Silicone Hydrogels and their use as Ophthalmic Drug Delivery Systems

Silicone Hydrogels and their use as Ophthalmic Drug Delivery Systems

By

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A Thesis Submitted to the School of Graduate Studies In Partial Fulfillment of the Requirements For the Degree Master of Applied Science

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ABSTRACT

Despite the long history of topical eye drops and their use in delivering therapeutic agents to the anterior of the eye, efficient sustained delivery continues to be an elusive goal. The robust and effective clearance mechanisms that the eye is endowed with are significant delivery challenges and result in short drug residence times and low ocular bioavailability. The work carried out in this thesis focused on developing, synthesizing and characterizing silicone hydrogels and evaluating their potential as drug eluting inserts for more effective delivery of ocular pharmaceuticals. The first strategy (Chapter 2) focused on incorporating a novel hydrogel additive, hyaluronic acid, to promote hydrogel-drug ionic interactions that can function to increase drug loading and subsequent release dosage. Hydrogels composed of a hydrophilic monomer, N,Ndimethlacrylamide (DMA) or 2-hydroxyethyl methacrylate (HEMA), and a hydrophobic monomer, methacryloxypropyltris(trimethylsiloxy)silane (TRIS), were used as model contact lenses. By combining ionic interactions with molecular imprinting techniques within a single hydrogel, it was shown that this can produce a compound effect on drug uptake and release. Although greater control over release dosage was achieved, there was limited capacity for these materials to delivery timolol for extended periods with drug release occurring rapidly over a period of 1-2 days. However, there were clear differences in the release duration from the p(DMA-co-TRIS) and p(HEMA-co-TRIS) hydrogel formulations. Therefore, the second study (Chapter 3) aimed to better understand the relationship between the hydrogel chemical composition and the resultant material properties on the drug release characteristics. A range of hydrogels were synthesized with varying hydrophilic and hydrophobic monomers, which were then characterized by their water content, transparency, optical haze and surface wettability. The previous generation materials were evolved by incorporating a modified siloxy methacrylate TRIS(OH), a methacrylated polydimethylsiloxane macromonomer (mPDMS) and a polymerizable silicone surfactant (ACR). The properties of the hydrogels were dramatically affected by the nature and relative contribution of hydrophobic and hydrophilic monomers. The release of dexamethasone (DEX), an anti-inflammatory medication, was shown to vary significantly depending on the hydrogel formulations; often displaying faster release in high water content materials and slow release in low water content hydrogels. The mechanism of diffusion for lipophilic DEX in these hydrogel systems appeared to be through the internal aqueous network channels within the bulk. Over the range of hydrogels formulations that were tested, the release from them varied from approximately seven days to greater than two weeks.

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DECLARATION OF ACADEMIC ACHIEVEMENT

Chapter 1: The literature review was researched, planned, prepared and written by Giuliano Guidi. Ben Muirhead prepared Figure 1-3 and Figure 1-5. Stefan Paterson assisted with the editing of the final draft.

Chapter 2: The hydrogel synthesis, characterization (water content, transparency, contact angle measurements), drug release testing and all subsequent data analysis was performed by Giuliano Guidi. The manuscript was also written solely by Giuliano Guidi with Myrto Korogiannaki proving insight into results discussion. Stefan Paterson assisted with publication formatting and final draft editing.

Chapter 3: In the third manuscript, Giuliano Guidi was again responsible for all hydrogel synthesis, characterization (water content, transparency, optical haze, surface wettability), drug release testing and all subsequent data analysis. Dr. Timothy Hughes provided valued insight and suggestions into potential monomers to evaluate and assisted in the drug release testing. Marlena Whinton provided advice on the incorporation of the polymerizable silicone surfactant and polymer extraction. The write-up was performed by Giuliano Guidi with Stefan Paterson providing assistance with final draft editing and formatting.

Chapter 1 : Literature Review

1.1 Topical Delivery

The use of eye drops for topical drug administration continues to dominate the treatment of ocular medical conditions, with over 90% of ophthalmic formulations being delivered in this manner. Their non-invasive nature and ease of use are primary reasons for their usage. However, topical administration has significant drawbacks and suffers from gross inefficiencies.

1.1.1 Clearance Mechanisms, Inefficiencies and Limitations

It is widely held that ophthalmic treatments delivered using topical eye drops suffer from short tear film residence time. The anatomy of the eye affords it unique structural systems and biological barriers that protect it from external factors. It is these natural barriers that undermine the effectiveness of eye drops as a delivery system. This subsequently results in low drug bioavailability, with only 1%-5% of the applied dose diffusing through the cornea to the target tissues (Ghate and Edelhauser, 2008; Gulsen and Chauhan, 2004; Le Bourlais et al., 1998; McNamara et al., 1999). Through a combination of lacrimation, drainage and absorption, a significant majority of the applied dosage is therefore quickly eliminated. The average volume of an eye drop can range from 20 μ L to 50 μ L, with the pre-corneal aqueous volume of the eye being approximately 7 μ L (Novack, 2009).Therefore, a significant excess tear film volume is generated when an eye drop is applied. The application of the drop usually causes eye surface irritation and induces a lacrimation response, which functions to immediately dilute the applied dosage. The excess tear fluid immediately begins draining through the nasolacrimal duct while overflow and cheek spillage occur due to blinking. Systemic absorption through the conjunctiva and the nasal mucosa where drainage is diverted accounts for approximately 95% of the applied dosage (Ghate and Edelhauser, 2008; White and Byrne, 2010). The above, in combination with continual tear turnover at a rate of 0.5-2.2 μ L/min, means that the majority of the applied drug is removed from the tear film within minutes (White and Byrne, 2010). Furthermore, the nature of the corneal epithelium layer with its tight cellular junctions acts as an additional barrier to diffusion (Järvinen et al., 1995). Figure 1-1 provides a schematic overview of the eye drop delivery and clearance process. It is obvious that despite the relatively large dose applied, the eye's protective mechanisms minimize drug bioavailability at the intraocular tissues.



Figure 1-1 – Flow chart of the eye drop delivery pathway and ocular drainage routes, adapted from *Järvinen et al.* and printed with permission from Elsevier (Järvinen et al., 1995).

As a consequence to the efficient clearance mechanisms of the eye, significant fluctuations in drug concentration and only a transient therapeutic effect can be achieved as indicated in Figure 1-2. Immediately following drop instillation, the concentration in the tear film reaches a maximum. However, due to the mechanisms described above, the drug concentration is very quickly reduced below the therapeutic threshold level. To address the pulsatile nature of drops, frequent application is often required to maintain drug concentration in the therapeutic window. Therefore, it is evident that, from a drug delivery standpoint, topical eye drops are not an ideal drug delivery method, and the eye is well equipped to minimize the effectiveness of such a system. A controlled release system capable of sustaining drug concentrations in the therapeutic window for a prolonged period of time would provide significant advantages.



Figure 1-2 – Diagram of the tear film drug concentration over time after application of eye drops and the ideal controlled delivery profile, adapted from Tieppo *et al.* and printed with permission from Elsevier. **A.** Eye drop installation results in pulsatile dosing peaks that provide transient therapeutic drug concentrations. This leads to the eye experiencing prolonged periods without any therapeutic effect. The maximum peak concentration is not very well controlled and in some cases can exceed the toxicity limit. **B.** A controlled release system would be able to deliver drugs in a manner that the concentration would remain within the therapeutics range. A contact lens capable of extended release could provide a controlled delivery profile.

The systemic absorption of a large fraction of the instilled drop represents significant drug wastage, and in the case of some drugs, has been shown to lead to undesirable side effects. As noted above, the inherent anatomical and physiological barriers that make drug delivery to the anterior of the eye challenging, mean that often higher concentrations and more frequent dosages of eye drops are necessary to accommodate (Urtti and Salminen, 1993). This increases the risk for systemic side effects. Timolol maleate drops, a widely used treatment option for open angle glaucoma, have been associated with cardiovascular and respiratory complications, in some cases leading to death (Korte et al., 2002). Other topical ophthalmic formulations such as brimonidine and cyclopentolate have also been shown to pose a risk for systemic toxicity (Bowman et al., 2004; Pooniya and Pandey, 2012). Such concerns are even more relevant in the treatment of young children and the elderly as both represent populations specifically susceptible (Diamond, 1997; Gray, 2006). Despite the development of novel alternative therapeutics that can treat ocular conditions effectively without the potential side effects, ongoing vigilance is required to mitigate the risks.

Patient noncompliance is another issue that hampers successful treatment of ocular diseases using eye drops. Some of the most common issues associated with noncompliance are forgetfulness, complications instilling the eye drop, and underestimating the importance of maintaining the prescribed regimen (Taylor et al., 2002). To address these issues, practitioners have focused on reducing the number of drops required per day, educating the patients on the consequences of missed dosages, and demonstrating proper drop technique (Taylor et al., 2002). Many of these

noncompliance issues are compounded in the elderly, who suffer from other conditions that often limit their mobility and dexterity. Therefore, simplifying the treatment modality to reduce the patient requirements and input would likely have great rewards in terms of treatment efficacy.

1.1.2 Anterior Delivery Improvement Strategies

Unique ocular delivery systems have been proposed to overcome the limitations of traditional topical formulations and improve the delivery parameters. Various strategies have been investigated for their potential to extend the drug residence time, increase corneal permeation, increase bioavailability, control the release and limit pulsatile dosing. Many of these novel systems have shown improved delivery over conventional eye drops, but very few have been widely implemented clinically as alternatives.

One interesting area that researchers have been investigating is altering the properties of formulations to increase the residence time of therapeutics. Much work has focused on the addition of specific compounds to drop formulations in order to promote increased bioavailability of therapeutics. Using additives that have mucoadhesive tendencies or an ability to increase viscosity are two major strategies that have been used to interact with the tear film and reduce the drainage rate. Examples of common additives with these properties include natural polymers such as hyaluronan, chitosan, hydroxypropylmethylcellulose, polyvinylpyrrolidone and polyvinylalcohol (Kaur et al., 2004; Uccello-Barretta et al., 2010). Many of these compounds exhibit both

mucoadhesive and viscosity boosting effects. The basis of such systems is the exploitation of the natural tear film layers shown in Figure 1-3 and the drainage mechanism described earlier. The natural tear film is composed of a small outer lipid layer, a middle larger aqueous layer and bottom mucin layer. Incorporation of naturally mucoadhesive polymers promotes association of the drop formulation with the mucin layer of the tear film. This delays the clearance time of the formulation because the rate of mucin turnover is slower than rate of tear turnover, thus promoting longer residence time and subsequent higher bioavailability (du Toit et al., 2011). Furthermore, the rate of lacriminal duct drainage depends heavily on the properties of the tear film. By adding agents to increase the viscosity of the eye drop, the ocular tear outflow rate can be reduced (Ding, 1998). This extends the contact time of the corneal surface with the drop formulation. Chitosan, a polysaccharide polymer with both mucoadhesive and viscoelastic properties in solution, was shown to increase the corneal residence time of the drug tobramycin by a factor of three in comparison to a commercial drop formulation (Felt et al., 1999). Further progress in this area has led to the development of *in situ* gelling formulations that show similar potential for improving corneal residence time of therapeutics. Such systems can be based on gelation that is triggered by pH, temperature and osmotic changes (Agrawal et al., 2012).



Figure 1-3 – Schematic of tear film composition layers, adapted from Ludwig and printed with permission from Elsevier (Ludwig, 2005).

Another strategy for improving eye drop delivery is the modification of the drug to increase its diffusion through the corneal layer. Although the corneal cell layer represents a significant barrier to ophthalmic drug diffusion, the physiochemical properties of the drug, such as lipophilicity, charge and size, play a significant role in how well it is able to permeate this layer (Järvinen et al., 1995). Lipophilicity, in particular, is one of the most important properties in determining the ability of drugs to diffuse through a medium, and this in some cases has been exploited to improve drug delivery. For hydrophilic drugs, the limiting step of penetration is the diffusion past the lipophilic epithelial layer, while for hydrophobic drugs it is the partitioning into the more hydrophilic stroma (Ghate and Edelhauser, 2008; Järvinen et al., 1995). Understanding how these factors influence corneal permeation can then be exploited to create prodrugs –

therapeutics that are administered in an inactive form – with optimal delivery properties. A primary example of this strategy is the treatment of glaucoma with prostaglandin analogues, where drugs are modified into an inactive form with properties that function to improve corneal diffusion (Hylton and Robin, 2003). Once the drug has permeated the cornea, it is then hydrolyzed into its free acid active form, which is able to reduce intraocular pressure at the target tissues (Hylton and Robin, 2003). Prostaglandin analogues used to treat glaucoma represent an equally if not more effective alternative to timolol maleate. It is clear that modification of actives can improve delivery by increasing the permeation ability of the therapeutic. However, this is not possible for every type of ophthalmic formulation, and again, the issues of patient compliance and systemic side effects are not addressed.

Material based delivery systems represent another broad alternative that uses solid implants to increase the bioavailability of ophthalmic drugs. Researchers have investigated inserts composed of a variety of different materials based on a myriad of technologies, ranging from degradable polymer shields and synthetic contact lenses, to nanoparticles and solid surgical implants, to control the release of therapeutics and improve their delivery (Kumari et al., 2010). Although there are significant advantages from a delivery perspective, there are other important factors that need to be considered for ocular inserts to be successful. Ideally, the sight path of the patient must not be impacted, the material must be compatible with the corneal epithelium, the system should be non-invasive and sufficiently comfortable to encourage patient use (Kumari et al., 2010). If the above criteria are met, then ocular inserts have the potential to provide a great advantage in improving drug delivery parameters and possibly reducing issues of patient compliance and systemic absorption. Despite great developments in the field of ocular compatible biomaterials capable of releasing therapeutics, many suffer from the inability to release these drugs for extended periods of time. A system capable of releasing therapeutics for very short durations from material inserts, although useful, would still suffer from issues of patient compliance. Thus, increased efforts are being put forth to develop an ocular insert that could deliver drugs for longer durations without the need for removal.

1.2 Contact Lenses for Drug Delivery

Contact lenses are one of the most widely used and most successful biomaterials that exist today. Since the original idea of using a glass lens on the front of the eye for vision correction in the 1800's, there has been significant growth and progress in the area of what would later be called contact lenses (Nicolson and Vogt, 2001). Currently, there are over 140 million users of these biomaterials worldwide and the market is expected to continue to grow in the coming years (Hui et al., 2012; Stapleton et al., 2007). Lens technology has come a long way since its conception, where significant developments have been made in terms of the design and material chemistry to greatly improve these vision correction systems. There are many considerations that need to be made when applying these materials in a biological environment to ensure comfort, safety and compatibility. Current technology focuses primarily on the use of soft synthetic hydrogel materials designed with unique properties that allow for the above criteria to be met.

1.2.1 Hydrogel Materials and Properties

The most recent advances in soft contact lens materials have split the industry in two directions: traditional/conventional hydrogel lenses, or extended wear silicone hydrogels. Conventional hydrogels can be divided into classes, those that are disposed of at the end of each day, known as daily disposables, and those that require post-usage cleaning to ensure sterility and remove deposits. While conventional hydrogel lenses remain a popular product for patients, they cannot be worn for extended durations due to their low oxygen permeability. The market demand for low maintenance lenses that could be worn continuously without the need for cleaning and disinfection, paved the way for the development of silicone hydrogels. Silicone hydrogels since their introduction in 1999 have rapidly captured a large fraction of market share and as of 2012 represent more than 60% of contact lens fittings being done (Nichols, 2013; Sankaridurg et al., 2013).

The chemistry of conventional hydrogel lenses is based on the use of hydrophilic water sorbing monomers such as HEMA, NVP and MAA, cross-linked to form a transparent polymer network (Nicolson and Vogt, 2001). These networks are capable of swelling significantly upon exposure to solvent or in the case of contact lenses, the tear fluid. The water uptake by these materials is what affords them comfort and the continuous aqueous phase allows for diffusion of the oxygen through the lens necessary for corneal health. This oxygen transmissibility is necessary to prevent corneal hypoxia, which has been associated with complications such as corneal swelling, epithelial microcycts and epithelial cell damage (Fonn et al., 2002). Despite the relatively high water content of these hydrogels, the oxygen permeability of these materials is not sufficiently high for them to be worn on an extended basis. Due to this risk of oxygen deprivation, in the past lens wearers were required to remove the lenses at the end of each day, soaking them in a cleaning solution overnight and placing them on the eye again in the morning. However, patients that did not follow the necessary cleaning regimen, or do so improperly, risked sight threatening complications such as microbial keratitis (Fleiszig and Evans, 2010). This led to the development of chemistry that was adaptable to high throughput manufacturing processes, that was capable for the production of cheap daily disposable lenses (Nicolson and Vogt, 2001). Disposable lenses eliminated the need for a cleaning regimen while maintaining the high degree of comfort that makes conventional lenses an attractive choice for contact lens wearers. However, due to the need for new lenses each day, daily disposables represent one of the more costly choices for soft hydrogel lenses.

Silicone hydrogels are the newest development in contact lens materials, combining comfort with oxygen permeability, with some lenses being approved for continuous wear for up to 30 days (Efron et al., 2007; Fonn et al., 2002; Morgan et al., 2011). The fundamental reason why conventional hydrogels were not appropriate for extended wear was their limited oxygen permeability. To overcome this, scientists introduced hydrophobic siloxane and fluoro monomers and polymers, which impart hydrogels with increased oxygen diffusivity and solubility respectively (Nicolson and Vogt, 2001). Examples of such compounds include methacryloxypropyl tris(trimethylsiloxy)silane (TRIS) and monomethacrylated polydimethylsiloxane. The ability of oxygen to transport through the bulk of these materials is referred to as oxygen permeability, (DK), measured in barrers (Efron et al., 2007; Nicolson and Vogt, 2001). Introduction of these new compounds ensured these materials had a significantly higher DK than traditional hydrogels. It was determined that the necessary permeability to avoid any hypoxia related complication of wearing a lens is 125 barrer per millimeter of thickness (Harvitt and Bonanno, 1999). This was an important milestone in the evolution of contact lenses as significant challenges were overcome to successfully merge hydrophobic and hydrophilic monomers without phase separation. Since their conception, silicone hydrogels have rapidly gained traction within the marketplace and now represent the majority of prescribed lenses (Nichols, 2013).

