Using Nanoparticle Drug Delivery Mechanisms to Improve Eye Moisture Over Extended Periods of Contact Lens Wear

Hasan Zaidi

Abstract

Millions of people around the world suffer from dry eye symptoms as a result of extended contact lens wear. The objective of this design document is to engineer a solution for chronic dry eyes. The solution must be safe, effective, easy to use, and affordable. The goal of the treatment is to decrease tear film osmolarity by 20 mOsmol/L. Three types of nanotechnologies were considered for this task. The candidate solutions were 1) hydrogel contact lenses infused with lubricant-loaded liposomes, 2) lubricant-loaded microemulsions applied as eye drops, and 3) lubricant-loaded niosomes applied as eye drops. All solutions use polyethylene glycol 400 as the primary active ingredient in the lubricant. The three solutions provide a safe treatment option that allows increased bioavailability of drug and increased retention time, as well as controlled release of drug. A combination of candidates 1 and 3 – namely, hydrogel contact lenses infused with lubricant-loaded niosomes – seems to be the best solution because of excellent drug delivery kinetics and minimal safety concerns. The success of this project would encourage further research in niosome-based and contact lens-based drug delivery. It would also allow this company to expand research and development and further specialize in ocular drug delivery.

Executive Summary

Millions of people around the world suffer from chronic dry eye symptoms as a result of extended contact lens wear. Contact lenses can cause dry eyes by disrupting the tear film on the ocular surface, and the resulting condition can be painful and even dangerous if left untreated. Current treatment methods include nighttime gel applications and eye drops, both of which have significant shortcomings. This project aims to solve the issue of dry eyes with a method that is safe, effective, and convenient over an extended treatment period.

Any meaningful and marketable proposal must be safe, comfortable, easy to use, long-lasting, and cost-effective. The safety must be guaranteed by ensuring that the candidate solutions can operate at the ocular pH of 6.5 and that they are isotonic with the ocular environment. The ease of use is determined by many non-technical factors, but a major one is the frequency at which the treatment must be applied. Accordingly, the time period over which the treatment is effective is determined by the bioavailability and residence time of the drug. The goal is to design a solution that need only be used a maximum of twice per day. The price of the treatment should be such that the treatment is reasonably attainable for a typical contact lens user. The cost should be within 50% of the cost of contact lenses. Ultimately, the overall objective of the treatment is to increase eye lubrication by approximately 6% over the course of several months.

Several nanoparticle-based drug delivery mechanisms were considered for this design. The advantages that nanoparticles have over conventional delivery mechanisms include enhanced drug permeation, controlled release, improved targeting specificity, and high customizability. The three

candidate solutions discussed are 1) hydrogel contact lenses infused with lubricant-loaded liposomes, 2) lubricant-loaded microemulsions applied as eye drops, and 3) lubricant-loaded niosomes applied as eye drops. A combination of solutions 1 and 3 is proposed. Hydrogel contact lenses infused with lubricant-loaded niosomes seem to be the best solution for the problem that this document aims to address. The niosome contact lenses are worn just like any other lenses, so ease of use is not a concern. The slow diffusion of niosomes from the lens and onto the ocular surface, along with the diffusion of lubricant from the niosomes and onto the ocular surface provides a steady, controlled release of drug that is expected to meet the 6% lubrication increase goal.

If this project is successful, it will introduce a novel treatment for chronic dry eyes. Competing pharmaceutical companies may try to match the treatment, and conventional eye drops would see a dip in sales. Research on niosome-based and contact lens-based drug delivery mechanisms would increase. The revenue of this company and the manufacturer will also increase significantly. The success of this project would encourage others to invest in this company, thereby allowing us to expand the business to other areas or to further specialize in ocular drug delivery.

Problem Statement

In this section, the issue of chronic dry eyes caused by extended contact lens wear will be analyzed in detail. The history of the condition and the treatments available will be briefly reviewed. Using that information, technical design objectives for potential treatments will be set forth. Based on those technical objectives, three candidate solutions will be proposed and one will be recommended for further development. The major design and implementation challenges of that solution will then be discussed. Finally, the implications of the success of the design proposal will be examined.

