilocarpine and drug-soaked lenses demonstrates similarly low elution times, though high loading could sometimes be achieved **[5.23, 25, 26]**.

A paper published in 2003 compared the uptake and release of cromolyn sodium, ketotifen fumarate, keterolac tromethamine, and dexamethasone sodium phosphate between silicone hydrogel lenses and traditional hydrophilic lenses further emphasizing the low potential for drug-soaked lenses **[5.29]**. This paper contained overwhelming evidence that both drug-soaked silicone hydrogel and traditional hydrogel lenses lack the significant control over drug release rates necessary for use as 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. An recent *in vivo* release study in rabbits used drug-soaked silicone hydrogel lenses to deliver ketotifen fumarate. The lenses released ketotifen fumarate from 13-24 hrs, but the release rate was initially very high (*instantaneous release rate upon insertion was ~500 μg/ hr*) but quickly decayed to ~40 μg/ hr **[5.30]**. This is a very inefficient delivery. Another device with similar loading of ketotifen fumarate used controlled delivery methods to maintain a constant ocular tear concentration in rabbit eyes for up to 26 hrs **[5.31]**.

Many other drugs have been loaded and released via drug-soaked lenses and are summarized in **Table 5.2** along with other methods. For instance, polymyxin B and phenylphrine both showed increased effectiveness when delivered from hydrophilic contact lenses via human and rabbit models **[5.24]**. Other drugs, such as acetazolamide **[5.32, 33]**, carbenicillin **[5.34]**, ciprofloxacin **[5.25, 35-38]**, cromolyn sodium **[5.25, 29]**, dexamethasone and its derivatives **[5.29]**, flurbiprofen **[5.39-41]**, fluorescein **[5.42]**, gentamicin **[5.34, 37]**, hyaluronic acid **[5.30, 31]**, hydroxypropyl methylcellulose **[5.43,**

44], idoxuridine **[5.25]**, kanamycin **[5.37]**, ketorolac tromethamine **[5.29]**, ketitofen fumarate **[5.29, 45]**, lovecabastine **[5.46]**, methazolamide **[5.33]**, ofloxacin **[5.37]**, phenylephrine **[5.24]**, polymyxin B **[5.24]**, prednisolone **[5.25, 47]**, timolol **[5.39]**, and tobramycin **[5.37]** have been loaded by soaking lens in drug solutions and supercritical drug solutions and released from different materials under a variety of conditions.

These drugs represent a wide variety of molecular weights and solubility values. The results of drug release from these lenses repeatedly show low drug loading and very quick elution times from both traditional lenses and silicone hydrogel lenses. However, a special case for longer elution times from drug-soaked lenses can be achieved by matching drug solubility to a similar lens material. Recently, a drug-soaked lens achieved longer release times by exploiting the solubility of a hydrophobic lipid, 1,2-dimyristoyl-sn-glycero-3-phosphocholine (*DMPC*), within a silicone hydrogel lens **[5.48, 49]**. The lipid was loaded very quickly by swelling the thin lens in a DMPC-isopropanol solution. Isopropanol is an exceptional solvent for the lens and dramatic swelling allowed for quick uptake, and the release of the hydrophobic lipid was slow due to it residing in the hydrophobic regions of the lens. The lens loaded only 33 μg of DMPC and release was Fickian with an exponentially decreasing release rate. Also, release was highly variable between individual lenses. The best performing lens released ~0.12 μg/ hr for the first 10 hrs, and then ~0.02 μg/ hr from 10-72 hrs **[5.48]**. Significant questions remain as per the effectiveness of such low amounts of DMPC and a commercial lens of this type providing end of day comfort, or comfort at the tail end of the duration of wear. It is unclear what amount of DMPC will either remain in the lens indefinitely or leach out at negligible concentrations. This is a common problem when designing systems based on solubility.

The reader is recommended to **Table 2** for additional details and comparisons between drug-soaked lenses.

When comparing the release data from contact lenses, the sink volume, sink medium, and mixing conditions become very important. Most drug-eluting lens systems described in the literature to date have used small volumes (*i.e., 2-4 mL*) of deionized water (*DI water*), saline, phosphate buffered saline (*PBS*), or artificial lacrimal solution (*ALS*). Such small volumes are usually not infinite sink environments and not well mixed and as a result confident comparison of release data is problematic. Drug elution commonly follows Fick's second law of diffusion, which means that a concentration gradient is the main driving force for elution. If an infinite sink is not achieved or similar release experiments performed, then different kinetics will be recorded and comparison will not be possible. Ideally, all release data should be taken in well mixed, infinite sink environments, where there are no significant concentration boundary layers and the concentration gradient is relatively constant throughout the release. This assures that there is no buildup of drug at the surface of the lens resulting in slower diffusion from the structure. Regardless of material, release medium, or delivery system, this will correspond to the fastest possible release. Using infinite sink conditions will allow true and accurate comparisons to be made between experimental data and the respective release systems. Since the precorneal volume is very small and the tear turnover fast, the infinite sink does not accurately predict release in vivo. In addition to infinite sink release profiles, there is a need to use in vitro microfluidic devices that accurately predict real ocular release rates. Therefore, using infinite sink conditions as a standardized model as well as generally

accepted release conditions will allow true comparisons between different lens release data and allow the further development of the field.

Release medium can greatly affect the elution of some drugs, and some release mechanisms are sensitive to the presence of ions common in ocular tear fluid. These conditions are best represented by using ALS as the release media in addition to proteins, such as lysozyme and albumin. Depending on the drug and lens studied, performing drug release in DI water can give rise to false kinetics of release. These inadequate models have slowed progress within the field by indicating that there is more potential for a mechanism of release to be used within a commercial drug-eluting contact lenses than is actually appropriate. Also, lens thickness is a significant factor when comparing drug release rates, lens loading and elution time for drugs. In Fickian release kinetics, the diffusion coefficient scales to the reciprocal of thickness squared, thus decreasing lens thickness by 10 will increase the release rate by a factor of 100.

In recent years, supercritical solvents have been of interest for many applications, and supercritical fluids has been used to load drug into contact lenses **[5.39]**. Supercritical CO_2-drug solutions were used to enhance loading of timolol maleate and flurbiprofen into four commercially available lenses. Timolol maleate was selected as a model hydrophilic drug, 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. The cumulative mass release of flurbiprofen from methafilcon A lenses loaded by soaking in supercritical CO_2 was 5-6x greater than the mass released from lenses soaked and loaded in a conventional aqueous solution **[5.39]**. Differences in loading were demonstrated and are shown in **Table 2**. This method controls release via

diffusion and did not extend drug elution time compared to control lenses but is interesting 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 **[5.25]**. In separate work, the effectiveness of supercritical solvents to load drugs within lenses was compared by soaking lenses in supercritical water-acetazolamide and supercritical ethanol-acetazolamide solutions. Acetazolamide loading increased when soaked in supercritical ethanol compared to supercritical water, loading 50 and 20 μg/ lens, respectively. Soaking a lens in a supercritical ethanol solution increased loading of timolol maleate by a factor of 20 when compared to soaking in an ethanol solution **[5.25]**. In this case, timolol maleate concentration within the lens was ~600 μg/ lens but was only slightly higher than published values using other methods. Acetazolamide loading was minor (*~100 μg/ lens*) using supercritical ethanol, which was much lower than previous work (*~1,500 μg/ lens*) **[5.50]**.

Flurbiprofen was loaded into a variety of lenses to a concentration of 80-1,200 μg/ lens by also soaking the lens in supercritical CO_2 **[5.40]**. 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 does not control release **[5.40]**. Other works also demonstrate that supercritical solvent may be an effective method to increase loading of some drugs **[5.26, 39, 40]**, but no control over release rate was observed indicating no true benefits over drug-soaked lenses in relation to controlled drug delivery. The application of supercritical fluid loading in addition to a controlled drug delivery

method **[5.40, 51]** could prove to be a powerful combination, though no combined effects were observed in these systems and release was not delayed. 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 **[5.40]**. Therefore, soaking in supercritical fluids is a variation in the drug-soaked method, and while it increases loading it does not increase release duration with little control over release.

Network design and size exclusion release strategies have also been used with drug soaking methods. Several controlled release mechanisms require changes in the polymer network for release to occur thereby requiring specific network design to promote drug release. Mechanisms that actively control mesh size or the free volume between polymer chains include expansion and contraction via pH, temperature, and other triggers as well as the controlled degradation of the network architecture. The common thread is that these methods control the flux of drugs via size exclusion where release depends on the mesh size, flexibility of chains, and the size or conformation of the drug. As drug molecules travel through a network, the motion can be modeled as discrete particles travelling through a field of random obstacles, where the obstacles are the polymer chains. As the concentration of these obstacles increases (i.e. the mesh size decreases), the transport of the particle is constrained. Eventually, as the crosslink density approaches infinity, no movement of the drug is observed. Steric interferences between the network and drug restrict drug transport. However, the relative mesh sizes of most hydrogel 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 effective method of

controlling release. In fact, without significant control over nanostructural morphology, it is unlikely that lenses with decreased mesh sizes can grant the same control over the release rate as other methods and maintain adequate mechanical and optical properties. Lenses under these conditions with a high amount of crosslinking and decreased mesh sizes will be rigid and inflexible affecting the fit and increasing lens discomfort for the patient. Also, for systems with expansion or contraction occurring on the chain level, this would lead to macroscopic changes in the lens affecting fit and optical quality.

In recent work, the concept of drug-soaked lens was altered by the presence of a bigger molecule to slow the release of loaded drug. In theory, drug elution would be slowed by a large diffusion barrier within the lens, limiting the free volume for transport. Such a lens was created when vitamin E was loaded into 5 different commercial lenses by soaking in a concentrated solution for 24 hours **[5.52]**. As a large molecule, the vitamin E constrained the free movement of timolol, dexamethasone 21-disodium phosphate, and fluconazole and increased 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 drug mass uptake which is repeatedly demonstrated within the paper for different molecules **[5.52]**. The rate of release is strongly dependent on the concentration of the diffusion barrier molecule. However, the barrier molecule also diffuses from the lens and as time increased, the effectiveness of the blockage decreased.

Loading of vitamin E was lens dependent with the greatest vitamin E affinity exhibited by Acuvue Oasys lenses. Decaying release rates of vitamin E into 2 mL of PBS

were found in all cases delivering lower doses over time. Oasys lenses were found to load ~6.5 mg Vitamin E. Drug release rates 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 [38]. Investigation of the loading and release of dexamethasone in a second article by the same authors demonstrated similar trends, and a mathematical model was developed to describe the kinetics of release [39]. Elution of dexamethasone reached 90% completion within a day of release [39].

Other methods have included the incorporation of specific chemistry or inclusion molecules along the polymer chains to increase the loading and control the release via soaked lenses. Ion-exchange methods have been used to control drug release from lenses. The mechanism depends on the ionic exchange of salt molecules between similarly charged molecules. Published work has demonstrated controlled release of azulene and naphazoline through ion-exchange [40-41]. 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 delay release via this method.

In other work, naphazoline, a cationic drug, was loaded into lenses composed of PHEMA and methacrylamide (MAm) with 2-methacryloxyethyl phosphate (MOEP) or

methacrylic acid (MAA) as ionic monomer [40]. The presence of the MAA increased loading in lenses at all concentrations, yet loading was minor. At 10 wt% ionic monomer, loading of the drug was found to be ~23 μmol and ~18 μmol with MAA and MOEP, respectively. Naphazoline release 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, though it exhibits low loading of 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. Work done by the same authors with azulene demonstrated similar patterns including low drug uptake and quick release time into saline [41].

Cyclodextrins are capable of forming high affinity complexes with certain drugs due to high concentration of hydroxyl groups inside the inclusion complex ring structure. Cyclodextrins have been used in a number of topical ophthalmic formulations and recently have been formulated into contact lenses and hydrogels **[5.53, 54]**. To date, only two articles present cyclodextrins as a method to control release of diclofenac sodium **[5.50]** and puerarin **[5.54]** from contact lenses. In the first article, cyclodextrins were grafted into PHEMA lenses by reacting functional groups of the cyclodextrins with the glycidal groups of co-monomer glycidal methacrylate (*GMA*) and then the lenses were loaded with diclofenac sodium (*DS*) by soaking in aqueous DS solution a . 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 lens. As GMA concentration in the lens increased from 0 to 360 μmol GMA/g lens, the higher loading was observed. The mass release rate of diclofenac decreased with increasing GMA content reaching completion ~11 days in ALS. However,

these lenses were significantly thicker than commercial lenses. Reducing these lenses to adequate thickness will greatly increase the release rate and decrease the loading of diclofenac.

The release of larger molecular weight molecules have also been investigated using drug-soaked methods. When a large molecular weight molecule is loaded by drug-soaked methods, the movement from the relatively unhindered solvent state into a constrained hydrogel becomes a significant obstacle to loading and often results in only small amounts of the molecule loaded into the lens. Small molecules undergo Brownian motion as they diffuse through a material and experience few constraints on their movement. 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 can be thought of as wormlike or occur through a statistical motion of coils and is 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 **[5.55]** demonstrating that as the molecular weight between crosslinks (M_c) approaches the polymer's persistence length (*i.e., the tail to tail length of a polymer*), the reptation of a polymer is severely reduced or eliminated.

This can be seen in recent work demonstrating very low loading and very short release times of macromolecular comfort agents. For example, numerous commercial lenses were soaked in a hyaluronic acid-containing Biotrue™ contact lens solution **[5.30]**. Overall, lens uptake of HA was very low, and HA was released within 30 minutes. A lens product marketed in Italy for daily wear uses similar reptation based release mechanisms to control the release of unknown molecular weight hyaluronic acid from methafilcon A lenses **[5.31]**.

One method to overcome the low loading of large molecular weight molecules is to disperse the molecule into the unpolymerized lens formulation, or pre-polymer. Once polymerization occurs the network will form around the molecules embedding them in the free volume within the polymer chains. This method can be used with high or low molecular weight molecules and is referred to within this review as direct embedding. While these are not drug-soaked lenses, the drug transport is similar the same as their drug-soaked counterparts, and the lenses can be considered to drug-soaked lenses with enhanced loading.

Currently, there is only one US marketed commercial lens formulated with direct embedding of a long chain comfort molecules. 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 macromolecule replenishing the tear layer. Release is controlled via solubility and reptation of the PVA in the Nelfilcon A network (*PVA network*). The reported release duration is ~16 hrs, at which time, the lens is then discarded, and a new lens is placed on the eye **[5.56, 57]**. Other work with long chain comfort agents demonstrated the release of PVP from poly(*HEMA-co-EGDMA*)

lenses capable of daily disposable wear **[5.58]**. The work showed release of PVP for ~3 days but with very little control demonstrated over the release rate.

Lastly, tailoring release through controlled polymer degradation has also been used and involves an increasing mesh size. Initially, drug elution is stopped via size exclusion but as the polymer degrades, the mesh size increases allowing more drug to elute. Such materials are usually poly(*lactic-co-glycolic acid*) (*PLGA*) or polylactic acid (*PLA*) since they are well studied, approved for use, can be controlled quite well, and have non-toxic degradation products.

Recent work using a biodegradable scaffolding as the mechanism for controlled release from lenses used a PLGA core embedded with ciprofloxacin and coated with a PHEMA shell **[5.59]**. The inner core thickness of PLGA measured 200-250 μm and was placed in another mold with HEMA monomer and cured, resulting in a PLGA center sandwiched between two layers of PHEMA. Thus, the completed 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 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 environments pupils can dilate up 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 standard deviation was observed in

the measurements. Each concurrent error bar completely overlapped with the preceding error bar. Given such significant deviation in measurements, any confident conclusions about release order are dubious and difficult to accept **[5.59]**.

5.5. Molecular Imprinting Strategies to Increase Loading and Delay Release

Molecular imprinting is one of the most promising and versatile methods to control drug delivery from contact lenses and has received considerable attention recently as a delivery mechanism. The following reviews **[5.60-63]** and articles **[5.64-75]** are recommended as background to the method.

The principle of molecular imprinting exploits non-covalent associations between drug and monomers or macromers to create macromolecular memory sites during the polymerization reaction. The drug is included in the formulation and influences the building of the polymer chains during the reaction. Functional monomers are typically selected for drug templates promoting intermolecular interactions, such as hydrogen bonding and ionic interactions. When polymerization occurs, the resulting polymer network has memory segments where the drug molecules have been templated into the network structure with functional chemistry oriented to bind the template drug. Thus, various polymer chains act to bind drug after the template drug has been removed. The orientation of the functional chemistry on differing polymer chains creates memory sites within the network that interact with drug molecules as they diffuse past. The drug undergoes Brownian motion as it diffuses in the free volume within the network and interactions between multiple chains producing the memory site causes the drug to be temporarily held, increasing the transport time as well as increasing the mean path length between the drug and the surface of the lens. However, just adding functional monomers

to a pre-polymer and drug solution will not necessarily create an imprinted network. The functional monomers must be in sufficient concentration to create the interactions in sufficient quantity to retard diffusion through the network. If the functional monomer concentration is too low, effective imprinting will not occur. Also, the average molecular weight between crosslinks (M_c) or the molecular weight between junction points within the network must be an optimal size as to allow drugs to easily pass through the network and small enough to allow effective interactions as the drug diffuses from the structure.

Molecular imprinting typically depends on drug molecules being dissolved in the monomer formulation or in a solvent instead of relying on other molecules to aid solubility. Surfactants or emulsifiers can, in theory, prevent the orientation of monomers with and around the drug molecule. Also, the best results for macromolecules in terms of release and loading can be seen if the macromolecule conformation does not vary significantly from solution to the bulk polymer network. In contact lenses where optical clarity is of paramount importance, the best results occur with miscible drugs and polymers, though use of immiscible drugs is not necessarily prohibited. Once the drug is dispersed and the polymer network formed, release depends on the interactions between the drug and the functional chemistry polymerized into the network as well as diffusion among crosslink structure and steric influences.

The first imprinted hydrogel created for use in contact lenses showing potential for contact lens industry was published in 2002 **[5.71]**. The gel released timolol to treat glaucoma by lowering 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 **[5.72]**. Results showed 300 μm thick films 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 correlated to the 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 **[5.73]**. 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 **[5.65, 76]**. The multiple monomers outperformed single monomers and loaded 6 times the amount of ketotifen fumarate over non-imprinted lenses. Using these lenses for in vitro releases in artificial lacrimal solution, controlled release of therapeutically relevant concentrations was demonstrated for 5 days **[5.65]**.

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 ketotifen fumarate using the best performing lenses from the 2005 paper **[5.66]**. 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 **[5.64]**.

Imprinted lenses were used to controllably release hyaluronic acid. This was the first imprinted contact lens for a large molecular weight molecule **[5.68, 69]**. Films 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 contact lens induced dry eye symptoms and increase wettability and the comfort of lenses.

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 traditional radically polymerized contact lenses and a 269% increase in loading other non-imprinted lenses **[5.75]**. 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 **[5.75]**.

In recent work, 120 KDa hydroxypropyl methylcellulose (*HPMC*) was used as the template macromolecule for development of comfort enhanced, molecularly imprinted, extended wear, silicone hydrogel contact lenses **[5.44]**. Using acrylic acid, significant control over the release rate was achieved. A linear release profile was observed in the release of 3,000 μg HPMC from 350 μm lenses for up to 60 days. Adjusting the functional monomer to template ratio (*M/T*) to M/T values of 0, 0.2, 2.8, 3.4 corresponded to HPMC release durations of 10, 13, 23, and 53 days, respectively. Altering the M/T ratio allowed

for significant control over the release rate and could be formulated to deliver the HPMC reservoir over the entire spectrum of lens wear. A lens with a thickness of ~100 μm and the HPMC content of 1,000 μg HPMC/lens was tested at physiological flow rate. The release reached completion in 60 days where the rate of release was observed to approximately constant at a rate of 16 μg/ day under physiological flow rates. A typical HPMC re-wetting eye drop delivers ~2.5 μg/ day, assuming 20 drops/ day.

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*) **[5.74]**. 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. Much work has been done with molecularly imprinting within contact lenses and future, *in vivo* data demonstrated the full potential of imprinted contact lenses **[5.77]**.

The use of molecular imprinting to produce lenses has mostly been limited to low molecular weight therapeutics and mildly hydrophilic/lypophilic drugs. The drugs have been used to treat anterior diseases with little progress in posterior treatments. Future work will show *in vivo* release of significant duration with enhanced drug residence time with substantial increases in bioavailability as well as a greater diversity of drugs released from imprinted lenses.

5.6. Carrier-Mediated Release (CMR) and Surfactant-Mediated Release (SMR) Strategies

Encapsulants are commonly used 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 drug release rate and increase loading. Drug is encapsulated into thermodynamically stable micelles or drug particles and mixed with a lens pre-polymer solution. The encapulsation process can be formulated as emulsions (*macro, micro, mini, nano*), colloids, suspensions, and particulates. The carriers can then elute from the hydrogel network releasing drug during and after elution. Release from colloid, emulsion-laden, and liposomal laden lenses have comparable mechanisms of release, though many reviews of the field discuss colloids, emulsions, and liposomes separately. The term carrier-mediated release (*CMR*) is coined by this review 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 systems that use surfactant as the carrier.

Carriers are best employed 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 the release of hydrophobic drugs from hydrophilic lenses or hydrophilic drugs from hydrophobic regions of lenses. Attempts to release hydrophilic drugs from hydrophilic lenses ultimately fail as the partitioning of the drug is too weak to form a stable carrier. CMR-based release is most commonly encountered from PHEMA lenses, which have been shown to release hydrophobic drugs such as lidocaine **[5.78-80]**, timolol **[5.81]**, and

cyclosporine A **[5.82]**. 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 **[5.78-80]**. Timolol is an anti-glaucoma drug used to control and reduce intraocular pressure, and cyclosporine A is used to treat ocular ulcers and keratoconjunctivitis.

In the lens pre-polymer, drug-carrier particles can be evenly distributed throughout the solution when the lens is formed. Forming a stable drug carrier often requires the addition of an oil phase, e.g. octadecyltrimethoxysilane and hexadecane. This oil phase, essential for many CMR systems, affects the 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 limiting particle size and loading. Loading of the minor phase must be kept low to prevent clarity loss. If the particle size and loading are sufficiently low (the exact value depends on the refractive index mismatch between the lens network 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 effective drug concentrations for more than 2-3 days.

However, CMR has several drawbacks that hinder it from being a dominant mechanism of ocular delivery from contact lenses. 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. In these systems, the release rate

decays as the drug is depleted from the carrier. Conceptually, the release rate is controlled through the rate limiting step of drug migration from areas of high solubility in the minor phase to the major phase were it is poorly soluble. Release rates decrease greatly as the concentration gradients that force the migration dwindle. Drug may also be sequestered in the particles for long periods with very low release rates. Published work in the field has shown poor control over release with a large fraction of the drug eluting quickly and quickly dropping below effective values.

Also, molecular weight of the drug is important in the design of CMR-based systems. A small molecule will not grant the same control of release as well as a large molecule and if a drug is too large, a stable structure will not form around the drug molecules. Without the stable structure, CMR is not an effective method of release. Also, many CMR studies, especially SMR-based vehicles, have shown sensitivity to the presence of ionic species present in lacrimal fluid **[5.75]**. Prolonged release times from experiments conducted in DI water were dramatically reduced in saline solutions and phosphate buffers. The ions interacted with the surfactant and collapsed the particle, resulting in very quick transport.

In 2004, a PHEMA lens was used to release lidocaine, which is hydrophobic **[5.79]**. The lidocaine, which is insoluble in hydrophilic materials, was encapsulated in the lenses with Brij 97 and the addition of an oil phase consisting of hexadecane and octadecyltrimethoxysilane. Lenses were 1,000 μm thick, far outside commercial tolerances, and took 24 hrs to polymerize. Considering lens thickness, loading was minor compared to other methods with 200 μg lidocaine/g 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 PHEMA lens did not significantly affect the release profile, probably due the mesh size of the hydrogel being much larger than the 50 nm particles. The release was not significant after 2-3 days, and release in DI water may be much different in salt solution, especially with SMR mechanisms, which are very sensitive to ions and pH. Also, as the films were much too thick for practical lens design, scaling the thickness down to an appropriate thickness would greatly reduce the loading of these systems and significantly reduce release times.

A subsequent article from the same group investigated liposomes in the delivery of lidocaine from PHEMA lenses **[5.78]**. The liposome served as a physical encapsulation mechanism where the lidocaine was trapped in the core of the liposome with release being controlled by the transport through the liposome. 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 was a drastic improvement compared to the 2004 article where loading of lidocaine was restricted to 200 μg lidocaine. After 3-4 days, the rate of drug release leveled to around 65% of theoretical loading and no further release was observed. Explanations for this include the possibility that the drug is sequestered in the liposomal drug carriers, 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 complete release. After the first day 40% of the loaded lidocaine (*600 μg*) was released. Also, 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 **[5.78]**. 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 and further partition the drug. The best performing lenses were those of type (*iv*). 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, although the release rate did decrease. For a period of 3 days, drug release was not detected from type (*ii*) lenses can be assumed to be due to the presence of the silica shell. The shell was not present in type (*iii*) lenses and no delay in release was observed. It can be assumed that the hydrophobic silica shell helped promote drug partitioning between the phases and thus slowed drug migration across the dominant phase. 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.

The SMR-lidocaine work described above shows promise using SMR as a delivery mechanism, particularly in lenses where a strong partitioning can be achieved. However, lidocaine is a model drug and extremely hydrophobic. The octanol-water partition coefficient or Log P for lidocaine is 245 **[5.83]**. A log P around 0 would indicate that a drug displays no preference for either phase, while a negative log P indicate the drug is predominately hydrophilic. Very few drug molecules will show this degree of

hydrophobicity, particularly for drugs used in ocular drug delivery, so the applicability of this method for commonly used drugs is uncertain.

In other work, timolol, an anti-glaucoma drug, was released from PHEMA lenses **[5.81]**. 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. 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 were 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 differences seen in release.

Removing the oil phase in the formulation (*iii*) matched the release profile of pure HEMA lenses for the first 40 days indicating the surfactant did not affect release. Using a post-cure sterilization 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 was 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 designs. The only benefit the SMR system displayed was extremely high loading.

Cyclosporine A, dexamethasone, and dexamethasone acetate were loaded into 100, 200, 400, and 800 μm thick PHEMA lenses by drug soaking **[5.82]**. 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 duration, but it did not significantly altering release rate. Release of cyclosporine from Brij 78 lenses delivered ~0.7-1 μg/ day when loaded with 8 wt% and 2 wt% Brij 78, 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 lenses without Brij 97 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 the release rate by 0.3 μg/ day. Such negligible

differences in release rates are not of great interest, but it would be feasible to 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 profiles were independent of surfactant concentration and structure.

These lenses released only 50-70% of the calculated loaded mass, presenting another concern with this system. It is unclear whether the failure of cyclosporine to completely release is due to the surfactant laden lenses sequestering up to 40% of the reservoir, the decaying release rate with 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 will deliver variable doses of drug over the duration of wear. Several articles promote the use of SMR technology as extended release options for ocular devices, even though 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 of hydrophobic drugs, which is vital for SMR-based release, would not be possible in silicone hydrogels. Hydrophilic drugs would have to be selected if SMR technology would be applied to silicone hydrogel contact lenses. To date, no release of drug from silicone hydrogel materials has been shown using SMR or CMR methods. 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 the loaded drug was lost in the sterilization step. This step is needed for most lenses before shipment to the consumer.

5.7. Conclusions

An exhaustive list of lenses, drugs, and methods are presented in this review of drug releasing contact lens literature. This review highlights how far the field has progressed since 1965 even though there are few drug releasing lens products on the market. However, most of the exciting developments have occurred within the past ten years, and these efforts have revitalized the field.

The majority of work to date has involved release of drug from drug-soaked lenses. Drug-soaked lenses have shown that bioavailability is increased when drugs are delivered from contact lenses compared to topical eye drops. However, it is clear that the benefit in bioavailability is not balanced by the very short release durations of drug-soaked lenses. Also, secondary to release duration is the significant time needed to load drug via soaking which can be much longer than the actual release time. Thus, topical eye drops still maintain 90% market share of ophthalmological treatments. The development of novel release mechanisms is making therapeutic contact lenses a convenient and commercially superior alternative to topical administration methods. There is tremendous room for growth in the field as the majority of molecules have not been used with these newest methods.

To conclude, it is important to provide a comparative evaluation of the best strategies. While the methods were delineated by mechanism in the text, Table II allows direct comparison of methods relating to particular drugs indicating the relative effectiveness of each method. For example, timolol release has been shown for all major methods discussed in this paper, and ketotifen fumarate and hyaluronic acid have also been used in various methods. Molecular imprinting is consistently one of the best methods in

terms of enhanced loading and tailorable control over release rate when factors are balanced such as lens thickness, material, and release media and conditions. The breakthrough of molecular imprinting technologies within drug-eluting contact lenses shows that tailorable and extended release for any duration of lens wear is no longer beyond the grasp of the field. Imprinting extends the drug release profiles providing more constant drug release for longer times while simultaneously increasing the potential drug reservoir within the lens to provide therapeutic amounts of drug over the duration of release. This has been the goal of drug-eluting contact lens research since 1965.

Carrier-mediated release has been demonstrated to work best for lenses releasing hydrophobic drugs from hydrophilic lenses, and lenses containing inclusion complexes have worked best with the release of hydrophilic drugs from hydrophilic lenses. Thus, these methods have not been proven beyond hydrogel lenses used for daily wear and daily disposable wear. Molecular imprinting has been shown to work for a wider range of drugs for the entire spectrum of lenses from hydrogels to silicone hydrogels, which are used for daily disposable and extended continuous wear, respectively. No other method has demonstrated the tailorability of release and enhanced loading that molecular imprinting demonstrates. Unlike other methods that can reduce lens clarity, molecular imprinting has been shown to produce lenses with excellent optical properties. In addition, imprinted lens have adequate mechanical properties for use as lenses and can be relatively easily incorporated into existing manufacturing schemes compared to other methods.

Therefore, while many controlled drug delivery strategies have not worked, a few have allowed unprecedented control over drug loading and release from contact lenses.

There is high potential in the future to treat ocular disease with significantly enhanced efficacy and efficiency.