In Figure 1-4, the relationship between oxygen transmissibility and equilibrium water content for conventional and silicone hydrogels is shown. It is clear that for conventional lenses, the transport of oxygen is dependent on the water content. In comparison, oxygen permeability of silicone hydrogels is not governed by water content but is in fact limited by increasing water content. This underlines that fact that oxygen transmission in silicone hydrogels is driven by the presence of the hydrophobic siloxanes in the lens material. However, as consequence of this, silicone hydrogels tend to have an inherent surface hydrophobicity that can result in tear film component deposition and subsequent discomfort (Santos et al., 2007; Weeks et al., 2011). To address the surface of lenses and included hydrophilic wetting agents like PVP in their products (Efron et al., 2007). These strategies function to improve the surface wettability and reduce the deposition of proteins. The newest developments in lens material technology have

allowed for the decoupling of this relationship and provide high oxygen permeability without compromising on water content, nor requiring the addition of wetting agents or surface coatings (Sindt and Longmuir, 2007). This is believed to be in part due to the movement away from TRIS based monomers that impart hydrophobic surface properties on the resultant hydrogel (Jacob, 2013).



Figure 1-4 – Relationship between oxygen permeability and water content for both silicone and conventional hydrogels taken from Efron *et al.* and printed with permission from Wolters Kluwer Health (Efron et al., 2007).

1.2.2 Drug Delivery Considerations and Potential Benefits

The well-established safety and public acceptance of contact lenses make these materials an attractive ocular insert alternative to therapeutic eye drops. Inherent advantages to using contact lenses for drug delivery include the potential for continuous wear of these materials allowing for extended drug delivery, the multiple ways drugs can be incorporated into these materials, and the advantageous delivery properties (Li and Chauhan, 2006).

To understand the function and advantages of such a system, consideration needs to be given to the importance of delivery conditions in the context of the biological environment. Figure 1-5 provides an overview of the delivery system within the tear film environment (Kim and Chauhan, 2008). A drug loaded lens placed on the cornea allows diffusion of the active therapeutics contained within the lens into both the post-lens tear film (POLTF) and the pre-lens tear film (PLTF). The usage of soft contact lenses has been shown to prevent mixing of the POLTF and PLTF and retard drainage of the tear fluid trapped beneath the lens (Creech et al., 2001; McNamara et al., 1999). This lack of drainage from the POLTF and minimal mixing ensures that the residence time of the drug in contact with the cornea dramatically increases and that the concentration gradient driving diffusion remains high. The combination of these factors has been shown to dramatically boost drug bioavailability (Li and Chauhan, 2006; Peng et al., 2012a). Moreover, this delivery mechanism means that the therapeutic concentration is maintained for longer periods of time, much like the controlled system as indicated in Figure 1-2. This is a significant improvement over the pulsatile nature of eye drops. It is evident that a lens insert would be significantly more effective than eye drops at delivering ocular therapeutics to the anterior chamber of the eye.



Figure 1-5 – Diagram of contact lens delivery system with the tear film divided into the POLTF and PLTF, adapted from Kim and Chauhan and printed with permission from Elsevier (Kim and Chauhan, 2008).

In addition to more efficient and effective delivery, a lens based system also addresses some of the issues of safety that are associated with topical eye drops. As alluded to previously, eye drops require significant dosages to reach therapeutic concentration levels at the target tissues due to the very short residence time of the applied drug in the pre-corneal tear fluid. A contact lens delivery system requires lower dosing levels to achieve the same therapeutic effect due to the more efficient delivery (Peng et al., 2012a; Peng et al., 2012b). Therefore, the amount of drug that would be cleared into the systemic circulation would presumably be less. Furthermore, this dosage would be applied over a significantly greater time interval, ensuring that the clearance into circulation would also be more balanced than the rapid clearance observed with eye drop systems. Therefore, a lens insert for drug delivery has the potential to significantly mitigate the risk for systemic side effects. Less drug wastage is another benefit of using such a system — with eye drops, the majority of the applied formulation is cleared, often onto the cheek, without contributing any therapeutic effect. By using a more efficient delivery system, the fraction of applied therapeutic contributing to treatment is significantly increased.

Patient compliance continues to be an issue that prevents successful treatment of ophthalmic diseases like glaucoma. There are a number of documented factors that contribute to adherence of an eye drop regimen. The requirement for application multiple times daily and or the use of multiple drugs in a combination therapy has been associated with reduced compliance. Reduced manual dexterity, forgetfulness and difficulty reading prescriptions have been connected with the poor compliance in the elderly. Side effects have also been shown to be associated with higher levels of regimen discontinuation (Stryker et al., 2010). Therefore, a lens based system that can reduce the need for multiple applications, as well as the need for continuous patient input, and that can mitigate the risk of side effects, has the potential to improve treatment success. Previously, materials that could be placed on the cornea for durations longer than a single day without complications did not exist. The development of silicone hydrogels, which allow for lenses to be worn for durations of up to 30 days continuously, opens the door for such a system. When coupled with the ability to delivery drugs for similar durations, this method could remedy many of the reasons for patient noncompliance. However, achieving such a sustained release continues to be a challenge for scientists.

1.2.3 Summary of Contact Lens Drug Delivery Strategies

The idea of using a contact lens as a means to deliver medically active substances can be traced back to 1965, where reference to such a system can be found in the initial patent filed for soft contact lens materials and an original publication submitted in the same year (Sedlavek, 1965; Wichterle, 1965). Despite decades passing, there are still significant challenges that continue to prevent the success of a clinically viable solution for contact lens-based drug delivery systems. Although much research has been conducted on the use of contact lenses to deliver therapeutics to the anterior chamber, such systems continue to be limited by one of the follow two factors: insufficient loading or release due to the limits of drug solubility and partitioning, or lack of controlled release and subsequent burst expulsion of the therapeutics from the hydrogel lens (White and Byrne, 2010). Researchers continue to evaluate the potential of commercially available lenses as drug delivery inserts and the impact of the underlying chemistry (Boone et al., 2009; Hui et al., 2008; Kim et al., 2010; Soluri et al., 2012). However, recent advances in the understanding of hydrogel polymer networks now allow for rational hydrogel designs that are able to control release kinetics and alter the loading and release capacity. Current research focuses on novel methods of hydrogel design and controlled delivery properties, such as incorporation of diffusional barriers (Kim et al., 2010; Peng et al., 2010), molecular imprinting (Alvarez-Lorenzo et al., 2002; Hiratani and Alvarez-Lorenzo, 2004; Hiratani et al., 2005; Hui et al., 2012; Venkatesh et al., 2008; White et al., 2011) and particle entrapment (Gulsen and Chauhan, 2004, 2005; Gulsen et al., 2005; Kapoor and Chauhan, 2008).

1.2.3.1 Drug Soaked Lenses

The most rudimentary form of incorporating drug into a contact lens is by soaking these materials in a solution that contains the drug. Drug from the loading solution is then transferred to the hydrogel material through a combination of diffusion and sorption (Kim and Chauhan, 2008). The loading and release kinetics of these systems are dependent upon a myriad of factors including the drug concentration, solubility in the solvent along with the material composition, water content and charge (Soluri et al., 2012). A significant body of research exists that has evaluated the importance of many of these factors when using a contact lens to treat ophthalmic conditions (Boone et al., 2009; Hui et al., 2008; Soluri et al., 2012).

Current commercial lens materials span a large chemical spectrum in terms of their composition. Conventional hydrophilic hydrogels and silicone hydrogels comprise the majority of soft contact lens materials that are available. However, significant variation exists within these two contact lens types with regards to the monomers used, the ratio of the contributing components, the overall hydrogel charge and the subsequent materials properties (Efron et al., 2007). Therefore, much effort has been put forth in understanding the importance of the material differences with respect to the release kinetics of different ophthalmic therapeutics

The rate and duration of the release appears dependant on multiple factors related to both the material and drug properties. In one study evaluating a range of commercially available silicone hydrogels, materials containing N,N,-dimethylacrylamide demonstrated prolonged release of dexamethasone in comparison to commercial lenses that do not incorporate this monomer. It also appeared that surface treatment of the lens may also be a factor in extending release from materials, although it was not determined how the surface treatment may impact the drug release (Hui et al., 2008). Another study evaluating commercial lenses for the delivery of ketotifen fumarate was able to show that the hydrogel charge is an important parameter when delivering this therapeutic (Soluri et al., 2012). While concentrations of drug that are released in many of these studies are therapeutically relevant, the systems do not demonstrate release for sufficiently long durations to be considered a viable alternative to topical eye drop treatment. Despite the lack of long term release, the possibility of using daily replaceable drug soaked lenses or reloadable lenses remains an option, but would likely be cost preventative.

In other cases, the use of commercial contact lenses has yielded release profiles that demonstrate prolonged drug release. Peng and Chauhan were able to show that commercial silicone hydrogels were capable of releasing cyclosporine A for durations of up to two weeks. In comparison, the conventional 1-day Acuvue lens showed sustained release for approximately one day. In this case the difference in release kinetics and duration were attributed to the drug's significantly higher partition coefficient in the silicone hydrogels (Peng and Chauhan, 2011). The higher partition coefficient observed is due to both the material properties and the drug properties. Cyclosporine is uniquely lipophilic and relatively large in molecular weight which suggests it will preferentially partition into a more hydrophobic hydrogel material, which may extend the release kinetics.

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It is evident that the duration of release differs significantly depending on the drug and the material. The results of such studies are a great starting point to understand the drug diffusion in contact lenses and the relevant factors that may alter the release kinetics. This information provides valuable insight that can be used when developing novel rational hydrogel designs.

1.2.3.2 Exploiting Diffusion

Developments in the field of drug delivery and polymer science have promoted the discovery of techniques that can improve the control over the release kinetics from hydrogels. Controlled systems are of particular interest when considering ophthalmic applications due to the eye's protection mechanisms. The tendency of commercial lenses to release hydrophilic drugs over a relatively short duration is well documented. Due to the unique properties of lens materials, large modifications of the bulk parameters are not usually a viable option to modify the release. Thus, scientists have proposed the incorporation of transport barriers within the hydrogel network to extend the release duration (Kim et al., 2010; Peng et al., 2010). Although this concept has been applied to other areas of mass transfer, this strategy was only recently evaluated for contact lens drug delivery.

There are a number of properties that need to be considered for a diffusional barrier based systems, for example: the material additive used as the diffusion barrier must be versatile in its ability to act as a barrier for a large number of ophthalmic drugs; the additive must not pose a risk of toxicity if it were to diffuse into the tear film and surrounding tissue; and incorporation of the additive must not compromise lens transparency. Vitamin E, an antioxidant, has shown significant promise as a diffusional barrier additive in commercial silicone hydrogel contact lens materials (Kim et al., 2010; Peng et al., 2010; Peng et al., 2012b). This bioactive molecule is particularly interesting due to its proven ability to help alleviate specific conditions of the eye (Bilgihan et al., 2000; Yilmaz et al., 2007). Studies have shown that loading of this compound into commercial contact lenses by soaking has the ability to extend the release of hydrophilic drugs by orders of magnitude. Dexamethasone 21-disodium phosphate, fluconazole and timolol maleate all demonstrated similar extended release underlining the importance of drug hydrophilicity (Peng et al., 2010). Peng et al. showed the loading of vitamin E within these lenses did not have any adverse effect on the transparency, however, a slight reduction in oxygen permeability and more significant reduction in ion permeability were observed. The mechanism of action for these diffusion barriers is likely to be either the formation of hydrophobic aggregates that force the drug compounds to diffuse over a longer tortuous path or adsorption onto the polymer gel which then acts as an impedance layer to drug diffusion from the gel phase of the lens. Although, the release from such materials did not exhibit zero-order kinetics, it is proof that the diffusion timescale of drugs from hydrogel materials can be altered by the incorporation of a hydrophobic barrier.

Further studies were able to demonstrate that vitamin E has the ability to extend the release for hydrophobic drugs as well, such as dexamethasone. The release duration of dexamethasone, for example, was increased by 9 to 16 times in the presence of vitamin E (Kim et al., 2010). However, the degree to which the release timescale was lengthened is still much less than with hydrophilic drugs. It was hypothesized that the relatively high viscosity of vitamin E may alter the ability of hydrophobic drugs to diffuse.

It is evident that the mechanism of drug diffusion within contact lenses is an area that can be exploited to improve control over the release profile. Alternatives to diffusion barriers, such as promoting charge based drug-polymer interactions, have also proven useful in modifying drug release from these materials. In a recent study, the cationic surfactant, cetalkonium chloride, was added to pHEMA based model lens materials to facilitate interactions with anionic drug compounds. Incorporation of this minimally toxic surfactant resulted in significant increases in both the drug release duration and loading partition coefficient (Bengani and Chauhan, 2013). An additional benefit of these modified materials was the reduced protein deposition observed. The use of ionic interactions to control drug delivery is not a new concept, but its application to contact lens drug delivery is a novel idea that further supports to importance of polymer-drug interaction for controlling release.

The volume of ongoing work into how to alter the mechanism and nature of drug diffusion in contact lenses underlines the usefulness of this area of study. Extending the release of ophthalmic drugs from both model and commercial materials using these strategies has great potential to increase of the efficiency of topical delivery.

1.2.3.3 Molecular Imprinting

Molecular imprinting is a technique whereby polymerization mediated interaction between functional monomers and a template molecule promote the formation of polymer networks with a tailored affinity and specificity for this template compound. Although this strategy was originally used primarily for highly cross-linked structures, its application to weakly cross-linked hydrogels has also been shown. This macromolecular memory is based on two primary mechanisms: shape specific cavities within the network that stabilize the template, and orientation of functional monomer groups to form noncovalent drug-functional monomer complexes (White and Byrne, 2010). When applied to drug delivery, this heightened interaction with the polymer network functions to increase the loading capacity and delay the release. Similar to the above diffusion strategies, the use of molecular imprinting must ensure that addition of functional monomer or template compound has no impact on the overall lens properties and lens transparency. Only recently has this strategy been applied to contact lens drug delivery, with investigation into the most relevant parameters that govern its efficacy including importance of functional monomer type, template nature, monomer to template ratio and release conditions (Ali and Byrne, 2009; Hiratani and Alvarez-Lorenzo, 2004; Hiratani et al., 2005; Hui et al., 2012; Karim et al., 2005; Venkatesh et al., 2008; White et al., 2011).

Researchers have evaluated a myriad of different functional monomers for their ability to promote increased loading and delayed release from contact lens materials. Methacrylic acid, acrylic acid, N,N-dimethylacrylamide and n-vinyl pyrrrolidone are some of the most common monomers that have used in such systems (White and Byrne,
2010). The choice of functional monomers to be incorporated within a system is highly dependent on the drug being imprinted. Variation in drug chemical functionality means that to promote ionic and/or non-covalent bond interactions with the network, consideration needs to be given to the compatibility of functional monomers. The widespread use of methacrylic acid in hydrogel systems that are imprinting timolol maleate supports this theory (Alvarez-Lorenzo et al., 2002; Hiratani and Alvarez-Lorenzo, 2002, 2004). It is believed that MAA is particularly useful when imprinting this drug because of the electrostatic and hydrogen bonding that is possible at physiological pH (Alvarez-Lorenzo et al., 2002). Using similar logic, other researchers have matched the antibacterial, Nofloxacin, with 4-vinyl pyridine and acrylic acid as functional monomers (Alvarez-Lorenzo et al., 2006). More elegant strategies have attempted to use a biomimetic basis and choose functional monomers that bear a chemical resemblance to the drug active site. Ribeiro et al. were able to show that hydrogels incorporating 4vinylmidazole and N-hydroxyethyl acrylamide to mimic the active site of the carbonic anhydrase inhibitors, acetazolamide and ethoxzolamide, exhibited significantly higher drug affinity and prolonged release (Ribeiro et al., 2011).

Incorporating hydrophilic long chain polymers within contact lenses has been shown to be of great benefit in maintaining a stable tear film and reducing the persistence of contact lens induced dry eye (Ali and Byrne, 2009; White et al., 2011). The ability of these wetting agents to mitigate protein deposition onto the lens has also been proven (van Beek et al., 2008b; Weeks et al., 2012). Similar to the delivery of active therapeutics, the delivery of these wetting agents from a lens system would improve delivery parameters and patient convenience relative to eye drops. A range of compounds have been explored for use in such a system, including hyaluronic acid, hydroxypropyl methylcellulose (HPMC), poly vinyl alcohol (PVA) and poly vinyl pyrrolidone (PVP). This technology has been developed commercially, with PVP being included in the silicone hydrogel, Acuvue Oasys, as an embedded wetting, and PVA being incorporated into the conventional hydrogel, Focus Dailies, as a releasable wetting agents (Van Beek et al., 2008a; van Beek et al., 2008b). However, the long term release of these wetting agents continues to be a challenge. Researchers have proposed molecular imprinting as a means to extend wetting agent release from soft hydrogel materials. Controlled release of HPMC over a period of 60 days from molecular imprinted silicone hydrogels was achieved using acrylic acid as a functional monomer (White et al., 2011). Another study obtained similar results while imprinting HA in model hydrogel materials (Ali and Byrne, 2009). In both cases, the release could be tailored by the choice of functional monomers and the ratio of functional monomer to template (M/T).

1.2.3.4 Particle Entrapment

A well-established drug delivery strategy to extend release in hydrogels is the entrapment of drug loaded particles within the polymer network. Under normal circumstances, the release of directly entrapped drug within a hydrogel is dependent on the partitioning of drug from the gel phase to the aqueous phase and subsequent diffusion. By incorporating nanoparticles containing active drug into a material, the drug release will be determined by first the diffusion from the particle and then from the bulk hydrogel. The ability to modify the chemistry of these particles allows greater control over the release kinetics and possibly targeting of the ideal rate for a particular application. It is evident that the use of particle laden hydrogels would have great value in contact lens drug delivery application. However, such a strategy must again ensure that the necessary lens properties and transparency are not compromised. To meet these obligations, the drug-loaded nanoparticle must be below 50nm in diameter and be capable of a high loading efficiency.

Various techniques exist for producing drug loaded nanoparticles, and some have been explored for use in a contact lens delivery application. A microemulsion is an established technique for synthesizing drug loaded nanoparticles that can be isolated and added to a bulk material. This method has been used to produce lidocane loaded nanoparticles with and without a silica shell, which were incorporated into basic pHEMA hydrogels (Gulsen and Chauhan, 2005). Although lidocane was used only as a model drug, the lens materials synthesized with the entrapped particles were able to maintain their transparency due to the particle size being less than 20 nm. Gulsen and Chauhan demonstrated these particle laden hydrogels were able to release lidocane for up to one week although no difference was observed between materials with and without the silica shell. While pHEMA hydrogels are not appropriate for extended wear, these results show that the inclusion of particles within conventional lens materials is able to prolong the release of a drug.