Initial Problem Description

Contact lenses are popular alternatives to glasses and are worn by over 30 million people in the United States alone (AOA, 2013). However, there are several issues associated with contact lens (CL) wear. According to one study, approximately one third of CL wearers discontinue wearing lenses within 6 years due to reported discomfort (Pritchard, Fonn, & Brazeau, 1999). Different studies found that one quarter to one third of CL wearers reported symptoms of dry eyes (Doughty et al., 1997). More recent studies have found similar results. This means that roughly 8 million CL wearers suffer from dry eye symptoms. The discomfort may be due to the environment or the lens itself, and the aspects of the lens that can contribute to discomfort consist of 1) the material, 2) the design itself (shape, etc.), 3) the fit and wear, and 4) lens care. Current CL designs divide the tear film (which naturally lubricates the eyes) on the eye surface into a pre- and post-lens tear film, which changes interactions between the eye and external substances such as a CL. These changes occur successively during each subsequent lens application, and can reduce the thickness of the tear film. Reduced tear film thickness has an increased evaporation rate as compared to normal tear film, so this is suspected to be the main contributor to eye dryness as a result of CL wear (Nichols et al., 2013). Current lenses do not do enough to mitigate this effect, and artificial tear drops do not offer a lasting lubrication of the eye surface.

Overall Analysis and Objectives

The purpose of this design document is to provide an engineering solution for eye dryness and discomfort caused by extended contact lens wear. In order to accomplish this goal, the solution must either attempt to preserve the tear film or compensate for the splitting of the tear film that occurs when traditional contact lenses are applied. Along with the overall objective, there are several sub-goals. First and foremost, quite obviously, is safety. Any solution to the issue of dry eyes will presumably come in contact with the eyes themselves, and if that solution is toxic, it will not matter how well it lubricates the eyes. Therefore, the solution must have outstanding biocompatibility with the environment of the human eye. While this is a major concern, it is not a major design challenge because there is a large body of research on this topic and solutions applied to the eyes already exist. The propositions in this document need only ensure that any novel substances introduced to an ocular treatment are not harmful to the eyes. Next, the solution must be comfortable and easy to use. The need for comfort is self-explanatory, and comfort will be ensured primarily by designing a treatment that has the same pH as the environment of the eye surface. The ease of use, however, is an understated requirement that is integral to the success of the solutions proposed in this document. One of the major problems with current solutions to dry eye symptoms is that they are inconvenient, especially for CL wearers. For example, someone with contact lens discomfort (CLD)[5] might have to apply eye drops several times a day and yet still feel uncomfortable. More importantly, if he/she forgets to bring the eye drops with them, then the eye drops will not be beneficial at all. Research has found that one cause for the discontinuation of CL wear is, in fact, inconvenience (Pritchard et al., 1999). Therefore, the solutions proposed in this document must be easy to apply and maintain. In addition, the solution must be long-lasting relative to current products available in the market such as conventional eye drops. For this document, the goal is to design a product that is intended to be used once a day or less frequently. Finally, the solution must be cost-effective. Assuming manufacturing companies adopt this design, consumers will not be able to buy it if it is too expensive. Acknowledging the fact that these designs will be more expensive to manufacture, the goal is to produce a solution that can be purchased by the end user for a price that is within 50% of the price per unit of its conventional competitors. In summary, the proposed solution must be safe, comfortable, easy to use, long-lasting, and cost-effective.

To achieve the aforementioned goals, a closer examination of the cause of eye dryness is required. The primary cause of dry eye symptoms associated with contact lenses is the splitting of the tear film into a pre-lens and post-lens tear film upon application of the CL. The tear film is a natural lubricant consisting of three major components: the inner mucin layer, the middle aqueous layer, and the outer lipid layer. The aqueous layer is approximately 8 μm thick, and it is composed of approximately 98% water, 1% inorganic salts, 0.2-0.6% proteins (globulins and albumins), and trace amounts of lysozymes, carbohydrates, and other organic molecules. This water-rich layer lubricates the eye and keeps it clean to avoid infections. The mucin layer (approx. 0.8 μm thick) helps the water layer spread evenly along the eye and remain adhered to the eye surface. The outer lipid layer (approx. 0.1 μm thick) is composed of cholesteryl esters, cholesterol, triglycerides, and phospholipids. This hydrophobic layer seals the aqueous layer, preventing it from evaporating and thus ensuring that the eye is properly moisturized (Tiffany, 2003).