5.8. Tables

Table 5.1. Drug-Eluting Contact Lenses

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); $^{\alpha}$ Release was stopped at 24 hrs regardless of release; $^{\beta}$ Soaked in Supercritical Fluid; ▪ PVAMA is derived from monoacrylated β-cyclodextrin and GMA.

Drug/Molecule Class; MW [Log P]	Method of Release	Lens Material [Thickness] (μm)	Loaded Drug/Molecule Released	Release Time (Medium)
Acetazolamide Anti-Glaucoma; 222 [-0.26]	Cyclodextrin	Poly(PVAMA▪) (200)	~1,500 μg/ lens	~4 days (5 mL Saline)
	Diffusion (Drug Soaked)	Sauflon PW	Not Reported	Up to 7.5 hrs (*in vivo* Leporine)
	Diffusion (Drug Soaked)	Balafilcon A	100 μg/ lens	30 mins (10 mL Saline)
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)
Carbenicillin Antibiotic; 378 [1.01]	Diffusion (Drug Soaked)	Sauflon 70	30-80 μg/ mL (tissue concentration)	Up to 2 hrs (*in vivo* Human)
		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)
		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⬩)
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⬩)
	Diffusion (Drug Soaked)	Vifilcon A	Not Reported	8-12 hrs (*in vivo* Human)
		Etafilcon A	944 μg/ lens	3 hrs (3 mL Saline)
		Vifilcon A	710 μg/ lens	
		PHEMA	417 μg/ lens	
		Polymacon	206 μg/ lens (11%)[α]	24 hrs[α] (2 mL Saline)
		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⬩)
		Lotrafilcon A	16 μg/ lens	
		Etafilcon A	420 μg/ lens	
		Etafilcon A	~1,000 μg/ lens	1.5 hrs (3 mL Saline)

Cromolyn Sodium Anti-Histamine; 484 [-4.3]	**Diffusion (Drug Soaked)**	**Polymacon**	**7,264 µg/ lens**	**≤ 1 hr (2 mL Saline)**
		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•)**
		Etafilcon A	**~1,000 µg/ lens**	**30 mins (3 mL Saline)**
		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•)**
		Poly(HEMA-co-EGDMA) and Brij 97/Brij 78/ Brij 700 (200 µm)	**50 µg/ lens**	**~10 days (3.5 mL PBS•)**
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•)**
	Vitamin E (Diffusion Barrier)	**Senofilcon A**	**80-120 µg/ lens**	**80-90% in 1-7 days (2 mL PBS•)**
		Lotrafilcon A		
		Lotrafilcon B		
	Diffusion (Drug Soaked)	**Alphafilcon A**	**118 µg/ lens**	**<4 hrs (3 mL PBS•)**
		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•)**
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•)**
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•)**
	Vitamin E (Diffusion Barrier)	**Senofilcon A**	**27 µg/ lens**	**34 Days (2 mL PBS•)**
		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)**
		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•)**
	Molecular Imprinting	**Poly(HEMA-co-DEAEM-co-PEG200DMA) (400)**	**70% in 11 hrs**	**5 days (1000 mL ALS•)**

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)**
Fluconazole Anti-Fungal; 306 [0.5]	**Vitamin E (Diffusion Barrier)**	**Senofilcon A**	**70 µg/ lens**	**90% in 2 Days (2 mL PBS•)**
		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[β])**	**Methafilcon A**	**~100 µg/ lens†**	**< 1 hr (10 mL Saline)**
		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•)**
		Hilafilcon B	**~800 µg/ lens†**	**3 hrs (80 mL DI Water)**
Gentamicin Antibiotic; 478 [-2.12]	**Diffusion (Drug Soaked)**	**Etafilcon A**	**186 µg/ lens**	**20-30 mins (3 mL Saline)**
		Sauflon 85	**10-30 µg/ mL Tissue Concentration**	**Up to 2 hrs (*in vivo* Human)**
Fluorescein Model; 332 [3.57]	**Diffusion (Drug Soaked)**	**Bionite**	**0.1% Fluorescein Solution**	**3.5 hrs (*in vivo* Leporine)**
		Soflens		
Homatrope Ocular Paralytic;	**Diffusion (Drug Soaked)**	**Sauflon**	**50 mg of 1% Solution**	**~10 hrs (*in vivo* Human)**
Hyaluronic Acid Therapeutic Comfort Agent, Corneal Healing Aid;	**Molecular Imprinting**	**Nelfilcon A (127)**	**200 µg/ lens**	**40 hrs (20 mL ALS•)**
	Diffusion (Drug Soaked)	**Polymacon**	**15 µg/ lens**	**~6-12 hrs (Saline at 3.8 µL/ min)**
		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**	

Timolol Anti-Glaucoma; 316 [0.68]	**pH Responsive Lenses**	**Poly(HEMA-co-MAA-BIS) (1,000)**	**~300 µg/ lens**	**~5 hrs (10 mL PBS')**
	Vitamin E (Diffusion Barrier)	**Silicone Hydrogel**	**100 µg/ lens†**	**50 days**
	SMR	**Poly(HEMA-co-EGDMA) (200 µm)**	**70 µg/ lens**	**2 days (3 mL PBS')**
	Vitamin E (Diffusion Barrier)	**Galyfilcon A**	**60-100 µg/ lens**	**80% in 0-4 days (2 mL PBS')**
		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')**
		Poly(DEAA-co-MAA-co-EGDMA) (300)	**~2.5 increase over non-imprinted lenses**	**8-24 hrs**
		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**
		Poly(MAA-co-EGDMA) (300)	**Not Reported**	**1-3 hrs**
		Poly(DEAA-co-MAA-co-EGDMA) (300)	**35 µg/ lens**	**30 min -1 hr (*in vivo* Leporine)**
	Diffusion (Drug Soaked)	**Nelfilcon A**	**~100 µg/ lens†**	**Not Reported**
		Omafilcon A	**Not Reported**	
		Methafilcon A	**~400 µg/ lens†**	
		Hilafilcon B	**Not Reported**	
		Balafilcon A	**600 µg/ lens**	**30 mins (10 mL Saline)**
Tobramycin Antibiotic; 467 [3.58]	**Diffusion (Drug Soaked)**	**Etafilcon A**	**239 µg/ lens**	**10 mins (3 mL Saline)**

Ketotifen Fumarate Anti-histamine; 425	**Diffusion (Drug Soaked)**	**Polymacon**	**151 µg/ lens**	**≤ 1 hr (2 mL Saline)**
		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)**
	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)**
		Poly(HEMA-co-PEG200EGDMA-co-AA-co-AM-co-NVP) (400 µm)	**2200 µg/ lens**	**5 days (30 mL ALS•)**
		Poly(HEMA-co-AA-co-AM-co-NVP) (400 µm)	**900 µg/ lens†**	**5 days (30 mL ALS•)**
Levocabastine Antihistamine; 421 [4.29]	**Diffusion (Drug Soaked)**	**PHEMA (200)**	**33 µg/ lens**	**6 days (*in vivo* Leporine)**
		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)**
		PHEMA	**100 µg/ lens**	
		Vasurfilcon A	**700 µg/ lens**	
		Etafilcon A	**750 µg/ lens**	**8 hrs (*in vivo* Leporine)**
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)**
		Poly(HEMA-co-EGDMA) and Brij 97 or Tween 80 (1000)	**10-50 µg/ lens**	**3 days (DI Water)**
Methazolamide Anti-Glaucoma; 236 [-1.5]	**Diffusion (Drug Soaked)**	**Sauflon PW**	**Not Reported**	**(*in vivo* Leporine)**
Naphazoline Vasoconstrictor; 210 [3.88]	**Ion-Exchange**	**Poly(HEMA-co-Mam-co-MOEP-co-EGDMA) (300)**	**2500 µg/ lens**	**4 hrs (10 mL Saline)**
Norfloxacin Antibiotic; 319 [1.09]	**Diffusion (Drug Soaked)**	**Etafilcon A**	**200 µg/ lens**	**1 hr (20 mL Saline)**
		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•)**
Ofloxacin Antibiotic; 361 [-0.34]	**Diffusion (Drug Soaked)**	**Etafilcon A**	**200 µg/ lens**	**10 mins (3 mL Saline)**
		Etafilcon A	**180 µg/ lens**	**1 hr (20 mL Saline)**
		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)**
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)**
		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)**
		Bionite	**0.5, 1, 4% Pilocarpine solution**	**4 hrs (3 mL DI Water)**
			0.5, 1% Pilocarpine Solution	**3-4 hrs (*in vivo* Human)**
			1% drops added while lens was worn	**Up to 24 hrs (*in vivo* Human)**
		Not Reported	**4% Pilocarpine Solution**	**Not Reported (*in vivo* Human)**
		Bionite	**400 µg/ lens**	**~3 hrs (*in vivo* Primate)**
		PHEMA	**1,200 µg/ lens**	**30 mins (5 mL DI Water)**
		Sauflon (70% water)	**2,300 µg/ lens**	
		Sauflon (85% water)	**1,750 µg/ lens**	
		Etafilcon A	**~3,000 µg/ lens**	**30 mins**
		Vifilcon A		
		PHEMA		
		Sauflon	**Not Reported**	**Effective for 7 hrs (*in vivo* Human)**
			700 µg/ lens	**2 hrs (*in vivo* Human)**
Polymyxin B Antibiotic; 1200 [2.03]	**Diffusion (Drug Soaked)**	**Bionite**	**0.25% Polymyxin Solution**	**Not Reported (*in vivo* Leporine)**
Poly(Vinyl Alcohol) Re-Wetting Agent; 40000-65000	**Diffusion (Reptation)**	**Nelfilcon A (100)**	**6 µg/ lens**	**24 hrs (DI water)**
		Nelfilcon A (100)	**-**	**16 hrs (*in vivo* Human)**
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)**
Prednisolone Corticosteroid; 360 [1.49]	**Diffusion (Drug Soaked)**	**Etafilcon A**	**~3,600 µg/ lens**	**< 90 mins (3 mL Saline)**
		Vifilcon A		
		PHEMA		**~2 hrs (3 mL Saline)**
		Helfilcon A	**2-3x increase over eye drops**	**1 hr (*in vivo* Leporine)**
Puerarin Anti-Glaucoma; 416	**Cyclodextrin**	**Poly(HEMA-co-βCD-co-TMATMP) (53)**	**385-1,000 µg/ lens**	**~6 hrs (*in vivo* Leporine)**

[1.97]		**Poly(PVAMA▪) (200)**	**~1,300 mg**	**8 hrs (5 mL Saline)**

Table 5.2. Advantages and Disadvantages of Selected Release Mechanisms

Method of Release	Advantage	Disadvantage
Drug-Soaked Lenses	**Easy to Produce from Pre-Existing Lenses** **Easy to Load with Small Molecular Weight Drugs** **Easy to Incorporate into Manufacturing Process**	**Low Drug Loading** **Short Elution Times** **Low Control Over Release Rate** **Difficult to Load High Molecular Weight Drugs** **Eye Drops Often More Convenient**
Supercritical Solvent Soaked Lenses	**Increased Drug Loading Compared to Drug Soaked Lenses** **Loads Poorly Soluble Drugs**	**Low Control Over Release Rate** **Short Elution Times** **Difficult to Incorporate into Manufacturing Process** **Difficult to Load High Molecular Weight Drugs**
Diffusion Barriers	**Easy to Load Small Molecules** **Easy-Medium Difficulty Incorporating into Manufacturing Process**	**Short Elution Times** **High Initial Burst Release** **Decaying Release Rate** **Barrier Elutes** **Barrier Loading Competes with Drug Loading** **Difficult to Load High Molecular Weight Drugs**
Inclusion Complexes	**Controls Release Rate** **Best Results for Small Molecular Weight Drugs** **Increased Drug Loading Compared to Drug Soaked Lenses** **Easy-Medium Difficulty Incorporating into Manufacturing Process**	**Sensitive to Ion Concentration (Ion Exchange)** **Insoluble in Silicone Hydrogel Formulations (Cyclodextrin)** **Inadequate Mechanical Properties** **Requires Low-Medium Alteration of Lens Formulation**
Direct Embedding	**Easy to Produce with Small Molecular Weight Drugs** **Easy to Incorporate into Manufacturing Process**	**Low Drug Loading** **Low Control Over Release Rate** **Loss of Optical Clarity** **Loss of Network Flexibility and Inadequate Mechanical Properties**
Molecular Imprinting	**High Control over Release Rate** **Increased Drug Loading** **High Variety in Drug Selection** **Easy-Medium Difficulty Incorporating into Manufacturing Process** **High Optical Clarity**	**Best with Miscible Drug/Lens Formulation** **Requires Low-Medium Alteration of Lens Formulation**
Carrier Mediated Release	**Loads Insoluble Drugs** **Best with Small Molecular Weight Drugs** **Releases Highly Hydrophobic Drugs from Hydrophilic Lenses**	**High Initial Burst Release** **Sensitive to Ion Concentration** **Decaying Release Rate** **Carrier Elutes** **Not Effective Releasing Hydrophilic Drugs** **Not Effective with High Molecular Weight Drugs**
Surfactant Mediated Release	**Loads Insoluble Drugs** **Best with Small Molecular Weight Drugs** **Releases Highly Hydrophobic Drugs from Hydrophilic Lenses**	**High Initial Burst Release** **Sensitive to Ion Concentration** **Surfactant Elutes** **Drug Must Fit Within Micelle** **Second Hydrophobic Phase Needed** **Not Effective Releasing Hydrophilic Drugs** **Loss of Optical Clarity** **Surfactant Release Can Cause Irritation and Toxicity**

5.9. Figures

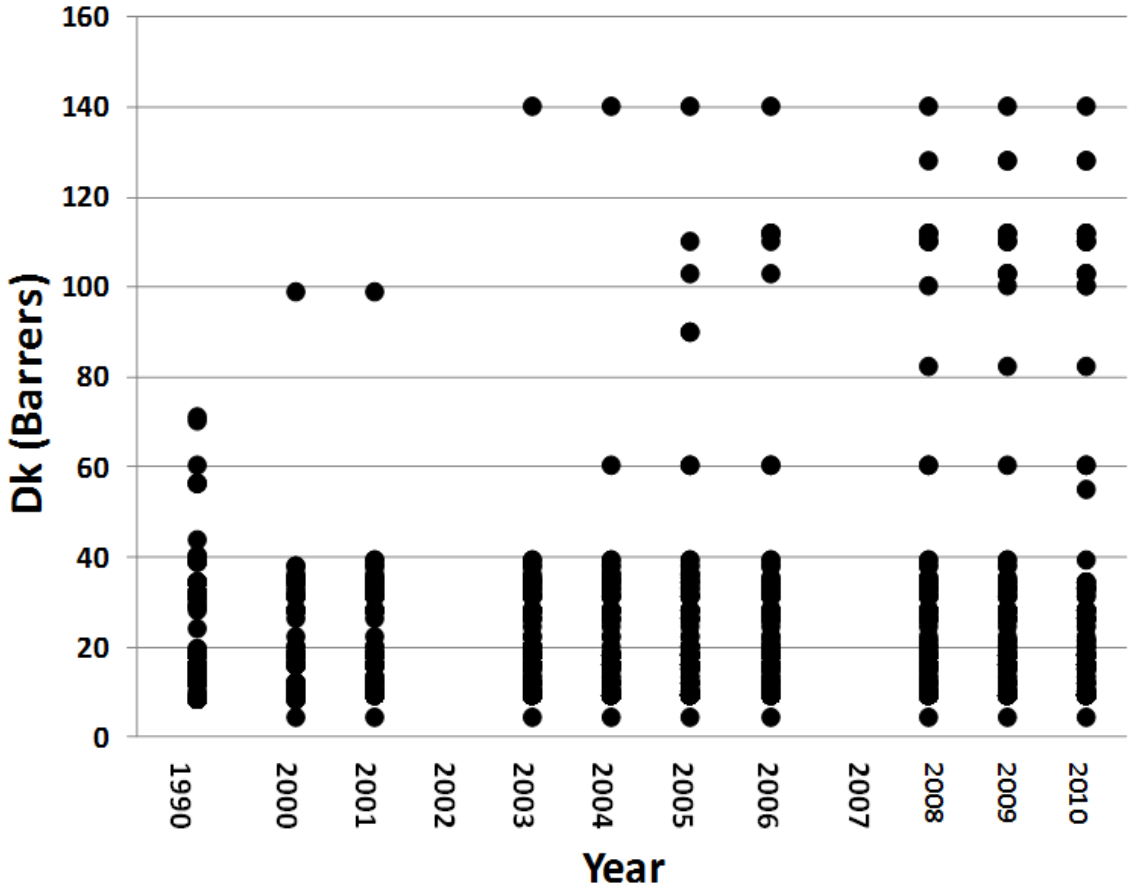

Figure 5.1. Trends in Oxygen Transport Values (Dk) of US Commercial Lenses in Hydrogel and Silicone Hydrogel Lenses

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.

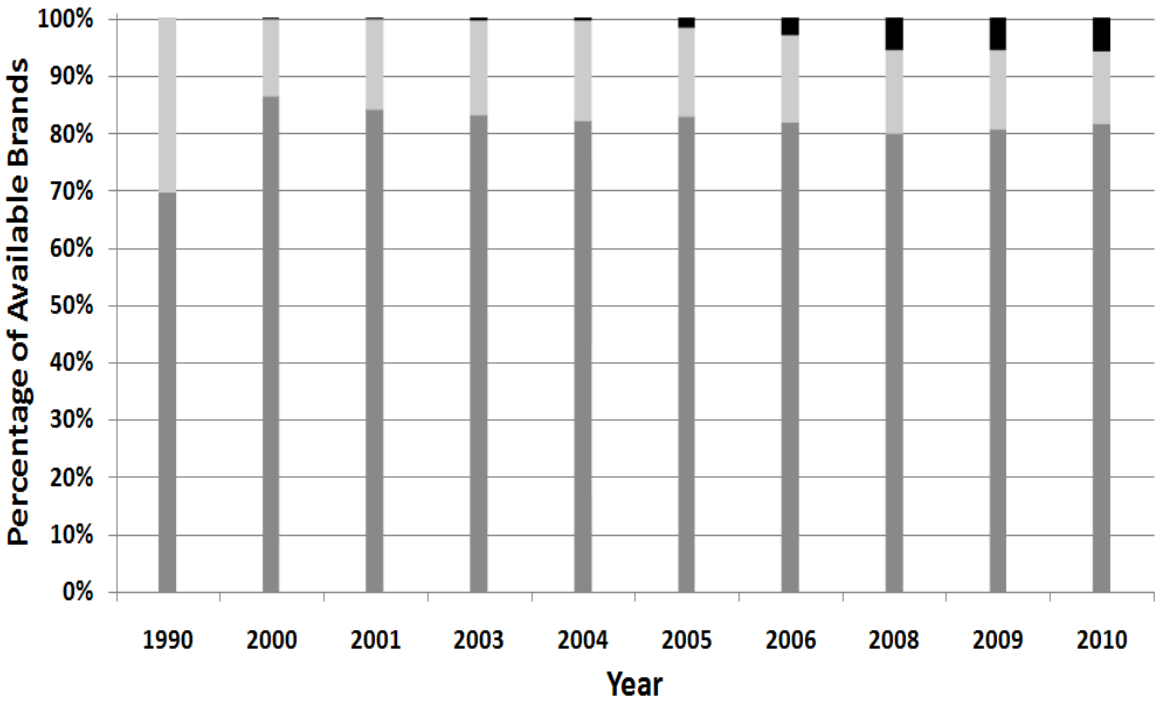

Figure 5.2. Percentage of US Commercial Lens Market Based on Material

Traditional hydrogel (■) lenses have, for the past two decades, made up at least ¾ 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 and are expected to continue as GP lenses are becoming a specialty lens.

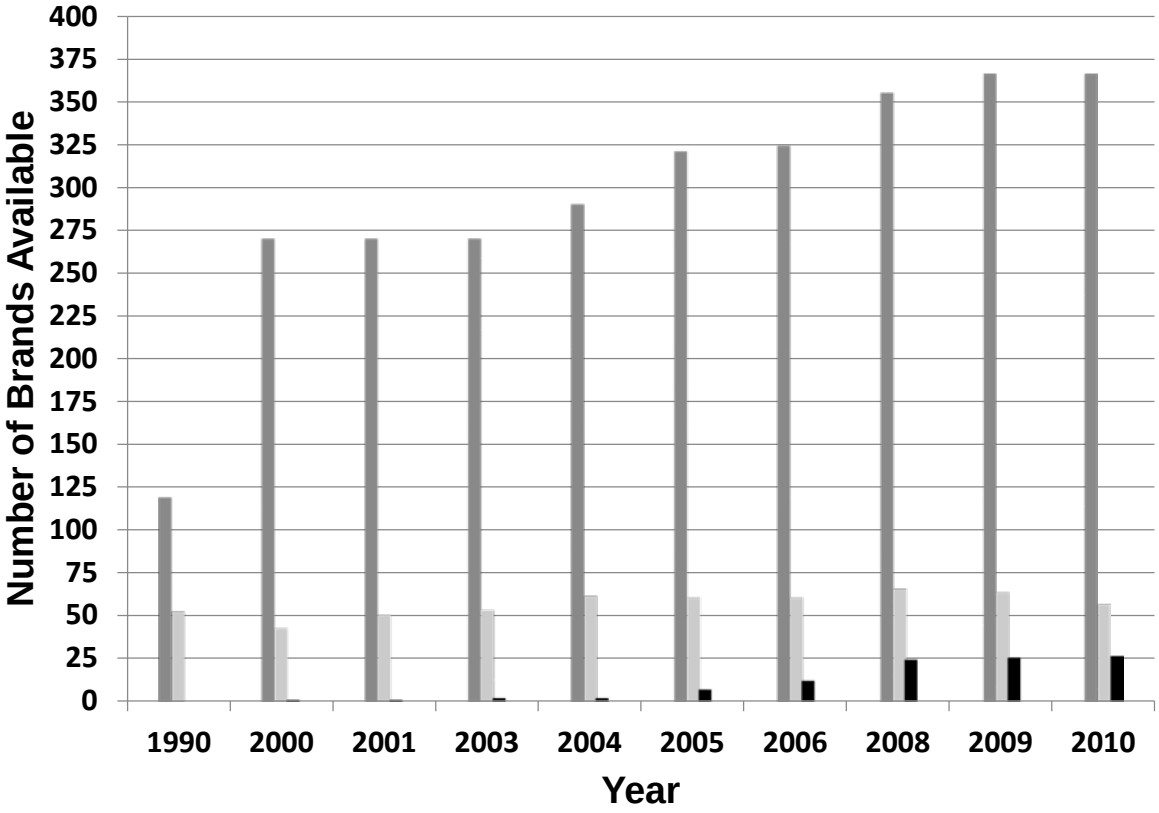

Figure 5.3. Number of Lenses Available in the US Lens Market Based on Material

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 but have exponentially grown. 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. There exists a consider gap in the technology of ocular drug delivery from silicone hydrogel contact lens materials.

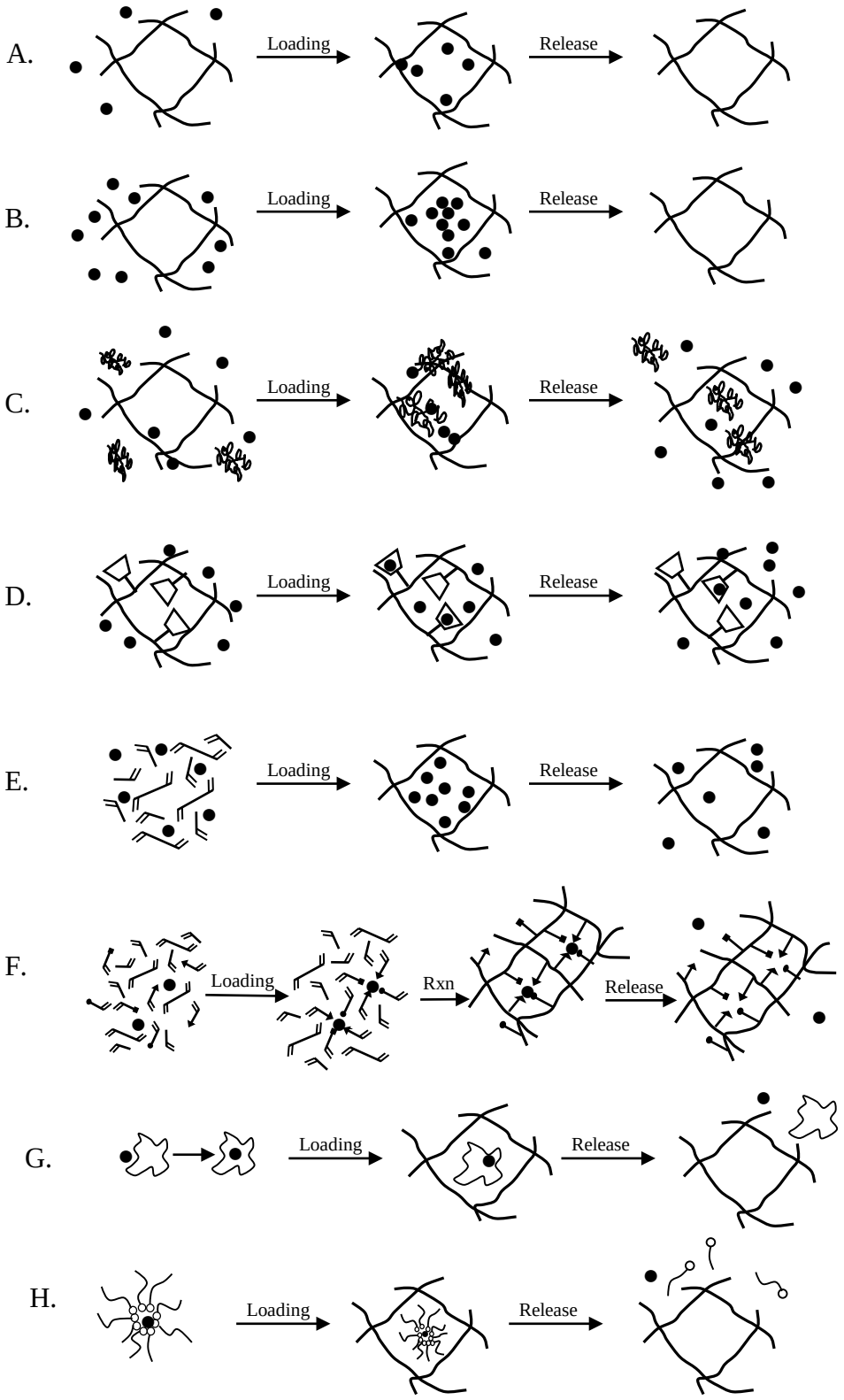
A.
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Figure 5.4. Demonstration of Release Mechanisms Used within Contact Lenses

Drug loading and release within contact lenses varies according to the method used. Therapeutic contact lenses have been produced by (A.) soaking lenses in a drug solution, (B.) soaking a lens in a supercritical fluid-drug solution to increase loading, (C.) including high molecular weight barrier molecules to slow elution of a small molecular weight drug, (D.) incorporating cyclodextrins into lens formulations to create inclusion complexes that slow the release rate, (E.) dispersing drug into the pre-polymer lens formulation or direct embedding of drug to increase drug loading, (F.) molecular imprinting drugs to control release rate and increase drug loading, (G.) addition of a carrier to load and release insoluble drugs as well as (H.) using micelles to disperse insoluble drugs for increased loading of insoluble drugs.

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CHAPTER 6

ENGINEERING THE CONTROLLED RELEASE OF COMFORT MOLECULES FROM CONTACT LENSES THROUGH MOLECULAR IMPRINTING

6.1. Introduction To Chapter 6

Administration of macromolecular comfort agents via eye drops is currently the most used method to overcome CLIDE discomfort. Comfort agents absorb water from the tear film and during blinking water is forced back onto the eye anterior surface, replenishing the tear film. In addition, the viscosity of the tear fluid can be altered by the presence of the macromolecule reducing the shear stress caused by blinking. However, drop volume, delivered dose, and patient compliance are highly variable with eye drop administration, and eye drops typically need to be instilled several times a day to maintain effective concentrations. For comfort eye drops, patients are advised to use drops as needed, and this can lead to extensive, inconvenient use with significant variations in comfort. Therapeutic molecules delivered via eye drops suffer from very low residence times with poor bioavailability and result in pulsatile concentration profiles in the tear fluid. In the last few years, therapeutic soft contact lenses have been demonstrated to be an ideal platform for the controlled delivery of numerous drugs as well as comfort molecules. Producing more comfortable contact lenses or comfort-enhanced lenses is a significant

goal, and this can be achieved by sequestering comfort molecules in the lens structure and/or releasing comfort molecule from the lens.

Soft contact lenses are the most convenient platforms to alleviate CLIDE symptoms, especially when compared to alternative methods of treatment such as eye drops, inserts, and ointments. Incorporation of comfort agents into commercial lenses has been shown to make lenses more comfortable. This has been done by physically sequestering comfort agents within the lenses. Commercial lens product lines, such as Johnson and Johnson® Acuvue lens series and Coopervision's Proclear lenses, have incorporated polyvinyl pyrrilidone (*PVP*) (*MW between 50-100 KDa*) into the lens that does not release. The PVP incorporated in the lens lowers the dehydration rate of the lens. Crosslinked hyaluronic acid (*HA*) networks within lenses can also reduce dehydration and protein adherence to the lens providing dual mechanisms of comfort.

While sequestering comfort agents inside the lens to increase water content of the lenses can promote comfort, controlled release of the comfort agent may offer several advantages. The release of the comfort agent can provide a comfort effect on the surface of the eye away from the lens, refresh the lens surface, and increase the effectiveness of the comfort agent. Released comfort agent mimics delivery from eye drops, but it can occur at a continuous rate, providing similar comfort at lower concentrations taking the dose out of the patient's hands for optimal efficacy and convenience. It is probable that controlled release of comfort agent can provide greater comfort in dry eyes than lenses with sequestered comfort agent.

One of the most promising methods to control the release rate of comfort molecule from lenses has been molecular imprinting. The first controlled release of HA from

molecularly imprinted Nelfilcon A lenses demonstrated release at a relatively constant rate for up 2 days, making them ideal for daily disposable lenses. Molecular imprinting is the creation of macromolecular memory within a polymer network, through the incorporation of functional monomers that non-covalently interact with the template molecule. Self-assembly occurs between the functional monomers (*M*) and the template (*T*) through non-covalent interactions and hydrogen bonding. By rational design of the M/T ratio and the diversity of chemistry, the interactions can be used to bind or delay the release of template molecules.