Alternative nanoparticle formulations have also been investigated and applied to contact lens drug delivery. Jung and Chauhan used emulsion thermopolymerization to synthesize propoxylated glyceryl triacrylate (PGT) and EGDMA based nanoparticles that contained timolol base. When incorporated into pHEMA hydrogel materials through direct addition to the monomer formulation, these materials exhibited extended release for over 1 month (Jung and Chauhan, 2012). It was observed that release from the PGT-timolol nanoparticles was highly temperature dependant. The authors concluded that the release may be governed by the hydrolysis of an ester linkage that forms between timolol and PGT during polymerization. More recently, studies focused on silicone hydrogel extended wear materials have come to the forefront. The same method mentioned above was applied to commercial and model silicone hydrogel materials, and the prolonged release found for pHEMA hydrogels was also observed in silicone hydrogels (Jung et al., 2013).

Drug-loaded liposomes represent an alternative to polymeric nanoparticles that can provide similar delivery advantages. Liposomes are lipid bilayer based vesicles and can be used as a vehicle for drug delivery, much like nanoparticles. Furthermore, the amphiphilic properties of these vesicles allow for the loading of both hydrophilic and hydrophobic drugs. The location of the drug in the liposome will vary depending on its lipophilicity. Hydrophilic drugs will be contained within the aqueous core or layers of the liposome, with lipophilic drugs being contained within the lipid bilayer (Gulsen et al., 2005; Mishra et al., 2011). Therapeutics have already been loaded into these charged vesicles and used directly on the corneal surface for ophthalmic drug delivery (Mishra et al., 2011). Current research in this area focuses on modifying the liposomes to improve the corneal penetration and adhesion by incorporating various polymer additives with bioadhesive and permeation inducing properties. The importance of such research relates to increasing the residence time and subsequent bioavailability of the drug being delivered. *Gulsen et al.* showed that it was also possible to disperse drug-loaded liposomes within a polymeric lens material while maintaining their stability. Furthermore, such a system was able to release the model drug, lidocaine, at therapeutically relevant concentrations for a period of up to 8 days (Gulsen et al., 2005). In this study, the sonication time could be used to control the size of the liposomes, and, thus, the transparency of the materials once these liposomes were incorporated into a hydrogel. It is evident that nanotechnology can play an important role in drug delivery and that, in the case of contact lens based systems, it can be used as a means of altering the release kinetics and diffusion timescale.

1.2.4 In Vivo Evaluation of Materials

Great progress has been made in the field of contact lens drug delivery in the past decade. The development of extended wear silicone hydrogels has spawned renewed interest in this field. The rational design of hydrogels and incorporation of nanotechnology has proven to be instrumental in improving the control over delivery kinetics and extending the duration of release. Recently, researchers have taken the next step to a viable lens delivery system by testing these advanced hydrogel systems in animal models to evaluate their clinical efficacy and advantage over topical eye drops.

Beagle dogs are often chosen as the subjects in the case of intraocular pressure studies due to their tendency to inherit open angle glaucoma, the most common human form of the disease (Gelatt and MacKay, 2001; Peng et al., 2012a). A dog model also

promised the potential to perform necessary physiological and pharmacological studies over the long course of disease progression. Furthermore, glaucomatous beagle dogs are a perfect model for a contact lens study due to the similarity in corneal shape that they share with humans. Unmodified commercial contact lenses can thus be used for *in vivo* testing. *Peng et al.* investigated the ability of commercial extended wear NIGHT&DAY lenses that were infused with vitamin E as diffusion barriers to reduce intraocular pressure in glaucomatous dogs. Researchers demonstrated that timolol loaded contact lenses that were replaced every 24 hours were equally effective in reducing the intraocular pressure as traditional timolol maleate eye drops (Peng et al., 2012a). The researchers were able to show that to achieve the same reduction in intraocular pressure, the contact lenses required only a third of the loading as would be delivered via an eye drop. This result underlines that a contact lens can increase the bioavailability of a therapeutic *in vivo*. However, the use of conventional lenses that are replaced every 24 hours is not ideal.

To further investigate the importance of extended release mechanisms on the efficacy *in vivo*, various studies have investigated the use of a silicone hydrogel delivery system continuously for more than 24 hours. Using ACUVUE TruEye commercial lenses with and without vitamin E diffusion barriers included, *Peng et al.* were able to show using glaucomatous beagles the same baseline reduction in intraocular pressure as eye drops could be obtained with 20% of the drug loading. Moreover, the use of vitamin E as a diffusion barrier can be integrated into the continuous wear lenses and deliver therapeutically relevant concentrations for up to 4 days (Peng et al., 2012b). This further

proves that a contact lens delivery system that is worn continuously can be effective in delivering drugs and achieving a therapeutic effect. It is also evident that there is a significant increase in bioavailability of the drug and a lower drug dosage can be used to obtain the same pharmacodynamics result.

1.3 Thesis Objectives and Scope

Using contact lenses as vehicles for drug delivery to treat a range of ocular conditions of the anterior eye is a potentially viable alternative to topical eye drops. Ongoing research suggests that there are a multitude of strategies that can be used to not only delivery drugs using contact lenses but achieve sustained release for multiple weeks. The objective of this research aims to investigate the importance of the hydrogel lens chemistry on the release of ocular therapeutics from model systems. The monomer formulations used to synthesize a hydrogel play a significant role in determining the material properties of the overall polymer. By developing hydrogel formulations that span a range of chemical space in terms of monomers and processing them in a similar manner to commercial lenses, we hoped to better understand the properties that are most advantageous for extended delivery and identify the monomers that promote these properties. The hypothesis was that by modifying the hydrogel chemistry by incorporating various monomers included HEMA, DMA, TRIS(OH), mPDMS and an acrylated silicone surfactant we could alter the overall polymer properties and morphology. By characterizing the materials in terms of their surface wettability,

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equilibrium water content, and drug release characteristics we could then understand the relevant properties to promote extended drug release. It was thought that the use of silicone hydrogels would provide more controlled release with the use of a lipophilic drug due to stronger hydrophobic associations. Furthermore, a silicone surfactant may better stabilize the phase separation between hydrophobic and hydrophilic monomers, resulting in smaller aqueous channel for which diffusion to occur through.

This research further attempted to evaluate the potential of non-tethered hyaluronic acid to modify drug release as a functional additive. Previously research in the Sheardown lab has suggested that HA has an ability to control the release of positively charged therapeutics. By combining the incorporation of HA with molecular imprinting we hoped to overcome the limited applicability of hydrogels that are not extracted while maintaining some control over the release that has been previously demonstrated. We hypothesized that the negative charge of hyaluronic acid may be a useful property to invoke ionic drug-hydrogel interactions that can provide controlled release.

References

- Agrawal, A.K., Das, M., Jain, S., 2012. In situ gel systems as 'smart' carriers for sustained ocular drug delivery. Expert Opin Drug Deliv 9, 383-402.
- Ali, M., Byrne, M.E., 2009. Controlled release of high molecular weight hyaluronic acid from molecularly imprinted hydrogel contact lenses. Pharm Res 26, 714-726.
- Alvarez-Lorenzo, C., Yañez, F., Barreiro-Iglesias, R., Concheiro, A., 2006. Imprinted soft contact lenses as norfloxacin delivery systems. J Controlled Release 113, 236-244.
- Alvarez-Lorenzo, C., Hiratani, H., Gómez-Amoza, J.L., Martínez-Pacheco, R., Souto, C., Concheiro, A., 2002. Soft contact lenses capable of sustained delivery of timolol. J Pharm Sci 91, 2182-2192.
- Bengani, L.C., Chauhan, A., 2013. Extended delivery of an anionic drug by contact lens loaded with a cationic surfactant. Biomaterials 34, 2814-2821.

- Bilgihan, K., Sengül Ozdek, C.O., gcaron, 2000. Topical vitamin E and hydrocortisone acetate treatment after photorefractive keratectomy. Eye 14, 231-237.
- Boone, A., Hui, A., Jones, L., 2009. Uptake and release of dexamethasone phosphate from silicone hydrogel and group I, II, and IV hydrogel contact lenses. Eye Contact Lens 35, 260-267.
- Bowman, R.J., Cope, J., Nischal, K.K., 2004. Ocular and systemic side effects of brimonidine 0.2% eye drops (Alphagan) in children. Eye (Lond) 18, 24-26.
- Creech, J., Chauhan, A., Radke, C., 2001. Dispersive mixing in the posterior tear film under a soft contact lens. Ind Eng Chem Res 40, 3015-3026.
- Diamond, J.P., 1997. Systemic adverse effects of topical ophthalmic agents. Implications for older patients. Drugs Aging 11, 352-360.
- Ding, S., 1998. Recent developments in ophthalmic drug delivery. Pharm Sci Technolo Today 1, 328-335.
- du Toit, L.C., Pillay, V., Choonara, Y.E., Govender, T., Carmichael, T., 2011. Ocular drug delivery - a look towards nanobioadhesives. Expert Opin Drug Deliv 8, 71-94.
- Efron, N., Morgan, P.B., Cameron, I.D., Brennan, N.A., Goodwin, M., 2007. Oxygen permeability and water content of silicone hydrogel contact lens materials. Optom Vis Sci 84, E328-E337.
- Felt, O., Furrer, P., Mayer, J., Plazonnet, B., Buri, P., Gurny, R., 1999. Topical use of chitosan in ophthalmology: tolerance assessment and evaluation of precorneal retention. Int J Pharm 180, 185.
- Fleiszig, S.M., Evans, D.J., 2010. Pathogenesis of contact lens-associated microbial keratitis. Optom Vis Sci 87, 225.
- Fonn, D., MacDonald, K.E., Richter, D., Pritchard, N., 2002. The ocular response to extended wear of a high Dk silicone hydrogel contact lens. Clin Exp Optom 85, 176-182.
- Gelatt, K.N., MacKay, E.O., 2001. Effect of different dose schedules of latanoprost on intraocular pressure and pupil size in the glaucomatous Beagle. Vet Ophthalmol 4, 283-288.
- Ghate, D., Edelhauser, H.F., 2008. Barriers to glaucoma drug delivery. J Glaucoma 17, 147.
- Gray, C., 2006. Systemic toxicity with topical ophthalmic medications in children. Paediatr Perinat Drug Ther 7, 23-29.
- Gulsen, D., Chauhan, A., 2004. Ophthalmic drug delivery through contact lenses. Invest Ophthalmol Vis Sci 45, 2342-2347.
- Gulsen, D., Chauhan, A., 2005. Dispersion of microemulsion drops in HEMA hydrogel: a potential ophthalmic drug delivery vehicle. Int J Pharm 292, 95-117.
- Gulsen, D., Li, C.-C., Chauhan, A., 2005. Dispersion of DMPC liposomes in contact lenses for ophthalmic drug delivery. Curr Eye Res 30, 1071-1080.
- Harvitt, D.M., Bonanno, J.A., 1999. Re-evaluation of the oxygen diffusion model for predicting minimum contact lens Dk/t values needed to avoid corneal anoxia. Optom Vis Sci 76, 712-719.

- Hiratani, H., Alvarez-Lorenzo, C., 2002. Timolol uptake and release by imprinted soft contact lenses made of *i* > N</*i*>, *i* > N</*i*>-diethylacrylamide and methacrylic acid. J Controlled Release 83, 223-230.
- Hiratani, H., Alvarez-Lorenzo, C., 2004. The nature of backbone monomers determines the performance of imprinted soft contact lenses as timolol drug delivery systems. Biomaterials 25, 1105-1113.
- Hiratani, H., Fujiwara, A., Tamiya, Y., Mizutani, Y., Alvarez-Lorenzo, C., 2005. Ocular release of timolol from molecularly imprinted soft contact lenses. Biomaterials 26, 1293-1298.
- Hui, A., Boone, A., Jones, L., 2008. Uptake and release of ciprofloxacin-HCl from conventional and silicone hydrogel contact lens materials. Eye Contact Lens 34, 266-271.
- Hui, A., Sheardown, H., Jones, L., 2012. Acetic and Acrylic Acid Molecular Imprinted Model Silicone Hydrogel Materials for Ciprofloxacin-HCl Delivery. Materials 5, 85-107.
- Hylton, C., Robin, A., 2003. Update on prostaglandin analogs. Curr Opin Ophthalmol 14, 65.
- Jacob, J.T., 2013. Biocompatibility in the Development of Silicone-Hydrogel Lenses. Eye Contact Lens 39, 13-19.
- Järvinen, K., Järvinen, T., Urtti, A., 1995. Ocular absorption following topical delivery. Adv Drug Del Rev 16, 3-19.
- Jung, H.J., Abou-Jaoude, M., Carbia, B.E., Plummer, C., Chauhan, A., 2013. Glaucoma therapy by extended release of timolol from nanoparticle loaded silicone-hydrogel contact lenses. J Control Release 165, 82-89.
- Jung, H.J., Chauhan, A., 2012. Temperature sensitive contact lenses for triggered ophthalmic drug delivery. Biomaterials 33, 2289-2300.
- Kapoor, Y., Chauhan, A., 2008. Ophthalmic delivery of Cyclosporine A from Brij-97 microemulsion and surfactant-laden p-HEMA hydrogels. Int J Pharm 361, 222-229.
- Karim, K., Breton, F., Rouillon, R., Piletska, E.V., Guerreiro, A., Chianella, I., Piletsky, S.A., 2005. How to find effective functional monomers for effective molecularly imprinted polymers? Adv Drug Del Rev 57, 1795-1808.
- Kaur, I.P., Garg, A., Singla, A.K., Aggarwal, D., 2004. Vesicular systems in ocular drug delivery: an overview. Int J Pharm 269, 1-14.
- Kim, J., Chauhan, A., 2008. Dexamethasone transport and ocular delivery from poly (hydroxyethyl methacrylate) gels. Int J Pharm 353, 205-222.
- Kim, J., Peng, C.-C., Chauhan, A., 2010. Extended release of dexamethasone from silicone-hydrogel contact lenses containing vitamin E. J Controlled Release 148, 110-116.
- Korte, J.M., Kaila, T., Saari, K.M., 2002. Systemic bioavailability and cardiopulmonary effects of 0.5% timolol eyedrops. Graefes Arch Clin Exp Ophthalmol 240, 430-435.
- Kumari, A., Sharma, P.K., Garg, V.K., Garg, G., 2010. Ocular inserts—Advancement in therapy of eye diseases. J Adv Pharm Technol Res 1, 291.

- Le Bourlais, C., Acar, L., Zia, H., Sado, P.A., Needham, T., Leverge, R., 1998. Ophthalmic drug delivery systems—recent advances. Prog Retin Eye Res 17, 33-58.
- Li, C.-C., Chauhan, A., 2006. Modeling ophthalmic drug delivery by soaked contact lenses. Ind Eng Chem Res 45, 3718-3734.
- Ludwig, A., 2005. The use of mucoadhesive polymers in ocular drug delivery. Adv Drug Del Rev 57, 1595-1639.
- McNamara, N.A., Polse, K.A., Brand, R.J., Graham, A.D., Chan, J.S., McKenney, C.D., 1999. Tear mixing under a soft contact lens: effects of lens diameter. Am J Ophthalmol 127, 659.
- Mishra, G.P., Bagui, M., Tamboli, V., Mitra, A.K., 2011. Recent applications of liposomes in ophthalmic drug delivery. J Drug Deliv 2011.
- Morgan, P.B., Efron, N., Helland, M., Itoi, M., Jones, D., Nichols, J.J., van der Worp, E., Woods, C.A., 2011. Global trends in prescribing contact lenses for extended wear. Cont Lens Anterior Eye 34, 32-35.
- Nichols, J., 2013. Contact Lenses 2012. Contact Lens Spectrum 28, 24-29.
- Nicolson, P.C., Vogt, J., 2001. Soft contact lens polymers: an evolution. Biomaterials 22, 3273-3283.
- Novack, G.D., 2009. Ophthalmic drug delivery: development and regulatory considerations. Clin Pharmacol Ther 85, 539-543.
- Peng, C.-C., Ben-Shlomo, A., Mackay, E.O., Plummer, C.E., Chauhan, A., 2012a. Drug delivery by contact lens in spontaneously glaucomatous dogs. Curr Eye Res 37, 204-211.
- Peng, C.-C., Chauhan, A., 2011. Extended cyclosporine delivery by silicone–hydrogel contact lenses. J Controlled Release 154, 267-274.
- Peng, C.-C., Kim, J., Chauhan, A., 2010. Extended delivery of hydrophilic drugs from silicone-hydrogel contact lenses containing Vitamin E diffusion barriers. Biomaterials 31, 4032-4047.
- Peng, C.C., Burke, M.T., Carbia, B.E., Plummer, C., Chauhan, A., 2012b. Extended drug delivery by contact lenses for glaucoma therapy. J Control Release 162, 152-158.
- Pooniya, V., Pandey, N., 2012. Systemic toxicity of topical cyclopentolate eyedrops in a child. Eye (Lond) 26, 1391-1392.
- Ribeiro, A., Veiga, F., Santos, D., Torres-Labandeira, J.J., Concheiro, A., Alvarez-Lorenzo, C., 2011. Receptor-based biomimetic NVP/DMA contact lenses for loading/eluting carbonic anhydrase inhibitors. J Membr Sci 383, 60-69.
- Sankaridurg, P., de la Jara, P.L., Holden, B., 2013. The Future of Silicone Hydrogels. Eye Contact Lens 39, 125-129.
- Santos, L., Rodrigues, D., Lira, M., Oliveira, M.E., Oliveira, R., Vilar, E.Y., Azeredo, J., 2007. The influence of surface treatment on hydrophobicity, protein adsorption and microbial colonisation of silicone hydrogel contact lenses. Cont Lens Anterior Eye 30, 183-188.
- Sedlavek, J., 1965. Possibilities of application of eye drugs with the aid of gel-contact lenses. Cesk Slov Oftalmol 21, 509-512.