Disruption of the tear film is a leading cause of eye dryness. When a CL is applied, the initial response of the eye is to increase tear production. However, the increased rate of tear production is

not sustainable, and eventually the tear system will be "fatigued." Decreased tear production increases the chances of CL deposits, which, along with other external substances, can lead to infections that cause discomfort. The ocular system then attempts to compensate for the disrupted homeostatic balance of the original tear film by establishing a new balance between the pre-lens and post-lens tear films. If the lipid layer of the new film is poor, there will be an increased rate of evaporation of the aqueous layer of the tear film. The loss of water on the lens surface would, in turn, increase the rate of osmotic draw of water towards the lens surface. As expected, this process will dehydrate the eye lens and weaken the epithelial surface. The result is eye discomfort that can become a serious medical issue if left untreated (Agarwal, 2006).

In order to determine the effectiveness of the three treatments proposed in this design document, there must be an objective way to quantify the extent of eye dryness. That method is osmolarity[9] testing. Osmolarity is the technical term used for the concentration of an osmotic substance in osmoles of solute per unit volume of solution. Ophthalmic applications generally use miliOsmoles per liter (mOsmol/L). Three popular ways of finding the osmolarity of a tear sample are determining its electrical impedance, vapor pressure, or freezing point depression. To measure the electrical impedance, a trained ophthalmologist would use a handheld device (provided by the manufacturer of the testing system) to collect 50 nL sample of the patient's tears. The electrical impedance osmometer (EIO) would then measure the electrical conductivity of the fluids in the tear sample and run calculations to display the results in the desired units. Advantages of the EIO include quick and simple application as well as the fact that the tests are reimbursable by Medicare. Disadvantages include the high cost of the EIO itself (approx. $9,500) and the relatively low precision of the instrument. Investigators have determined that the EIO is useful for distinguishing between patients with dry eyes and patients without dry eyes, but not for determining the degree of dryness between two patients with dry eyes. A vapor pressure osmometer (VPO) functions by measuring the vapor pressure of 5 µL sample of tears. The lower the vapor pressure, the higher the concentration of solutes in solution. The VPO method is quicker and more reliable than the EIO method, but its major drawback is the large volume of tears required for the sample (5 µL). To put that in perspective, a healthy eye only has 7 to 10 µL of tears, while a dry eye has significantly less. Additionally, collecting such a large sample without triggering the tear reflex – which invalidates a reading – requires considerable skill. For these reasons, it is recommended that VPO only be used as a secondary diagnostic test. The last method, and the one that would be used for determining the effectiveness of the designs in this document, is freezing point depression. Freezing point depression osmometry (FPDO) operates on a principle similar to that of the VPO and only requires a 0.2 µL tear sample. Despite drawbacks such as high cost, high technical challenge, and low accessibility of proper equipment, FPDO is the industry standard because of the high precision and accuracy of its readings (Narayanan, 2011).

The higher the osmolarity reading of the tear sample, the drier the eye from which the sample was taken. A reading of 290 mOsmol/L or below indicates healthy eyes. 290 to 316 mOsmol/L suggests "borderline or intermittent" dry eye. A reading of 316 mOsmol/L or greater indicates dry eyes (hyperosmolarity). Typically, even the driest eyes will have an osmolarity well below 400 mOsmol/L. It is important to remember that these are guidelines and that the best way to measure eye dryness and improvement in eye lubrication over time is to track intra-patient readings (Narayanan, 2011). Studies have shown that CL wearers typically have tear osmolarity in the approximate range of 280-330 mOsmol/L (Muselier-Mathieu et al., 2013). CL wearers with dry eye

symptoms typically have tear osmolarity readings between 300 and 340 mOsmol/L (Lemp et al., 2011). Research suggests that sustained eye lubrication can have a compounding effect because proper eye lubrication encourages tear film repair (Benelli, Nardi, Posarelli, & Albert, 2010). Therefore, the goal of the designs proposed in this document is to decrease the tear osmolarity of a dry eye by 10 mOsmol/L within 30 days and by an additional 10 mOsmol/L (total -20 mOsmol/L relative to original readings) after several months of treatment. In nontechnical terms, this is roughly equivalent to increasing eye lubrication by 6% (20/316) over the course of the treatment.