Other work has included more passive, diffusion-controlled methods of release. CIBA Vision® Focus Dailies® (*Nelfilcon A*) are currently the only comfort molecule eluting lens on the market with a delayed elution rate of PVA for ~15-20 hours from the daily disposable lens. Poly(*HEMA-co-EGDMA*) films released PVP for 2-3 days, with potential use as a daily wear lens. In both of these materials, transport is based solely on network structure and comfort molecule concentration and size. For imprinted systems, release rate can be further tailored by macromolecular memory. Thus, the focus has been on comfort molecule release from traditional hydrogel lens materials which are used for daily wear.

Development of silicone hydrogels allowed the production of continuous, extended wear lenses. Silicone hydrogel lens materials have been approved by the FDA for long durations of wear. For example, Air Optix® NIGHT & DAY® Aqua silicone hydrogel lenses may be worn for up to 30 nights of continuous wear. Extended comfort in these types of lenses is extremely important since they reside on the surface of the eye for long periods of time, and extended comfort molecule release may be the best option for these types of lenses. To achieve 30 day release, application of controlled release methods such

as molecular imprinting will be needed. Molecular imprinting applied to silicone hydrogel contact lenses may lead to delayed release and enhanced comfort molecule loading. In this paper, we present research on the extended wear silicone hydrogel contact lens with controlled release of hydroxypropyl methylcellulose (*HPMC*) using molecular imprinting. HPMC is a common comfort agent and rheology modifier used in over the counter eye drops.

There has been very little work highlighting the release of comfort molecules from silicon hydrogel lenses. Previous work involving silicone hydrogel lenses has not demonstrated significant loading or extended release of comfort agents. Soaking a variety of both silicone hydrogels and hydrogel commercial contact lenses in a HA solution did not load sufficient amounts of HA and release was complete in well under an hour. Work with much lower molecular weight molecules showed release was generally quick with the majority (*i.e., 60-80%*) of the loaded molecules eluting within 1 hour or within 3-4 days.

6.3. Engineering Lotrafilcon B Silicone Hydrogel Material For The Continuous And Extended Release Of A Macromolecular Comfort Agent

This project started as a collaboration with CIBA Vision®, Inc to incorporate and control the release rate of a macromolecular polysaccharide comfort agent to alleviate sensations of contact lens associated discomfort (*CLAD*) and contact lens induced dry eye (*CLIDE*) for one of the flagship silicone hydrogel lens materials. Silicone hydrogels are complex, biphasic materials that are very sensitive to any deviation from the base formulation. As a result, it is difficult to incorporate any therapeutically relevant of a free comfort molecule. Additionally, incorporating any effective intelligent drug release is very difficult without compromising important physical properties of the contact lens. The

specific aim of the collaboration was to engineer the LFB lenses to controllably release a specific comfort agent macromolecule at measurable mass rate for the entire duration of lens wear: 30 days. Given previous success controlling the release of hyaluronic acid (*HA*) from a hydrophilic contact lens, it was hypothesized that the most promising method to attain the desired goal was the incorporation of molecular imprinting into the hydrophilic phase of the LFB lenses.

6.3.1. Description Of Lotrafilcon B Silicone Hydrogel Material

Lotrafilcon B (*LFB*) is a patented contact lens material used in CIBA Vision, Inc. lens brands, such as Air Optix® and others. The material is a mixture of the proprietary silicone hydrogel macromer, Betacon Macromer, referred to hereafter as macromer, methacryloxypropyl-tris-(trimethylsiloxy) silane (*TRIS*), and dimethyl acrylamide (*DMA*). The thickness of the commercial LFB lens varies depending on the power of the lens, but can be approximated as 100 µm center (*swollen*) thickness. The water content of the lens is 33%. The low water content and hydrophobic nature of the TRIS and macromer limits the maximum loading and potential comfort agents that can be loaded into the lens. An effective comfort agent must be hydrophilic to provide comfort and sequester water, but an agent displaying too high a preference for water will not disperse into the lens formulation and will not controllably release from the lens. For this reason, hydroxypropyl methylcellulose (*HPMC*) was selected as the most promising comfort agent as it demonstrates a wide range of solubility.

6.3.2. Results And Discussion For Extended Release Of HPMC

Several methods to control comfort agent mass release were used to control the mass elution rate of both HA and HPMC. The methods discussed within this section are

solution-soaked lenses, direct embedding lenses, lenses with higher degrees of crosslinking, and molecularly imprinted lenses. Other methods, such as altering the hydrophobic/hydrophilic co-monomer balance, the addition of a co-solvent or co-solvent blend, the use of emulsifiers or surfactants, etc. were explored in the course of this project as well but are not discussed in this section.

The results of the comfort agent evaluation in **Chapter 3** were used to select hyaluronic acid (*HA*), hydroxypropyl methylcellulose (*HPMC*), and carboxymethylcellulose (*CMC*) as the three primary comfort agents for use in this project as the three most effective comfort agents to promote comfort. Selection of HPMC as the primary comfort agent of interest in this work was made after demonstration that HA and CMC were both incompatible with the LFB formulation. Several diverse molecular weights of HPMC were available for use, but 120 KDa was identified as the ideal molecular weight as higher molecular weights of HPMC did not provide sufficient increases in comfort property contribution to make the corresponding loss of lens physical properties worthwhile.

6.3.2.1. Release From Pre-Fabricated Lenses Soaked In Comfort Agent Solution

The first step of this work was to assess the feasibility of loading HA/HPMC into a pre-fabricated lens. This is the ideal case as it does not affect the synthesis or manufacturing process. However, synthesizing an optically clear lens and soaking the lens in either aqueous solution did not result in a sufficient reservoir of comfort agent loaded into the lens to deliver comfort to the eye. The mass uptake of various masses of the comfort agent from the solutions are presented in **Table 7.2**. Mass loading of the comfort agent was determined via difference in mass uptake. By far, HPMC demonstrated the greatest

loading. Loading of the 120 KDa HPMC did not exceed 0.2 μg/lens after soaking in a solution for a week. The highest loading was seen for 10 KDa HPMC. As the smallest molecular weight, the least resistance is seen to diffusion of HPMC in the lens. Release occurred in less than 30 minutes for the 10 KDa case, and for molecular weights above 10 KDa, very little HPMC release was observed. The loading of 10 and 1800 KDa hyaluronic acid (*HA*) was found be much lower and cannot be confidently said to have loaded any mass of HA at all even after a week of soaking. This was due to high water solubility of hyaluronic acid. When lenses soaked in the HPMC solutions for a week, the lenses were placed in 50 mL of DI water at room temperature (*temperature = 20ºC*), and the mass release profile is shown in **Figure 6.1**. A total of 2.5 μg ± 2 μg of 10 KDa was all that observed to release from the lens. No mass of 90 or 120 KDa HPMC was observed to release. Release of 10 KDa was statistically complete well within 30 mins, essentially within 10 mins.

The values are very low from a drug delivery perspective and indicate that soaked lenses are not a feasible option for the development of therapeutic contact lenses for long chain molecules. The mass loaded into the lens was determined via the mass difference between the dry lens and the saturated, soaked lens. However, this is a very unreliable method and potentially results in very large error for the calculation of loading of macromolecules into the hydrogel materials. Loading of HPMC and other high molecular weight polymers through adsorption is best explained as a thermodynamically unfavorable process. HPMC loaded into the hydrogel network would be more confined and adapt a much different conformation from the HPMC in the surrounding solution. The energy required for high molecular weight molecules to adapt a conformation change at the surface

of the hydrogel and reptate deeply into the lens makes it unfeasible as a loading option. For smaller molecular weight molecules, some loading may be demonstrated for molecules within silicone hydrogel lenses, but release will be short in duration without control leading to a Fickian or exponentially decaying release rate.

6.3.2.2. Release From Direct Embedded Lenses

Dispersing comfort agent into the pre-polymer formulation and synthesizing the lens, referred to hereafter as direct(*ly*) embedded lenses, allowed for a much greater mass loading of comfort agent into the contact lens as compared to the soaked lenses. Hyaluronic acid (*MW = 1800 KDa*) was dispersed into an LFB formulation adjusted to be as hydrophilic as possible. This was the only method found to disperse the HA into the hydrophobic formulation without instantaneous phase separation. Even with this modification to the formulation, phase separation occurred slowly but still within 10 minutes. In addition the synthesized lens was found to be unusable as for clinical application due to its rigidity and was completely opaque (*transmittance ~0%*).

A therapeutically minor mass (*~150 μg HA*) of 1.8 MDa HA was loaded into 500 μm thick lens. When the dry lens was placed into 50 mL of DI water at 20ºC, the mass dispersed within the lens swelled to a much greater extent than the lens and was visibly observed to expand beyond the lens surface. The expansion of the HA when exposed to the release media was very fast and caused physical damage to the rigid lens. The elution of HA was essentially done within 10 mins (***Figure 6.2A***), and the stress induced by the swelling HA chains dispersed with the lens caused catastrophic structural failure of the lens (***Figure 6.2B***). It was decided at this point that incorporating HA into the silicone hydrogel

material for adaption as contact lens materials was impractical and not feasible for the scope of this project and abandoned for the completion of the work.

HPMC of 120 KDa molecular weight was loaded into unaltered LFB formulation in a similar manner as the HA work. A greater mass (*800 μg*) of 120 KDa HPMC was loaded into the formulation, and the formulation was synthesized into different lenses. Release was performed in 250 mL of DI water (*temp = 34ºC*). There was a very high initial rate of mass release during the first 24 hours, where approximately 80% of the loaded mass eluted (***Figure 6.3***). The remaining mass eluted in a somewhat linear, stable manner for the remaining 3-4 days at a rate of approximately 55-40 μg of HPMC/day. Significant impacts on both the optical clarity and qualitative tensile properties were observed.

In addition, separate lens formulations were prepared incorporating HPMC comfort agent of lower molecular weight, specifically 90 and 10 KDa HPMC. It was shown in **Chapter 3** for the first time empirically that lower molecular weight comfort agents do not provide equivalent contributions to sensations of comfort as higher species of the same comfort agent. In fact, the contributions of 120 KDa HPMC and 90 KDa are 1100% and 800% greater than the contribution of 10 KDa HPMC, respectively. The hypothesis suggested that a higher mass loading of lower molecular weight HPMC could be achieved within the lens with a reduced detrimental impact on the optical clarity and tensile modulus. The maximum mass loading of 120 KDa HPMC while maintaining appropriate optical clarity levels was found to be 1000 μg/lens. It was found that the maximum mass loading of 90 and 10 KDa HPMC before optical clarity dropped below minimum levels was higher and found to be 1500 μg and 4000 μg/lens, respectively. A series of lenses incorporating 90 KDa and 10 KDa at a concentration of 800 μg/lens were synthesized to compare the

control over the mass release rate (***Figure 6.3***). The rate of release of 90 KDa HPMC was found to be statistically identical to the release rate of 120 KDa. The rate of release of 10 KDa was found be faster (*~700 μg/day*), achieving complete release approximately within a day. This is appropriate as 10 KDa HPMC would adapt a much smaller compact and linear conformation within the lens and be less likely to encounter local steric hindrances that would delay the larger Gaussian coil conformation that 120 KDa HPMC adapts.

A disperse mixture of 10, 90, and 120 KDa HPMC were incorporated to a LFB silicone hydrogel contact lens simultaneously. It was hypothesized that the presence of the larger volume 120 KDa HPMC would serve as diffusion barriers for the lower molecular weight comfort agents. The mass loaded of each species was 800 μg/lens. The mass release profile is shown in **Figure 6.4**. The release of 10 KDa HPMC was not statistically significant or not affected at all.

It was made clear through experimentation that this method of controlling HPMC release was insufficient to attain a tailorable release rate for the full 30 day duration of wear. In addition, the silicone hydrogel contact lens material is highly complex and sensitive to alteration and incorporation of the comfort agent. Including a therapeutically significant reservoir of comfort agent within the bulk of the contact lens result resulted in devastating drops in both the optical clarity and tensile modulus of the lenses. It was decided that the formulation and resulting polymer matrix had to be adjusted to incorporate crosslinking co-monomers or new chemistries in order to achieve the desired result.

6.3.2.3. Release From Crosslinked Lenses

The release duration of HPMC was also affected by adding the additional crosslinking molecules to the formulation as expected. The presence of crosslinkers

resulted in significant improvements in lens clarity and reduced swelling, but insufficient control over the mass release duration was not demonstrated to control HPMC mass release for 30 days. By increasing the crosslinking monomer to template mass ratio (*xLer/T*) (*shown in* ***Figure 6.5*****)**, the initial rate of HPMC mass release is delayed by the decreased mesh size. As the percentage of crosslinker is increased, the initial mass release rate (*mass release <10-15%*) is decreased. However, once approximately 10 mass percent of the HPMC reservoir within the lens was released from the lens, the release rate increased, and the balance of the reservoir is completely release over the next 4-7 days regardless of the xLer/T mass ratio. After the initial delay, no statistically significant control over HPMC release mass was observed.

The addition of the crosslinking molecules greatly increased the tensile modulus beyond the practical application of the material as contact lenses. This is a common problem when trying to control the release of free molecules within the lens by increasing the number of steric barriers and crosslinks. This has been documented in other work in our lab and significant discussion of the penalty paid for control of the mass release rate by sacrificing desirable contact lens physical properties.

6.3.2.4. Release From Molecularly Imprinted Lenses

Figure 6.6 demonstrates the varied release rates that can be designed by altering the functional monomer to template (*M/T*) ratio. Increasing the M/T ratio decreases the release rate and extended the time to complete release from ~2 days (*85% in less than 1 day, control, non-imprinted, no additional crosslinker*) to 50 days (*imprinted lens with M/T ratio of 3.4 containing additional crosslinker*). It is important to note that the delayed release was not due to the additional crosslinking within the lens. A non-imprinted lens

with additional crosslinker released all HPMC in less than 10 days. For all lenses with additional crosslinker, the crosslinking content was kept approximately constant and the release was significantly decreased as M/T ratio increased. In perfect sink environment, the longest releasing lenses delivered ~60 μg HPMC/day for 50 days. In **Figure 6.7**, the average daily mass release rate for diverse M/T ratios is demonstrated showing that there is an optimal M/T value to control the rate of release of 120 KDa HPMC from the contact lens. Both the mass release rate and the variance beyond that value increases are seen to increase drastically in a manner highly consistent with molecularly imprinting.

One of the traditional ways of demonstrating molecular imprinting is by reloading the template and demonstrating enhanced loading over control polymers. However, given the very high molecular weight of our template molecule (*HPMC*), this is not a feasible method as all binding will be on the surface of the lens, and the template will not enter the bulk structure. In other work, delayed release of high molecular weight hyaluronic acid was significantly improved through the use of multiple functional monomers, highlighting a synergy between the imprinting monomers providing controlled release. With the significant dependence of release on M/T ratio at low amounts of functional monomer, we hypothesize that molecular imprinting, and not random hydrogen bonding, is the primary reason for the decreased transport observed.

To match commercially available silicone hydrogel lens thicknesses, it was necessary to reduce the swollen lens thickness to 100 μm. In addition, it was desirable to reduce thickness to potentially increase the clarity of the lenses. However, decreasing thickness will reduce the HPMC content and increase the release rate. It is well understood that release rate will be proportional to the thickness and that thinner lenses will have an

increased rate of release compared to a thicker lenses. It was found that decreasing the thickness limited the loading of HPMC to ~1000 μg/lens. Optical clarity was measured on 100 μm thick lenses at various M/T and xLer/T weight ratios (**Figure 6.8**). **Figure 6.8** demonstrates to maintain greater than 90% transmittance, which is an acceptable commercial optical clarity value, the design variables xLer/T and M/T must stay between 1.0 and 3.5 and 3 and 6, respectively. Therefore, lenses can be produced with therapeutic amounts of HPMC with high optical clarity for commercial use as contact lenses. These lenses also have a water uptake of ~30%.

6.3.2.5. Microfluidic Device Release

The next step of this work was to perform a dynamic release study on the thin lenses as is shown in **Figure 6.9**. Imprinted lenses were formulated to xLer/T of 1.5 and M/T of 3.5 and a HPMC content of 1,050 μg/lens. This is the same lens composition as the lens exhibiting a 52 day HPMC release duration in **Figure 6.6**, except it contained a third of the HPMC (*i.e., an equivalent xLer/T and M/T ratio*). In addition, release of 120 KDa HPMC was demonstrated for the unaltered LFB formulation, M/T ~ 0.5, M/T ~ 1, and M/T ~2. The mass release profiles for each release curve are approximately linear.

HPMC release from the thin lens in a perfect sink environment reached completion in 10-12 days. However, the perfect sink model is the fastest possible release, and release in the eye will be slowed due to the reduced sink and physiological conditions. Within an ocular flow rate, the thin lens released HPMC at a linear rate of ~16 μg HPMC/day for 60 days (***Figure 6.9***). The microfluidic device pioneered by our laboratory models the physiological flow rate of the eye (*i.e., 3 μL/min*) and was used to more accurately predict the *in vivo* lens release profile.

6.3.2.5. Correlating Release Rate To Comfort

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% comfort agent concentration*). Drops are applied as needed, and 20 drops a day yields a delivered mass 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®, El Monte, CA*) 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 cumulative mass delivered from the eye drops is 1000 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 alleviate CLIDE symptoms.

Using the concept of comfort property contribution (*CPC*) as described in **Chapter 4**, it is possible to compare the theoretical comfort contribution of ocular tear fluid concentrations of different comfort species using the derived residence time relationships with comfort agent species, comfort agent molecular weight, and solution concentration in addition to the comfort index values presented in **Chapter 4**.

6.4. Engineering Polydimethylsiloxane Silicone Hydrogel Materials For The Release Of A Macromolecular Comfort Agent From A Daily Disposable, 24 Hour Wear Contact Lens

It was discussed previously that adapting the technology used to control the rate of HPMC release from the LFB material to silicone hydrogels prepared with a relatively simpler telechelic PDMS-macromer rather the complex functionalities found within the LFB Betacon Macromer would be of special interest and a valuable demonstration of the versatility and high value the principles of the molecular imprinting to all commercial silicone hydrogel lens materials. Also, recent trends within the lens market has shown a consumer preference for the daily disposable lens technologies, and user surveys consistently rank these lens modalities as more comfortable than the extended wear lenses.

A series of experiments were conducted varying the silicone macromer among a group of 5 diverse silicone macromers. The 5 selected silicone macromers were used to create HPMC-imprinted silicone hydrogel contact lenses, and the mass release of 120 KDa HPMC was measured at the same M/T values. The HPMC release profiles from each series of imprinted lenses were used to assess any potential relationship between the nature of the macromer used in the synthesis of the lens and the corresponding release rate. In addition, physical properties of each series of lens (*such as optical clarity, tensile modulus, surface tension, etc*) were correlated with the polymer morphology and average phase diameter to provide a fundamental understanding of the relationship between the phase distribution and the properties of the lens materials.

After the successful demonstration of the extended release of 120 KDa HPMC from imprinted LFB lenses over a broad and tailorable period of wear, it was desirable to

evaluate the ability of molecular imprinting and the engineered LFB lenses to control the release rate of HPMC in different release media, different lens wear modalities, and from different material platforms. For the engineered lens, the most important demonstration was that the release rate would remain consistent when release was performed in both DI water as was shown in **Figure 6.10** and in release media containing salts and other ions that can interfere with the formation, duration, and strength of hydrogen bonds and other non-covalent interactions and can cause microscopic changes in the lens morphology, particularly at the surface of the lens.

This effect of salts and ions on the release rate from contact lenses has been documented both in previous works published by the Byrne lab and by others in the field. However, the presence of salts within the release media can have unpredictable, but potentially enormous, impacts on the release rates of template molecules from the paired lens material. One particularly notable example is the release of diclofenac sodium (*DS*) from imprinted hydrogel contact lens materials. In the work, a high degree of control over the release of DS was demonstrated by altering the molar M/T ratio for select imprinted systems when release was performed in DI water, but when imprinted and the control lenses were placed in salt/ion solutions, no statistically significant difference was observed in the mass release profiles. The presence of the salts and other ions disrupted the interactions between the template and the high affinity site, eliminating all control over the template mass release rate. However, this was not the case for the release of dexamethasone from similarly engineered PDMS-based silicone hydrogels. The presence of ions and salts and other molecules did not affect the release rate to any noticeable degree. Similarly, the

elution of HA from imprinted contact lenses showed very minor effects from the presence of the salts in the release media and was easily compensated for by tailoring the M/T ratio.

Given the diversity of responses and the importance that the controlled release mechanism work in salt solutions (*such as the lacrimal tear film*), it is important that the release of HPMC from an imprinted lens is demonstrated in both DI water and salt solutions. It is hypothesized that the low water content of the silicone hydrogel lenses (*which results in a very low uptake of salt into the bulk of the lens material*), the high molecular weight of the HPMC as template (*which potentially allows the template HPMC to interact with more than one high affinity binding sites simultaneously*), and the non-ionic functional groups present on the template macromolecule (*ionic functional groups are orders of magnitude more probable to demonstrate any significant change in behavior due to the presence of ions than are non-ionic functional groups*) result in no noticeable effect in the mass release profiles. As there is no significant difference in the mass release profiles over the 7 day long period between any of the release media, the majority of release demonstrations that follow will be performed in DI water to maintain consistency with previous work.

In addition, current trends in the lens field demonstrate that daily disposable lenses are quickly becoming the consumer preferred modality due to the higher comfort experienced by the user. Therefore, it is highly desirable that the technology developed with the LFB system be adapted to a silicone hydrogel daily disposable system and engineered to demonstrate similar levels of control. Closer examination of the LFB data presented in **Figure 6.6** shows that there was very little control over the release of HPMC within the first 24-48 hours of release, and very similar mass was released during the 1st 24

hours. At the time, this was not a matter of concern as the desired release duration was well in excess of 24 hours. However, it was hypothesized that the high molecular weight between crosslinks prevented significant levels of control over the mass release rate within the first 24 hours and that this effect could be overcome by incorporating lower molecular weight macromers.

One major benefit of the decision to use lower molecular weight macromers was to demonstrate the versatility of molecular imprinting amid diverse silicone hydrogel materials. **Section 6.3** described the extended release of HPMC from a complex commercial silicone hydrogel material. These results were highly successful and important to the field. However, Lotrafilcon B (*LFB*) is a very complex, very specific, highly individualized material. The PDMS-based Betacon macromer is the key component of the lens material. In fact, the primary difference between all of the current commercially available silicone hydrogel lens materials in the US is the silicone macromer. Each of the silicone macromers are highly specific and individualized, incorporating numerous types of functional groups, are formulated to diverse molecular weight, etc, but each of the macromers, regardless of manufacturer, is still based upon a single root material, specifically, PDMS. If an intelligent drug delivery mechanism was adapted to a specific commercial lens material, there would be significant potential difficulties translating the technology between such highly diverse materials. However, it would be much simpler task if the controlled release mechanism was adapted to a common ancestor-type material and then engineered into the more complex materials.

It could be argued that the versatility of imprinting comfort agents can be inferred that it was effectively and successfully incorporated into such a specialized silicone

hydrogel. If a system can be incorporated into such a difficult and complex material, logically a simpler, less specific material would be easily engineered to include the release mechanism. Aside from the fact that a demonstration is usually more valuable than the same inference, in this sense, describing the telechelic PDMS-based silicone macromers as simper macromers refers to the relative homogeneity of structure and uniformity of functionality and inter-molecular forces, etc the macromer exerts on the surrounding chemical environment. It is not to imply that complex network structures cannot be formed, etc. In fact, relatively small changes in the reactive end groups, molecular weight, or average functionality of a given PDMS-based macromers can result in significant differences in the reactivity and conformation of the macromer and, thus, of the morphology of the crosslinked polymer three dimensional network.

In addition to the LFB macromer received from CIBA Vision® (*Atlanta, GA*), four simple PDMS, telechelic macromers were purchased from Gelest® (*Morrisville, PA*). The macromers were of various molecular weights. Two (*DMS-V08 and DMS-V21*) were vinyl-terminated, or divinyl functional crosslinkers. The remaining two (*DMS-R11 and DMS-R18*) were methacryloxypropyl-terminated. The major distinction between the end groups is the relative reactivity of the carbon-carbon double bond toward a propagating radical. Acryloxypropyl-terminated macromers are readily polymerized via radical chemistry and are easily polymerized via photopolymerization chemistry and kinetics (*complete conversion is attained within 2 minutes*). The vinyl-terminated macromers are less reactive and cannot be polymerized via photopolymerization methods. Instead, a peroxide-based catalyst must be used and cured under much slower thermal-based initiation and propagation kinetics (*gelation and complete conversion is completed in 1-6 hours*).

7.4.1. Release Of 120 KDa HPMC In DI Water

DMS-R11 and DMS-R18 macromers were used at similar ranges as the LFB Betacon macromer in their respective formulations. The Betacon macromer had a molecular weight of 7 to 9 KDa. This is significantly greater than either the DMS-R11 and DMS-R18 macromers, which possess an average molecular weight of approximately 1 and 5 KDa, respectively. Formulations including the DMS-R11 macromer were created at various M/T ratios in accordance to molecular imprinting principles as discussed in previous sections. Release was performed in a large volume of release media within the Sotax Dissolution Apparatus under the same conditions used for the release of HPMC from LFB lenses. The lenses were tested for both modules of lens wear: daily disposable (*high degree of control of the release rate for the first 24 hours*) and extended continuous wear (*high degree of control over the release rate for a full 30 days*). The results of these studies performed in DI Water can be seen in **Figures 6.11** and **6.12**, respectively. As can be seen, the extended release is statistically similar to the extended release from LFB lenses shown in **Figure 6.6**. There was no measurable difference in HPMC loading or optical clarity between the DMS-R11 lenses and LFB lenses.

6.4.2. Release Of 120 KDa HPMC In Artificial Lacrimal Fluid, Saline Solution, And Phosphate-Buffered Saline Solution

Additionally, it was highly desirable to determine the effect that different release media would have on the effectiveness of the molecularly imprinted memory sites. Other work has shown that certain controlled release mechanisms particularly those that rely on non-covalent or ionic interactions are particularly susceptible to the presence of salts and other molecules commonly found within the tear film. Overall, the hydrophobic nature of

silicone hydrogel materials prevent any significant mass uptake of salts into the bulk of the lens where it would have the potential to interfere with high affinity interactions between comfort molecules and the respective memory sites or disrupt the formation of hydrogen bonds that are vital to the effectiveness of molecular imprinting principles to control the release rate of the template molecule.

To this end, the lens release experiments were repeated with the same lens formulations as in DI water, but the artificial lacrimal fluid (*ALF*), 0.9% sterile saline solutions (*0.9% NaCl*), 5% sterile saline solutions (*5% NaCl*), and phosphate-buffered saline (*PBS*) solutions were chosen in turn to act as the release media intern. The ALS solution had a greater diversity of specific salt ions than the other solutions, but the overall concentration of salt in the other solutions, particularly the 5% NaCl solution was greater than the ALS salt content, providing a more stringent test condition. As can be seen **Figure 6.13**, the presence of the salt ions in the release media had no noticeable effect on the release rate of HPMC. Though this effect was not unexpected, it could easily be a special case arising from the high molecular weight of the template molecule allowing HPMC to interact with several macromolecular memory sites simultaneously and encountering a greater number of steric obstacles and interferences to the reptation and diffusion of the comfort agent from the lens material that are not experienced by smaller template molecules.

In short, though the data in **Figures 6.13** was found to support our hypothesis, it is not conclusive as, though no interference was detected from the presence of the salt in the release media, the extreme molecular weight of the template molecule could have masked a potentially significant effect on the strength, duration, and occurrence of hydrogen bonds

between the HPMC chain and the functional monomers incorporated into the polymer network due to normal, passive diffusion barriers. This effect if present would be detrimental to the controlled release of low molecular weight template molecules.

6.5. Structure And Property Relationship

A basic physical characterization of the LFB contact lenses was performed by measurement of lens swelling when the dry lenses were placed to water, through evaluation of the percent transmittance of visible light through the synthesized lens, and by calculation of the tensile modulus of the engineered lenses. These three essential test represent a robust general characterization of the lenses and are absolutely necessary if the produced lenses are to be shown to be viable as a commercial products, but they are not sufficient for full characterization. More intensive set of test are performed later in this chapter to fully characterize the physical and surface properties of each produced lenses.

In general, the incorporation of HPMC into LFB lenses resulted in drastic decreases in each of the 3 evaluated properties, well below the minimal acceptable levels for use as commercial products. However, it was seen that by applying the principles of molecular imprinting to the lens formulations containing 120 KDa HPMC reduced the detrimental effect of incorporating the comfort agent. This trend is most readily observable in the evaluation of optical clarity of the HPMC-containing lenses. It was initially hypothesized that the incorporation of the functional monomers necessary for imprinting strategies helped solubilize and disperse the HPMC within the lens and prevent instances of high local swelling, which would reduce the lens clarity. However, the demonstration of similar trends in the evaluation of tensile moduli values and the occurrence of lens swelling in water indicate that a more subtle and significant structure property relationship is occurring

within the polymer matrix. However, other than the qualitative demonstration that imprinting improved the performance of the lenses in all 3 properties, this structure property relationship was not fully investigated within the LFB series, but is fully vetted in a later section of this chapter. The behavior between the tensile modulus, lens clarity, and lens swelling and the extent of molecular imprinting to the specific lens formulation is described below.

6.5.1. LFB Lens Modulus Measurements

Modulus values were also determined, which depended strongly on the xLer/T ratio. Modulus values for the lenses were as follows: (*i*) LFB lenses: 1.48±0.25 MPa, (*ii*) LFB lenses prepared with additional crosslinkers and no HPMC (*equivalent amount of crosslinker*):12±9 MPa and (*iii*) LFB lenses with additional crosslinkers (*xLer/T 1.5*) and 1000 μg HPMC/lens: 8.9±4.3 MPa. As expected, the modulus of the crosslinked lenses increased with additional crosslinking content and decreased when HPMC was added. The modulus can be reduced by small decreases in xLer/T, and small variations in M/T ratio and xLer/T will lead to large variations in release rate, while still producing an optically clear lens. A decrease in M/T and xLer/T will increase the release rate, and an increase in both of these parameters will decrease the release rate.