- Sindt, C.W., Longmuir, R.A., 2007. Contact lens strategies for the patient with dry eye. Ocul Surf 5, 294-307.
- Soluri, A., Hui, A., Jones, L., 2012. Delivery of ketotifen fumarate by commercial contact lens materials. Optom Vis Sci 89, 1140-1149.
- Stapleton, F., Keay, L., Jalbert, I., Cole, N., 2007. The epidemiology of contact lens related infiltrates. Optom Vis Sci 84, 257-272.
- Stryker, J.E., Beck, A.D., Primo, S.A., Echt, K.V., Bundy, L., Pretorius, G.C., Glanz, K., 2010. An exploratory study of factors influencing glaucoma treatment adherence. J Glaucoma 19, 66.
- Taylor, S.A., Galbraith, S.M., Mills, R.P., 2002. Causes of non-compliance with drug regimens in glaucoma patients: a qualitative study. J Ocul Pharmacol Ther 18, 401-409.
- Uccello-Barretta, G., Nazzi, S., Zambito, Y., Di Colo, G., Balzano, F., Sansò, M., 2010. Synergistic interaction between TS-polysaccharide and hyaluronic acid: implications in the formulation of eye drops. Int J Pharm 395, 122.
- Urtti, A., Salminen, L., 1993. Minimizing systemic absorption of topically administered ophthalmic drugs. Surv Ophthalmol 37, 435-456.
- Van Beek, M., Jones, L., Sheardown, H., 2008a. Hyaluronic acid containing hydrogels for the reduction of protein adsorption. Biomaterials 29, 780-789.
- van Beek, M., Weeks, A., Jones, L., Sheardown, H., 2008b. Immobilized hyaluronic acid containing model silicone hydrogels reduce protein adsorption. J Biomater Sci Polym Ed 19, 1425-1436.
- Venkatesh, S., Saha, J., Pass, S., Byrne, M.E., 2008. Transport and structural analysis of molecular imprinted hydrogels for controlled drug delivery. Eur J Pharm Biopharm 69, 852-860.
- Weeks, A., Luensmann, D., Boone, A., Jones, L., Sheardown, H., 2012. Hyaluronic acid as an internal wetting agent in model DMAA/TRIS contact lenses. J Biomater Appl 27, 423-432.
- Weeks, A., Subbaraman, L.N., Jones, L., Sheardown, H., 2011. The Competing Effects of Hyaluronic and Methacrylic Acid in Model Contact Lenses. J Biomater Sci Polym Ed 23, 1021-1038.
- White, C.J., Byrne, M.E., 2010. Molecularly imprinted therapeutic contact lenses. Expert Opin Drug Deliv 7, 765-780.
- White, C.J., McBride, M.K., Pate, K.M., Tieppo, A., Byrne, M.E., 2011. Extended release of high molecular weight hydroxypropyl methylcellulose from molecularly imprinted, extended wear silicone hydrogel contact lenses. Biomaterials 32, 5698-5705.
- Wichterle, O., 1965. Cross-linked hydrophilic polymers and articles made therefrom, in: Office, U.S.P. (Ed.).
- Yilmaz, T., Aydemir, O., Ozercan, I.H., Ustundag, B., 2007. Effects of vitamin e, pentoxifylline and aprotinin on light-induced retinal injury. Ophthalmologica 221, 159-166.

Chapter 2 : Modification of Timolol Release from Imprinted Silicone Hydrogels using Hyaluronic Acid

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Objectives: To incorporate hyaluronic acid as a negatively charged novel additive to modify the drug release of a positively charged drug, timolol, from silicone hydrogel materials, while maintaining many of the essential lens properties.

Main Scientific Contributions:

- Successfully incorporated non-tethered hyaluronic acid into silicone hydrogels and demonstrated its potential to alter the uptake and release characteristics of a positively charged therapeutic
- Proved that this can be combined with molecular imprinting strategies to generate a compound boosting effect on the drug release dosage
- Demonstrated that the reduction in transparency of hydrogels containing HA can be mitigated as the thickness is reduced

Abstract

The ability of hyaluronic acid (HA) to act as a functional additive in silicone hydrogels to alter the uptake and release of timolol maleate was investigated. Model silicone hydrogels were prepared using two primary formulations: 2-hydroxyethyl methacrylate (HEMA) with methacryloxypropyltris(trimethylsiloxy)silane (TRIS) in a 9:1 (wt:wt) ratio or N,N-dimethylacrylamide (DMA) with (TRIS) in a 1:1 (wt:wt) ratio. Ethylene glycol dimethacrylate (EGDMA) was used as the crosslinker for both formulations. HA and timolol maleate were added to the hydrogel formulations during the synthesis step. This generated molecularly imprinted networks after the timolol template was removed during a wash step. Successfully imprinted materials were then used for drug loading and release studies. Release data showed that in both formulations, HA has the ability to act as a functional additive in these networks, increasing the drug loading and subsequent release. HA, although different than typical functional monomers used in molecular imprinting, can be a useful additive to modify drug delivery properties of silicone hydrogels.

2.1 Introduction

Application of ophthalmic therapeutics to the anterior region of the eye is dominated by the use of topical eye drops, which is a well-established and proven delivery method (Lang, 1995). However, this system suffers from inherent delivery inefficiencies and can result in systemic side effects (Davies, 2000; Korte et al., 2002; Urtti, 2006). The efficacy of eye drops, which represent 90% of ophthalmic treatments, is hampered by low tear film residence time which subsequently results in low bioavailability, with less than 5% of the applied drug diffusing through the corneal epithelium to the target tissues (Ghate and Edelhauser, 2008; Gulsen and Chauhan, 2004; Le Bourlais et al., 1998; McNamara et al., 1999). Furthermore, the 95% of drug that is either cleared into systemic circulation or overflows from the eye, not only represents significant waste, but opens the door for toxicity in distant organs (Diamond, 1997; Salminen, 1990). Patient compliance is another major issue, limiting the efficacy of current treatment paradigms, particularly in diseases where regular installation of drops is necessary, such as glaucoma (Schwartz and Quigley, 2008). To address the limitations of this delivery method, researchers have evaluated alternative controlled delivery systems with the capability of increasing the bioavailability, reducing the possibility for systemic side effects, and eliminating issues of patient compliance. A variety of technologies have been explored ranging from drug carrying nanoparticles and liposomes, to drug eluting inserts and contact lenses (Alonso and Sánchez, 2003; Ciolino et al., 2009b; Kaur et al., 2004; Kim et al., 2008; Kopecek, 2009; Lavik et al., 2011; Sahoo et al., 2008; White and Byrne, 2010; Xinming et al., 2008). The widely accepted usage of contact lenses in the eye coupled with their theoretical ability to increase the residence time and subsequent bioavailability of therapeutics makes them attractive candidates for an alternative delivery system (Gulsen and Chauhan, 2004; Hehl et al., 1999; Li and Chauhan, 2006; Wu et al., 2010).

An ideal clinical solution would be for the lens to deliver drugs for multiple weeks. With the rising popularity of extended wear silicone-based hydrogels, the use of a drug-eluting contact lens that can be worn for these durations is a very real possibility (Fonn et al., 2002; Nichols, 2009). However, for such a system to be successful, the release duration must match the duration of wear. This means designing a hydrogel system that is able to control the release of drugs, while maintaining the original properties of the lens. Researchers have proposed a myriad of hydrogel designs, some of which fulfill these requirements and are capable of such a sustained release. Traditional techniques include soaking of the gels in a drug solution to facilitate uptake or the direct entrapment of therapeutic within the hydrogel network (Boone et al., 2009; Ciolino et al., 2009a). Recently more sophisticated hydrogel designs based on molecular imprinting, diffusion barriers and particle-laden hydrogels have come to the forefront (Hiratani et al., 2005; Jung et al., 2013; Peng et al., 2010; White and Byrne, 2010).

Molecularly imprinted hydrogel systems are a relatively new concept. This technique involves polymerizing functional monomers in the presence of a template, with the template being removed post-polymerization to create unique cavities (Alvarez-Lorenzo and Concheiro, 2004; Byrne et al., 2002; Mosbach and Ramström, 1996; Sellergren and Allender, 2005). Once the cavities are exposed to the template – often by

immersing the hydrogel in a template-containing solution – the functional groups present in these cavities are able to interact non-covalently with the template. Through these molecule specific interactions, the drug loading and release kinetics from hydrogel systems can be altered. Figure 2-1 visually depicts the creation of molecule specific cavities within a polymer network. It is evident that such systems would be particularly useful for contact lens based delivery, where the release duration must be extended to fit the wear duration of the lens. Research has demonstrated the ability of molecular imprinting to increase loading capacity of the template compound and extend the release duration from some hydrogel systems. Different functional monomers such as acrylamides, methacrylic acid, acetic acid, N-vinyl pyrolidone have been evaluated for template binding affinity, and have showed that the loading and release properties can be dependent on the functionality of the various monomers (Hiratani and Alvarez-Lorenzo, 2002, 2004; Venkatesh et al., 2008; Venkatesh et al., 2007). Additional studies have focused on optimizing synthesis parameters, such as degree of crosslinking and monomer to template ratio, to further refine the loading capacity and delivery profile (Alvarez-Lorenzo et al., 2002; Karim et al., 2005). In the area of molecularly imprinted contact lenses, researchers have demonstrated the ability to imprint a wide variety of compounds in hydrogels, including both ocular therapeutics and long-chain polymer comfort molecules (Ali and Byrne, 2009; Alvarez-Lorenzo et al., 2002; Efron et al., 2007; Hiratani and Alvarez-Lorenzo, 2002; Karim et al., 2005; Venkatesh et al., 2007). However, there is a limited body of research focusing specifically on silicone hydrogels, which represent the most prescribed lens type as of 2008 and which show the greatest promise for extended delivery due to their potential to be worn continuously for 4 weeks (Efron et al., 2007; Fonn et al., 2002; Nichols, 2009).



Figure 2-1 – Polymer network drug loading through soaking in basic hydrogels systems (left) and molecularly imprinted systems (right) demonstrating the higher loading capacity associated with template molecule specific memory cavities.

Therefore, the aim of this study was to evaluate the potential of silicone hydrogels for a contact lens drug delivery application. More specifically, it was intended to explore the potential of these hydrogel materials as molecularly imprinted networks, and to investigate the impact of including a long chain negatively charged comfort molecule into the polymer as a functional additive in place of copolymerization with functional monomers. Previously, the negative charge of the functional monomer, methacrylic acid, appeared to be a determining factor in generating the timolol template specific cavities based on ionic interactions (Hiratani and Alvarez-Lorenzo, 2002). The highly negatively charged wetting agent, hyaluronic acid (HA), was incorporated into the polymer to determine if it could function in a similar manner to these monomers, altering the release of timolol. To ensure the study would suit a contact lens delivery system, the drug release parameters were analyzed, while making certain that many of the essential properties of silicone hydrogel lenses remained intact.

2.2 Materials and Methods

2-hydroxyethyl methacrylate (HEMA), N,N-dimethylacrylamide (DMA), ethylene glycol dimethacrylate (EGDMA) and timolol maleate were all purchased from Sigma-Aldrich (Oakville, ON). 3-Methacryloxypropyltris(trimethylsiloxy)silane (TRIS) was purchased from Gelest Inc. (Morrisville, PA). Irgacure 184 was generously supplied by BASF Chemical Company (Vandalia, IL). Hyaluronic Acid (HA) 7.5 kDa was purchased from LifeCore Biomedical (Chaska, MN). Plexiglas G-UVT for casting molds was supplied by Altuglas Internationional (Bristol, PA). All other reagents were purchased from Sigma-Aldrich unless otherwise stated.

2.2.1 Hydrogel Synthesis

Model silicone hydrogels were prepared by UV-initiated free radical polymerization of a mixture of hydrophilic water sorbing monomers, DMA or HEMA, and a hydrophobic silane monomer, TRIS. All monomers were passed through inhibitor remover packed columns to ensure removal of monomethyl ether hydroquinone (MMEQ) prior to usage. All polymers were initiated with Irgacure 184 (0.1 wt.%) and crosslinked with EGDMA (3.33 wt.%). As an example of the polymerization procedure, the method used for composition entry 4 in Table 2-1 is provided. Timolol maleate (0.3 wt.%) was dissolved in 3 grams of a 1:1 weight ratio of DMA and TRIS solution. HA was added to the monomer solution as a functional additive and the mixture was stirred vigorously for

30 minutes to evenly disperse all components. Irgacure 184 was dissolved in the formulation, and the solution was immediately injected into a UV-transmittant acrylic plated mold with a 1mm Teflon spacer. The mold was then placed in a 400W UV chamber (Cure Zone 2 Con-trol-cure, Chicago, IL) for 15 minutes to facilitate polymerization. The hydrogel was then transferred to (100 mL) of PBS (pH of 7.4) for 30 minutes for partial hydration and then cut into discs with a diameter of 5/16" (7.94 mm) using a cork borer. All discs were then transferred to a 40°C oven to dry before subsequent wash release and characterization.

Material Composition	HA (mg)	Timolol (mg)		
1 (Control)	-	-		
2 (HA Included)	3	-		
3 (Timolol Imprinted)	-	9		
4 (HA and Imprinted)	3	9		
5 (HA Included – higher)	7.5	-		
6 (Timolol Imprinted – higher)	-	15		
7 (HA and Imprinted – higher)	7.5	15		
^a Base formulation of [DMA]:[TRIS]:[EGDMA] – [1.5g]:[1.5g]:[0.1g]				
^b Base formulation of [HEMA]:[TRIS]:[EGDMA] – [2.7g]:[0.3g]:[0.1g]				

Table 2-1 – Hydrogel compositions evaluated for p(DMA-*co*-TRIS) and p(HEMA-*co*-TRIS) base formulations.

2.2.2 Imprinting

Molecularly imprinting was accomplished by removing the template drug and unreacted monomer from the hydrogel by soaking the punched discs in 1mL of PBS (pH of 7.4) at 37°C with the wash solution being replaced at regular intervals. Soaking was carried out until all possible release had occurred; complete release was confirmed by the lack absorbance spectra in the UV wavelength range (200nm-400 nm) using a UV-Vis Spectrophotometer (Spectramax Plus 384, Molecular Devices, Corp, Sunnyvale, CA). Once all template had been removed, successfully imprinted hydrogels were then dried in a 40 °C oven for a minimum of 24 hours.

2.2.3 Swelling Behavior

The equilibrium water content (EWC) of each material was measured by comparing weights of dry and fully hydrated sample discs after 48 hours in MilliQ at 37 °C. Dry weight (M_D) was obtained by measuring the mass of hydrogels discs after being dried in a 40 °C oven for 24 hours. Hydrated weights (M_H) were obtained by removing the hydrated discs from MilliQ water, patting the discs dry with a soft tissue to remove any residual water droplets on the surface and then weighing the discs. All weights measurements were taken post-imprinting. Equation 2-1 was used the calculate the equilibrium water content of the hydrogels

$$EWC\% = \frac{M_H - M_D}{M_H} \cdot 100$$
 (Equation 2-1)

2.2.4 Transmittance

The transparency of the synthesized hydrogels was evaluated through light transmittance as measured by UV-Vis spectrophotometry. Discs of 5.55 mm diameter were hydrated in 100 μ L of Milli-Q water in the bottom of 96-well plates for 24 hours,

after which the transmittance was measured between 400-700 nm, the visible wavelength range. The value at 600nm was quoted as a representation of the visible spectrum.

2.2.5 Surface Wettability

The surface wettability of hydrogels was analyzed by measuring the contact angle using the captive bubble technique on a goniometer apparatus (Ramé-Hart NRL 100-00 Contact Angle Goniometer). Discs were attached to a microscope slide using double sided tape and then submerged in Milli-Q water within a glass tank. A syringe was then used to place a bubble on the surface of the submerged hydrogel and the contact angle was measured. All measurements were taken after hydrogels had been successfully imprinted and hydrated to equilibrium for 48 hours.

2.2.6 Drug Loading, Release and Analysis

Timolol maleate was loaded into hydrogels by soaking imprinted discs in drug-PBS (pH 7.4) uptake solutions at a concentration of 0.2 mg/mL and 1 mg/mL. Dry imprinted hydrogels were transferred to 1 mL of uptake solution for a period of 6 days. Drug-loaded hydrogels were then blotted dry and immediately used for release. Drug release experiments were conducted by soaking the drug-loaded discs in 1 mL of PBS (pH 7.4) at 37 °C, transferring the discs to fresh PBS at regular intervals to maintain sink conditions. The dynamic drug concentration in PBS was tracked by UV-Vis spectrophotometry at 295 nm. Drug loading and release experiments were carried out in triplicate as a minimum.

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2.3 Results and Discussion

2.3.1 Hydrogel Properties

2.3.1.1 Equilibrium Water Content

The water content of hydrogels used for contact lenses is an important parameter for on-eye comfort. Synthesized materials were evaluated to determine the impact of including both HA and imprinting therapeutic on this property (Table 2-2). When no drug or HA was incorporated into the gels, there was a clear difference in the EWC of the p(HEMA-co-TRIS) and the p(DMA-co-TRIS) gels with respective measures of $26.9\% \pm$ 0.7 and $31.8\% \pm 0.6$ (P < 0.000001). It is important to note the values obtained for these model hydrogels are within range of the EWC for commercially available silicone contact lenses (Efron et al., 2007). The above trend remains consistent regardless of the addition of HA as functional wetting agent or addition of the template drug timolol maleate. The variation between hydrogel compositions within a particular monomer formulation appeared to be minimal. Hydrogels with the addition of HA or imprinting of timolol as in composition 2 and 3 respectively, showed no difference in EWC for both p(HEMA-co-TRIS) (P > 0.5) and p(DMA-co-TRIS) (P > 0.1) materials. When added simultaneously as in composition 4, no difference in the EWC was observed in comparison to controls for the p(HEMA-co-TRIS) formulation (P > 0.05). In comparison, there was an small observable difference in the EWC for composition 4 of the p(DMA-co-TRIS) formulation (P < 0.004). The result of an ANOVA test performed on all the compositions for the p(HEMA-co-TRIS) formulation suggests that, regardless of the 4 compositions explored, there was no change in the EWC (P > 0.5). This lack of change can be explained by the fact HA has limited solubility in the monomer solutions, so only relatively low concentrations (0.1-0.25 wt.%) of the wetting agent can be added to the polymer formulations. And while previous studies have shown that HA incorporation can be used to increase the EWC for similar hydrogel formulations, those studies incorporated methacrylated HA or dendrimer-linked HA post-polymerization, as opposed to the direct entrapment performed in this study (van Beek et al., 2008; Weeks et al., 2012a; Weeks et al., 2012b).

 Table 2-2 – Comparison of essential lens properties (±SD) for material compositions 1-4

 of both p(DMA-co-TRIS) and p(HEMA-co-TRIS) formulations.