6.5.2. Optical Clarity Of HPMC-Laden LFB Lenses At Various M/T And xLer/T Ratios

Optical clarity of the produced lenses were evaluated by measuring the percent transmittance of visible light through the lenses. Measurements of purchased commercially available contact lenses were used to identified the minimum optical clarity necessary for contact lens use. Statistical evaluation of the sample results produced an estimate of 80%

transmittance for the entire visible light spectrum. In most lenses, the transmittance of visible light is greatest for the longer wavelengths, approaching near 100% transmission. Exponentially greater levels of absorbance occur in the blue range of light and are of special concern for optical clarity testing. Transmittance levels can be high, yet the polymer may not be optically clear, exhibiting significant levels of haze. This is due to the tendency of the low wavelengths of light to diffract through the polymer and appear white or cloudy. Haze proved to be a significant problem throughout the project, and was managed in a similar manner as controlling the optical clarity and transmittance.

When incorporating 120 KDa HPMC into the LFB lenses, significant losses of optical clarity were observed even at minimal HPMC content. For example, incorporating 250 μg of 120 KDa HPMC into the LFB contact lenses lowered the percent transmission to below 50%. A LFB lens with the full 1000 μg 120 KDa HPMC loaded into the lens resulted in a drop in clarity of about 80-90%. It was evident that to maintain sufficient levels of optical clarity that the LFB formulation would have to be altered. Various carriers and emulsions were used to minimize the detrimental effect of the 120 KDa HPMC on the ocular clarity of the lenses, but proved to inadequate to properly control the effect. 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.

Additional crosslinking monomers were selected to reduce the swelling of the HPMC-laden contact lenses and added to the pre-polymer lens formulations that would act

as physicals limitations and prevent the polymer network from expanding. Several crosslinking monomers of various molecular weight and concentration were added to the LFB formulation. The presence of crosslinkers in the lens led to significant improvements in clarity, but increased the tensile modulus well beyond the useable limitations. In addition, as discussed in a previous section, the use of crosslinking monomers failed to provide the desired tailorable control over the release rate. To control the release rate, the principle of molecular imprinting was applied, and two design variables (*xLer/T and M/T*) were adjusted to engineer the lens as necessary to attain the appropriate release rates. By adding the functional monomer, acrylic acid (*AA*), improvements in optical clarity were observed. A full factorial design of experiments was employed to investigate the relationship between the lens optical clarity and the two design variables. The results of this study is shown in **Figure 6.8**. The interplay of the two design variables was first hypothesized to increase clarity by dispersing the HPMC within the bulk of the lens. However, similar relationships demonstrated between the swelling of the lens and the tensile modulus seemed to indicate a more complex structural effect.

6.5.3. Swelling Of HPMC-Laden LFB Contact Lenses In Water

Substantial amounts of swelling were seen when incorporating HPMC into the LFB lenses. The only crosslinking monomer in the unaltered LFB formulation is the Betacon Macromer, which is very long. When the HPMC-laden LFB lenses are placed in water, the 120 KDa HPMC absorbs significant mass of water and increases in volume, attaining a large Gaussian coil. This expansion results in the elongation of the macromer, which can expand up to 4-10 times. When 700 μg of HPMC was incorporated into the LFB formulation, the volume of the hydrated lens increased by a factor of 8.5 over the dry lens

volume. The addition of crosslinking monomers to the formulation greatly restricted the lens swelling as predicted. The equilibrium weight swelling ratio was significantly reduced from 8.5 to 1.4 for lenses (*700 μg HPMC/lens*). The swelling ratio for the HPMC-imprinted lenses were seen to swell to a very minor degree between 1 and 1.1.

6.6. Incorporating Trehalose Into Lens For Controlled Release of Both

Hydroxypropyl methylcellulose is an effective ocular comfort agent where the primary mechanism of action for comfort contribution is the increase in tear solution viscosity due to the presence of the HPMC, and secondly, the relatively mild water retention properties of each chain. The HPMC comfort agent is particularly effective combating the propagators of lens discomfort when incorporated into the bulk of the lens by reducing the rate and mass of protein adhesion, the rate of lens dehydration, and increase the wetting of the lens surface. These are major propagators of discomfort and are the predominant causes of discomfort at the end of the day/wear. However, HPMC provides little additional comfort at the beginning of wear, making HPMC more effective at providing comfort as lens wear continues beyond the first 6 hours of wear. Moreover, other comfort agents are more effective in the retention of water than HPMC. This is important for initial wear period where the loss of tear fluid/water volume is the predominant propagator of discomfort at the initiation of lens wear.

For this reason, it was desirable to engineer the HPMC-eluting lens to include an additional comfort agent into the contact lens for release during the first 4-8 hours of lens wear to ensure high initial levels of comfort. The molecule selected for this purpose was the disaccharide trehalose. Trehalose has well documented water retention properties. The water retention of dry, powdered trehalose was measured in the same matter as the

macromolecular comfort agents in **Chapter 4**. The water retention properties of trehalose were found to be extremely high for the small molecule, binding 28 water molecules per trehalose molecule. This value is similar to those found for low molecular weight hyaluronic acid. The trehalose had minimal effect on the other comfort properties investigated. The comfort index for trehalose was found to be 98, primarily to the high water retention value. However, this is desirable as an initial wear comfort agent.

It was found that trehalose dihydrate was completely insoluble in the DMS-R11 silicone hydrogel contact lens formulation. It was decided that the presence of water was causing the incompatibility with the hydrophobic formulation solution. The trehalose dehydrate was dried in an oven for 24 hours at 34ºC to remove the water content from the powder. The dry trehalose was still incompatible with the lens pre-polymer solution. Trehalose displayed minimal solubility until glacial acetic acid was added as a co-solvent to 10 mass percent of the formulation. With the addition of the acetic acid, the dried trehalose was almost instantly dispersed into the lens pre-polymer formulation to high concentrations. Optically clear lenses containing 500 μg trehalose were then synthesized in the same matter as the HPMC lenses, and the lenses were placed in the oven overnight at 30ºC to remove the ethanol and acetic acid from the cured lens. The high compatibility between acetic acid and trehalose indicated that a high affinity would be demonstrated between the template trehalose and the functional monomer, acrylic acid (*AA*).

Trehalose release was performed first in a static sink volume of 250 mL of DI water and then repeated in a second static sink volume of 250 mL 0.9% sterile saline solution. Trehalose concentration in the release media was determined via a colorimetric assay. It was found in the large volume, static sink that the duration of mass release was very short

in the control lens, i.e. less than 10 mins. However, by altering the ratio of acrylic acid to trehalose ($M_{Acrylic\ Acid}/T_{Trehalose}$) from 0 up to 8, the release duration was extended from 10-30 mins up to 6-8 hours (***Figure 6.14***). No statistical difference was observed between the release rate measured in either release media, DI water or saline solution (***Figure 6.15***). After this demonstration and a similar demonstration in the release of hydroxypropyl methylcellulose earlier in **Chapter 6**, sufficient support for the hypothesis that the effect of the salt ions present in the release media was found that no further release studies were performed in the saline solution.

Release of trehalose was also measured in a small volume, continuous flow sink model. The trehalose mass release was not affected by the different sink conditions (***Figure 6.16***). This was unexpected, but this effect is easily understood by the solubility of trehalose in water. Trehalose is practically infinitely soluble in DI water. The microfluidic device has a steady state release media reservoir of approximately 200 μL. If the trehalose –eluting lens was continuously exposed to a fresh release media, the concentration driving force is infinitely high and remains unchanged. Once the eluting molecule achieves a measurable concentration in the release media, the driving force can be greatly reduced. However, the high solubility of trehalose allows the driving force to remain high and relatively unchanged. As a result, the release rate measured in the large volume, static sink is statistically the same as that measured in the small volume, continuous flow sink model. This observation is unique to highly soluble molecules. The release rate of a hydrophobic molecule would be very different in the two models, i.e. initially a faster but gradually decreasing mass release rate would be seen in the large volume, static sink than the slow,

but relatively linear and constant release rate found in the small volume, continuous flow sink.

Optically clear lenses were synthesized containing both 500 μg 120 KDa HPMC and 500 μg trehalose. The primary propagator of discomfort with initial lens wear is the sensation of dryness and disturbance the tear film and tear volume. Trehalose has extremely high water binding property for its relative molecular weight. After the first 6-10 hours, other propagators of discomfort like protein and lipid adhesion to the surface of the lens become the dominant propagators of discomfort. It was hypothesized that the short release rate of the trehalose would provide high initial comfort early in lens wear when the sensation of dryness is predominant. After the release of trehalose is complete, significant mass of HPMC is still releasing providing relief from major propagators. It is hypothesized that release of multiple molecules simultaneously is the most promising method to ensure high comfort for the full duration of lens wear.

6.7. Release Of A Cocktail Of Comfort Molecules

Simultaneous release of both comfort agents was measured in 250 mL of DI water. It was found that the presence of the large volume of HPMC in the bulk of the lens formulation helped reduce the rate of trehalose mass release slightly and extended the release duration by 1-2 hours (***Figure 6.17***). The size of the HPMC served as a steric hindrance for the transport of the trehalose, but trehalose is of insufficient molecular weight to effect the release of HPMC. In addition, hydrophobic molecules were added to the lens formulation that would reside in the hydrophobic sections of the contact lens material. The hydrophobic molecules were selected to alleviate other propagators of discomfort. The first cocktail of molecules for the combination release devices were 120 KDa HPMC, trehalose,

prednisolone, and ibuprofen (***Figure 6.18***) and a second group of 120 KDa HPMC, trehalose, aspirin, and chloramphenicol (***Figure 6.19***) were chosen to show the diversity of the engineered technology.

6.8. Conclusions

The release of comfort molecules is the most promising method to ensure high comfort during contact lens wear. For this purpose, novel lens technologies were developed for the controlled delivery of 120 KDa HPMC from both extended and daily wear contact lenses. With the high level of control over the mass release rate demonstrated through the application of molecular imprinting, it was decided that while HPMC is a superior comfort agent for the relief of the predominant propagators of end of wear, HPMC contributes little comfort for the primary propagators of discomfort experienced during the initial stages of lens wear such as foreign body response and sensations of dryness. As such, additional comfort molecules were selected and incorporated into the lenses to address multiple propagators of discomfort. The two groups of molecules were 120 KDa HPMC, trehalose, prednisolone, and ibuprofen and 120 KDa HPMC, trehalose, aspirin, and chloramphenicol. This technology is a major breakthrough for the field as no other report has shown release of this number and diversity of comfort molecules.

6.9. Tables

Table 6.1. Theoretical Mass Loading And Release Time Of Untinted LFB Lenses Soaked In Aqueous 0.1, 1, 10 Wt% Solutions Of Various Comfort Agents

Comfort Agent		Theoretical Mass Loaded From Drug Solutions (mg/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	0.01	0.2	0.1	0.4	0.7	0.6	0.01	0.02	0.04	None Detected
	1800 KDa	0.01	0.09	0.01	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	0	0	0.08	0.04	0.01	0.01	0.2	0.1	None Detected
PVA	500 KDa	0.02	0.01	0.01	0.04	0.06	0	0.01	0.09	0.04	None Detected

6.10. Figures

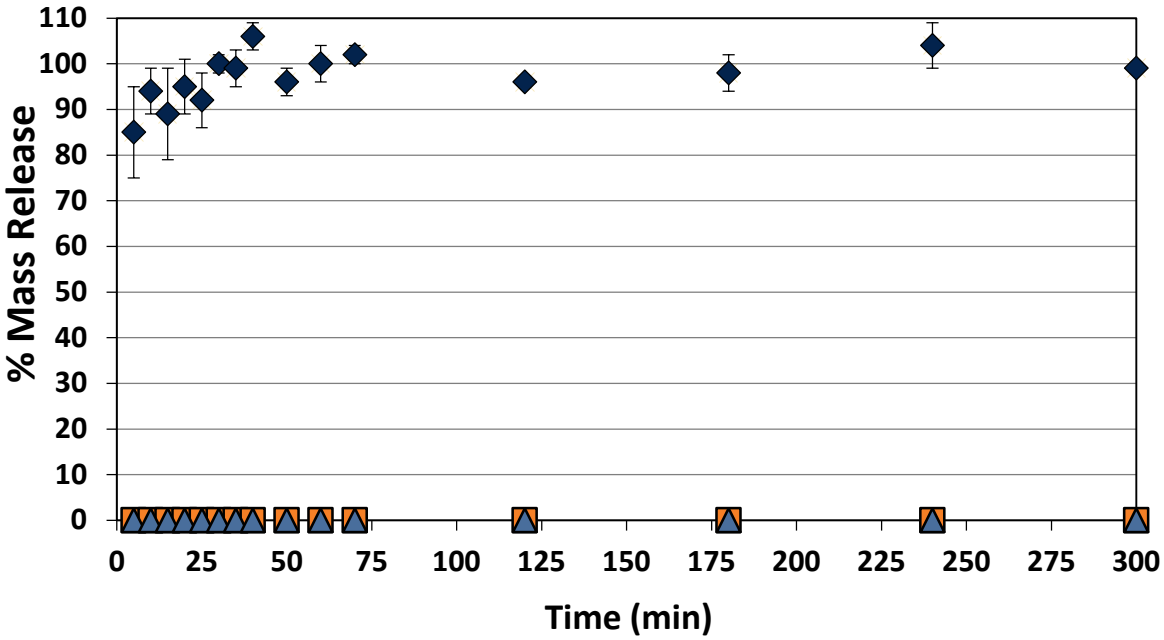
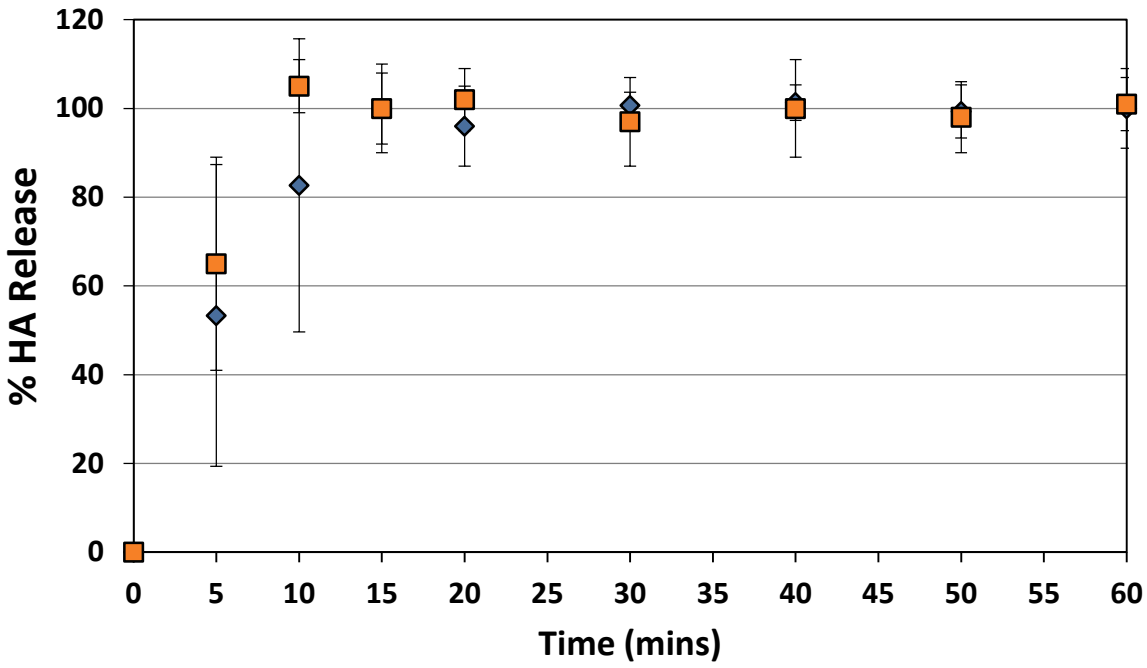


Figure 6.1. HPMC Soaked LFB Lenses: Release From LFB Lenses After Soaking 7 Days In 1 Wt% HPMC Solutions

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.

A.


120
100
80
60
40
20
0
% HA Release
0
5
10
15
20
25
30
35
40
45
50
55
60
Time (mins)

B.

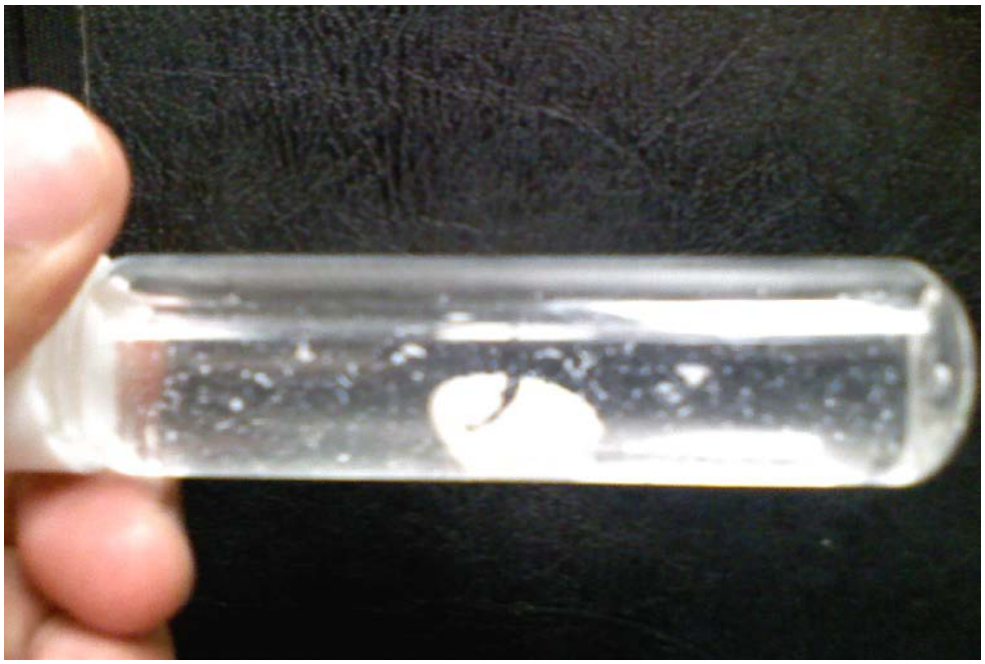


Figure 6.2. Release Of HA From LFB Networks Synthesized With HA

Hyaluronic acid of 1800 KDa molecular weight 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 (7.2A). Both the film and the lens sample were completely opaque. The expansion of HA while hydration occurred and the violent kinetics of release caused catastrophic physical damage to the lens as demonstrated by the crack in the lens shown in Figure 7.2B.

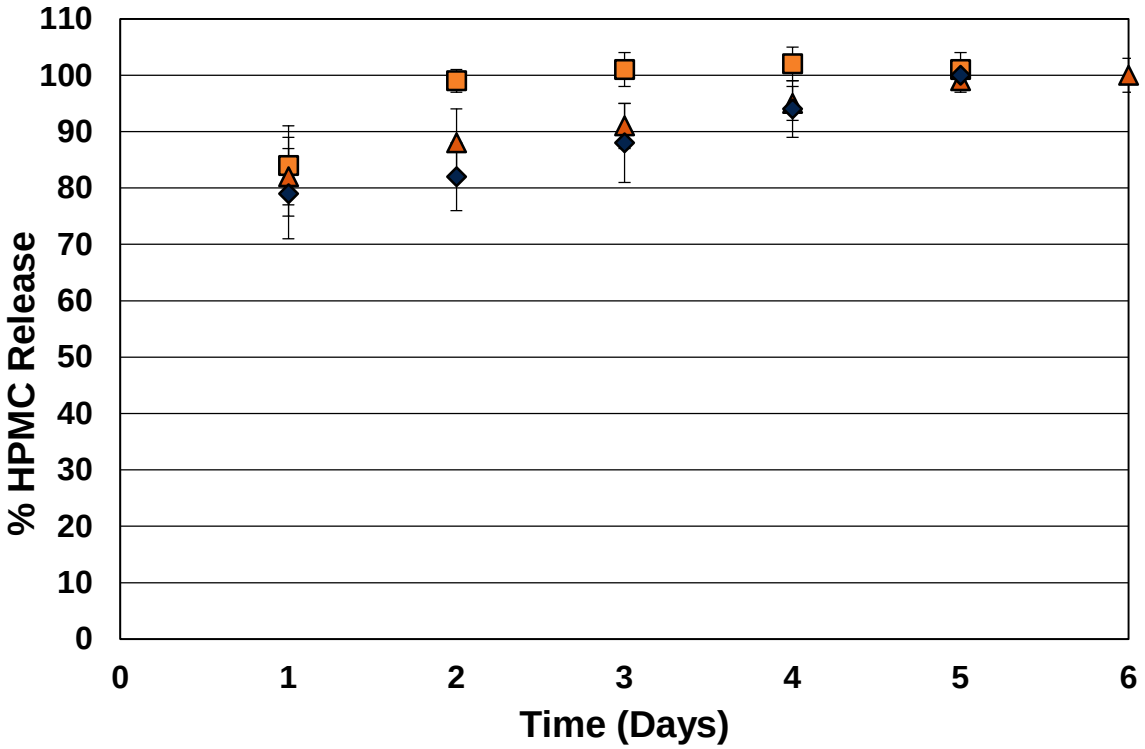


Figure 6.3. Release Of 10 KDa, 90 KDa, And 120 KDa HPMC From CIBA Vision® LFB Control Lenses

Release of 800 µg of 120 KDa HPMC from (◆) CIBA Vision's 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*).

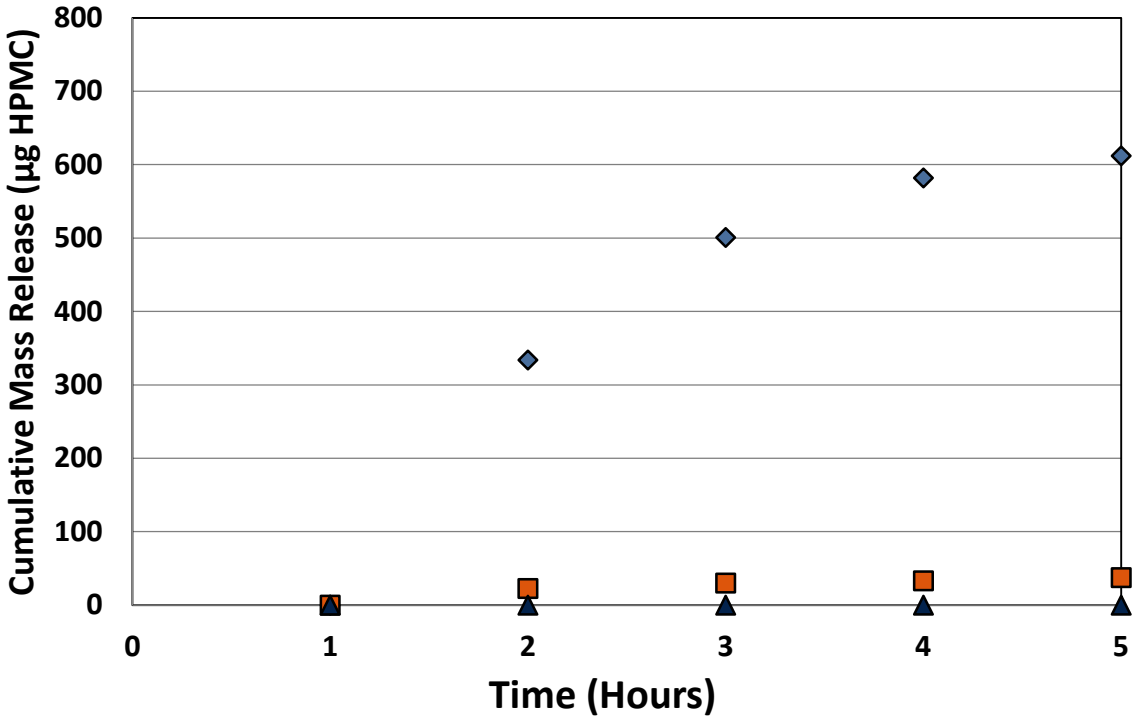


Figure 6.4. Release Of Polydisperse Molecular Weight HPMC From LFB Lenses Synthesized With Polydisperse HPMC

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.

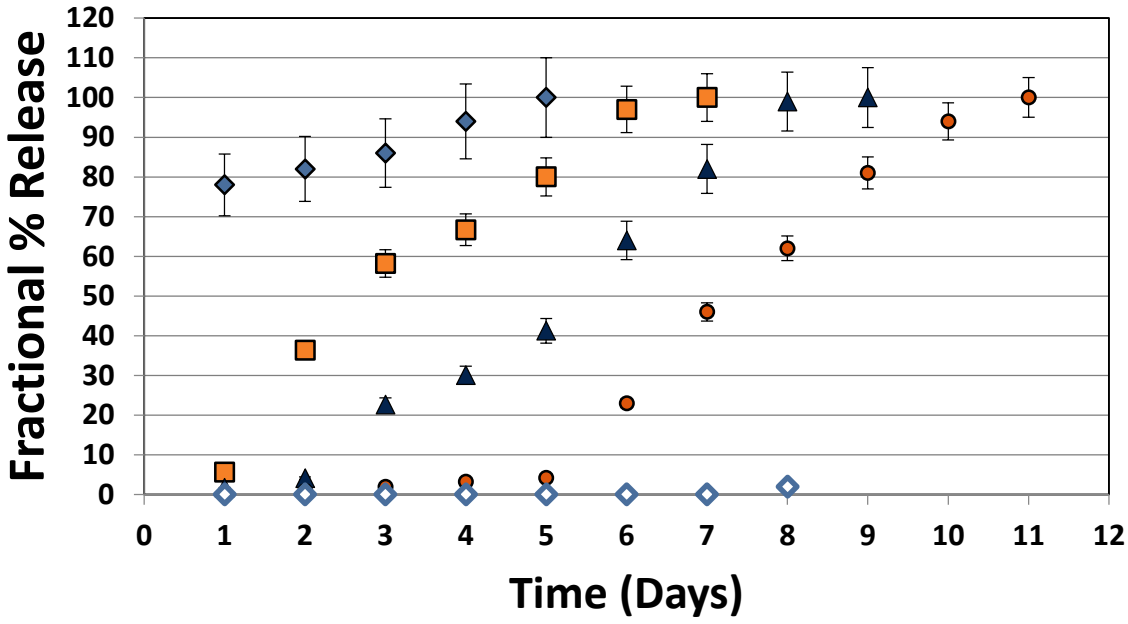


Figure 6.5. Effect Of Crosslinkers On The Release Of 120 KDa HPMC From LFB Lenses Synthesized With HPMC

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 2750 µg HPMC (◆), xLer/T ratio of 0.019 with 2800 µg HPMC (■), xLer/T ratio of 0.237 with 2700 µg HPMC (▲), xLer/T ratio of 1.02 with 2600 µg HPMC (●), and xLer/T ratio of 1.75 with 2600 µg HPMC (◇). 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.

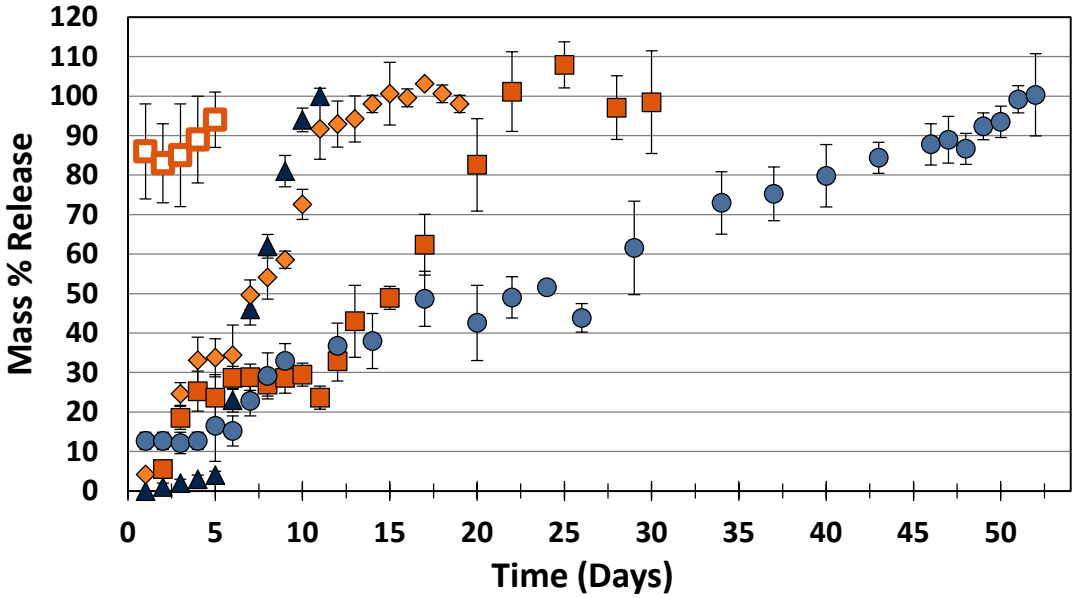


Figure 6.6. Fractional Release Of HPMC From Imprinted LFB Lenses

Hydroxypropyl methylcellulose (*120 KDa*) was incorporated into various lens formulations included the control LFB material (▣). The measured release duration from the control lens was found to reach completion over the course of 3-4 days. However, the majority of the HPMC mass release occurred within the first 24 hours of release. A small amount (*10-15%*) may trickle out over the next 24-72 hours but, statistically, the release is essentially complete within the first day. By adding a small amount of crosslinker (*xLer*) to a xLer/T ratio of about 1.5, the release rate for the control lens (▲) was lowered, and the duration of mass release was extended to 10 days. By applying the principles of molecular imprinting and formulating the lens formulation of (◆) 0.2, (■) 2.8, and (●) 3.4, the release rate was extended to 15 days, 25 days, and 52 days respectively.