Material	Equilibrium Water	Contact Angle (°)	Light Transmittance	
Composition	Content (%) (n=9)	(n=6)	at 600nm (%) (n=5)	
1 – DT	31.8 ± 0.6	44.5 ± 3.5	96.2 ± 2.8	
2 – DT	31.4 ± 0.6	47.9 ± 2.3	80.0 ± 5.6	
3 – DT	31.8 ± 0.5	48.8 ± 3.8	96.6 ± 2.1	
4 - DT	32.3 ± 0.3	43.4 ± 2.2	76.7 ± 2.2	
1 – HT	26.9 ± 0.7	41.2 ± 1.3	77.1 ± 2.1	
2 - HT	27.0 ± 0.6	45.1 ± 2.1	49.1 ± 5.5	
3 – HT	26.8 ± 0.6	44.3 ± 1.3	71.6 ± 2.8	
4 – HT	26.5 ± 0.5	41.0 ± 2.4	48.8 ± 2.2	
^a HT denotes p(HEMA-co-TRIS) formulation and DT denotes p(DMA-co-TRIS)				
formulation		_		

2.3.1.2 Surface Wettability

Hydrogel wettability is another important parameter when considering the use of contact lenses. Ideally, the surface of the lens must be sufficiently wettable to maintain a stable tear film, which in turn promotes comfort. Using the captive bubble technique, the

contact angle was measured for hydrogel compositions 1-4 to further evaluate the impact of adding the wetting agent and therapeutic. As with EWC measurements, the presence of HA or timolol imprinting had no impact on the contact angle of hydrogels for both p(HEMA-co-TRIS) (P > 0.21) and p(DMA-co-TRIS) (P > 0.05) materials. This result is contradictory to previous studies, which have indicated that including hydrophilic wetting agents can moderate the surface wettability and thereby increase the comfort for lens wearers (van Beek et al., 2008; Weeks et al., 2012a). In this case because the materials are put through an extraction step post synthesis, a fraction of the HA added will be released as shown in previous studies (Weeks et al., 2013). One plausible explanation is that the HA which is releasing is likely concentrated on the surface, which would have the greatest effect on surface wettability.

2.3.1.3 Transparency of Hydrogel

Transparency is an essential property of any hydrogel to be used in a contact lens application. Therefore, it was necessary to determine the degree to which the addition of wetting agent affected the light transmittance. In addition, molecular imprinting requires the addition of the template therapeutic to the monomer formulation during synthesis, and this could affect transmittance as well. Despite the fact that the template would later be removed, hydrogel samples were analyzed to ensure that the direct entrapment of timolol did not significantly compromise the transparency. Light transmittance measurements of hydrogels for both monomer formulations were evaluated and results are included in Table 2-2 The p(HEMA-*co*-TRIS) materials were significantly less transparent than the p(DMA-co-TRIS) materials (P < 0.00001). The addition of timolol in synthesized materials had no significant impact on transparency for p(DMA-co-TRIS) materials (P >0.9), but reduced transparency when included in p(HEMA-co-TRIS) materials (P < P0.001). The p(DMA-co-TRIS) materials correspond to expectations as the relatively high solubility of timolol maleate in the monomer solution was hypothesized to prevent any loss in transparency. A possible explanation for reduced transparency observed with the p(HEMA-co-TRIS) materials when imprinted with timolol is that these particular monomers when combined are known to be susceptible to phase separation as evidenced by the low amount of TRIS monomer in the materials (Nicolson and Vogt, 2001). This means that the properties of hydrogels produced from this formulation are likely less consistent when fabricated. Therefore, it is possible that the difference in transparency is not necessarily the result of timolol imprinting. This hypothesis is further supported by the lack of statistical difference (P > 0.8) when comparing material compositions 2 and 4 for the p(HEMA-co-TRIS) formulation. In contrast, the presence of HA resulted in a reduction in the transparency for both p(DMA-co-TRIS) (P < 0.0001) and p(HEMA-co-TRIS)TRIS) (P < 0.001) materials. The low limit of solubility for the long hydrophilic chains of HA in the monomer formulations is likely preventing it from being fully solubilized. This in turn may be resulting in light refraction caused by insolubilized particulate being trapped within the gel.

Material Composition	Light Transmittance at 600nm (%)	
2 (HA Low) - DT	81.3 ± 3.1	
5 (HA High) – DT	65.1 ± 0.3	
2* (HA Low) – DT	86.0 ± 1.7	
5* (HA High) – DT	72.2 ± 0.4	
3 (Timolol Low) – DT	96.6 ± 2.3	
6 (Timolol High) – DT	98.1 ± 1.0	
^a The use of * denotes materials produced with a		
thickness of 0.5mm		

Table 2-3 – Effect of lens thickness on hydrogel transparency (±SD) measured by
spectrophotometry with n=6.

The nature of this effect was further evaluated using the p(DMA-*co*-TRIS) material and comparing higher levels of HA and timolol maleate in hydrogel compositions 5 and 6 respectively. Transmittance results in Table 2-3 show that even at higher levels, drug concentration continues to have no effect on transparency (P > 0.1). However, there is a direct correlation between increasing HA concentration and reduced transmittance (P < 0.0001). It should be noted these discs are significantly thicker than commercial lenses; a reduction in thickness will likely result in a less pronounced drop in transparency. A comparison of gels containing the same concentration of HA with a thickness is decreased both for low concentrations in composition 3 (P < 0.02) and at higher concentrations in composition 5 (P < 0.000001). This phenomenon is supported by previous studies by White *et al.* evaluating the same effect with hydroxypropylmethylcellulose (HPMC) in hydrogel materials (White et al., 2011). These

results support the hypothesis that as the model lens thickness is decreased to more representative values, the impact of HA on reducing transparency diminishes.

2.3.2 Dynamic Release

2.3.2.1 Imprinting Release

Drug release studies were carried out to compare materials that were not imprinted with template therapeutic, those that were imprinted with timolol, those that contained HA and those that were imprinted and included HA as a functional additive. This allowed for a comparison of the release kinetics of hydrogel compositions 1-4 and provided insight as to whether the use of a negatively charged wetting agent could increase the loading and alter the release kinetics. As HA is added prior to the imprinting stage, it is possible that a certain amount of it would be released during the template wash stage. This is supported by studies carried out by Ali and Byrne showing that HA can be released from similar hydrogel materials (Ali and Byrne, 2009). To accommodate for any loss of HA during the wash stage, materials were loaded using two uptake solutions, one comprised of timolol maleate (0.2 mg/mL) in PBS (pH 7.4) and another containing a dual solution with both HA and timolol maleate at a concentration of 0.2 mg/mL in PBS (pH 7.4). This would ensure that any quantifiable change in drug release caused by HA could be traced back to be either a result of adding it to the polymer or loading it from the soaking solution.



Figure 2-2 – Drug release profile for p(DMA-*co*-TRIS) formulation loaded with 0.2mg/mL timolol maleate. Error represented as (±SD) with n=3.



Figure 2-3 – Drug release profiles for p(HEMA-*co*-TRIS) formulation loaded with 0.2mg/mL timolol maleate. Error represented as (±SD) with n=3.

Figures 2-2 and 2-3 show that for each respective monomer formulation, all hydrogel compositions are governed by similar release kinetics. However, there are clear differences in the amount of drug being released based on the material composition: control hydrogels that have no modification (composition 1) lead to the lowest amount of drug released; hydrogels that have HA added to the monomer solution during synthesis (composition 2) show noticeably higher release than the control non-imprinted materials; timolol imprinted hydrogels (composition 3) show higher release than controls as expected based on the literature; and hydrogels that were both imprinted and contain HA (composition 4) show the highest release, representative of a summative effect caused by combining both strategies within a single hydrogel. The above trends are consistent in both monomer formulations which further supports this trend. Table 2-4 summarizes the total timolol release observed for compositions 1-4 and underlines the significant difference between controls and modified hydrogels. Although HA addition and timolol imprinting both independently increased total release compared to control, the total release produced by each strategy is the same. This applies for both p(HEMA-co-TRIS) (P > 0.6) and p(DMA-co-TRIS) (P > 0.1) materials.

Material Composition	p(DMA <i>-co-</i> TRIS) Total Release (ug/mg dry gel)	p(HEMA-co-TRIS) Total Release (ug/mg dry gel)		
r	Release (µg/ing ar j ger)	Release (µg/ing ar y ger)		
1 (Control)	0.16685 ± 0.00812	0.19987 ± 0.02028		
2 (HA)	$0.24366 \pm 0.00713^*$	$0.25435 \pm 0.00846*$		
3 (Timolol Imprinted)	$0.25459 \pm 0.00446*$	0.26870 ± 0.04033		
4 (HA+Timolol Imprinted)	$0.31019 \pm 0.02269^*$	$0.40070 \pm 0.00540^{*}$		
^a The use of $*$ denotes release is significantly different than control hydrogels (p<0.05)				

Table 2-4 – Comparison of total drug release amounts (±SD) for compositions 1-4 of both p(DMA-*co*-TRIS) and p(HEMA-*co*-TRIS) formulations with n=3.

Figure 2-4 compares of the release from the materials loaded with the dual solution of both HA and timolol maleate at 0.2 mg/mL. It is evident that the trend observed in the release from these materials is the same as those loaded with only timolol maleate. This suggests it is the HA that is added within the material during synthesis that is producing this effect. If it were the HA within the loading solution that was generating the observed change in drug release, the trend would not be consistent in release results for both loading solutions.



Figure 2-4 – Drug release profiles for p(DMA-*co*-TRIS) formulation loaded with HA and timolol at 0.2mg/mL. Error represented as (±SD) with n=3.

This result is likely to be caused by the significant negative charge associated with HA. Previous studies have shown that negatively charged carboxyl groups can be incorporated into hydrogels to improve the loading capacity and slow the release of timolol in ophthalmic hydrogels (Hiratani and Alvarez-Lorenzo, 2002; Venkatesh et al., 2008). Although not tethered to the polymer network, HA could function in the same manner. It is believed that the functional monomers with carboxyl groups will have electrostatic charge interactions with timolol at physiological pH because both components will carry charge (pKa timolol 9.21; pKa carboxyl groups 4.2) and will be suitable counter ions (Alvarez-Lorenzo et al., 2002). It is through these specific charge interactions, that HA likely increases the amount of timolol that is loaded into the hydrogel. The higher level of drug release is, thus, likely a manifestation of the higher

drug loading that is taking place. This method of action would likely explain the ability of HA alone to increase the release without the imprinting of timolol.

The results further suggest that the effect of imprinting and the effect of adding HA are separate and can act independently. Additionally, they can be combined within a single hydrogel to produce a release that is summative of the two individual effects. To our knowledge, this study is the first to show that a negatively charged wetting agent like HA can be used as a functional additive, in a similar fashion to functional monomers, to increase the loading capacity of silicone hydrogels.

2.3.2.2 Imprinting Release - Higher Uptake Concentration

It is evident that at low concentrations of drug loading (0.2 mg/mL timolol), HA could promote increased drug release when added to hydrogels during synthesis. However, based on the hypothesized function of HA, the inclusion of a specific concentration of wetting agent would only allow for a set number of electrostatic interactions. Therefore, it was important to evaluate this effect at much higher timolol loading concentrations that may be required in a clinical environment. At low loading concentrations these interactions appeared to be significant enough to produce a quantifiable difference in the amount of drug released. At higher loading concentrations, the interactions that boost uptake may be insignificant compared to the diffusive uptake, and, thus, produce no difference in comparison to controls.

Figure 2-5 shows the release results for hydrogel compositions 1,5,6,7 after loading in 1 mg/mL of timolol in PBS (pH of 7.4). Referring back to the hydrogel

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composition tables, both the timolol template concentration and the HA concentration were increased for hydrogels 5 and 6 respectively; for simplicity, these studies were carried out on only the p(DMA-co-TRIS) monomer formulation. Imprinting with timolol template continued to generate higher drug release compared to non-imprinted materials (P < 0.00001). The addition of HA to the control hydrogels continued to boost release over the control (P < 0.006), but the degree of this effect was significantly reduced at these higher loading concentrations and not significant when HA was added to timolol imprinted materials (P > 0.6). This validates the hypothesis that the use of HA as a functional additive to increase the timolol loading and subsequent release becomes less relevant at higher loading concentrations. At higher loading concentrations of timolol maleate, the relative contribution to drug uptake from normal diffusion likely outweighs the electrostatic interactions with HA. It is possible that the effect would be more pronounced as the concentration of HA added to the polymer was increased, but as noted previously, the low solubility of HA in the pre-polymer solution remains a limiting constraint. However, it is not clear why imprinting timolol template continues to generate an increased drug release while the addition of HA does not.



Figure 2-5 – Timolol Release profiles for p(DMA-*co*-TRIS) formulation loaded with 1mg/mL drug-PBS solutions. Error represented as (±SD) with n=6.

Despite the fact that at higher loading concentrations, including HA does not produce a significant increase in the amount of drug released, such high concentrations may not be required. The use of a typical 0.25% timolol maleate drop formulation applied twice daily will result in approximately 50 μ L total volume being added to each eye (Gulsen and Chauhan, 2004). Assuming a maximum of 5% of this formulation penetrates the cornea, the total amount of drug delivered to the target tissues would be approximately 6.25 μ g per day. With an estimated contact lens mass of 22.3 mg, the delivery from hydrogels loaded with a 0.2 mg/mL solution of timolol maleate based on these results would be approximately 4.0 μ g per day while those loaded with 1 mg/mL would be 20 μ g per day (Peng and Chauhan, 2011). This suggests that high loading concentrations may not be required to reach clinically relevant drug release levels. Thus, HA as a functional additive may allow for loading at concentrations appropriate for a contact lens based delivery system to be clinically viable. Furthermore, such systems can be tailored to reach specific drug release targets based on the concentration of the loading solution used.

Over the majority of the cases explored, 90% of the total release occurs within the first three days and the presence of HA does not appear to significantly extend the release from these imprinted polymers. For a clinically viable solution, it would be ideal to achieve prolonged release that matches with the extended wear of silicone hydrogels. The use of daily therapeutic hydrogels that release drugs for a period of 1-2 days would not address issues of patient compliance that many of these treatments already suffer from. This underlines the need to produce hydrogel systems capable of extended release with zero-order kinetics. To generate such solutions, it is essential to further evaluate ways in which drug release can be controlled from these systems.

2.4 Conclusion

Using hyaluronic acid as a functional additive within hydrogel polymers allowed for an increase in the loading of timolol through electrostatic interactions, and worked simultaneously with molecular imprinting to boost the uptake of therapeutic. Incorporating low concentrations of HA into the polymer network resulted in the release of higher amounts of timolol from the hydrogels compared with hydrogels that did not contain HA. However, at higher loading concentrations, incorporated HA did not lead to increased timolol uptake. These results suggest that it is possible to use HA as an
alternative to functional monomers to increase the loading of timolol. However, the HA concentration included within the hydrogels in comparison to template loading concentration is an important consideration for such a system. Despite the reduced ability of HA to increase uptake at higher loading concentration, therapeutic release amounts may only require relatively low loading concentrations. Overall, transparent drug loaded hydrogels that contain HA as a functional additive, have potential for use as anterior eye delivery systems.

References

- Ali, M., Byrne, M.E., 2009. Controlled release of high molecular weight hyaluronic acid from molecularly imprinted hydrogel contact lenses. Pharm Res 26, 714-726.
- Alonso, M.J., Sánchez, A., 2003. The potential of chitosan in ocular drug delivery. J Pharm Pharmacol 55, 1451-1463.
- Alvarez-Lorenzo, C., Concheiro, A., 2004. Molecularly imprinted polymers for drug delivery. J Chromatogr B 804, 231-245.
- Alvarez-Lorenzo, C., Hiratani, H., Gómez-Amoza, J.L., Martínez-Pacheco, R., Souto, C., Concheiro, A., 2002. Soft contact lenses capable of sustained delivery of timolol. J Pharm Sci 91, 2182-2192.
- Boone, A., Hui, A., Jones, L., 2009. Uptake and release of dexamethasone phosphate from silicone hydrogel and group I, II, and IV hydrogel contact lenses. Eye Contact Lens 35, 260-267.
- Byrne, M.E., Park, K., Peppas, N.A., 2002. Molecular imprinting within hydrogels. Adv Drug Del Rev 54, 149-161.
- Ciolino, J.B., Dohlman, C.H., Kohane, D.S., 2009a. Contact lenses for drug delivery, Semin Ophthalmol. Informa UK Ltd UK, pp. 156-160.
- Ciolino, J.B., Hoare, T.R., Iwata, N.G., Behlau, I., Dohlman, C.H., Langer, R., Kohane, D.S., 2009b. A drug-eluting contact lens. Invest Ophthalmol Vis Sci 50, 3346-3352.
- Davies, N.M., 2000. Biopharmaceutical considerations in topical ocular drug delivery. Clin Exp Pharmacol Physiol 27, 558-562.
- Diamond, J.P., 1997. Systemic adverse effects of topical ophthalmic agents. Implications for older patients. Drugs Aging 11, 352-360.
- Efron, N., Morgan, P.B., Cameron, I.D., Brennan, N.A., Goodwin, M., 2007. Oxygen permeability and water content of silicone hydrogel contact lens materials. Optom Vis Sci 84, E328-E337.

- Fonn, D., MacDonald, K.E., Richter, D., Pritchard, N., 2002. The ocular response to extended wear of a high Dk silicone hydrogel contact lens. Clin Exp Optom 85, 176-182.
- Ghate, D., Edelhauser, H.F., 2008. Barriers to glaucoma drug delivery. J Glaucoma 17, 147.
- Gulsen, D., Chauhan, A., 2004. Ophthalmic drug delivery through contact lenses. Invest Ophthalmol Vis Sci 45, 2342-2347.
- Hehl, E.-M., Beck, R., Luthard, K., Guthoff, R., Drewelow, B., 1999. Improved penetration of aminoglycosides and fluoroquinolones into the aqueous humour of patients by means of Acuvue contact lenses. Eur J Clin Pharmacol 55, 317-323.
- Hiratani, H., Alvarez-Lorenzo, C., 2002. Timolol uptake and release by imprinted soft contact lenses made of< i> N</i>,< i> N</i>-diethylacrylamide and methacrylic acid. J Controlled Release 83, 223-230.
- Hiratani, H., Alvarez-Lorenzo, C., 2004. The nature of backbone monomers determines the performance of imprinted soft contact lenses as timolol drug delivery systems. Biomaterials 25, 1105-1113.
- Hiratani, H., Fujiwara, A., Tamiya, Y., Mizutani, Y., Alvarez-Lorenzo, C., 2005. Ocular release of timolol from molecularly imprinted soft contact lenses. Biomaterials 26, 1293-1298.
- Jung, H.J., Abou-Jaoude, M., Carbia, B.E., Plummer, C., Chauhan, A., 2013. Glaucoma therapy by extended release of timolol from nanoparticle loaded silicone-hydrogel contact lenses. J Control Release 165, 82-89.
- Karim, K., Breton, F., Rouillon, R., Piletska, E.V., Guerreiro, A., Chianella, I., Piletsky, S.A., 2005. How to find effective functional monomers for effective molecularly imprinted polymers? Adv Drug Del Rev 57, 1795-1808.
- Kaur, I.P., Garg, A., Singla, A.K., Aggarwal, D., 2004. Vesicular systems in ocular drug delivery: an overview. Int J Pharm 269, 1-14.
- Kim, J., Conway, A., Chauhan, A., 2008. Extended delivery of ophthalmic drugs by silicone hydrogel contact lenses. Biomaterials 29, 2259-2269.
- Kopecek, J., 2009. Hydrogels: From soft contact lenses and implants to self-assembled nanomaterials. J Polym Sci, Part A: Polym Chem 47, 5929-5946.
- Korte, J.M., Kaila, T., Saari, K.M., 2002. Systemic bioavailability and cardiopulmonary effects of 0.5% timolol eyedrops. Graefes Arch Clin Exp Ophthalmol 240, 430-435.
- Lang, J.C., 1995. Ocular drug delivery conventional ocular formulations. Adv Drug Del Rev 16, 39-43.
- Lavik, E., Kuehn, M., Kwon, Y., 2011. Novel drug delivery systems for glaucoma. Eye 25, 578-586.
- Le Bourlais, C., Acar, L., Zia, H., Sado, P.A., Needham, T., Leverge, R., 1998. Ophthalmic drug delivery systems—recent advances. Prog Retin Eye Res 17, 33-58.
- Li, C.-C., Chauhan, A., 2006. Modeling ophthalmic drug delivery by soaked contact lenses. Ind Eng Chem Res 45, 3718-3734.