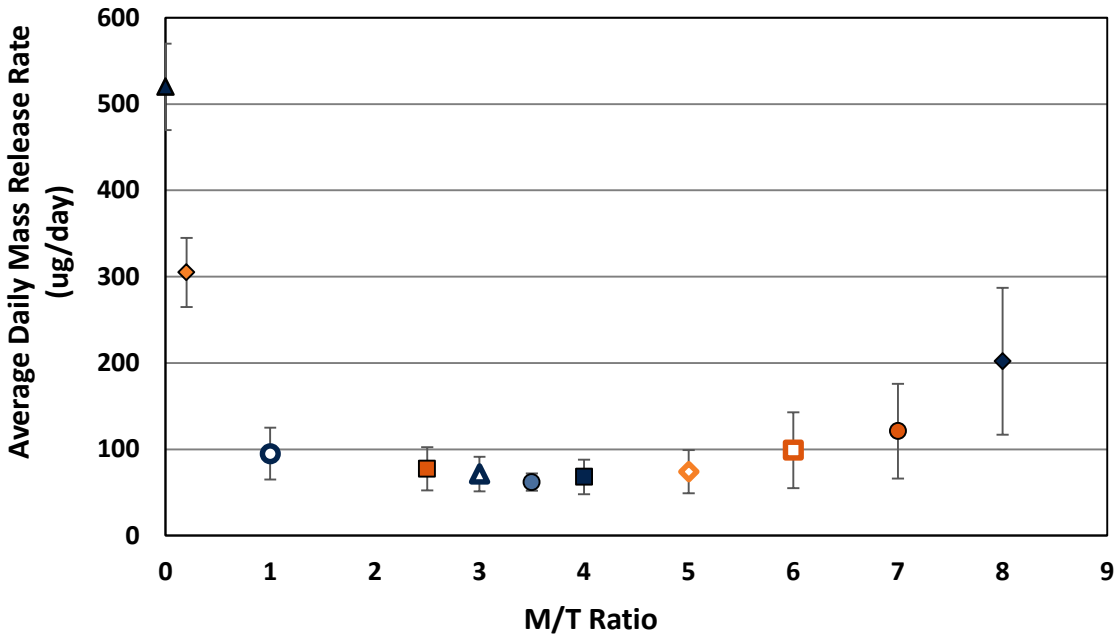


Figure 6.7. Average Daily Mass Release Rate Variation With Increasing M/T Ratios

A series of HPMC-eluting lenses were synthesized according to the principles of molecular imprinting of different M/T mass ratios. A sharp decrease was observed in the mass release rate at relatively low M/T ratios. As the M/T ratio increases, the release rate was observed to increase again in a manner consistent with molecular imprinting. As the M/T was increased further, the mass release rate achieved a minimal value, but as the M/T ratio was increased to still greater values the release rate began to increase to higher values in a manner consistent with molecular imprinting effect.

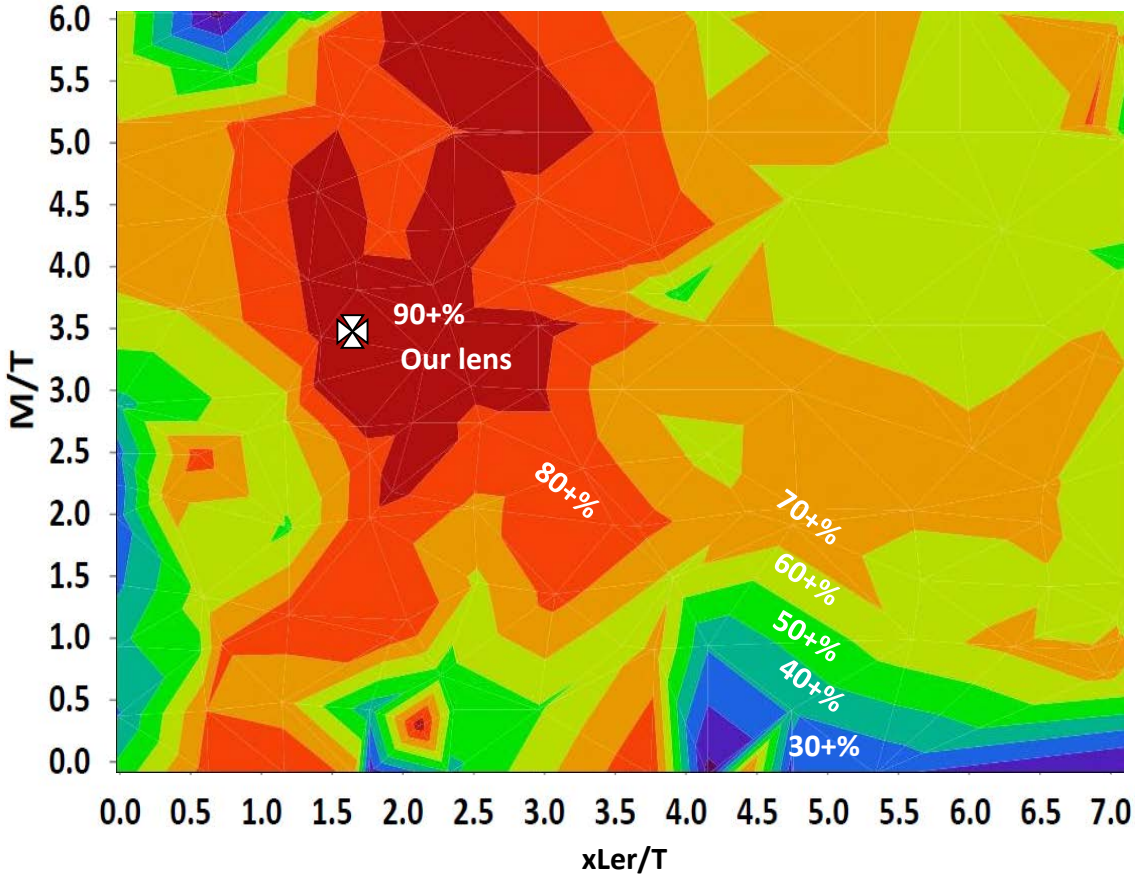


Figure 6.8. Optical Clarity Of Imprinted Lenses

Optical clarity of 100 μm thick LFB lenses imprinted With 120 KDa HPMC. There is a wide range of compositions that will lead to an optically clear lens. The release and optical clarity data indicates that the crosslinker amount (*xLer/T*) can be decreased.

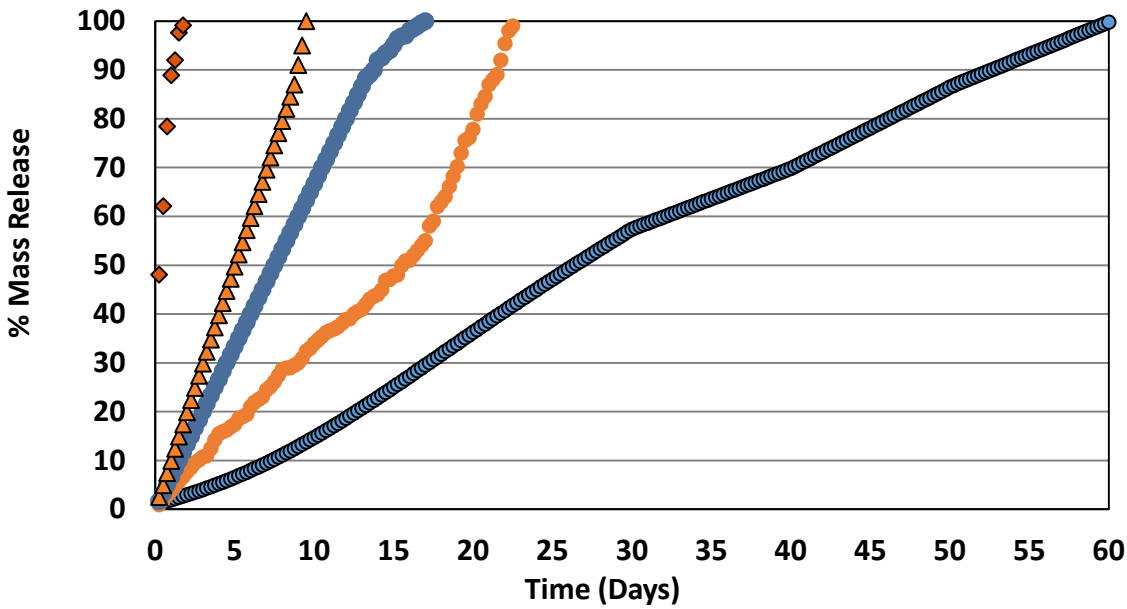


Figure 6.9. Release Of 120 KDa HPMC Tinted LFB Lenses In A Small Volume, Continuous Flow Sink Model

The release rate was measured for the samples in **Figure 6.6** using the microfluidic device instead of the large volume, static sink used previously. The microfluidic device contains a volume of release media of approximately 175 µL, whereas the large volume, static sink contained 250 mL of release media. The differences in release rate are due to the differences in driving force and occurrence/magnitude of the equilibrium-based kinetics.

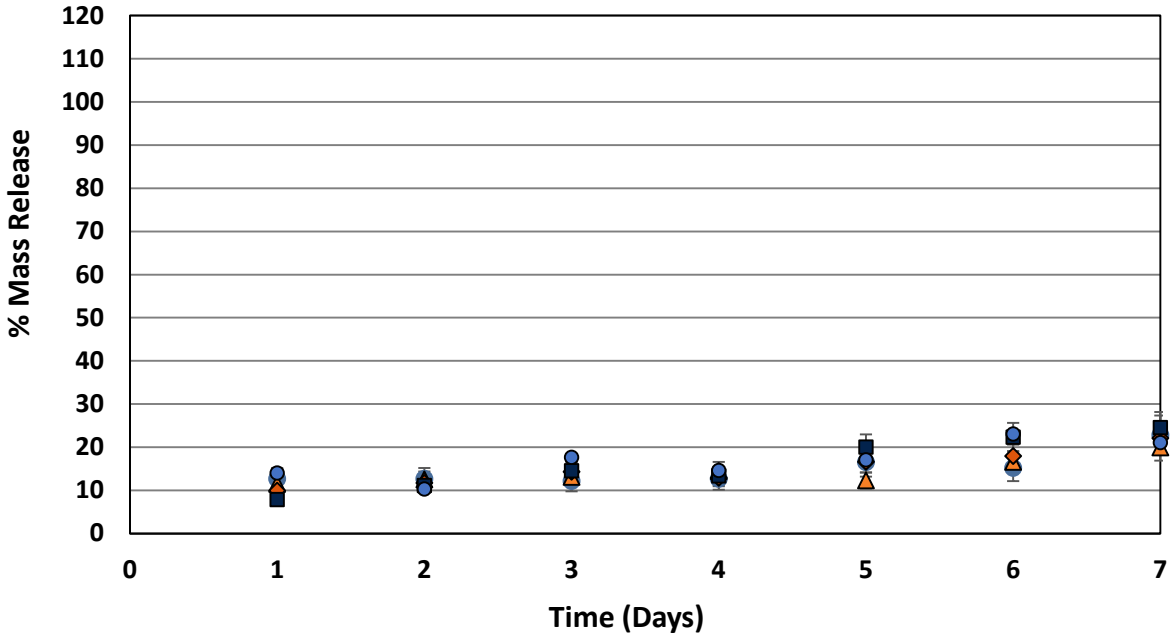


Figure 6.10. Release Of 120 KDa HPMC In Different Release Media

Release of 120 KDa HPMC was performed in different types of release media including (■) DI water, (●) artificial lacrimal solution (*ALS*), (◎) 0.9% sterile saline, (▲) 5% sterile saline, and (◆) phosphate buffered saline (*PBS*) in 250 mL volume. No statistically significant difference is observed between the media.

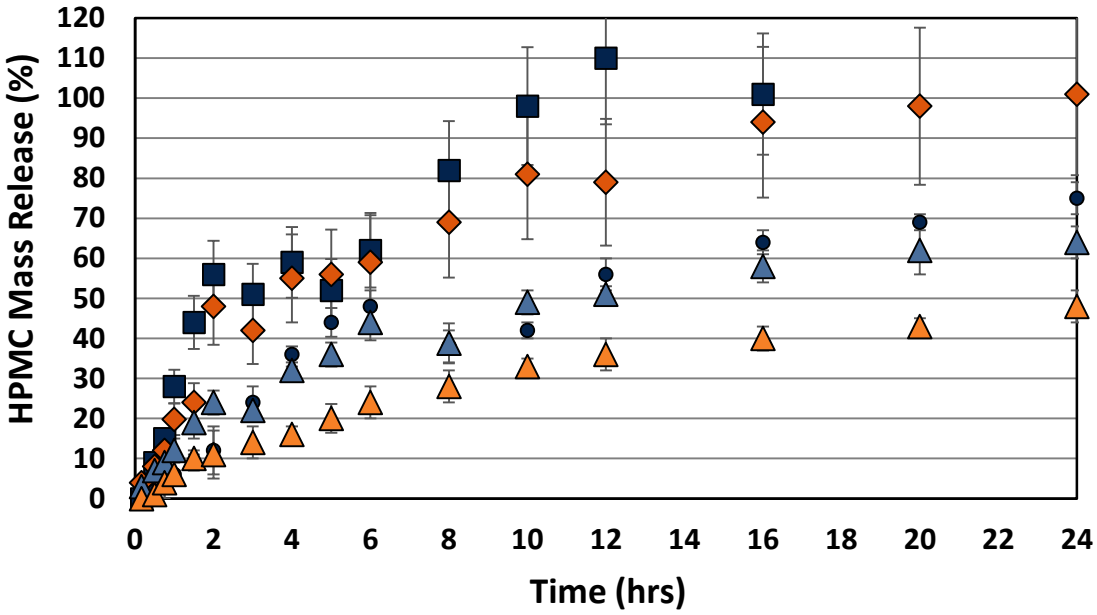


Figure 6.11. DMS-R11 Daily

Trehalose was incorporated and released from imprinted lenses at various M/T ratios. The ratios include (■) 0, (◆) 1, (●) 2, (▲) 3, (▲) 4. At M/T ~ 4, a linear steady release rate was observed.

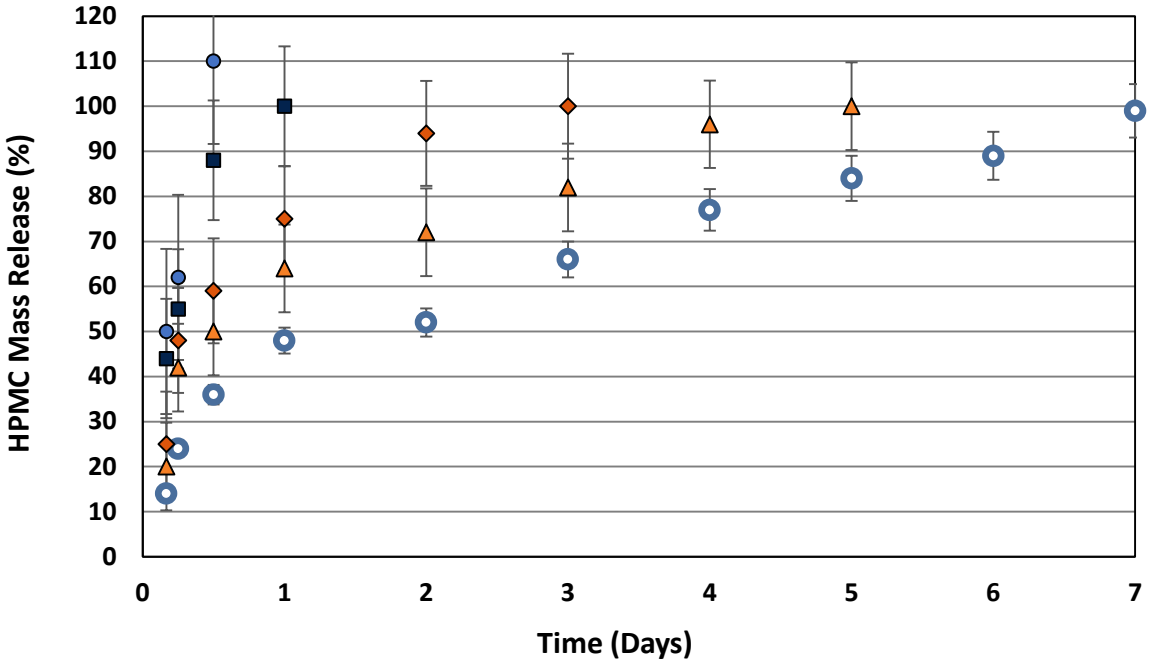


Figure 6.12. Extended Release From Imprinted DMS-R11 Contact Lenses

HPMC (*120 KDa*) was incorporated and released from imprinted DMS-R11 lenses at various M/T ratios. The ratios include (●) 0, (■) 1, (◆) 2, (▲) 3, (◎) 4. At M/T ~ 4, a relatively linear and steady release rate was observed.

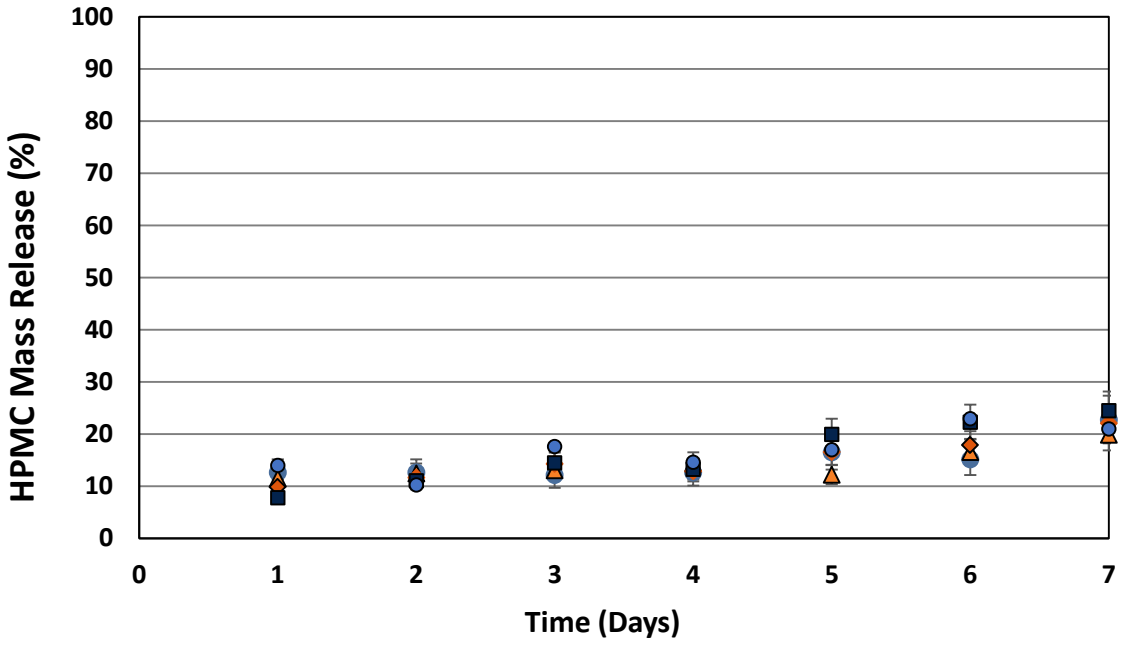


Figure 6.13. DMS-R11 Lenses Release Of 120 KDa HPMC In Different Release Media

Release of 120 KDa HPMC was performed in different types of release media including (■) DI water, (●) artificial lacrimal solution (*ALS*), (◎) 0.9% sterile saline, (▲) 5% sterile saline, and (◆) phosphate buffered saline (*PBS*) in 250 mL volume. No statistically significant difference is observed between the media.

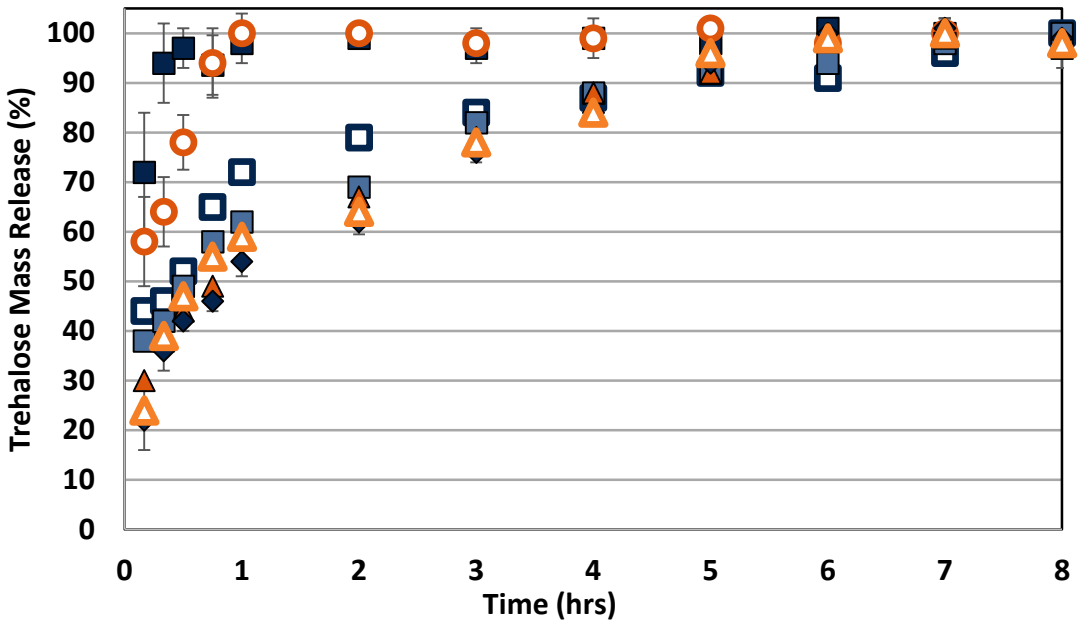


Figure 6.14. Mass Release Of Trehalose From Imprinted Lenses

Trehalose mass release profiles were observed from imprinted lenses formulated as a (■) control lens and at various M/T ratios including (◎) 0.5, (▣) 2, (▣) 3, (▲) 4, (◆) 5, (△) 6. As the M/T ratio increased, the delay in release rate was less and less significant between samples. Beyond M/T ~ 3, there is very little statistical significance.

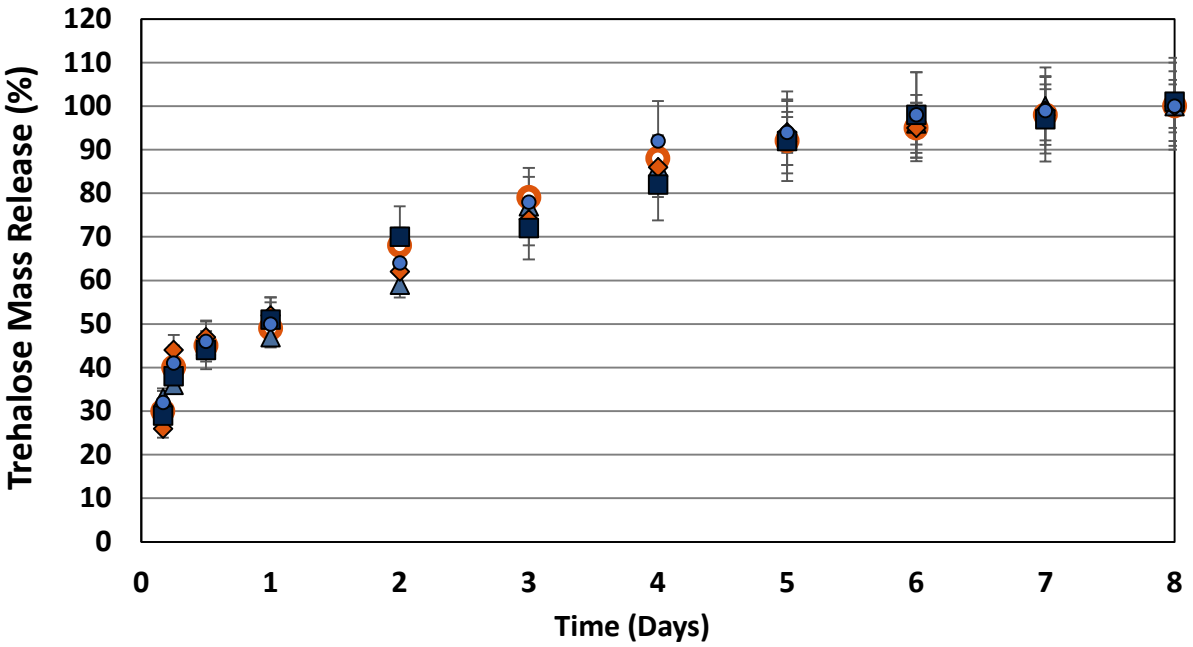


Figure 6.15. Mass Release Of Trehalose From Imprinted Lenses In 250 mL Of Different Release Media

Release of trehalose was performed in different types of release media including (■) DI water, (●) artificial lacrimal solution (*ALS*), (◎) 0.9% sterile saline, (▲) 5% sterile saline, and (◆) phosphate buffered saline (*PBS*) in 250 mL volume. No statistically significant difference is observed between the media.

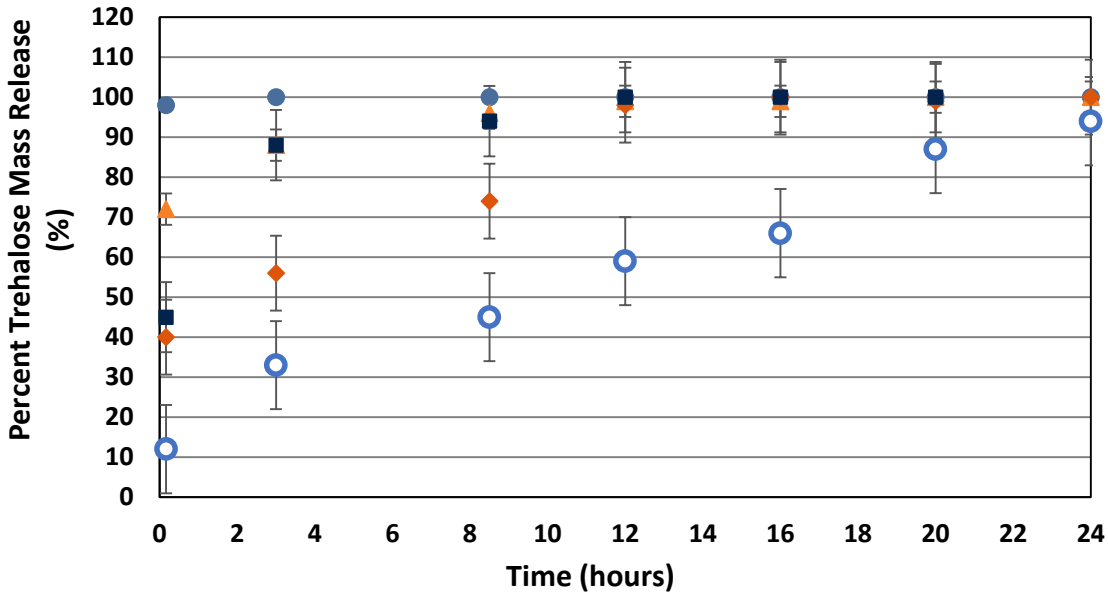


Figure 6.16. Trehalose Release In The Microfluidic Device

Trehalose was incorporated and released from imprinted lenses at various M/T ratios. The ratios include (●) 0, (▲) 1, (■) 2, (◆) 3, (◎) 4. At M/T ~ 4, a linear steady release rate was observed.

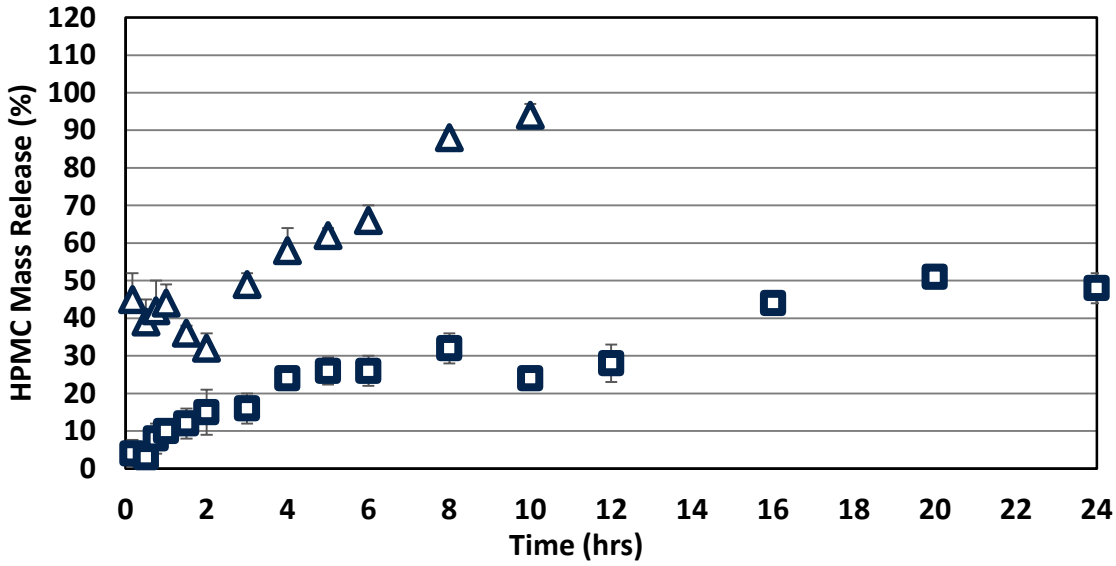


Figure 6.17. Simultaneous Release Of 120 KDa HPMC And Trehalose From Imprinted Lenses

(△) Trehalose and (□) 120 KDa HPMC were both incorporated into imprinted lenses (*500 μg of each/lens*) for simultaneous release from a single contact lens. Trehalose was incorporated for its high water retention properties and was intended to alleviate sensations of dryness, which is the primary propagator of discomfort during initial wear. The release duration of trehalose was desired to be completed within the first 6-12 hours. As lens wear continues, other propagators of discomfort become predominant.