- McNamara, N.A., Polse, K.A., Brand, R.J., Graham, A.D., Chan, J.S., McKenney, C.D., 1999. Tear mixing under a soft contact lens: effects of lens diameter. Am J Ophthalmol 127, 659.
- Mosbach, K., Ramström, O., 1996. The emerging technique of molecular imprinting and its future impact on biotechnology. Nat Biotechnol 14, 163-170.
- Nichols, J., 2009. Contact Lenses 2008. Contact Lens Spectrum 24, 24-32.
- Nicolson, P.C., Vogt, J., 2001. Soft contact lens polymers: an evolution. Biomaterials 22, 3273-3283.
- Peng, C.-C., Chauhan, A., 2011. Extended cyclosporine delivery by silicone–hydrogel contact lenses. J Controlled Release 154, 267-274.
- Peng, C.-C., Kim, J., Chauhan, A., 2010. Extended delivery of hydrophilic drugs from silicone-hydrogel contact lenses containing Vitamin E diffusion barriers. Biomaterials 31, 4032-4047.
- Sahoo, S.K., Dilnawaz, F., Krishnakumar, S., 2008. Nanotechnology in ocular drug delivery. Drug Discov Today 13, 144-151.
- Salminen, L., 1990. Review: systemic absorption of topically applied ocular drugs in humans. J Ocul Pharmacol Ther 6, 243-249.
- Schwartz, G.F., Quigley, H.A., 2008. Adherence and persistence with glaucoma therapy. Surv Ophthalmol 53, S57-S68.
- Sellergren, B., Allender, C.J., 2005. Molecularly imprinted polymers: A bridge to advanced drug delivery. Adv Drug Del Rev 57, 1733-1741.
- Urtti, A., 2006. Challenges and obstacles of ocular pharmacokinetics and drug delivery. Adv Drug Del Rev 58, 1131-1135.
- van Beek, M., Weeks, A., Jones, L., Sheardown, H., 2008. Immobilized hyaluronic acid containing model silicone hydrogels reduce protein adsorption. J Biomater Sci Polym Ed 19, 1425-1436.
- Venkatesh, S., Saha, J., Pass, S., Byrne, M.E., 2008. Transport and structural analysis of molecular imprinted hydrogels for controlled drug delivery. Eur J Pharm Biopharm 69, 852-860.
- Venkatesh, S., Sizemore, S.P., Byrne, M.E., 2007. Biomimetic hydrogels for enhanced loading and extended release of ocular therapeutics. Biomaterials 28, 717-724.
- Weeks, A., Luensmann, D., Boone, A., Jones, L., Sheardown, H., 2012a. Hyaluronic acid as an internal wetting agent in model DMAA/TRIS contact lenses. J Biomater Appl 27, 423-432.
- Weeks, A., Morrison, D., Alauzun, J.G., Brook, M.A., Jones, L., Sheardown, H., 2012b. Photocrosslinkable hyaluronic acid as an internal wetting agent in model conventional and silicone hydrogel contact lenses. J. Biomed. Mater. Res., Part A 100, 1972-1982.
- Weeks, A., Subbaraman, L.N., Jones, L., Sheardown, H., 2013. Physical entrapment of hyaluronic acid during synthesis results in extended release from model hydrogel and silicone hydrogel contact lens materials. Eye Contact Lens 39, 179-185.
- White, C.J., Byrne, M.E., 2010. Molecularly imprinted therapeutic contact lenses. Expert Opin Drug Deliv 7, 765-780.

- White, C.J., McBride, M.K., Pate, K.M., Tieppo, A., Byrne, M.E., 2011. Extended release of high molecular weight hydroxypropyl methylcellulose from molecularly imprinted, extended wear silicone hydrogel contact lenses. Biomaterials 32, 5698-5705.
- Wu, Y., Carnt, N., Willcox, M., Stapleton, F., 2010. Contact lens and lens storage case cleaning instructions: whose advice should we follow? Eye Contact Lens 36, 68-72.
- Xinming, L., Yingde, C., Lloyd, A.W., Mikhalovsky, S.V., Sandeman, S.R., Howel, C.A., Liewen, L., 2008. Polymeric hydrogels for novel contact lens-based ophthalmic drug delivery systems: A review. Cont Lens Anterior Eye 31, 57-64.

Chapter 3 : Evaluating the Impact of Hydrogel Chemistry on Dexamethasone Release

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Objectives: To elucidate the relationship between the monomers used in hydrogel formulations and the resultant drug release kinetics of dexamethasone.

Main Scientific Contributions:

- Successfully synthesized a number of silicone hydrogels of varying chemical compositions while maintaining many essential contact lens properties
- Demonstrated changing dexamethasone release (7-16 days) based on monomer formulation
- Proved that the diffusion rate of lipophilic dexamethasone is largely dependent on the water content of hydrogel materials

Abstract

The relationship between the delivery of dexamethasone (DEX) and the composition of silicone hydrogel materials was investigated. Two hydrophilic monomers (2-hydroxyethyl methacrylate or N,N-dimethylacrylamide), a siloxy methacrylate based (1-(bis(trimethylsiloxy)methylsilyl)propoxy-3-metacryloxy-2-propanol, monomer a polysiloxane (monomethacryloxypropyl terminated polydimethylsiloxane) and a polymerizable silicone surfactant (Silmer ACR A008-UP) were used to synthesize hydrogels of variable composition. The materials properties, such as surface wettability and equilibrium water content, were highly dependent on polymer formulation. All DEX loaded hydrogels showed uptake that was driven primarily by sorption to the polymer phase. Furthermore, a positive correlation between loading mass and equilibrium water content was established. The drug release duration from the hydrogels ranged from one to greater than two weeks depending on the monomer combination and relative contribution of hydrophilic and hydrophobic monomers. Higuchi model rate constants for the release showed strong correlation with the equilibrium water content, signifying that the release is likely controlled by aqueous phase diffusion.

3.1 Introduction

Currently, the use of the eye drops continues to dominate the topical treatment of ocular medical conditions, with over 90% of ophthalmic formulations being delivered in this manner (Peng et al., 2012b). Their non-invasive nature and ease of use are primary reasons for their usage. However, topical administration suffers from a number of inefficiencies including, rapid formulation drainage and absorption, short tear film residence time, and low ocular bioavailability of the drug (Ghate and Edelhauser, 2008; Järvinen et al., 1995). The summation of these delivery barriers leads to only 1-5% of the applied formulation contributing to a therapeutic effect (Ghate and Edelhauser, 2008; Lang, 1995). To accommodate, frequent drop administration is required, in many cases multiple times per day. This leads to further issues of patient noncompliance, which can undermine the effectiveness of an eye drop treatment regimen (Taylor et al., 2002). Furthermore, upwards of 90% of the applied drug formulation is absorbed into systemic circulation, which has the potential to result in detrimental side effects (Bowman et al., 2004; Korte et al., 2002; Pooniya and Pandey, 2012). The clear drawbacks and disadvantages of eye drops from a drug delivery standpoint have prompted the investigation of alternative delivery strategies, one of which is the use of contact lenses as a delivery vehicle. Contact lenses are one of the most successful biomaterials to date with over 140 million users worldwide (Hui et al., 2012; Stapleton et al., 2007). Although their primary function is vision correction, their unique properties make them attractive as a potential therapeutic delivery system.

Drugs that are used to treat conditions of the anterior eye can be incorporated within contact lenses and eluted from the lens by diffusion into the tear film. When a lens is positioned on the anterior surface of the eye, it divides the tear film into two sections, a post-lens tear film (POLTF) and a pre-lens tear film (PLTF). The drug can then diffuse from the hydrogel network into both sections. Due to the limited mixing between the two areas and resultant delayed turn over time of the POLTF, the drug concentration in contact with the cornea can be sustained for periods of up to 30 minutes (Creech et al., 2001; McNamara et al., 1999). Owing to this prolonged tear film residence time, the drug bioavailability can potentially be increased to 50% of the applied dosage (Li and Chauhan, 2006). This leads to reduced drug wastage and has the potential to improve the effectiveness of the treatment. Moreover, the increased delivery efficiency can allow for lower doses, possibly resulting in lower systemic drug concentrations, thereby mitigating the risk for harmful side effects. In the case of silicone hydrogel lenses, the potential exists for them to be worn for periods of up to 30 days continuously (Efron et al., 2007). If delivery can be sustained for extended durations, this offers a means to reduce the issue of patient noncompliance associated with repeat administrations. The above delivery advantages combined with the comfort of contact lenses underlines their attractiveness as an alternative ophthalmic delivery method.

A significant body of research in the area of contact lens drug delivery has focused on the use of commercial lens materials as a means of providing a therapeutic effect (Boone et al., 2009; Hui et al., 2008; Karlgard et al., 2003; Peng et al., 2012a; Phan et al., 2013; Soluri et al., 2012). Many of these studies have focused on evaluating various

types and brands of lenses in the quest to determine which lens properties are most advantageous for higher drug partitioning and extended release. These studies have investigated a number of different ophthalmic drugs ranging from dexamethasone and timolol maleate, to cyclosporine A and nantamycin, which are used as treatments for a range of conditions, including glaucoma, dry eye, ocular inflammation and infections (Kim et al., 2008; Kim et al., 2010; Peng and Chauhan, 2011; Phan et al., 2013). Such studies have demonstrated that monomer composition, hydrogel charge and drughydrogel partitioning are important factors that govern drug delivery from commercial contact lenses (Boone et al., 2009; Kim et al., 2010; Soluri et al., 2012). However, the limited availability of proprietary information regarding the chemical formulation of these lenses makes it difficult to understand the relationship between hydrogel formulation chemistry and delivery characteristics. Thus, it is proposed that an evaluation of dynamic drug release from synthesized model silicone hydrogels with known molar fractions of common established monomers will provide valuable insight into this relationship. This information will be extraordinarily beneficial when rationally designing subsequent silicone hydrogel release systems capable of sustained release.

Silicone hydrogels, unlike conventional hydrogels, are approved for continuous wear for up to 30 days due to their high oxygen permeability (Jones and Powell, 2013; Jones et al., 2003). This makes them particularly suitable as a lens based delivery system since they provide the opportunity to deliver therapeutics for extended periods without posing a risk for corneal surface hypoxia. Dexamethasone (DEX) was chosen as the deliverable drug based on its lipophilic nature, which lends itself to high corneal

penetration and a comparably longer release timescale than hydrophilic drugs (Kim and Chauhan, 2008). Its anti-inflammatory effects make it potentially useful in a bandage lens application to treat corneal wounds. To determine the impact of incorporating silicone based monomers within the lens on drug transport, DEX was incorporated into a range of polymers where the hydrophilic monomers (2-hydroxyethyl methacrylate (HEMA, 1) or N,N'-dimethylacrylamide (DMA, siloxy methacrylate monomer 2)), ((1-(bis(trimethylsiloxy)methylsilyl)propoxy-3-metacryloxy-2-propanol (TRIS-OH, 3)), a methacrylated polysiloxane macromonomer (mPDMS, 4), and a polymerizable silicone surfactant (ACR, 5) were systemically adjusted. By analysing the release of DEX from these materials, it was possible to correlate the duration of drug delivery and drug release kinetics to the chemistry of polymer formulation.



Figure 3-1 – Chemical structures of monomer components used in model silicone hydrogel contact lenses

These two silicone based monomers are two commonly used to enhance the oxygen permeability of lens materials (Nicolson and Vogt, 2001). Previous generations of silicone hydrogel lenses often incorporated internal wetting agents or were surface plasma coated to address the reduced surface wettability that comes with introducing hydrophobic silicone compounds (Nicolson, 2003; Sindt and Longmuir, 2007). However, new continuous wear lenses have an optimized chemistry that allows them to be inherently wettable, eliminating the need for additives (Jacob, 2013). In this work, the incorporation of a polymerizable silicone surfactant, ACR, is proposed as a method of improving the wettability of these model materials while eliminating the need for wetting agents or coatings (Khan, 2013). Incorporating non-tethered surfactants in contact lenses as a means of beneficially altering the release properties has also been recently documented (Bengani and Chauhan, 2013; Kapoor and Chauhan, 2008). A polymerizable surfactant was chosen to ensure permanent enhanced lens wettability and mitigate possible eye irritation that could accompany non-tethered surfactant incorporation. Analyzing the DEX loading and release parameters will provide a fundamental understanding of how the lens chemistry affects and mediates drug transport in these hydrogel systems.

3.2 Materials and Methods

2-hydroxyethyl methacrylate (HEMA), N,N-dimethylacrylamide (DMA), ethylene glycol dimethacrylate (EGDMA) and Dexamethasone (DEX) were all purchased from Sigma-

Aldrich (Oakville, ON). 1-(bis(trimethylsiloxy)methylsilyl)propoxy-3-metacryloxy-2propanol (TRIS(OH)) and monomethacryloxypropyl terminated polydimethylsiloxane (mPDMS) were purchased from Gelest Inc. (Morrisville, PA). Silmer ACR A008-UP was supplied by Siltech Corp. (Mississauga, ON). Irgacure 184, the photoinitiator (PI) was provided by BASF Corp (Vandalia, IL). Plexiglas G-UVT for acrylic molds was provided by Altuglas (Bristol, PA). All other reagents were purchased from Sigma-Aldrich unless otherwise stated.

3.2.1 Hydrogel Synthesis

Model hydrogel lenses were formed through free radical bulk polymerization of various monomer mixtures. All individual monomers had the inhibitor, monomethyl ether hydroquinone (MMEQ), removed by passing through packed columns of appropriate inhibitor remover acquired from Sigma-Aldrich prior to mixing. Monomers were then combined in the molar ratios according to those outlined in Table 3-1 and mixed for approximately 10 minutes, after which point 1 mg of PI was added and stirred vigorously to ensure complete dissolution. Monomer mixtures were then injected into a UV-light transmittant acrylic plated mold with a Teflon spacer of 500 μ m thickness and placed in a 400W UV chamber (Cure Zone 2 Con-trol-cure, Chicago, IL) for 10 minutes to facilitate polymerization. Upon removal from the mold, the polymers were hydrated in MilliQ water for 24 hours before punching into discs with different diameters using a cork borer. Hydrogel discs with diameters of 7/32", 5/16" and 7/16" were used for drug delivery, transparency and contact angle measurements respectively. All discs were then transferred to a 1:1 H₂O:methanol (v./v.) solution to extract any residual unreacted

monomer and initiator for 48 hours and dried at room temperature afterward. Complete extraction was then confirmed by lack of absorbance in the UV wavelength range using a UV-VIS spectrophotometer (Varian Cary 50 Bio).

3.2.2 Hydrogel Formulations

The molar feed compositions of the various hydrogels synthesized are summarized in Table 3-1. Control formulations included pHEMA, p(HEMA-*co*-TRIS(OH)) and p(DMA-*co*-TRIS(OH)) hydrogels. To increase the similarity between model materials to commercial lens formulations two approaches were taken:

- Incorporating an oxygen permeability enhancing monomer, mPDMS
- Incorporating a potential surface wettability enhancing monomer, ACR

mPDMS was added to the formulation as a replacement for an equivalent molar fraction of TRIS(OH) in control materials. ACR was added at 5 or 10 mol%, while keeping the ratio of hydrophilic monomer (DMA or HEMA) to hydrophobic monomer (TRIS(OH)) constant.

Hydrogel Formulation ^a	(DMA or HEMA)	TRIS(OH)	(ACR)	(mPDMS)
pHEMA (0.2mL H ₂ O)	97.0	-	-	-
p(DMA-co-TRIS(OH))	77.6	19.4	-	-
p(DMA-co-TRIS(OH)-co-ACR)	73.6	18.4	5	-
p(HEMA-co-TRIS(OH))	94.0	3.0	-	-
p(HEMA-co-TRIS(OH)-co-ACR)	89.2	2.8	5	-
p(HEMA-co-TRIS(OH)-co-ACR)	84.3	2.7	10	-
p(HEMA-co-TRIS(OH)-co-mPDMS)	77.6	9.7	-	9.7
p(DMA-co-TRIS(OH)-co-mPDMS)	77.6	9.7	-	9.7
^a All monomer mixtures contained 3 mol% EGDMA and 1 mg of PI (Irgacure 184).				

Table 3-1 – Summary of monomer molar percent composition for synthesized hydrogels

3.2.3 Swelling Behavior

The equilibrium water content (EWC) of synthesized hydrogels was evaluated post-extraction. Discs were weighed in a dry state after being placed in a 40°C oven for 24 hours and then transferred to room temperature for 48 hours. Dry discs were then placed in 1 mL of PBS (pH 7.4) and incubated at room temperature for an additional 48 hours. Hydrated discs were then removed from the aqueous solution, patted with KimWipes to remove any surface water droplets that remained and weighed. The EWC of each hydrogel composition was then determined using equation 3-1, where M_H is the hydrated mass and M_D is the dry mass of the hydrogel discs. All measurements were done in triplicate.

$$EWC\% = \frac{M_H - M_D}{M_H} \cdot 100$$
 (Equation 3-1)

3.2.4 Transmittance and Optical Haze

The percent of light transmittance for each hydrogel formulation was measured using a UV-VIS spectrophotometer (Varian Cary 50 Bio). Hydrogel discs post-extraction were hydrated in MilliQ water for a minimum of 48 hours. Materials were then directly transferred to the bottom of a 96-well plate with 100 μ L of MilliQ water to ensure sustained hydration of the discs. Light transmittance was then measured in the visible light spectrum range from 400nm-700nm. Values were quoted at 600 nm as a representation of the visible spectrum.

The tendency of the synthesized hydrogels to scatter light was analyzed using a hazemeter ((BYK Gardner, Germany). Dried discs were hydrated for a minimum of 48 hours after extraction. Hydrogels were then removed from the MilliQ water and immediately patted on the surface using KimWipes to remove residual water droplets, then placed within the beam path of the hazemeter and light scattering percent was measured.

3.2.5 Surface Wettability

The wettability of the hydrogel surface was analyzed by measuring the contact angle using the captive bubble technique. Hydrated discs were placed on top of a holder and then submerged in PBS (pH 7.4) within a glass chamber. After a 5 minute waiting period to ensure rehydration, a syringe was then used to place an air bubble underneath the hydrogel materials and a goniometer (OCA 35, dataphysics) was used to measure the captive bubble contact contact angle. All measurements were done in triplicate.

3.2.6 Drug Delivery Studies

3.2.6.1 Drug Loading

Hydrogels were loaded with DEX by soaking in a drug solution. Dried hydrogel discs were placed in $1.5mL \ 1:1 H_2O$:methanol solution containing 1mg/mL DEX. The amount of drug loaded was quantified using UV spectrophotometry by measuring the change in UV absorbance of the DEX solution at 241 nm after 24 and 48 hours of incubation. A calibration curve was used to covert absorbance to concentration. After

loading was complete, hydrogels were then dried at room temperature for 60 hours to remove the remaining cosolvent.

3.2.6.2 Drug Release

The dried drug loaded hydrogel discs were then placed in 1.5mL PBS (pH 7.4) and incubated at 37°C. The release of DEX was quantified over time using UV spectrophotometry by measuring the absorbance of the releasate at 241 nm. To ensure infinite sink conditions, the release solution was replaced with fresh PBS at each time point. Both loading and release studies were carried out with 6 discs for each hydrogel formulation evaluated.

3.3 Results and Discussion

3.3.1 Impact of Hydrogel Composition on Material Properties

3.3.1.1 Equilibrium Water Content

A comparison of the material properties for each of the hydrogel formulations is shown in Table 3-2 and Table 3-3. It is evident that the overall hydrogel composition had a direct impact on the equilibrium water content of the resultant hydrogel. Using pHEMA as a control material for reference, the introduction of the silane, TRIS(OH), resulted in a reduction of the water content (P<0.007). This result is expected due to the hydrophobic nature of TRIS(OH), as unlike HEMA it has a limited capacity for aqueous association and functions to increase oxygen permeability at the expense of water content. A comparison of the p(HEMA-co-TRIS(OH)) hydrogel with the p(DMA-co-TRIS(OH)) hydrogel demonstrates that despite the higher silicone monomer content (3% vs. 19.4%), the latter is able to absorb more water (P<0.0002). This is likely due to the more hydrophilic nature of DMA (logP 0.18) in comparison to HEMA (logP 0.3) (Baggiani et al., 2006)³³. This is an important result as it demonstrates that the tendency of silicone components to reduce the water content can be overcome by the use of more hydrophilic monomers. The incorporation of mPDMS resulted in a slight reduction in the water content of the p(DMA-co-TRIS(OH)) base hydrogel formulation (P<0.007). This is expected due to the more hydrophobic nature of mPDMS compared to TRIS(OH). In contrast, the addition of a polymerizable silicone surfactant (ACR) to the hydrogel formulation caused a slight increase in the equilibrium water content. There appeared to be a direct relationship between mole fraction of the ACR and the water content of the resultant material. The cause of the increased swelling in aqueous solution is likely the hydrophilic pendant oligo(ethyleneoxide) chain contained within the surfactant. Across the span of hydrogel formulations evaluated, all but one exhibited EWC of approximately 20%-35%, which closely resembles that of commercial silicone hydrogel lens materials (Efron et al., 2007).

It appears that the relative hydrophilicity of the overall polymer formulation determines the water content of these hydrogels. The ability of hydrophilic monomers to promote water uptake depends on the octanol/water partition coefficient. There is an inverse relationship between the logP value of the monomer used and the water content of a resultant hydrogel. However, the incorporation of silicone based monomers appears to reduce the water content of the hydrogel due to their inability to interact with water. Thus, for silicone hydrogels, a balance must be struck between hydrophilic and hydrophobic components to ensure sufficient water content, while maintaining high enough silicone content to facilitate oxygen permeability.

Hydrogel Formulation	Equilibrium Water Content (%)	Contact Angle (°)
pHEMA	26.6 ± 1.3	31.5 ± 1.9
p(DMA-co-TRIS(OH))	32.1 ± 0.9	37.4 ± 3.7
p(DMA-co-TRIS(OH)-co-ACR) 5%	34.6 ± 0.7	36.8 ± 0.1
p(HEMA-co-TRIS(OH))	21.0 ± 0.7	31.1 ± 2.5
p(HEMA-co-TRIS(OH)-co-ACR) 5%	23.7 ± 0.3	36.4 ± 1.7
p(HEMA-co-TRIS(OH)-co-ACR) 10%	26.1 ± 1.4	33.7 ± 1.3
p(HEMA-co-TRIS(OH)-co-mPDMS)	11.3 ± 1.9	28.3 ± 2.6
p(DMA-co-TRIS(OH)-co-mPDMS)	26.9 ± 0.3	33.6 ± 1.0

Table 3-2 – Summary of equilibrium water content (n=3) and captive bubble contact angle (n=3) (\pm SD) for each hydrogel formulation.

3.3.1.2 Captive Bubble Contact Angle

The surface wettability of the hydrogels was analyzed using captive bubble contact angle method to analyze the static captive bubble contact angel. Table 3-2 results show that the contact angle ranged from approximately 28°-38° depending on the hydrogel formulation. Despite higher water content and increased hydrophilicity of water sorbing monomer, the p(DMA-co-TRIS(OH)) hydrogel displayed a less wettable surface than control pHEMA (P<0.5). A similar result was observed with the p(HEMA-co-

TRIS(OH)) material as well (P<0.4). A comparison of the chemistry shows DMA based hydrogels contained significantly more silicone monomer than comparable HEMA based hydrogels. This suggests that the relative silicone monomer contribution to the overall hydrogel is a determining factor in the surface wettability of model lenses. The incorporation of mPDMS did not appear to alter the surface wettability of DMA or HEMA containing hydrogels. This was not an anticipated result because not only is mPDMS a more hydrophobic monomer than TRIS(OH) but the molar percent of silicone in these formulation was increased compared to controls. It is possible that the difference in hydrophobicity between TRIS(OH) and mPDMS is not sufficiently significant to alter the surface wettability. The addition of the ACR surfactant did not appear to have any significant effect on surface wettability of the hydrogels as measured by captive bubble. Using similar techniques, commercial lenses have been shown to have contact angles ranging from 17°-22° (Read et al., 2011). The large difference in contact angle range may be attributed to the hydrogel shape difference along with specialized surface treatments and wetting agents associated with the commercial lenses.

3.3.1.3 Transparency and Optical Haze

Transparency is an essential property of any contact lens based application. However, silicone hydrogels in particular are known to suffer from phase separation, which, if significant, can manifest as opacity (Nicolson and Vogt, 2001). To ensure the synthesized hydrogels had optical properties that were suitable for use as a contact lens thereby ensuring the relevance of the data, the light transmittance was evaluated. The results are shown in Table 3-3. It is evident that all materials exhibited high light transmittance values between 90% and 100% at 600nm, except for the p(HEMA-*co*-TRIS(OH)-*co*-PDMS) hydrogel. The reason for the minimal transparency of this formulation is that phase separation occurs during polymerization presumably due to the fact that the HEMA monomer is less compatible with the polysiloxane mPDMS, than the DMA, resulting in an opaque polymer. It should be noted that this sample also had the lowest water content of all samples (11.3%), suggesting that phase separation may also affect the ability of the materials to take up water.

Optical haze is characterized as the degree of scattering as light passes through a film. Quantifying haze allows separation of directly transmitted light from scattered light, which may be an important property of contact lens materials. Using a Hazemeter, the tendency of the synthesized hydrogels to scatter light as it passes through was analyzed. Results in Table 3-3, demonstrate low levels of light scattering for the majority of the hydrogel compositions. The P(DMA-*co*-TRIS(OH)-*co*-mPDMS) hydrogel appeared to cause slightly more light scattering relative to comparable hydrogels not containing mPDMS (P<0.04), although the same sample also showed lower transparency compared with other formulations. The opaque p(HEMA-*co*-TRIS(OH)-*co*-mPDMS) showed extremely high optical haze, which is to be expected considering its lack of transparency.

Hydrogel Formulation	Light Transmittance (%)	Optical Haze (%)
pHEMA	98.5 ± 1.9	2.59 ± 1.12
p(DMA-co-TRIS(OH))	97.0 ± 4.9	5.40 ± 1.04
p(DMA-co-TRIS(OH)-co-ACR) 5%	94.8 ± 8.0	3.89 ± 0.53
p(HEMA-co-TRIS(OH))	93.1 ± 7.8	2.87 ± 0.57
p(HEMA-co-TRIS(OH)-co-ACR) 5%	90.7 ± 4.4	5.90 ± 0.20
p(HEMA-co-TRIS(OH)-co-ACR) 10%	96.6 ± 0.9	4.47 ± 0.55
p(HEMA-co-TRIS(OH)-co-mPDMS)	3.4 ± 0.9	90.87 ± 0.05
p(DMA-co-TRIS(OH)-co-mPDMS)	93.4 ± 7.4	9.43 ± 1.66

Table 3-3 – Summary of light transmittance (1	$(n=6)$ and optical haze $(n=3)$ $(\pm SD)$ for each
hydrogel for	ormulation

3.3.2 Impact of Hydrogel Composition on Drug Delivery Properties

To understand the impact that the hydrogel composition has on the drug delivery properties, comparisons were made between the different hydrogel formulations and their respective DEX loading and release parameters.

3.3.2.1 Dexamethasone Loading and Percent Release

By measuring the change in concentration of the DEX solution over the duration of the loading study, the amount of drug taken up by each hydrogel disc was determined. Due to the relative lipophilicity of DEX and subsequent low solubility in aqueous solvents, a 1:1 H₂O:methanol solvent solution was used to ensure higher concentrations of DEX could be used. *Kim et al.* demonstrated that the drug uptake in hydrogels can be modeled as a two component system: the drug which is held in the solvent solution volume of the hydrated gel, and the fraction of drug that is adsorbed to the polymer phase (Kim et al., 1992; Ribeiro et al., 2011b). Therefore, depending on the relative swelling and affinity of the drug for certain monomers that are incorporated in the formulations, the total drug loading will vary. The amount of DEX taken up into each hydrogel is shown in Table 3-4. Drug loading was higher when DMA was used with mPDMS compared with HEMA in similar monomer molar compositions (P<0.000004). This is in accordance with previous studies that showed DMA containing commercial hydrogels tend to load significantly more drug from soaking solutions (Hui et al., 2008).

From the calculated drug loading, the polymer matrix/cosolvent partition coefficient for each respective hydrogel was approximated using equation 3-2, where V_S is the volume of cosolvent contained within the hydrogel at equilibrium, V_P is the volume of dried polymer, M_P is the mass of dry hydrogel, $C_{L,i}$ is the initial concentration of the loading solutions and $C_{L,f}$ is the final concentration of the loading solution.

$$K = \left(Drug \ Loading \left(\frac{\mu g}{mg} \ dry \ gel \right) \cdot M_p - V_S \cdot C_{L,f} \right) / \cdot V_P \cdot C_{L,i}$$
(Equation 3-2)

All evaluated hydrogels had estimated partition coefficients that were greater than 1. This implies that the primary avenue through which loading occurs in these systems is sorption to the polymer phase. Hydrogels that contained DMA – which typically had greater swelling in 1:1 H₂0:methanol solvent compared to HEMA-containing hydrogels – generally tended to have higher partition coefficients. One plausible explanation is that the partitioning of drug onto or into the gel phase depends not only on the affinity for particular monomers, but also on the ability of DEX to contact the polymer phase within the bulk network. This is further supported by the fact that when the DMA contribution is reduced and the ACR surfactant is incorporated, the overall loading again increases (P<0.000001). The DEX contained within the drug loading solution can only interact with the fraction of the internal polymer phase with which it is in contact with. Thus, as the swelling of a hydrogel increases, there is likely more surface area for sorption of DEX to occur.

Hydrogel Formulation	DEX Loading (µg/mg dry gel)	Partition Coefficient (K)	Percent Release (M _t /M _o)
pHEMA	16.62 ± 0.95	16.10 ± 1.09	44.4 ± 2.3
p(DMA-co-TRIS(OH))	17.75 ± 0.44	20.29 ± 0.58	43.5 ± 1.2
p(DMA-co-TRIS(OH)-co-ACR) 5%	21.51 ± 0.59	26.90 ± 0.85	38.2 ± 1.9
p(HEMA-co-TRIS(OH))	14.40 ± 0.84	18.26 ± 1.25	39.5 ± 3.8
p(HEMA-co-TRIS(OH)-co-ACR) 5%	16.92 ± 1.79	19.85 ± 2.21	40.3 ± 4.6
p(HEMA-co-TRIS(OH)-co-ACR) 10%	15.52 ± 0.55	17.23 ± 0.65	49.5 ± 6.5
p(HEMA-co-TRIS(OH)-co-mPDMS)	7.29 ± 0.62	6.85 ± 0.70	25.8 ± 3.3
p(DMA-co-TRIS(OH)-co-mPDMS)	15.69 ± 1.30	19.42 ± 1.81	34.9 ± 3.7
p(HEMA-co-TRIS(OH)-co-ACR) 5% p(HEMA-co-TRIS(OH)-co-ACR) 10% p(HEMA-co-TRIS(OH)-co-mPDMS) p(DMA-co-TRIS(OH)-co-mPDMS)	16.92 ± 1.79 15.52 ± 0.55 7.29 ± 0.62 15.69 ± 1.30	19.85 ± 2.21 17.23 ± 0.65 6.85 ± 0.70 19.42 ± 1.81	$40.3 \pm 49.5 \pm 25.8 \pm 34.9 \pm $

Table 3-4 – Dexamethasone loading amount, partition coefficient and fraction of total possible release for all hydrogel formulations (±SD) with n=6.

The total loading amount is compared to the total release amount after 16 days to determine the percent of drug release, shown in Table 3-4. It is clear that in all cases, a large fraction of the loaded DEX remained trapped within the hydrogel network, ranging from approximately 50%-75% depending on the formulation. To understand the reason for this, consideration must be given to the difference in loading and release conditions.

Loading was facilitated using an organic-containing solvent system, while the release of DEX was carried out in PBS. The use of a methanol/water mixture not only improves the solubility of DEX, but increases the swelling of the hydrogels in comparison to in PBS. Despite a lower partition coefficient than if PBS was used as the solvent, a higher drug concentration inside the hydrogel can be achieved. When subsequent hydrogels were then transferred to PBS for release, the releasate solution was constantly changed to mimic infinite sink conditions. Despite the constant concentration gradient driving drug flux out of the hydrogel, a large fraction remained entrapped within the network unable to diffuse out. It is possible that because the loading and release are conducted in different solvents, the drug that is taken up may be absorbed into the polymer phase in areas that are not permeated when PBS is used, such as the silicone domains, and can result in the DEX being trapped within the polymer phase. This is an important result as it undermines the potential efficiency of lens systems for delivery. It is well documented that eye drops lead to significant drug wastage, but these results show that this is also the case for lenses loaded with a lipophilic drug using an alternative solvent to PBS. However, the drug wastage that is observed using contact lens materials in this study is still significantly less than the wastage associated with the use of eye drops. The release studies were carried out for a period of two weeks, although the results suggest that in some cases DEX was still being released after 16 days (Figure 3-2). Therefore, there was no relationship determined between hydrogel formulation and the percent total release.

3.3.2.2 Release Rate Approximation

In order to quantify the DEX release rate and better understand the diffusion processes that are occurring in these systems, the release data were fit to the Higuchi equation which has been used to model Fickian diffusion in similar hydrogel materials (Ribeiro et al., 2011a). Previous studies have made use of approximating the release as square root kinetics, where M_t is the drug released at time t, M_o represents the total amount of drug released from the hydrogel, and K_R represents the release rate constant.

$$\frac{M_t}{M_o} = K_R \cdot t^{0.5}$$
 (Equation 3-3)

This equation was applied to the experimental release data up to an M_t/M_o ratio of <0.6 and regression analyses performed on the constructed linear curve for each hydrogel formulation. The release rate constant, K_{R} , for each respective hydrogel formulation was calculated using this method and summarized in Table 3-5. It is clear that the release rate varied significantly depending on the hydrogel formulation.

Hydrogel Formulation	Higuchi Rate Constant (K _R)
pHEMA	0.426 ± 0.007
p(DMA-co-TRIS(OH))	0.527 ± 0.006
p(DMA-co-TRIS(OH)-co-ACR) 5%	0.602 ± 0.024
p(HEMA-co-TRIS(OH))	0.322 ± 0.005
p(HEMA-co-TRIS(OH)-co-ACR) 5%	0.392 ± 0.009
p(HEMA-co-TRIS(OH)-co-ACR) 10%	0.488 ± 0.009
p(HEMA-co-TRIS(OH)-co-mPDMS)	0.309 ± 0.009
p(DMA-co-TRIS(OH)-co-mPDMS)	0.481 ± 0.009

Table 3-5 – Estimated rate constants (±SD) based on Higuchi model.

3.3.2.3 Comparison of DMA and HEMA Drug Release

The release profiles for p(DMA-co-TRIS(OH)), p(HEMA-co-TRIS(OH)) and control pHEMA formulations are shown in Figure 3-2. It is evident that DEX was released from pHEMA at a much faster rate than from the p(HEMA-co-TRIS(OH)) hydrogel based on both the rate constant data and the release profiles. The addition of the hydrophobic siloxy methacrylate appears to extend drug release, even when incorporated at low mole fractions. However, the release is also dependant on the hydrophilic monomer used. The p(DMA-co-TRIS(OH)) hydrogel had a much faster release rate than the p(HEMA-co-TRIS(OH)) formulation, similar to that of the pHEMA control hydrogel. This is despite the significantly higher molar fraction of the hydrophobic silane. Therefore, DMA as a monomer produced less resistance to diffusion than HEMA. However, the diffusion pathway must be considered. There was a correlation between increased material swelling and DEX release rate. The order of materials in terms of the highest content water was p(DMA-co-TRIS(OH)>pHEMA>p(HEMA-co-TRIS(OH)), which is the same order for DEX release rate. This suggests that the water content of materials is also a determining factor for the timescale of drug release.