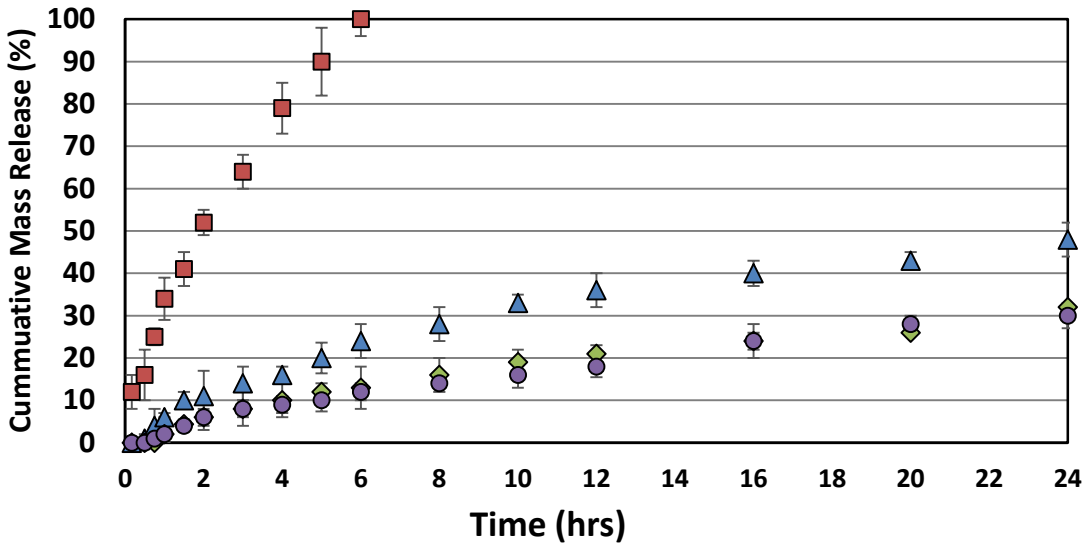


Figure 6.18. Release Of A Cocktail Of A Diverse Selection Of Comfort Molecules

A set of comfort molecules were selected to demonstrate the diversity of the engineered imprinted lenses to deliver a diverse cocktail of comfort molecules simultaneously. The group of molecules included (▲) 120 KDa HPMC, (■) trehalose, (◆) prednisolone, and (●) chloramphenicol.

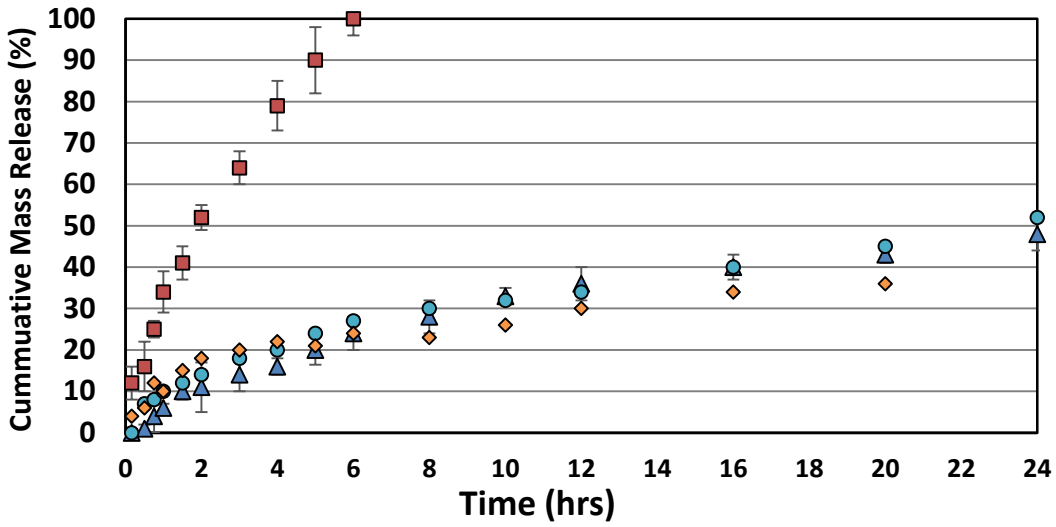


Figure 6.19. Release Of A Second Cocktail Of A Diverse Selection Of Comfort Molecules

A second set of comfort molecules were selected to demonstrate the diversity of the engineered imprinted lenses to deliver a diverse cocktail of comfort molecules simultaneously. The second group of molecules included (▲) 120 KDa HPMC, (■) trehalose, (●) aspirin, and (◆) chloramphenicol.

CHAPTER 7

NOVEL AUTOMATON FOR IN VITRO MEASUREMENT OF THE MASS RELEASE RATE OF MOLECULES FROM CONTACT LENSES

7.1. Introduction To Chapter 7

The Byrne Lab has pioneered the use of both large volume, static sink models and small volume, continuous flow sink devices, referred to as microfluidic devices, to accurately determine the release kinetics from drug-eluting contact lenses and to predict the mass release profile under physiological conditions. The most recent published device design has represented a major contribution to the field. However, there are several drawbacks of the design that could be improved upon with the design of a novel device. The conception, development, fabrication, programming, and evaluation of a novel heat exchanger-based automaton for the performance of *in vitro* dynamic mass release studies is described in this chapter.

7.2. Models Of Sink And Previously Developed Technology

In the 45 years since the field's inception, there is a long list of different sink models and conditions that have been used by different investigators. **Table 7.1** provides an outline some of the advantages and drawbacks of some commonly used models for *in vitro* dynamic release studies. In general, the most models used within the field can be divided among the following categories: *in vivo* animal (*e.g., rat, rabbit, dog/beagle, and ape*), *in vivo* human, *in vitro* small volume, static sink, *in vitro* large volume, static sink, and *in*

vitro continuous flow models. A brief discussion outlining the small volume, static sink, large volume, static sink, and continuous flow sinks is provided below.

7.2.1. Small Volume, Static Sink

Historically, the small volume, static sink model has been the most commonly used model when performing dynamic mass release studies. However, a recently published paper has shown conclusively that this model is actually incapable of accurately demonstrating the true kinetics of release, i.e., kinetics free of any equilibrium effects on the concentration-driving force between the drug reservoir in the bulk of the lens and the release media, of molecules from the lens. This model has been criticized for incorrectly indicating that certain technologies for lens release have value as to the production of therapeutic contact lenses. When the technology is performed later under with an *in vivo* model, the technology is shown to be without value. This results in loss on the invested capital and the failure to further progress the growth of the field.

7.2.2. Large Volume, Static Sink

This argument is gradually gaining increased attention within the field and use of more accurate models is becoming more frequently. The most popular alternative to the small sink *in vitro* model is the large volume, static sink. This model is superior to the small sink model in-so-much as accurate kinetics of release can be determined confidentially. This is because the concentration gradient driving force remains more or less constant throughout the experiment since no boundary layer of the eluting molecule is formed. The driving force between the bulk of the lens and the surface of the lens is therefore identical to the driving force between the bulk of the lens and a point infinitely far away from the lens. This condition is often referred to vernacularly as a “perfect” sink or an infinite sink.

Results from separate studies can only be confidently compared when both studies are performed under infinite sink conditions. This is the only way to accurately evaluate various release strategies and determine their relative value. Unfortunately, this condition results in the fastest possible release rate and is not an accurate model for the eye.

7.2.3. Continuous Flow Sink Devices

The eye is best described as a small volume, pseudo-infinite sink. For this reason, Pate, Tieppo, and Byrne have been the predominate developers of a small volume, continuous flow sink device, generally referred to as a microfluidic device, designed to provide a flow rate of release media approximating the physiological flow rate of the tear fluid into a minimally sized *(175 μL*) reservoir surrounding a drug-eluting lens. The development of this device was a response to an unmet need within the field for a method to accurately predict the *in vivo* mass kinetics from an *in vitro* device. A diagram of the device is provided in **Figure 7.1**.

This device has been used repeatedly for the analysis of several eluting lens technologies by our lab. Reports detailing the release of ketotifen fumarate, hydroxypropyl methylcellulose (*HPMC*), dexamethasone, trehalose, diclofenac sodium, and others have been published incorporating data from the device. The microfluidic device has been a valuable development of for the field. However, there are several drawbacks associated with the microfluidic device that leave room for the development of more advanced devices. The major of these drawbacks are that the device is not reusable and tends to age with experimentation. Each device must be made uniquely for each experiment and discarded afterwards. This introduces a small possibility for variation and error between studies. Also, the fluid flow is horizontal instead of the vertical flow seen under *in vivo*

conditions. The reservoir within the device is approximately 175 μL and completely surrounds the lens. Actual ocular conditions include 20-40 μL of tear fluid, and the flow mostly stays among the peripheral of lens rather than over the top. Also, there is no blinking motion within the device. Last of all, in the current microfluidic device, there is no convenient method to control the temperature of the device and is therefore usually operated at ambient temperatures of 20ºC, instead of the more accurate ocular temperature of the surface of the eye, 34ºC.

A novel automaton device was designed and fabricated to incorporate solutions to these drawbacks. The automaton was based upon a custom heat exchanger design and a servo-based mechanism to reproduce the blinking motion as well as a method to allow for controlled, variable flow rates of release media through the device. The automaton is referred to as the heat exchanger device for the duration of this text. Two distinct designs for the heat exchanger, referred to as Design 1 and Design 2, respectively, were created.

7.3. Production Of The Novel Device

The production of the device required the custom manufacture and assembly of several pieces and the adaptation of parts from diverse sources. In addition, the operation of the device necessitated the programming of an Arduino® microcontroller to operate the timing, activity, and range of motion of the various mechanical and digital components and collect data from the attached modules. To simplify the control and adjustment of the various operation variables of the device, a custom Apple® iPad app compatible with Apple® operating system iOS 7 was created using Adobe® InDesign software and loaded onto an Apple® iPad with Retina Display, 4th generation tablet. Wi-Fi and Bluetooth low

energy (BLE) shields were added to the microcontroller to allow for simpler or remote adjustment of the experimental parameters or to access the recorded data within the device.

7.3.1. Materials And Methods

Two heater exchanger glass devices were ordered for use as the main bodies segments in the design and fabrication of an improved microfluidic device. Two novel designs were created by the author and submitted to the Auburn University Glass Shop (*Auburn, AL*) for custom manufacture. All pieces of glassware used in the custom fabrication of the heat exchangers, including glass flasks, tubes, rods, and plates, were procured, received, and stored by the Glass Shop. The glass was heated until it could be reshaped to match the design schematics provided by the author without altering the glass thickness and then allowed to cooled. The final thickness of the glass walls was 3 mm and uniform through the devices. The finish devices were then steam cleaned and picked up by the author. The device was then used as received by the author will no further alteration of the glass surface. A third unprocessed flask identical to those used to form the globe of the heat exchangers was purchased from the Glass Shop to use as a mold to create a model eyelid from a two component silicone mold material.

Two different mold materials were purchased during the completion of this study. The first was a brushable, soft silicone mold material (*Rebound™ 25*) purchased from Smooth-On®, Inc (*Easton, PA*). The second was a high modulus silicone elastomer (*Sylgard® 184 Silicone Elastomer Kit*) procured from Dow Corning® Corporation (*Midland, Michigan*).

9.3.1.1. Electronic And Programming Materials And Parts

Various electronic, construction, and robotic-assembly sets and parts necessary in the assembly and production of the devices were procured from various suppliers and are listed here. Jameco® Electronics (*Arndt Electronics, Belmont, CA*) for included Standard HI-Tec® Servo HS-311 and HS-422 (*Hitec RCD USA, Inc., Poway, CA*), Arduino® Uno R3 microcontrollers (*Smart Projects, Strambino, Italy*), Arduino® Starter Kit which included USB cable, breadboard, solid core jumper wires of various lengths, resistors of various strength, capacitors of various capacity, transistors, and other pieces not used in the assembly (*Smart Projects, Strambino, Italy*).

In addition, Arduino®-compatible accessories for the microprocessor were procured, including 3 Arduino®-compatible shields [*Arduino® Wi-Fi Shield (Smart Projects, Strambino, Italy), RedBearLab Bluetooth Low Energy (BLE) Shield (Red Bear Company Limited, Hong Kong, China), and Seeed Studio® Grove Sensor Shield (Seeed Technology, Inc, Shenzhen, China)*], Seeed Studio® Grove System-compatible environmental sensor modules [*Oxygen Sensor Module, Button Module, Temperature Sensor Module, Temperature Probe Module, Real Time Clock Module, Buzzer Sensor Module, Barometric Pressure Sensor Module, and MQ2 Gas Sensor Module*] as well as 4 pin Grove connector cables of various lengths (*Seeed Technology, Inc, Shenzhen, China*). Additional modules were purchased individually and included a Virtuabotix® Temperature And Humidity DHT11 Sensor Module (*Virtuabotix® LLC, Colorado Springs, CO*) and modules to compose the device user interface consisting of a 20x4 LCD Screen Module, a Standard Numeric Keypad Module, and Push Button and Switch Modules (*Smart Projects, Strambino, Italy*). The base for the each automaton, including the servo mounts, was

assembled from pieces adapted from an Erector® Super Construction Set *(Meccano® Joint Stock Company, Calais, France*).

Other materials procured for the construction of the device included a Cole-Parmer® Masterflex® peristaltic pump (*Cole-Parmer® Instrument Company, Vernon Hills, Illinois*) fitted with a Masterflex® L/S Easy-Load II Pump Head selected to be capable of producing flow rates between 0.01 and 10 mL/min. Masterflex® L/S silicone 6 mm inner diameter tubing was used connected to the device and loaded through the pump. Also, the same tubing connected the device to a Cole-Parmer® Polystat® H6L Sealed Circulation Heating/Cooling Bath set at 34ºC.

7.3.1.2. Materials For Lens Synthesis

Dimethyl acrylamide (*DMA*) and 3-methacryloxypropyl-tris-(trimethylsiloxy)silane (*TRIS*) were purchased from Sigma-Aldrich® (*St. Louis, MO*), and the silicone macromer, 1 KDa methacryloxypropyl-terminated polydimethylsiloxane , was bought Gelest®, Inc (*Morrisville, PA*). Darocur® 1173 (2-hydroxy-2-methyl-1-phenyl-propan-1-one), the photo-initiator, and all additional monomeric materials, including acrylic acid (*AA*), poly(*ethylene glycol*) (*200*) dimethacrylate (*PEG200DMA*), and ethylene glycol dimethacrylate (*EGDMA*), were all purchased from Sigma-Aldrich® (*St. Louis, MO*). Different pharmaceuticals and comfort agents were selected to represent a diverse subset of molecular weights and solubility's were all purchased through Sigma-Aldrich® and include hydroxypropyl methylcellulose (*HPMC*) (*MW = 120 KDa*), trehalose, aspirin, ibuprofen, acetaminophen or paracetamol, naphazoline hydrochloride or naphozoline HCl (*2-(1-naphthylmethyl)-2-imidazoline hydrochloride*), and chloramphenicol. All compounds were used as received. Glacial acetic acid, 12 Molar hydrochloric acid (*HCl*),

and diphenylamine (*DPA*) were ordered from Sigma-Aldrich® for use in a photo-calorimetric assay to determine the mass of 120 KDa HPMC and trehalose in the release media.

7.3.2. Assembly And Programming Of The Automation

An model of an eyelid was composed of a model silicone mold material. The two component Rebound™ 25 silicone mold material was mixed at an equal mass ratio and decanted into a round bottom Petri dish. A 60 mm round bottom flask was placed into the material to form the inside shape of the eyelid. It was allowed to cure at ambient temperatures for 24 hours before removal from the model. Once removed, it was cut in half to form 2 eyelids.

The Wi-Fi and BLE shields were mounted onto the Arduino® Uno microcontroller in that order, followed by the Grove shield on top. Servo mounts were assembled from pieces adapted from an Erector® model kit. Once installed on the mounts, the servos and various other modules were connected to Arduino® Uno microcontroller. The heat exchanger was held in place next to the servo mounts via a mounting clamp and hoses connecting the heat exchanger to a Cole-Parmer® recirculating temperature bath (*temperature = 34ºC*), and another connecting the heat exchanger to the Cole-Parmer® Masterflex® peristaltic pump. Schematics for the custom heat exchanger body designs are shown in **Figure 7.2**. In Design 1, rods were connected to the two servos with a crossbar bridging the two, and the eyelid glued to the horizontal crossbar. In Design 2, a 3 mm axel rod was inserted through the heat exchanger and curved back over the top of the heat exchanger. The eyelid was glued to the axel as shown in the diagram. The axel was then connected to a single servo. The modules and environmental sensors were then placed

around the device as appropriate and connected to the Arduino® microcontroller via a 4-pin Grove connector wire and the Grove shield. The various modules and shields attached to the microcontroller. In addition, a novel tablet application, or app, was written as a convenient user interface and a screenshot of the introductory page for setting the protocol of the experiment is shown in **Figure 7.3**.

7.3.3. Synthesis Of PDMS Lenses

Lenses were produced by mixing individual monomers of the formulation. The monomers were kept refrigerated at 4°C. A typical formulation consisted of 1300 mg of PDMS-macromer referred to as DMS-R11, 1300 mg of TRIS, and 1300 mg of DMA (*referred to as the base formulation*). The base formulation was equal parts of these monomers and used to calculate ratios of other components. The template molecule was added to the base formulation to attain a desired concentration of within the synthesized lens. Equal masses of the crosslinkers (*xLer(s)*) EGDMA and PEG200DMA were added according to a previously selected mass ratio (*xLer/T*). To maintain acceptable tensile modulus values, the xLer/T mass ratio typically used for most of the lens formulations was approximately 1 to 1.5. For a typical xLer/T ratio of 1.5 lens formulation, the mass fraction of the crosslinkers fell between 0 and 10 wt% of the base formulation and >5% of the total formulation. Imprinting monomers were then added to achieve a desired mass ratio for the monomer to template (*M/T*) added to the formulation usually representing a range between 0 and 10 wt% of the base formulation. Often, ethanol was necessary to fully disperse the monomers and added to the formulation in a mass fraction of up to 20% of the total formulation. For trehalose-containing formulation, glacial acetic acid was used instead of ethanol. The photo-initiator, Darocur® 1173, was added to the solution to a concentration

of 1% of the total formulation. The samples were thoroughly mixed by sonication for 30 minutes. The formulations were exposed to high shear mixing for up to 1 minute and sonicated for at least 15 minutes to remove any dissolved air or air bubbles.

A fixed aliquot volume was pipetted into polypropylene (*PP*) lens molds provided by CIBA Vison®, Inc. 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 (*Lumen Dynamics® Mississauga, Ontario, Canada*) with an intensity of approximately 25 mW/cm^2 for a duration of 1.5 minutes. Out of mold lenses were ~220 μm thick (*center thickness*) and water swollen lenses were ~350 μm thick (*center thickness*) unless otherwise noted. Thinner lenses were produced with a swollen center thickness of ~100 μm using a Thomas spherical joint pinch clamp tightened around the mold. Once cured, the lens molds were opened and placed into an oven at 25ºC for an hour to remove the solvent remaining in the lens. This prevented the tearing of the lens during removal from the mold. The lenses were then removed from the molds and used immediately in dynamic release studies.

7.3.4. Dynamic Release Studies Under Large volume, Static Sink Conditions

Dynamic release studies were conducted to measure how long each therapeutic contact lens would release *in vitro*. The studies were conducted under large volume, static sink conditions using a Sotax® Dissolution Apparatus (*Sotax® AG Joint Stock Company, Allschwil, Switzerland*) in which loaded lenses were placed in 250 mL of DI water (*pH 6.4*). In the Sotax® Dissolution Apparatus, the release media was kept stirred at a constant rate of 30 rpm by paddles at a constant temperature of 34°C. The average weight of the lenses out of the mold was 35 mg ± 6 mg.

7.3.5. Dynamic Release Studies Under Physiological Flow Rates Using The Previous Microfluidic Device Design

A 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 minutes and poured onto a glass plate within a circular mold. Within the mold were 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 was then cured at 60°C under a vacuum for 6 hours. The PDMS was removed from the mold and then the needles and marble were removed. A slightly smaller marble hemisphere (*15.2 mm wide x 4.35 mm high*) was placed under the mold and a syringe pump was used to pump DI water through the mold at the physiological flow rate of 3 μL/min. The inner chamber contained 175 μL of DI water. The lens was placed in the device, sealed, and the concentration was measured every 10-12 hrs. A schematic of the microfluidic device is presented in **Figure 7.1**.

7.3.6. Dynamic Release Studies Under Physiological Flow Rates Using The Novel Heater Exchanger Design

Once the device was assembled and programmed and ready for use, a lens was placed on the front, center of the device. The desired protocol was set through the interface app (*mainly the duration of release was set to 24 hours, the blink rate was set to 6 blinks/min*) and the Cole-Parmer® pump was set to the desired flow rate (*usually 2 mL/min*) and the protocol allowed continue unabated. The release media fluid was collected at pre-determined, specific intervals, and the mass concentration of the eluting molecule determined via the appropriate procedures presented below.

7.3.7. Determining The Mass Concentrations Within The Release Media Of Selected Molecules

HPMC concentration in the release medium was determined via High Performance Liquid Chromatographer (*HPLC*) (*Shimadzu® Corporation, Nakagyo-ku Kyoto, Japan*) equipped with a refractive index detector. The mobile phase was deionized water, and a flow rate of 1 mL/min was maintained by the HPLC. A standard curve of refractive index and known HPMC concentrations was established. Percent mass release curves were plotted for each lens.

HPMC and trehalose concentrations could be calculated from a photo-calorimetric assay technique recommended by United States Pharmacopeia (*USP*) exploiting the colorimetric reaction between the secondary hydroxyl functional groups between the saccharide molecules and diphenylamine. A concentration calibration equation for the Biotek® Spectrometer was calculated to determine the mass of the molecule present. Samples of the release media (*2 mL in volume*) were taken at specific intervals during the dynamic release studies and added to a diphenylamine, hydrochloric acid, and glacial acetic acid solution and heated at 110ºC in an oil bath for 30 minutes. At the end of the 30 minutes, the sample solutions were removed from the oil bath and immediately placed in a chilled water bath for 30 minutes. Three aliquots (*200 µL in volume*) of the final reacted solution were pipetted into an organic solvent resistant 96 well plate, and the absorbance measured at wavelength of 630 nm.

Solution concentrations of aspirin, ibuprofen, acetaminophen, naphozoline HCl, and chloramphenicol are determined by UV-Vis Spectroscopy. Dilutions of a standard solution of each molecule were formulated and used to create a calibration for the Biotek®

Spectrometer for the characteristic wavelength where the maximal absorbance occurred. The wavelengths associated with each molecule are as follows: aspirin - 230 nm, ibuprofen – 290 nm, acetaminophen – 250 nm, naphozoline HCl – 350 nm, and chloramphenicol – 490 nm.

7.4. Results And Discussion

The first section of the experimental work focused on evaluating the performance, reliability, and repeatability of the device by varying different operating parameters, such as flow rate and blink rate and to demonstrate that no water was lost, etc. Afterwards, contact lenses were placed upon the device, and dynamic release studies performed to find the mass release profile of the molecules from the lens. A diverse range of molecules selected to represent a spectrum of different molecular weights and solubility's were incorporated into contact lenses used to demonstrate the versatility of the device design. The mass release profiles obtained by using the heat exchanger device were compared to the profiles obtained from the Sotax® Dissolution Apparatus and the previous microfluidic device design.

7.4.1. Setting Experimental Protocols

Several experimental protocols were programmed into the Arduino® microcontroller during the assembly of the devices and can be selected at the onset of the experiment. The pre-installed protocols vary according to the experimental design variables. The variables control the blinking motion, such as study duration (*time periods of 1 min, 1 hour, 12 hours, 18 hours, 24 hours, 2 weeks, and 30 days were all pre-installed with the default selection to 24 hours*), blink rate [(*blinks/min*) *with a default setting of 6 blinks/min*), interval between blinks [(*fixed or random*) *with a default setting of fixed*], sleep

period (*yes/no, with a default setting of no*) and duration (*if applicable, duration is 8 hours*), etc. The sleep setting is designed to represent a subject wearing a lens while asleep by placing the eyelid in the "closed" position for the duration of the selected period. In addition to the preset protocols and variable options, the device's user interface, in the form of either a tablet app (***Figure 9.3***) or a more conventional LCD screen, keypad, and push buttons, offers the option of creating an unique user protocol by inputting custom values for each variable. The default protocol is referred to as the standard protocol (*all variables have the default value*). The values are as follows: study duration: 24 hrs, blink rate: 6 blinks/min, interval between blinks: fixed interval of 10 seconds, sleep period: no, computer usage: no, and record data: yes. In the current device design, the release media continuously flowed over the lens in a manner designed to approximate natural tear flow conditions.

7.4.2. Troubleshooting Device And Testing For Design Flaws

Once both heat exchanger devices were completely assembled, performance evaluation experiments designed to troubleshoot the setup and design and determine the reliability of the device, etc were undertaken. The first of these tests was to simply run the device without a contact lens present and using DI water for the release media for 24 hours under the standard protocol to demonstrate that no mechanical malfunctions or water leaks, etc would occur and that the digital components, such as the servos and microcontroller would not fail under extended usage. At the end of the experiment, the recovered volume of water was found to match the input volume, indicating that no significant loss of the release media occurred. However, it was found by varying the flow rate of the DI water through the heat exchanger that friction between the model eyelid material and the device surface could prevent the motion of the device if it was not kept lubricated by the tear flow.

The minimum flow rate necessary to maintain reliable operation of the device was 0.2 mL/min. The maximum flow rate was likewise measured at 10 mL/min. The flow rate interval between 0.2 and 10 mL/min is referred to the operating range. One minor flaw in Design 1 was found with the fluid collection pan. When manufactured, the pan was attached at an angle 30º below the horizon, as shown in the schematic found in **Figure 7.2**. This angle caused the collected release media to spill from the pan. This fault was easily accounted for, however, by placing a collection funnel and flask under the pan to catch the run-off.

To test the lens adhesion to the device, the experiment was repeated under the standard protocol with a contact lens placed on the front surface of the device. During the experiment, the lens was found to adhere well once placed. Some care is necessary to ensure that high contact is achieved when placing the lens, and no air bubbles are present under the contact. Though the lenses used in the test showed excellent adhesion, it is possible that lenses with very high tensile moduli may have some difficulty. Within the operating range, the lens remained in place and hydrated. Below the operating range, the lens dehydrated, and the friction from the eyelid motion caused the lens to fail to adhere to the device surface. Above the operating range, the lens began floating in the flow and would slip down the device. Within the operating range, the flow of release media around the lens was very interesting in an unexpected way. The lens thickness was much greater than the thickness of the stream. As a result, the water flowed around the edges of the lens rather than over the top of the lens except at the very highest flow rates. During the blinking motion, the model eyelid would wet the surface of the lens with the release media. The fluid would then drain off the lens, while flow was maintained around the edges. The same

phenomena is observed for tear flow around a lenses placed on the ocular surface. This effect reinforced the potential of the heat exchanger to more accurately reproduce the physiological conditions experienced by a lens worn on the eye.

Both devices were shown to be stable and consistent in their performance evaluations and possessed a high degree of repeatability within the operating conditions. The operating flow range was found to be between 0.2 and 10 mL/min. When a lens was placed on the surface, the release media flow profile was consistent at all time periods and the lens remained firmly in contact with the surface. In addition, the Arduino® microcontroller recorded important information such as the number of blinks occurring during the experiment, the exact times of each blink motion, the intervals between each blink, the precise start time and end time, and more in a text file that can be accessed remotely through the internet and stored to a remote location. The device was deemed to be ready for use performing dynamic release studies.

7.4.3. Using The Device To Perform Mass Release Studies

After the evaluation of the device demonstrated that it was feasible to perform dynamic release studies with high confidence, the highest priority was to perform a dynamic release mechanism DMS-R11 lenses were synthesized to incorporate various molecules to perform dynamic release studies with the heat exchanger device. Dynamic release studies were performed in all three release devices: the large volume, static sink model (*Sotax® Dissolution Apparatus*), the small volume continuous flow model (*microfluidic device*), and the variable, continuous flow model (*heat exchanger device*). Release profiles attained from the two more conventional environments, the Sotax® large

volume, static sink and the small volume continuous flow microfluidic device, were used to evaluate the variable, continuous flow device.

The first molecule selected for incorporation into the DMS-R11 lenses was ibuprofen as it is highly compatible with the silicone hydrogel material and could be loaded into the lens formulation at very high concentrations without affecting the lens properties. Also, the ibuprofen solution concentration within aliquot samples of the release media is easily found, and the high hydrophobic nature of the molecule gave the release experiments a high degree of repeatability. However, ibuprofen is a very hydrophobic molecule and, when released from a drug-eluting lens, the release kinetics are very sensitive to the sink volume conditions. This effect in particularly strong in the release of hydrophobic molecules and was observed in the release kinetics of ibuprofen. Care was taken to identify reliable release kinetics in each model.

7.4.3.1. Release Of Ibuprofen From DMS-R11 Control Lenses

An extended and relatively constant daily mass release of ibuprofen was produced in a large (*600 mL*) static volume of DI water within the Sotax® Dissolution Apparatus for an extended duration (*25% mass released during 72 hours*). The volume of DI water was replaced daily. However, it was observed that a similar mass of ibuprofen (*25 μg*) was released each day, strongly indicating that the ibuprofen release rate was artificially reduced. Previous work indicated that the most probable explanation was that the concentration driving force was experiencing equilibrium-based conditions. To test this hypothesis, an additional series of dynamic release studies were performed in the 600 mL static sink, but with the replacement intervals were gradually reduced from 24 hours to 12, 6, 2, and 1 hour. The resulting mass release profiles can be seen in **Figure 7.4**.

The average mass release rate increased drastically between the various media replacement intervals, increasing approximately by order of magnitude (*shown in **Figure 7.5***). The mass release per day increased from 37 µg/day (*volume was replaced daily*) to 230 µg/day (*volume was replaced hourly*). The relationship between the average daily mass release rate and the volume replacement interval was used to estimate the mass release at continuous flow or under "perfect" sink conditions by extrapolating to a replacement interval of zero hours. The mass release rate found under "perfect" sink conditions corresponds to the fastest possible rate of release for ibuprofen and was estimated to be 260 µg/day.

The mass release profile under physiological flow rates was found by placing a lens in the microfluidic device. The mass release of ibuprofen at 24 hours was found to be 0.11 µg (***Figure 7.6***). The small volume of the DI water reservoir within the microfluidic device had a very strong effect on the release rate of ibuprofen due to its very low water solubility. The release rate under 3 µL/min flow conditions was found to be 4.6 µg/hour. Both the mass release rate found under the large volume, static sink condition and the mass were used to release rate found under the physiological flow rates were used to estimate the minimal release rate of ibuprofen from the lens material and was found to be 0.066 µg/min.