Figure 3-2 - DEX release profiles for base hydrogel formulations. Error is represented by (±SD) with n=6.

To further understand the mechanism of release, further exploration of the fundamental diffusion within the hydrogel system must be considered. Previous studies have suggested that the diffusion of DEX within contact lens materials is governed by a combination of free drug in the aqueous phase of the hydrated gel and the drug bound to the polymer (Bengani and Chauhan, 2013). This can be quantitatively described by the differential mass balance equation shown below.

$$\frac{\partial c_g}{\partial t} = D_f \frac{\partial^2 c_f}{\partial y^2} + D_b \frac{\partial^2 c_b}{\partial y^2}$$
(Equation 3-4)

Therefore, the overall hydrogel concentration (C_g) changes over time with the free concentration within the aqueous phase (C_f) , and bound concentration to the polymer phase (C_b) . D_f and D_b, correspond the drug diffusivity in the aqueous phase and from the

polymer surface respectively. Considering this model of drug diffusion in the context of the above results, the rate limiting component is likely the diffusion of the drug from the aqueous phase within the network. Based on the drug loading partition coefficients, there is a large amount of DEX interaction with the polymer phase. This sorption will be present both on the external surface of the hydrogel and the internal bulk network, once the materials are dried post-loading. While drug desorption from the outer surface will occur rapidly because it will be exposed to infinite sink conditions, the drug diffusion internal to the hydrogel network will be more complex. For diffusion of absorbed DEX within the bulk network to occur, it must first partition into the aqueous phase once the polymer is hydrated. Therefore, upon hydration, there will be a large concentration gradient established between the polymer and aqueous phases. As a result, a dynamic equilibrium will be quickly established between these two phases. However, the partitioning will be limited by the solubility of DEX in the aqueous phase. Assuming free DEX concentration reaches its solubility maximum upon hydration (100 µg/mL), the relationship between release rate and aqueous fraction can then be explained by the fact that in hydrogels with increased water content, more total free drug mass will be available for diffusion from the internal bulk network. If the overall diffusion was limited by desorption from the polymer to the aqueous phase, the release profile would not be dependent on the water content of the hydrogel material. However, based on these assumptions, the release profile should remain linear, which is not the case. The rapid diffusion of surface sorbed DEX in combination with a changing diffusion gradient in the bulk phase over time is a plausible explanation for the initial burst release observed in Figure 3-2.

3.3.2.4 Effect of mPDMS on Drug Transport

Incorporating a polysiloxane macromonomer by substitution of part of the TRIS(OH) monomer with mPDMS was also expected to impact the drug delivery properties of such systems. Figure 3-3 shows the dynamic DEX release from the p(DMAco-TRIS(OH)) formulation relative to comparable hydrogel compositions that contain mPDMS. The incorporation of the mPDMS resulted in a lower amount of DEX released (P<0.0000009) but did not impact the release kinetics. Considering the percent release data located in Table 3-4 and the nature of the mPDMS properties, this is likely a manifestation of an increased tendency of DEX to stay associated with the polymer phase containing mPDMS. The lipophilicity of DEX will likely cause it to have stronger association with more hydrophobic monomers. Despite the opacity of the p(HEMA-co-TRIS(OH)-co-mPDMS) hydrogel, evaluating the DEX release kinetics provided further insight on the impact of polymer composition. Both the release rate and total amount of the DEX released was significantly reduced when HEMA was used in place of DMA (P<0.0000002). The use of HEMA instead of DMA resulted in significantly lower water content, and further supports the importance of hydrogel water content on controlling the drug release kinetics. This yielded a much slower rate of DEX release with close to zeroorder kinetics. The lower percent of DEX release further corresponds with the aforementioned hypothesis that DEX will form stronger associations with a more hydrophobic polymer phase.



Figure 3-3 – DEX release profiles for hydrogels with and without incorporating polysiloxane mPDMS. Error is represented as (±SD) with n=6.

Consideration of the above release profiles provides further insight into the diffusion mechanism that governs DEX transport in these model contact lenses. In the case of the p(HEMA-*co*-TRIS(OH)-*co*-mPDMS) hydrogel, it believed that the diffusion gradient between the absorbed drug in the polymer phase and the aqueous phase is maintained longer relative to the other hydrogels analyzed. The reason for this is because this formulation has the lowest equilibrium aqueous volume, therefore the mass of absorbed drug required to diffuse in order to reach the solubility limit of DEX internally within the network is lower. It can then be concluded that a sufficiently large concentration gradient driving diffusion from the polymer phase to the aqueous phase to maintain constant free DEX concentration in the aqueous phase will result in a release that is stable and approximately zero-order. This trend of slower release from materials

with lower aqueous volume fraction supports the hypothesis that release is controlled by the diffusion from the aqueous phase of the hydrated material. This suggests that the ideal lens delivery system must maintain a balance between the comfort that accompanies higher water content and the extended release associated with less hydrated materials.

3.3.2.5 Effect of ACR Surfactant on Drug Transport

The release of DEX from hydrogels containing the surfactant ACR was characterized and the dynamic release profiles compared in Figure 3-4. Release data clearly showed increasing rate of release as the molar fraction of the surfactant was increased. The profiles appeared to converge upon a universal mass of drug released per mass of gel, regardless of the chemical composition. As mentioned previously, the incorporation of the polymerizable surfactant was shown to increase the equilibrium water content of resultant materials in PBS. These results agree with the purposed hypothesis of aqueous phase diffusion being the limiting factor that governs overall release rate. In all cases there is a clear period of burst release followed by a period of prolonged DEX release. Similar results were obtained for p(DMA-*co*-TRIS(OH)-*co*-ACR) hydrogels (data not shown).



Figure 3-4 – DEX release profiles for hydrogel formulations containing the polymerizable surfactant ACR. Error is represented by (±SD) with n=6.

3.3.3 Mechanism of Release

Despite a number of imposed assumptions of the Higuchi model, it is a reasonable method to analyze release data and infer a general mechanism of release. To confirm our hypothesis of aqueous controlled diffusion and gain a better understanding of the release mechanism, the rate constants were compared to equilibrium water content in Figure 3-5. Upon observation it is evident that the hydrogel formulations exhibited a positive correlation between the water content and release rate. A regression analysis yielded an R^2 value of 0.91, which further supports this assertion. This approximately linear relationship confirms the importance of water content in governing the rate of DEX release. Although this underlines the importance of release through the aqueous phase, to

understand the impact of the sorption/desorption component of diffusion, more complex models must be applied. Despite the prolonged release observed in these model hydrogels, the thickness is an important parameter of diffusion and the fabrication method employed results in materials that are thicker than typical commercial lenses (500 μ m *vs*. 100 μ m). Therefore, as thickness is reduced, the surface area to volume ratio of these hydrogels will increase. Considering the hypothesized mechanism of diffusion, this altered ratio will result in the surface desorption component of diffusion contributing a greater proportion of the overall mass of drug released. As a result, more rapid rates of drug release would be observed using hydrogels with a more representative thickness.



Figure 3-5 – Higuchi release rate constant for DEX as a function of equilibrium water content. Error is represented by (±SD).

3.4 Conclusion

Based on these results, it is clear that hydrogel chemistry has a significant impact on the resultant release characteristics. Within the range of formulations investigated, 90% of the release occurred over a time duration of approximately 5-16 days. Hydrogels that contained greater silicone contents or used a hydrophilic monomer with a higher octanol/water partition coefficient appeared to release at a slower rate and in some cases showed lower overall DEX release. The incorporation of the polymerizable silicone surfactant, ACR, tended to increase the rate of DEX release. In this study, the water content of the resultant hydrogels appeared to be a determining factor in overall rate of release, suggesting a primary mechanism of diffusion is through the aqueous phase within the hydrogel networks. The rapid desorption of DEX from the exterior surface of the hydrogel is likely a contributing factor to the observed burst release in many of the hydrogel formulations. While a range of monomers was used in these studies, there are a multitude of others that are currently being used in commercial lenses. For a more complete understanding of the relationship between hydrogel chemistry and the lipophilic drug release characteristics, more variation in the hydrogel chemistry must be explored. Overall, these results show that drug release kinetics from contact lens hydrogels can be modified based on the formulation chemistry and these results provide some insight into how the drug eluting contact lens may be altered to ensure the optimal release properties.

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References

- Baggiani, C., Baravalle, P., Giovannoli, C., Tozzi, C., 2006. Binding behaviour of pyrimethanil-imprinted polymers prepared in the presence of polar co-monomers. J Chromatogr 1117, 74-80.
- Bengani, L.C., Chauhan, A., 2013. Extended delivery of an anionic drug by contact lens loaded with a cationic surfactant. Biomaterials 34, 2814-2821.
- Boone, A., Hui, A., Jones, L., 2009. Uptake and release of dexamethasone phosphate from silicone hydrogel and group I, II, and IV hydrogel contact lenses. Eye Contact Lens 35, 260-267.
- Bowman, R.J., Cope, J., Nischal, K.K., 2004. Ocular and systemic side effects of brimonidine 0.2% eye drops (Alphagan) in children. Eye (Lond) 18, 24-26.
- Creech, J., Chauhan, A., Radke, C., 2001. Dispersive mixing in the posterior tear film under a soft contact lens. Ind Eng Chem Res 40, 3015-3026.
- Efron, N., Morgan, P.B., Cameron, I.D., Brennan, N.A., Goodwin, M., 2007. Oxygen permeability and water content of silicone hydrogel contact lens materials. Optom Vis Sci 84, E328-E337.
- Ghate, D., Edelhauser, H.F., 2008. Barriers to glaucoma drug delivery. J Glaucoma 17, 147.
- Hui, A., Boone, A., Jones, L., 2008. Uptake and release of ciprofloxacin-HCl from conventional and silicone hydrogel contact lens materials. Eye Contact Lens 34, 266-271.
- Hui, A., Sheardown, H., Jones, L., 2012. Acetic and Acrylic Acid Molecular Imprinted Model Silicone Hydrogel Materials for Ciprofloxacin-HCl Delivery. Materials 5, 85-107.
- Jacob, J.T., 2013. Biocompatibility in the Development of Silicone-Hydrogel Lenses. Eye Contact Lens 39, 13-19.
- Järvinen, K., Järvinen, T., Urtti, A., 1995. Ocular absorption following topical delivery. Adv Drug Del Rev 16, 3-19.
- Jones, L., Powell, C.H., 2013. Uptake and release phenomena in contact lens care by silicone hydrogel lenses. Eye Contact Lens 39, 29-36.
- Jones, L., Senchyna, M., Glasier, M.-A., Schickler, J., Forbes, I., Louie, D., May, C., 2003. Lysozyme and lipid deposition on silicone hydrogel contact lens materials. Eye Contact Lens 29, S75-S79.

- Kapoor, Y., Chauhan, A., 2008. Ophthalmic delivery of Cyclosporine A from Brij-97 microemulsion and surfactant-laden p-HEMA hydrogels. Int J Pharm 361, 222-229.
- Karlgard, C., Wong, N., Jones, L., Moresoli, C., 2003. In vitro uptake and release studies of ocular pharmaceutical agents by silicon-containing and p-HEMA hydrogel contact lens materials. Int J Pharm 257, 141-151.
- Khan, M., 2013. Novel Silicone-Based Materials to Limit Bacterial Adhesion and Subsequent Proliferation. Open Access Dissertations and Theses Paper 7954.
- Kim, J., Chauhan, A., 2008. Dexamethasone transport and ocular delivery from poly (hydroxyethyl methacrylate) gels. Int J Pharm 353, 205-222.
- Kim, J., Conway, A., Chauhan, A., 2008. Extended delivery of ophthalmic drugs by silicone hydrogel contact lenses. Biomaterials 29, 2259-2269.
- Kim, J., Peng, C.-C., Chauhan, A., 2010. Extended release of dexamethasone from silicone-hydrogel contact lenses containing vitamin E. J Controlled Release 148, 110-116.
- Kim, S.W., Bae, Y.H., Okano, T., 1992. Hydrogels: swelling, drug loading, and release. Pharm Res 9, 283-290.
- Korte, J.M., Kaila, T., Saari, K.M., 2002. Systemic bioavailability and cardiopulmonary effects of 0.5% timolol eyedrops. Graefes Arch Clin Exp Ophthalmol 240, 430-435.
- Lang, J.C., 1995. Ocular drug delivery conventional ocular formulations. Adv Drug Del Rev 16, 39-43.
- Li, C.-C., Chauhan, A., 2006. Modeling ophthalmic drug delivery by soaked contact lenses. Ind Eng Chem Res 45, 3718-3734.
- McNamara, N.A., Polse, K.A., Brand, R.J., Graham, A.D., Chan, J.S., McKenney, C.D., 1999. Tear mixing under a soft contact lens: effects of lens diameter. Am J Ophthalmol 127, 659.
- Nicolson, P.C., 2003. Continuous wear contact lens surface chemistry and wearability. Eye Contact Lens 29, S30-S32.
- Nicolson, P.C., Vogt, J., 2001. Soft contact lens polymers: an evolution. Biomaterials 22, 3273-3283.
- Peng, C.-C., Ben-Shlomo, A., Mackay, E.O., Plummer, C.E., Chauhan, A., 2012a. Drug delivery by contact lens in spontaneously glaucomatous dogs. Curr Eye Res 37, 204-211.
- Peng, C.-C., Chauhan, A., 2011. Extended cyclosporine delivery by silicone–hydrogel contact lenses. J Controlled Release 154, 267-274.
- Peng, C.C., Burke, M.T., Carbia, B.E., Plummer, C., Chauhan, A., 2012b. Extended drug delivery by contact lenses for glaucoma therapy. J Control Release 162, 152-158.
- Phan, C.-M., Subbaraman, L.N., Jones, L., 2013. In Vitro Uptake and Release of Natamycin From Conventional and Silicone Hydrogel Contact Lens Materials. Eye Contact Lens 39, 162-168.
- Pooniya, V., Pandey, N., 2012. Systemic toxicity of topical cyclopentolate eyedrops in a child. Eye (Lond) 26, 1391-1392.
- Read, M.L., Morgan, P.B., Kelly, J.M., Maldonado-Codina, C., 2011. Dynamic contact angle analysis of silicone hydrogel contact lenses. J Biomater Appl 26, 85-99.
- Ribeiro, A., Veiga, F., Santos, D., Torres-Labandeira, J.J., Concheiro, A., Alvarez-Lorenzo, C., 2011a. Bioinspired imprinted PHEMA-hydrogels for ocular delivery of carbonic anhydrase inhibitor drugs. Biomacromolecules 12, 701-709.
- Ribeiro, A., Veiga, F., Santos, D., Torres-Labandeira, J.J., Concheiro, A., Alvarez-Lorenzo, C., 2011b. Receptor-based biomimetic NVP/DMA contact lenses for loading/eluting carbonic anhydrase inhibitors. J Membr Sci 383, 60-69.
- Sindt, C.W., Longmuir, R.A., 2007. Contact lens strategies for the patient with dry eye. Ocul Surf 5, 294-307.
- Soluri, A., Hui, A., Jones, L., 2012. Delivery of ketotifen fumarate by commercial contact lens materials. Optom Vis Sci 89, 1140-1149.
- Stapleton, F., Keay, L., Jalbert, I., Cole, N., 2007. The epidemiology of contact lens related infiltrates. Optom Vis Sci 84, 257-272.
- Taylor, S.A., Galbraith, S.M., Mills, R.P., 2002. Causes of non-compliance with drug regimens in glaucoma patients: a qualitative study. J Ocul Pharmacol Ther 18, 401-409.

Chapter 4 : Conclusions

The work of this thesis attempted to design novel silicone hydrogel materials containing hyaluronic acid to alter drug release, but also to understand the fundamentals of drug diffusion in these systems and how it is impacted by the nature of the formulation chemistry. Although HA was successfully incorporated into materials without compromising many of the essential lens properties, it was not able to alter release kinetics from the first generation hydrogels. It did however increase the release dosage from the model lens materials, likely due to hydrogel-drug ionic interactions between negatively charged HA and positively charged timolol maleate. This demonstrates that ionic charges can be exploited in these silicone hydrogels to promote increased loading affinity of the network.

In the second study the materials were further developed by incorporating other monomer components, such as mPDMS, ACR and TRIS(OH), to achieve a more commercially representative contact lens model. The monomer composition and relative hydrophobicity/hydrophilicity of components was shown to be a significant factor in DEX partitioning, release rate and the amount of irreversibly absorbed drug. By estimating the Higuchi rate constants for each respective sample that was tested it was demonstrated that the release rate was highly dependent on the water content of the hydrogel models which in turn was largely determined by the monomer formulation. The incorporation of silicone or silane based monomers tended to reduce the water content of hydrogels due to their lack of water associative capacity. However, a comparison between HEMA and DMA showed that it is possible to overcome this by using hydrophilic monomers with a greater propensity to promote water uptake. Overall, these results underline that it is possible to rationally design hydrogels with modified release characteristics and that the hydrogel composition plays an important role in the loading and release properties.

Moving forward, it is important to consider factors outside the hydrogel delivery system such as the drug properties and the release conditions when investigating the possibility of contact lenses as an alternative to eye drops. From the above studies, it is evident that the lipophilicity of a drug is an important factor that governs that solubility in a loading solution, its tendency to sorb onto or into the polymer and the rate at which it is able to diffuse from the network. The results suggest that lipophilic drugs have greater potential due to their ability to release for extended periods relative to hydrophilic therapeutics. In the future, modifying the release conditions to better resemble to ocular tear film and using hydrogel geometry that is identical to commercial lenses would provide more insight on how release would occur in vivo. This is an important step in determining the usefulness of contact lenses for drug delivery because although differences in kinetics can be identified during in vitro experiments, the duration of release may change dramatically depending on the releasate volume, hydrogel thickness and the sink conditions that are applied. The results obtained from this thesis work suggest that silicone hydrogels with lower water content can provide extended release that may be applicable to a range of ocular conditions of the anterior eye. It is likely that only once more realistic release conditions are examined, that the true potential of these systems for extended delivery can be realized.

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Appendix



Figure A-1 – chemical structures of hyaluronic acid, timolol maleate and dexamethasone



Figure A-2 – release raw data fit to Higuchi model for each hydrogel formulation, demonstrating reasonable linear fit as expected.

Lower Limit	Upper Limit
0.408	0.444
0.504	0.55
0.453	0.75
0.312	0.33
0.373	0.409
0.453	0.523
0.292	0.327
0.459	0.503
	Lower Limit 0.408 0.504 0.453 0.312 0.373 0.453 0.292 0.459

Table A-1 –	95%	confidence	interval	of	estimated	rate	constants	for	each	hydrogel
formulation.										