The combination of the large volume static and the small volume microfluidic device allowed a fairly robust, if labor intensive, brute force evaluation and characterization to calculation the range of mass release rates it was possible to achieve from ibuprofen-eluting lenses. The release profiles can be seen in **Figure 7.4-7.7**. With this range of release rates determined, characterization of the variable flow heat exchanger device was performed by placing a lens on the front, center surface. A series of experiments

performed at different flow rates were conducted with the device at 34ºC with a blinking rate of 6 blinks/min. The flow rates selected were 0.2, 2, 5, 10 mL/min. Trial and error evaluations showed that the lowest flow rate where the DI water release media formed a continuous stream around the lens was ~2 mL/min, and 2 mL/min was considered to be the default flow rate. The mass release profiles at each respective flow rate are shown in **Figure 7.7**.

The results were extremely interesting. It was found that mass release profiles representative of the entire range of rates possible for release of ibuprofen could be achieved by varying the flow rate of release media through the heat exchanger device (***Figure 7.8***). The mass release profiles found at 0.2 and 10 mL/min closely corresponded to the minimum and maximum release rates estimates found from mass release profiles determined by the other two devices. This is a very exciting and potentially very valuable property of the heat exchanger device as it could mimic a variety of conditions. After the conclusion of each experiment, the device was carefully washed, and the solution collected to check for ibuprofen deposits on the surface of the glass. None were found.

The effect of the blinking motion was also evaluated by varying the blink frequency of dynamic release experiments with a fluid flow rate of 2 mL/min and temperature of 34ºC. The blink frequencies used were 0, 1, 6, and 15 blinks/min (***Figure 7.9***). There was a significant effect on the release rate as the frequency of blinking was increased. The release profiles determined with no blinking motion and a rate of 1 blink/min were statistically the same. The release rate observed was approximately 2.2 µg/hr. This rate was approximately a third of the release rate observed previously (*6 µg/hr*) with the same flow rate and a blinking rate of 1 blink/sec. The difference is explained by the wetting of the

surface of the lens caused from the eyelid material spreading the release media across the top of the lens. At lower blink rates, the lens surface dried out in a manner reminiscent of that observed when a lenses placed on the human eye. Increasing the blink rate to 15 blinks/min resulted in a greater level of hydration of the surface of the lens and increased the mass release to 8 µg/min (*4x greater that the release without blinking*).

The heater exchanger device was shown to have high value for *in vitro* determination of the mass release profile of ibuprofen from the lenses. The device was shown to have numerous advantages over the previous continuous flow device design. The release rates for ibuprofen in the large volume, static sink model were by far the greatest, as was expected. However, a surprising result was found comparing the release profiles from the heat exchanger device and the microfluidic device. It was expected that the release rate from the microfluidic device would be greater than that found in the heat exchanger. There is a greater volume of release media within the microfluidic device with a high degree of contact with the lens and for longer periods than seen in the heat exchanger. However, this was not the case, except for at the very lowest flow rates available on the heat exchanger device. The best explanation of this phenomena was by the very low solubility of ibuprofen in water. Within the microfluidic device, there is a reservoir of 175 µL would be greater than that found in the heat exchanger. However, this was not the case, except for the lowest flow rates available on the heat exchanger device. The best explanation of this phenomena was by the very low solubility of ibuprofen in water. Within the microfluidic device, there is a reservoir of 175 µL of release media in the device, which gradually being renewed through a slow flow rate of fresh media.

This results in a steady concentration of the eluting molecule within the fluid reservoir, lowering the concentration-based driving force by a small fraction, whereas the novel design of the heat exchanger device introduced a smaller volume of release media with lower degree and duration of contact with the lens, but the fluid was always kept fresh and no steady concentration of ibuprofen could build up around the lens to lower the release rate. Thus, the concentration gradient driving force was always kept high. For a highly hydrophobic molecule, this could result in a higher rate of release in the heat exchanger device than seen in the microfluidic device. However, it is probable that the reverse would be observed with the release of a more water soluble molecule.

7.4.3.2. Release Of 120 KDa HPMC From Imprinted DMS-R11 Lenses

To fully demonstrate the value of the device, the release of other molecules of different molecular weights and solubility's from DMS-R11 lenses was performed to show the versatility of the device. HPMC (*120 KDa*) was selected as a template molecule and incorporated into imprinted lenses at various M/T ratios. Release of HPMC from imprinted molecules in the Sotax® Dissolution Apparatus and microfluidic device were presented and discussed in **Chapter 6** and can be seen in **Figure 7.10** and **Figure 7.11**. The release profiles found from the heat exchanger device under the standard protocol were found and can be seen in **Figure 7.12**.

HPMC-imprinted DMS-R11 lenses were synthesized to various M/T mass ratios in **Chapter 6,** and dynamic release studies were performed in a large volume, static sink (*250 mL DI water*). Application of molecular imprinting principles to the silicone hydrogel material resulted in control over the biphasic structure and polymer morphology and therefore the physical properties of the lens and granted a high degree of control over the

mass release rate of HPMC from the lens. The imprinted DMS-R11 lenses were designed for use as daily disposable lenses, and it was demonstrated that the release rate be tailored to delivered varied amounts of HPMC in a 24 hour period. The M/T mass ratios used to formulate the lenses were 0, 1, 2, 3, and 4, and the corresponding hourly mass release rates were found to be 87.5, 66, 33, 25, and 10.5 µg/hr, respectively. Lenses of the same compositions were created and placed in the microfluidic device for determination of the mass release under small sink, continuous flow conditions (***Figure 7.11***). The mass release rate of HPMC under these conditions were found to be as follows: 26.5 µg/hr (*M/T = 0*), 21.3 µg/hr (*M/T = 1*), 11.9 µg/hr (*M/T = 2*), 5.4 µg/hr (*M/T = 3*), and 2.3 µg/hr (*M/T = 4*).

Identical HPMC-imprinted lenses were placed on the heat exchanger device, and the release conditions were set to the standard protocol (*temperature= 34ºC, blink rate = 6 blinks/min, and flow rate = 2 mL/min*). The average mass release rate was shown to decrease with increasing M/T ratios (***Figure 7.12***), as was also demonstrated in both the Sotax® Dissolution Apparatus and in the microfluidic device. However, the release rates were significantly lower than observed in the other models. The average mass release rate per hour were found to be 10.2 µg/hr (*M/T = 0*), 6.8 µg/hr (*M/T = 1*), 4.9 µg/hr (*M/T = 2*), 1.91 µg/hr (*M/T = 3*), and 0.87 µg/hr (*M/T = 4*). The microfluidic mass release rates were found to approximately 3 times larger than those determined with heat exchanger device, and the Sotax® release rates were found to be 10-25 times greater than those found from the heat exchanger device.

7.4.3.3. Release Of Other Diverse Molecules From DMS-R11 Control Lenses

In addition, a selected set of diverse molecules (*trehalose, aspirin, acetaminophen, prednisolone, naphozoline HCl, and chloramphenicol*) were incorporated into DMS-R11

and placed on the heat exchanger device. The selected molecules represented diverse solubility's and are as follows: trehalose dehydrate - 689 mg/mL, aspirin - 3 mg/mL, acetaminophen - 13 mg/mL, prednisolone – 0.5 mg/mL, naphozoline HCl - 170 mg/mL, and chloramphenicol - 2.5 mg/mL. Evaluation was performed under the standard protocol (*temperature= 34ºC, 1 blink/10 sec, and a flow rate of 2 mL/min*). To avoid repetitive discussion, the profiles are presented in **Figure 7.13**. Demonstration of the release profiles without the additional analysis and discussion performed and provided in the ibuprofen section (***Section 7.4.3.3.***) was sufficient to show the high value of the heat exchanger device. The mass release rate correlated strongly to the solubility of the molecule in water. The mass release duration of trehalose dihydrate was extended by up to 8-12 hours, approximately 2 times longer, than the same duration seen from the microfluidic device (*discussed in **Chapter 6***). No loss of drug due to adhesion to the surface was observed for any of the presented molecules. With these molecules, 120 KDa HPMC, and ibuprofen, the potential high value of the variable flow rate device design demonstrated the versatility for the *in vitro* characterization of drug-eluting lenses. Different sink conditions were shown to be approximated in a single device by altering the flow rate and blink rate variables, the first time such a demonstration has been shown.

The release rates for 120 KDa HPMC were found to be greatest in the Sotax® Dissolution Apparatus (*large volume, static sink, temperature = 34°C*) followed by the small volume, continuous flow microfluidic device (*small volume, continuous flow, temperature = 20°C*) and then by the heat exchanger variable flow, continuous flow device (*flow rate of 2 mL/min, 6 blinks/min, and temperature = 34°C*). As discussed in **Section 7.4.3.1.**, ibuprofen demonstrated a separate trend where the release rate found in the heat

exchanger device were greater than the release rates found in the microfluidic device. It was discussed that the low water solubility of ibuprofen resulted in an artificially low concentration gradient driving force, while the continuous flow of pure DI water produced in the heat exchanger device allowed for a higher driving force for the release rate. The behavior observed with 120 KDa HPMC is consistent with this explanation.

7.4.4. Release Of Multiple Molecules From A Single, Imprinted Contact Lens Under The Conditions Of The Heat Exchanger Device

Molecularly imprinted lenses incorporating multiple molecules into a single lens were described in **Chapter 6**, and the mass release within the Sotax® Dissolution Apparatus are presented in **Figure 7.14**. The final demonstration of lens release on the heat exchanger device was from these lenses. The combination of molecules selected were 120 KDa HPMC, trehalose, ibuprofen, and prednisolone. The individual mass release profiles of trehalose, ibuprofen, and prednisolone from DMS-R11 control lenses were presented in **Figure 7.13**. Release of 120 KDa HPMC from imprinted DMS-R11 lenses with a M/T ratio of 4 were presented in **Figure 7.12**. The combination of molecules were incorporated into imprinted lenses where acrylic acid (*AA*) was used as a hydrophilic functional monomer and equal masses of methacrylic acid (*MAA*) and 4-vinylphenol (*4-VP*) were used for imprinting within the hydrophobic phase. The M/T ratio for both phases [*AA/(120 KDa + trehalose) and (4-VP+MAA)/(ibuprofen + prednisolone)*] were individually set at 4. Greater detail about the identification of these M/T ratios are provided in **Chapter 6.** The release conditions followed the standard protocol. The results are shown in **Figure 7.15.** The mass release rates for each molecule are 2 µg/hr (*120 KDa HPMC*), 8 µg/hr (*trehalose*), 3 µg/hr (*prednisolone*), and 4.3 µg/hr (*ibuprofen*). However, further study is

needed defining the relationship between the release profiles determined between the different environmental models and the *in vivo* release profiles.

7.5. Potential For Further Development

This chapter focused on the production and evaluation of a novel variable flow, continuous flow, blinking device for the *in vitro* approximation of *in vivo* ocular conditions. The design of the device tried to incorporate methods to overcome drawbacks observed with the previous microfluidic device technology. The results produced with the device are very exciting and supports that the development of similar automaton devices is potentially very valuable to the field. However, both of the designs described within the chapter are still within the prototype stage. There were several observed points where an improvement to the current prototype design could be implemented to improve the versatility and performance of the next generation prototype. These points are described below.

The rate of the model tear flow was determined via a Cole-Parmer® peristaltic pump and, once selected, the flow rate was constant during the entire experiment duration. Though no problems were observed in the operation of the pump or device, it is not desirable that the peristaltic pump remain independent of regulation from the Arduino® microcontroller. Future device designs and protocols will incorporate some pumping module(s), allowing the microprocessor to regulate both the operation and the instantaneous pump flow rate as well as allowing the microprocessor to record the pump performance and fluid flow rate in a text file. Such a module would consist of either an Arduino®-compatible variable flow pump or of an Arduino®-compatible stepper motor converted into a centrifugal pump.

7.6. Conclusions

The heat exchanger release device is shown to have high potential value as application as a novel device to measure mass release profiles from drug-eluting contact lenses. The prototype was found to be capable of producing flow rates between 0.1 and 10 mL/min and flow could be altered easily through manipulation of the peristaltic pump. The novel design improved upon previous work by as the device is reusable, whereas the previous device had to created specifically for each experiment and discarded afterward, in addition, other improvements included that the device was capable of reproducing vertical fluid flow in a manner similar to that experienced by a lens placed on the eye, eliminating the reservoir of release media volume that surrounds the lens, the addition of a variable blinking action that rewets the lens surface in a similar manner as the eye, ability to set a desired temperature, the attachment of several environmental sensor modules, and other advantages. Varying the flow rate of the device was shown to reproduce release profiles characteristic of large volume, static sinks and of small volume sinks. Release of a diverse set of molecules were demonstrated to release without any complications. Though the potential value was demonstrated, several observations for potential improvements to the device operation and versatility were found and noted for the creation of future prototypes.

7.6. Tables

Table 7.1. Advantages Of Release Devices

Model	Example Device	Advantages	Drawbacks
Small Volume, Static Sink	**Sample Vial Centrifuge Tube**	**Simple**	**False Kinetics**
Large Volume, Static Sink	**Sotax® Dissolution Apparatus**	**True Kinetics**	**Not Good Model For *In Vivo* Conditions**
Small Volume, Continuous Flow Sink	**Microfluidic Device**	**Better Approximation For *In Vivo* Conditions**	**No Definite *In Vivo* Correlation**
Variable Flow, Continuous Flow Sink	**Heat Exchanger Device**	**Variable Flow Better Approximation For *In Vivo* Conditions Blinking Mechanism Ability To Approximate Diverse Models**	**No *In vivo* Correlation**

7.7. Figures

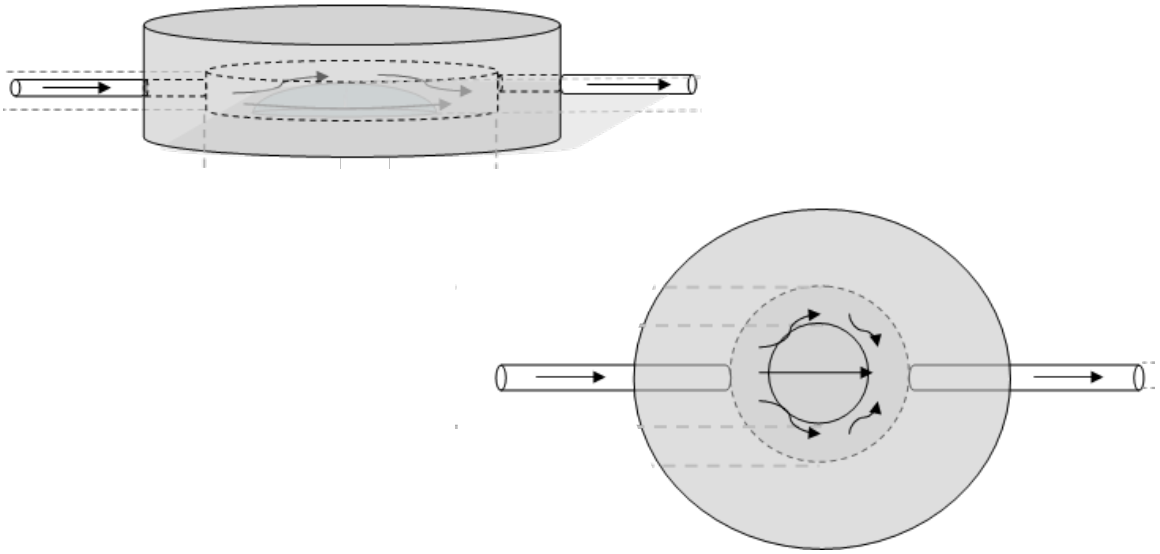
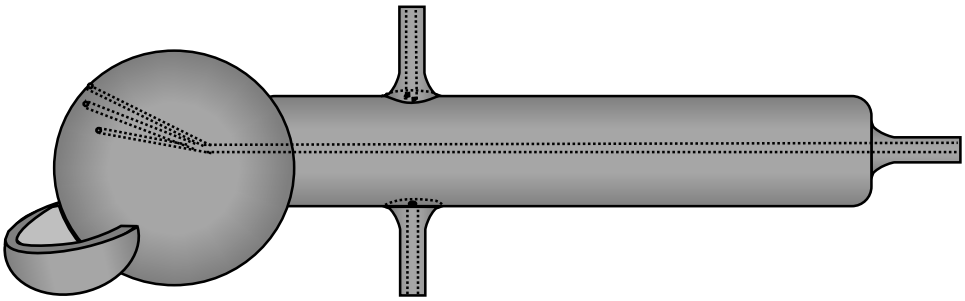


Figure 7.1. Schematic Of The Microfluidic Device

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.

A.



B.

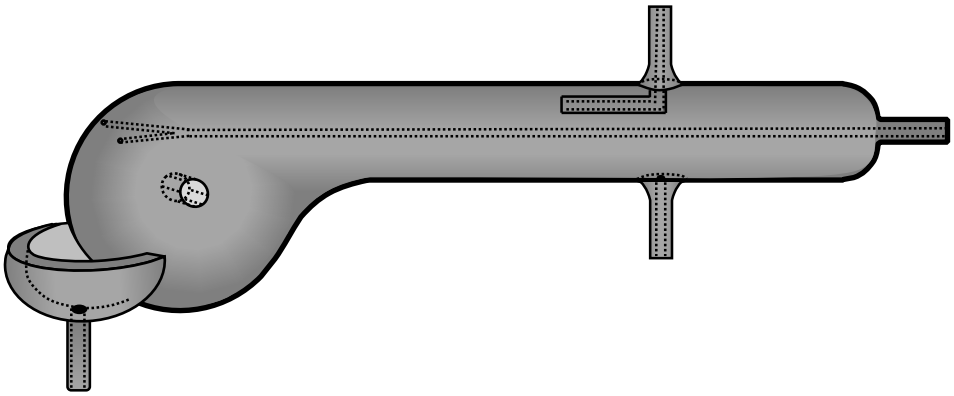


Figure 9.2. Schematic Of The Heat Exchanger Glass Body

The schematic for the glass heat exchangers for both Design 1 and Design 2 are shown in **Figures 9.5A** and **9.5 B**, respectively. The measurements are as follows:

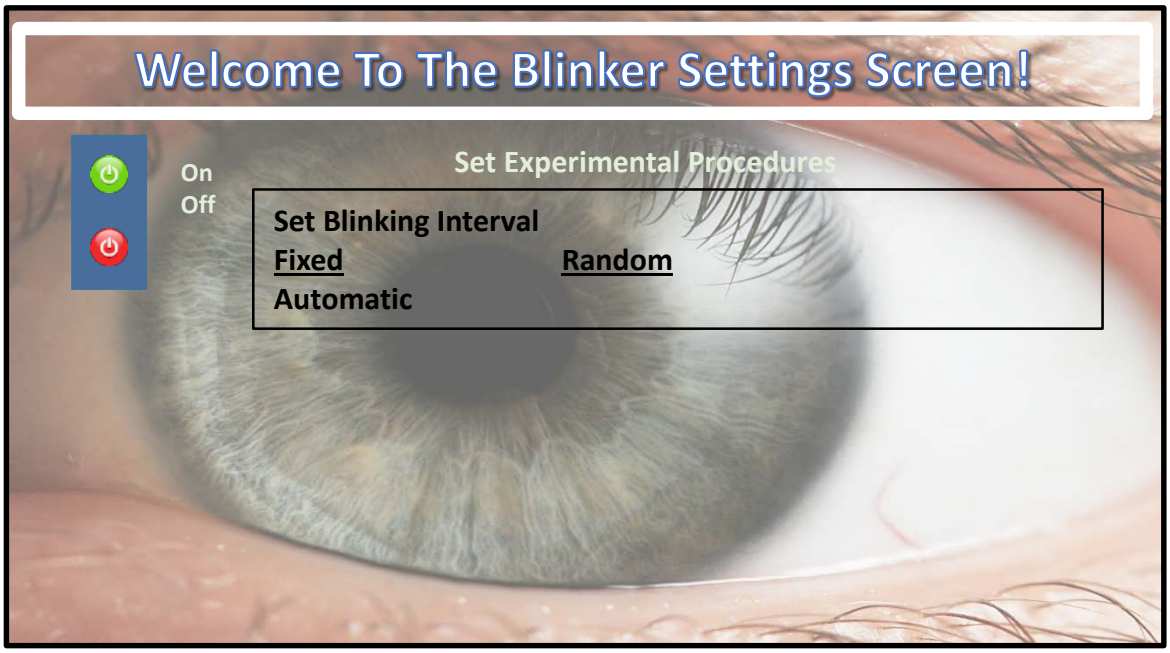


Figure 7.3. iPad/Tablet App User Interface Screen

A tablet app was created with Adobe® InDesign (Creative Suite 6) software and loaded onto an Apple® iPad, 4th generation with Retina Display to allow for the operation of the heat exchanger device via a Bluetooth connection between the tablet and the Arduino® microcontroller via the RedBearLab Bluetooth Low Energy (*BLE*) Shield installed on the microcontroller. The user interface allowed the desired experimental protocol to be set including experiment duration, blink rate, interval between blinks, periods of sleep, computer usage, etc via either pre-programmed protocols or by setting custom values.

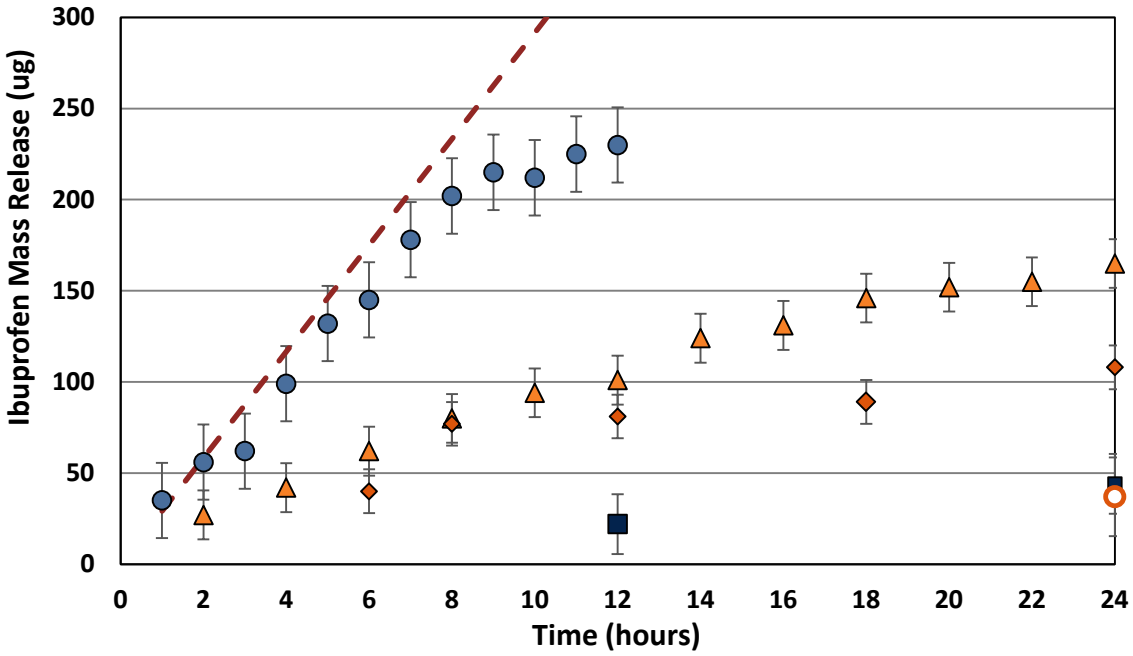


Figure 7.4. Demonstration Of The Effect Of Equilibrium Between The Release Media And The Lens Reservoir On The Mass Release Rate Of Ibuprofen Over A 24 Hour Period In A Large Volume, Static Sink

Dynamic mass release experiments showing the mass release profile of ibuprofen from DMS-R11 control lenses within the Sotax® Dissolution Apparatus with a large volume (*600 mL*) of static release media (*DI water*). Initially, the release media was completely exchanged daily (◎) for 3 days (*only first 24 hours shown*), and the mass release rate was found to be relatively constant over the 72 hour period at an average rate of 37 µg/day or 1.5 µg/hr. However, the low water solubility of ibuprofen in water necessitated a series of experiments to confirm that no equilibrium effects were artificially delaying the release rate. The media replacement interval for the 600 mL of DI water was increased over each series from 24 hours to 12, 6, 2, and 1 hour. A large increase in the mass release rate was observed as is shown in Figure 9.10. The mass release rates increased from 1.5 µg/hr (◎, *24 hours*) to 1.8 µg/hr (■, *12 hours*), 6 µg/hr (◆, *6 hours*), 10 µg/hr (▲, *2 hours*), and 25

µg/hr (●, *1 hours*). The release rate at a replacement interval of 0 hours or continuous flow of fresh release media was found by extrapolation to be 29 µg/hr (▬ ▬ ▬, 0 hours). The rate of 29 µg/hr was assumed to be the fastest possible rate of release for ibuprofen from the DMS-R11 control lenses. Great care was taken to ensure that the proper kinetics of release were found for the release of ibuprofen in later experiments.

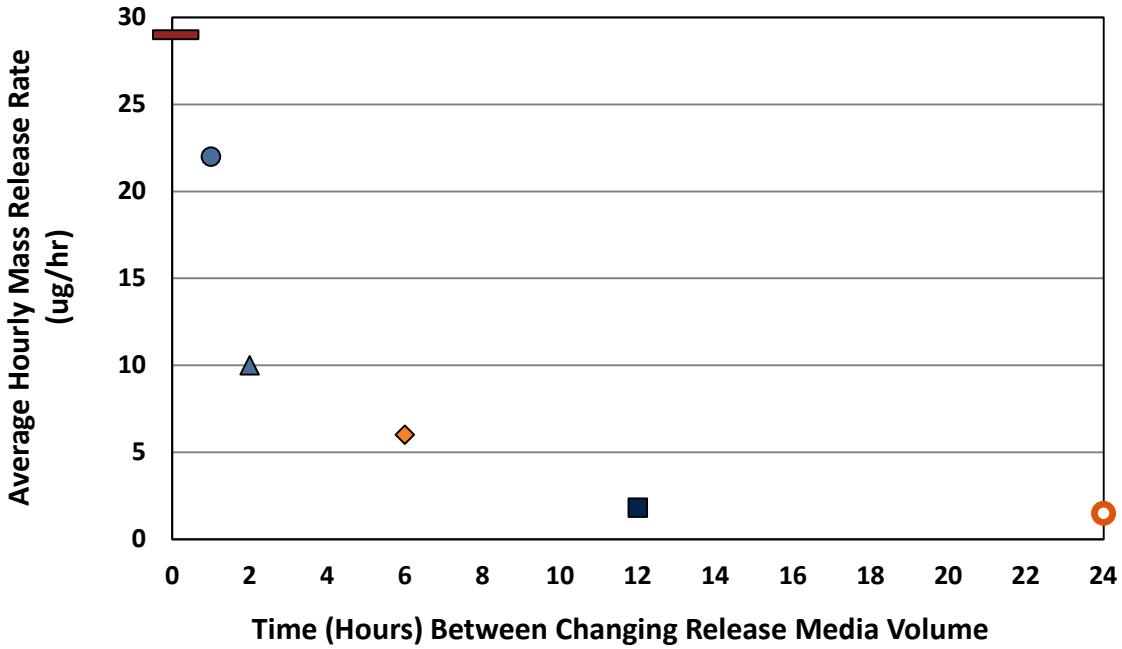


Figure 7.5. Release Of Ibuprofen For 24 Hour Period In A Large Volume, Static Sink

Average hourly release rate of ibuprofen in 600 mL of static DI water (*temperature= 34ºC*). A power law relationship is evident between the time interval and mass release rate. The represented data points are 24 hours (●), 12 hours (■), 6 hours (◆), 2 hours (▲), 1 hour (●), and an extrapolated value for 0 hours (▬).

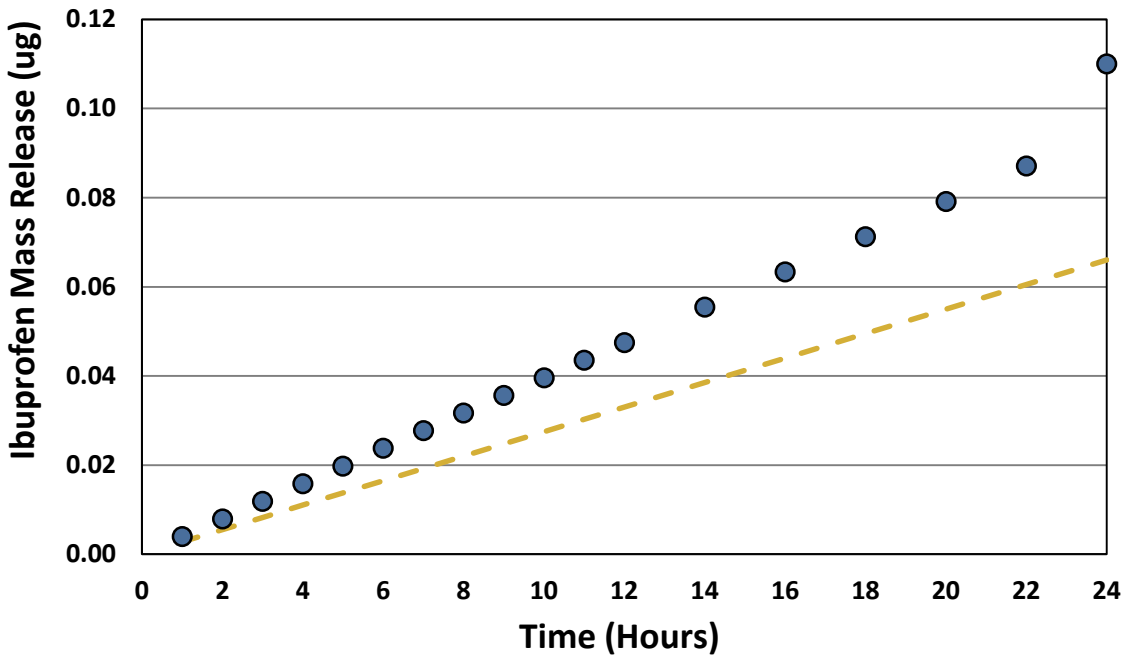


Figure 7.6. Ibuprofen Mass Release Under Small Volume, Continuous Flow Model

The mass release of ibuprofen within the (●) microfluidic device (*temperature = 20ºC*). The average hourly mass release rate was found to be approximately 3.5 µg/hr. The release rates found in the 600 mL of release media and in the 175 µL reservoir within the microfluidic device were used to estimate the (▬) lowest possible release rate of 2.3 µg/hr.

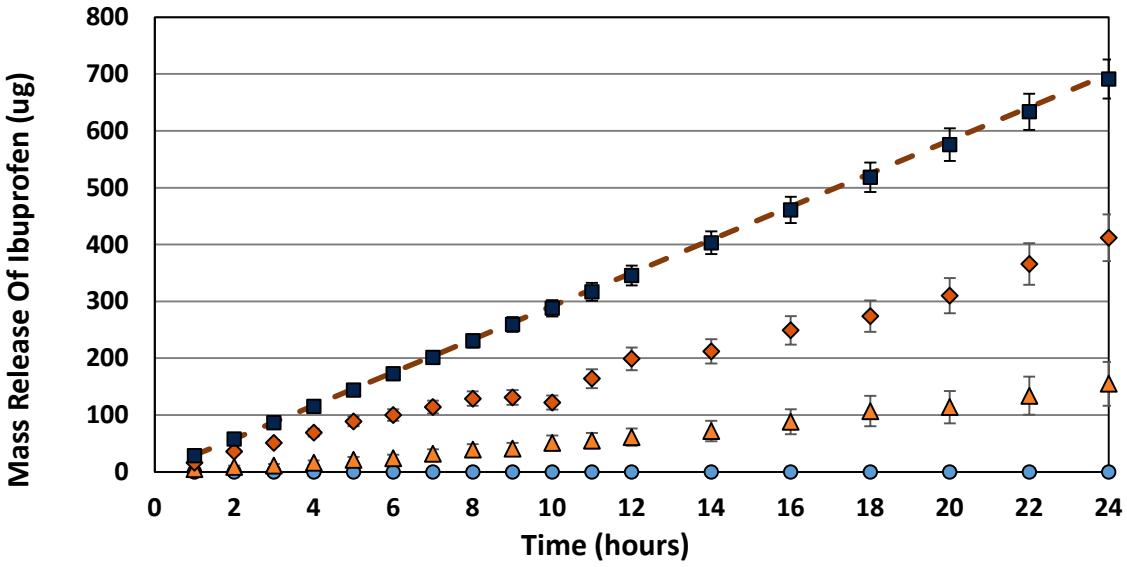


Figure 7.7. Ibuprofen Mass Release Profiles Undergoing Various Volumetric Flow Rates

Ibuprofen mass release profiles are shown eluting from DMS-R11 control lenses when placed on the front, center of the heat exchanger device. Experiments were performed to evaluate the release of ibuprofen at different volumetric flow rates were conducted with the device at 34ºC and a blinking rate of 6 blinks/min. The flow rates selected were 0.2 (●), 2 (▲), 5 (◆), and 10 mL/min (■). The mass release rates were 3.42 µg/hr, 6.5 µg/hr, 17.2 µg/hr, and 29 µg/hr, respectively. An important observation was that the flow rate at the 0.2 mL/min approximated the ibuprofen release rate observed with the microfluidic device (*3.5 µg/hr*), while the mass release rate (*29 µg/hr*) found with largest flow rate (*10 mL/min*) tested on the heat exchanger device approximated the estimated fastest possible release rate of ibuprofen (*29 µg/hr*). This indicated that a wide variety of sink conditions could be recreated due to the variable flow rates available to the new device.

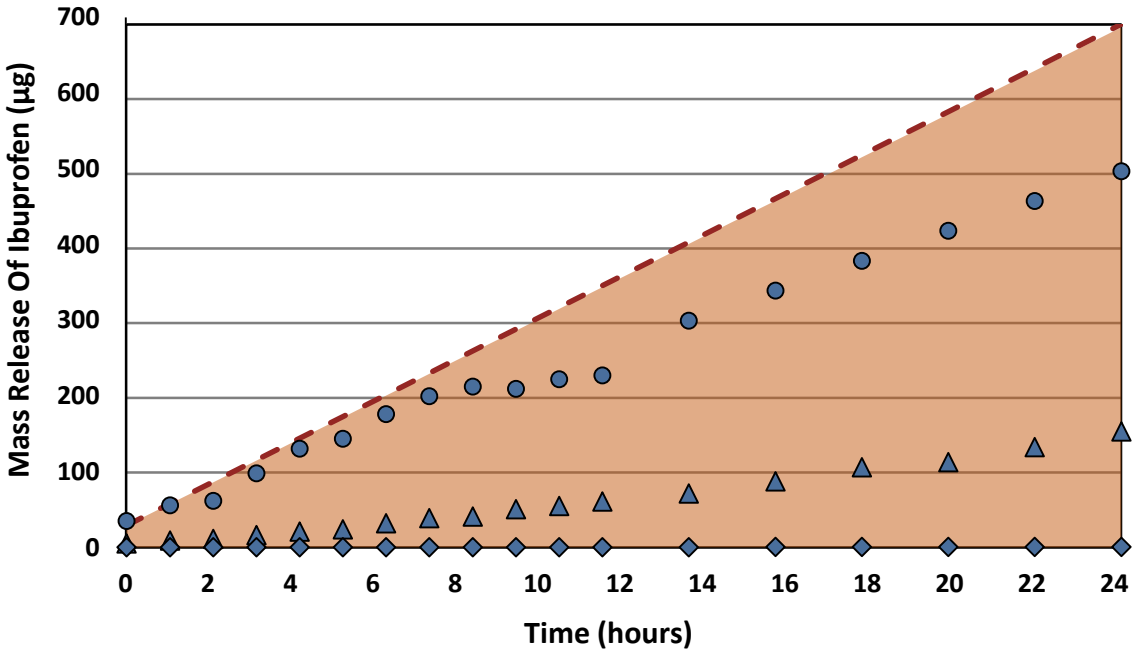


Figure 7.8. Comparison Of Mass Release Profiles For Ibuprofen Within The Sotax® Dissolution Apparatus, The Microfluidic Device, And The Heat Exchanger Device

The mass release profiles of ibuprofen obtained from the various *in vitro* devices are presented for easy comparison. The devices and the respective release conditions are the (●) Sotax® Dissolution Apparatus with large volume (*600 mL*), static sink model (*temperature = 34°C*) with complete release media replacement every hour, (▲) the heater exchanger variable flow, continuous flow device (*temperature = 34°C, blink rate of 6 blinks/min, flow rate of 2 mL/min*), and the small volume, continuous flow (◆) microfluidic device (*temperature = 20°C, flow rate of 3 µL/min*). It is evident that the devices result in very different mass release profiles. However, the shaded area (▯) represents the mass release profiles obtained by altering the volumetric flow rate of the DI water through the device. The estimated maximum mass release rate of ibuprofen from the DMS-R11 control lens is represented by the dotted line (▬ ▬ ▬). The heat exchanger

device is demonstrated to have high value for the release of ibuprofen, as several different sink conditions were approximated in a single, reusable device.

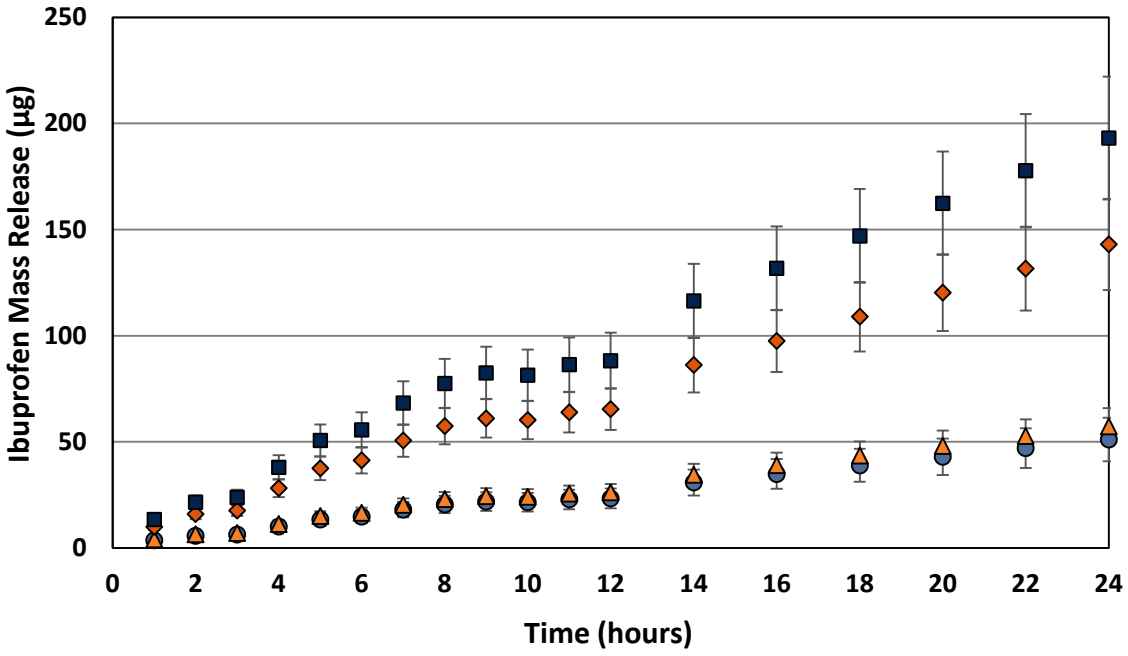


Figure 7.9. Comparison Of Mass Release Profiles Within The Heat Exchanger Device Experiencing Different Blink Rates

The effect of the blinking mechanism on the mass release profile was evaluated by varying the blink rate between (●) 0, (▲) 1, (◆) 6, and (■) 12 blinks/min. A significant impact on the mass release profile of ibuprofen was achieved by this control over the blink rate. Increasing the blink rate from 0 blinks/min to 12 blinks/min increased the average mass release rate by a factor of 4. The motion of the model eyelid was observed to wet the surface of the lens with the release media in a manner reminiscent of the phenomena observed *in vivo* with the actual eyelid. The thickness of the lens was much greater than that of the fluid film, resulting in a tendency for the fluid to flow around the sides of the lens rather than across the surface. This resulted in lower degrees of contact between the fluid film and the lens as well as the gradual dehydration of the greater fraction of the lens surface area. At 2 mL/min flow rate, the lens visibly dried out during lower blink rates, whereas the greater

blink rates maintained a higher degree of contact between the release media and the lens, allowing a greater rate of mass release.

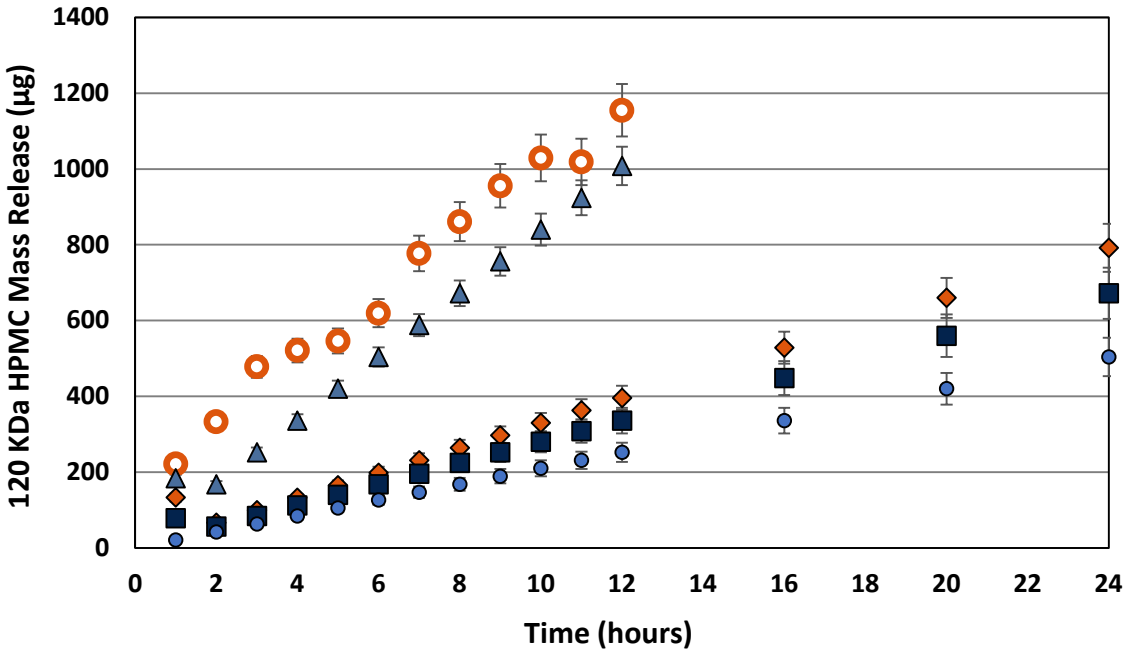


Figure 7.10. Mass Release Profiles For 120 KDa HPMC From DMS-R11 Imprinted Lenses In The Sotax® Dissolution Apparatus

HPMC (*120 KDa molecular weight*) was incorporated into DMS-R11 imprinted lenses where the functional monomer selected to create high affinity memory sites was acrylic acid. The process of imprinting and the selection and development of these lenses is described in much greater detail in **Chapter 6**. HPMC-imprinted lenses were synthesized at different M/T ratios, including (◎) 0, (▲) 1, (◆) 2, (■) 3, and (●) 4 and placed in 250 mL of DI water (*temperature = 34°C*). The mass release rate decreased 93.5 µg/hr, 84 µg/hr, 33 µg/hr, 28 µg/hr, and 21 µg/hr.

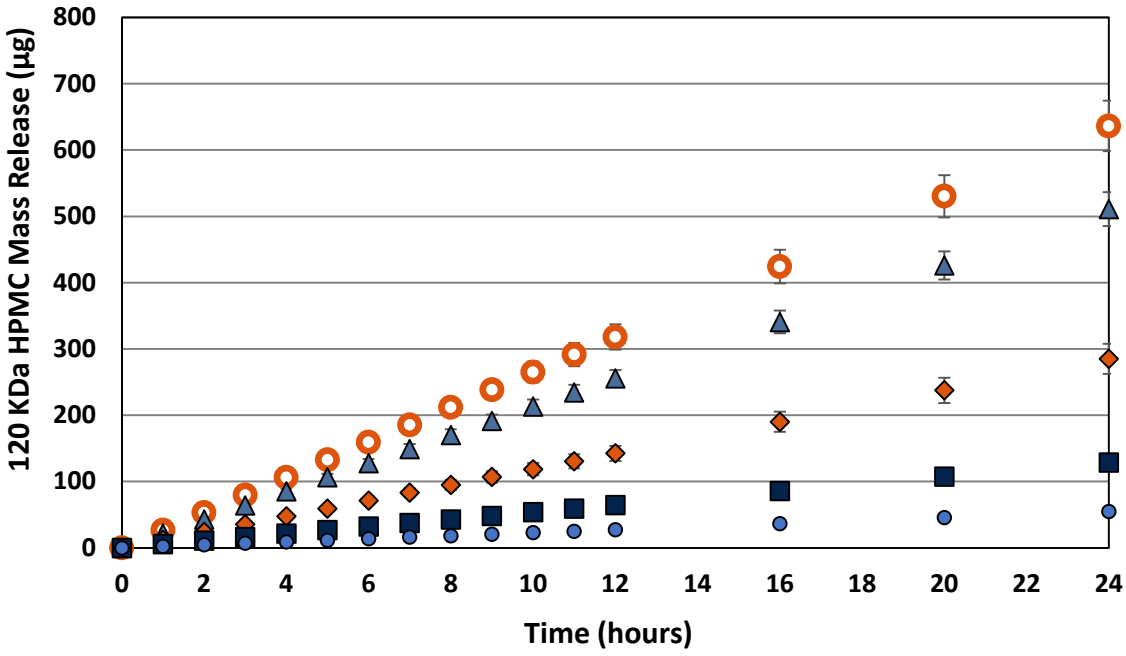


Figure 7.11. Mass Release Profiles For 120 KDa HPMC From DMS-R11 Imprinted Lenses In The Microfluidic Device

Identical HPMC-imprinted lenses [*with M/T ratios of* (◎) 0, (▲) 1, (◆) 2, (■) 3, *and* (●) 4] to those evaluated in **Figure 7.10** were placed in the small volume, continuous flow microfluidic device (*temperature = 20°C, flow rate of 3 µL/min*). The mass release rate was shown to decrease with increasing M/T ratio in a similar manner seen in **Figure 7.10**. The release rate within the small volume, continuous flow was, on average, 5 times slower than the release rate observed in the Sotax® Dissolution Device. The release rates for each lens series were found to be 26.5 µg/hr (*M/T – 0*), 21.3 µg/hr (*M/T – 1*), 11.9 µg/hr (*M/T – 2*), 5.4 µg/hr (*M/T – 3*), and 2.3 µg/hr (*M/T – 4*).

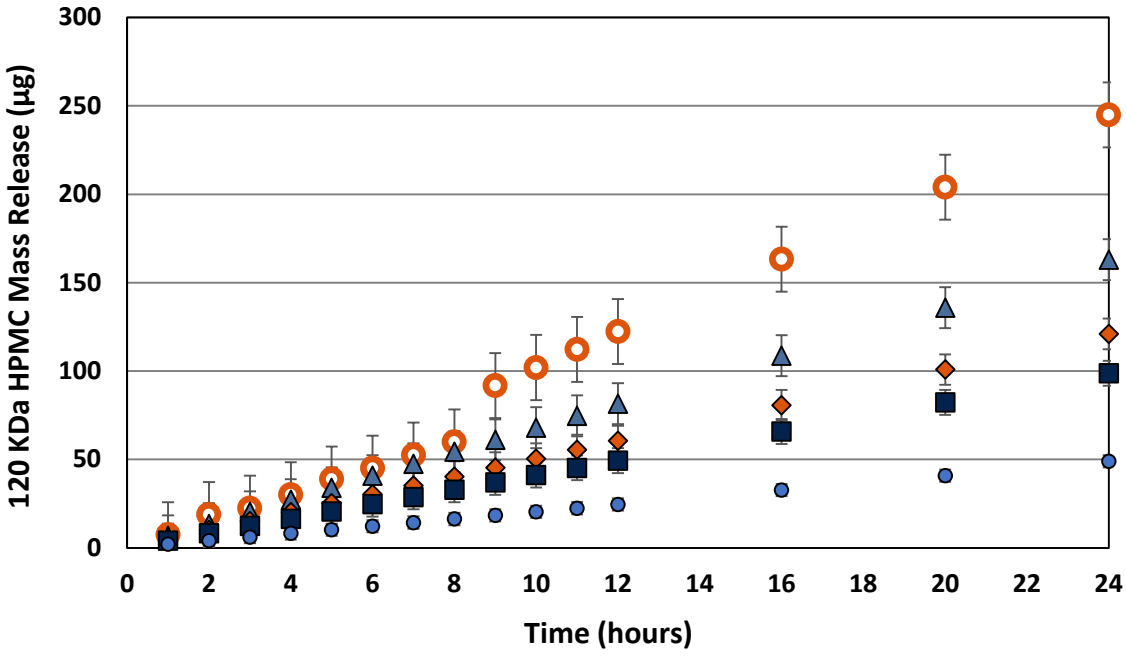


Figure 7.12. Mass Release Profiles For 120 KDa HPMC From DMS-R11 Imprinted Lenses In The Heat Exchanger Device

The same series of HPMC-imprinted lenses [*M/T ratios of* (◎) 0, (▲) 1, (◆) 2, (■) 3, *and* (●) 4] were evaluated for mass release under the novel heat exchanger device (*temperature = 34°C, blink rate of 6 blinks/min, flow rate of 2 mL/min*). The mass release rates were found to be approximately half of the respective rates found from the microfluidic device. The mass release rates were found to be 10.2 µg/hr (*M/T – 0*), 6.8 µg/hr (*M/T – 1*), 5.0 µg/hr (*M/T – 2*), 4.1 µg/hr (*M/T – 3*), and 2.0 µg/hr (*M/T – 4*).

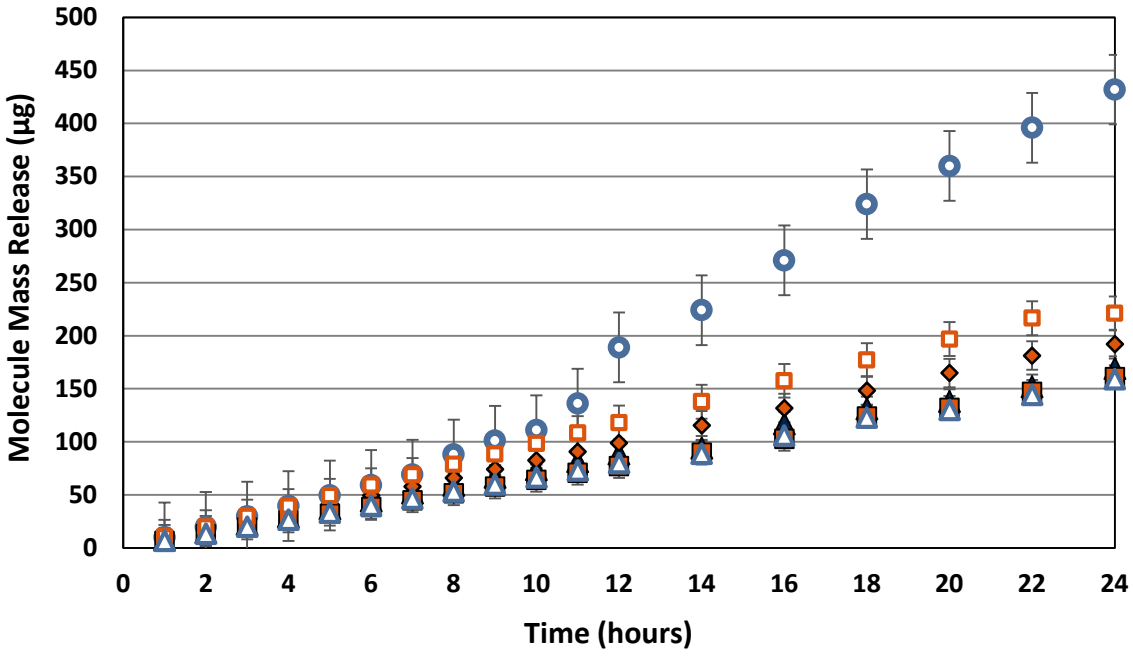


Figure 7.13. Mass Release Profiles Of A Set Of Diverse Molecules From DMS-R11 Control Lenses In The Heat Exchanger Device

Mass release profiles for release of (◎) trehalose, (▲) aspirin, (◆) acetaminophen, (■) prednisolone, (▣) naphozoline HCl, and (△) chloramphenicol from DMS-R11 control lenses under the standard protocol conditions of the heater exchanger device. The average hourly mass release rate under 2 mL/min flow conditions were found to be 18 µg trehalose/hr, 7 µg aspirin/hr, 8 µg acetaminophen/hr, 6.7 µg prednisolone/hr, 9 µg naphozoline HCl/hr, and 6.6 µg chloramphenicol/hr.

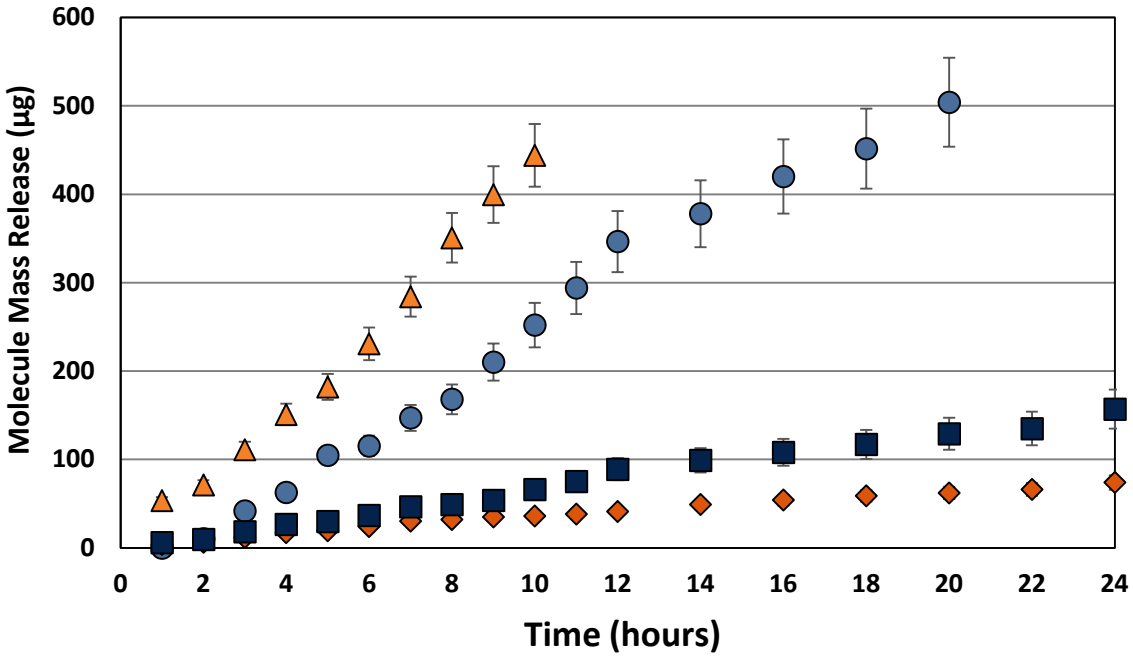


Figure 7.14. Mass Release Profiles Of A Diverse Molecules From A Single Imprinted, DMS-R11 Lenses Within The Sotax® Dissolution Apparatus

A set of 4 diverse molecules were incorporated into a molecularly imprinted DMS-R11 lens. The molecules included (▲) trehalose, (●) HPMC, (■) ibuprofen, and (◆) prednisolone. Trehalose and HPMC memory sites form primarily in the hydrophilic phase, while memory sites for ibuprofen and prednisolone are predominantly located in the hydrophobic areas. The hydrophilic imprinting monomer selected was acrylic acid, well to hydrophobic imprinting monomers were selected and included methacrylic acid and 4–vinylphenol. The mass ratio of acrylic acid to hydrophilic template was formulated to a value of 4. Both the mass ratio of methacrylic acid to prednisolone and the mass ratio of 4–vinylphenol to ibuprofen were individually set to a value of 2. The synthesized lenses had high optical clarity and adequate mechanical properties. Once the solvent was removed from the cured lenses, the lenses were transferred to the Sotax® Dissolution Apparatus and placed in 600 mL of DI water (*temperature = 34ºC*) where dynamic mass release studies

were performed. To ensure proper sink environment for both the ibuprofen and prednisolone, the release media was replaced hourly. This also ensured sufficient sample volume to determine the solution concentration of all molecules. As expected, the highly hydrophilic templates, trehalose and 120 KDa HPMC, had much greater mass release rates than the 2 hydrophobic molecules. The average hourly release rate for the molecules are 44 μg trehalose/hr, 25 μg 120 KDa HPMC/hr, 6.5 μg ibuprofen/hr, and 3 μg prednisolone/hr.

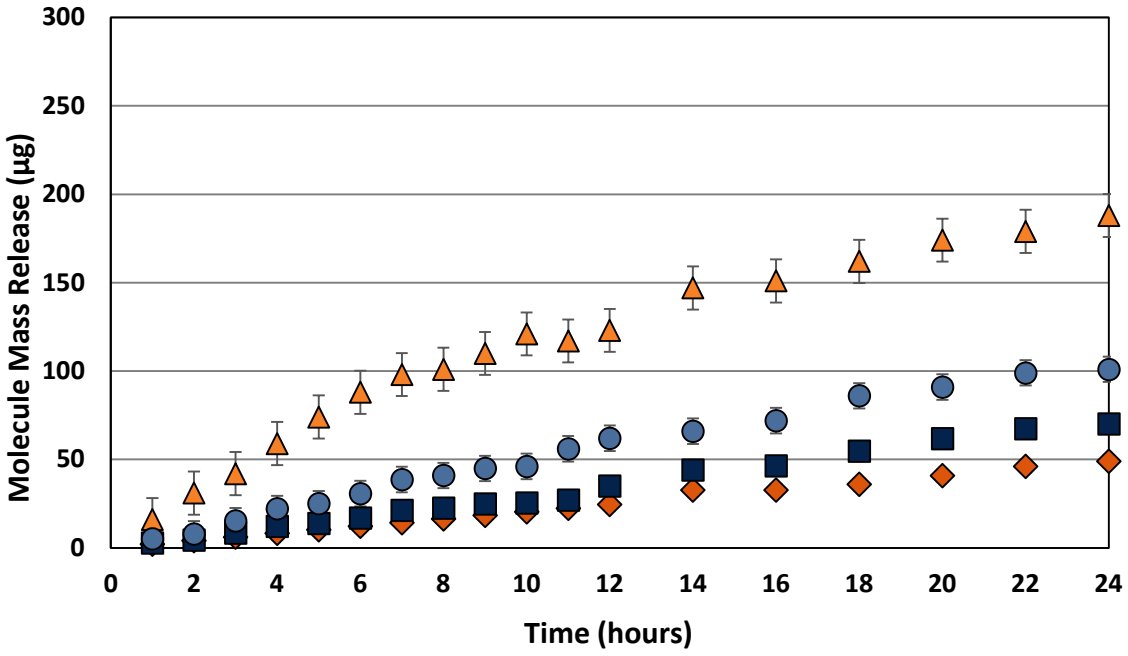


Figure 7.15. Mass Release Profiles Of A Diverse Molecules From A Single Imprinted, DMS-R11 Lenses Within The Heat Exchanger Device

The same formulation for the molecularly imprinted, DMS-R11 contact lenses containing a mixture of 4 diverse molecules shown in **Figure 7.14** were place on the heat exchanger device, where the dynamic release studies were repeated under the standard protocol for the device. The molecules included (▲) trehalose, (●) HPMC, (■) ibuprofen, and (◆) prednisolone. The average hourly release rate for the molecules were found to be 7.8 µg trehalose/hr, 25 µg 120 KDa HPMC/hr, 6.5 µg ibuprofen/hr, and 3 µg prednisolone/hr.