To treat dry eye symptoms as a result of CL wear, there are several possible solutions, but considerably fewer practical ones at this time. As the discussion on the structure and function of the tear film suggests, eye treatments that aim to improve aspects of the three layers could theoretically provide solutions to the stated problem. However, only the lipid layer and the aqueous layer are practically relevant from an engineering perspective, at least in the context of this design document. The function of the mucin layer is to ensure that tears adhere to the eye, but if there are not enough tears present, then the mucin layer becomes irrelevant. The aqueous layer is of greater interest since it is the main functional structure that moisturizes the eye. Along with the outer lipid layer, which preserves the aqueous layer, the aqueous layer will be the main target of the drug delivery system proposed to treat eye dryness. There are several reasons for this decision. Firstly, the outer layers are, quite simply, the most accessible layer in terms of drug delivery. Secondly, they play the major roles in lubricating the eye, so treatments can have significant effects on eye lubrication. Thirdly, the technology that is proposed to treat dry eye symptoms is readily available in drug delivery systems with the proper physical and chemical characteristics. The availability of the materials means that less capital needs to be spent on research and development, which ultimately makes the solution more economical for all parties involved. Fourthly, the effectiveness of the proposed solutions is likely because they are based on existing treatments for ocular conditions such as glaucoma. The volume of academic sources available on the topic also suggests that any potential issues with the design can be eliminated eventually. Therefore, the aqueous layer and the lipid layer should be targeted when designing a treatment for dry eye symptoms. This means that the conceptual objective of the treatment will be to preserve and/or enhance the lipid layer of the tear film and to enhance the aqueous layer. The substance used to achieve this goal must be inert, isotonic with the eye, and able to maintain ocular pH. The reason for the inertness is obvious: any reaction with substances on the eye surface would likely be detrimental to the health of the eye. The requirement of being isotonic is because a significantly improper osmotic pressure would either dehydrate the eyes, worsening the existing condition, or over-stimulate the tear ducts, causing a painful stinging sensation and eventually fatiguing the tear system.

The other aspect of the design is the method with which the two layers will be treated. Considering the limitations set by the goal (cost, ease of use, etc.) and the fact that the eye – a sensitive organ – is being treated, there are only two general classes of delivery mechanisms that are practical: drug solution-loaded lenses and eye drops. Both methods can be engineered to be cost effective and comfortable. Both methods can also be administered by CL wearers by themselves. As mentioned earlier, eye drops can be a hassle, but if the engineering objective of extended treatment period can be met, the eye drops would only have to be administered once or twice a day at maximum. Likewise, the drug-loaded contact lenses offer a solution that can be designed to meet all the goals set forth by this project. To recap, the candidate solutions will use eye drops or drug-loaded contact

lenses to target the lipid layer and aqueous layer of the tear film and help maintain them, which will ultimately preserve eye moisture and increase eye comfort for long-term CL wearers.

Historical and Economic Perspectives

Contact lenses and their related issues have become prevalent relatively recently, after practical lenses began to be commercialized in the early 1950s. After that, the industry moved from various glass contact lenses to plastic lenses, which were made from a gas permeable, but relatively non-porous (by today's standards) material known as polymethyl methacrylate. Drastic advances were then made with the advent of hydrophilic hydrogel lenses in 1959 (Wichterle & Lim). Silicone hydrogel lenses, the current industry standard, were first introduced in 1999 and commercially launched in 2002. The latest major development in CL design occurred in 2010, with the commercialization of custom-manufactured silicone hydrogel lenses. The general trend with each successive design was an increase in water permeability, decreasing the potential for dry eye symptoms (Heiting, n.d.a).

The understanding of dry eye conditions emerged around the same time as the commercialization of contact lenses, when E. Wolff first described the structure of the tear film in 1946. He found that the film has three layers: mucin, aqueous, and lipid. Studies in 1973 and 1997 by Frank J. Holly and Scheffer Tseng, respectively, further explored the function of the tear film. Based on the structure and function, they concluded that dry eye symptoms had several causes, one of them being the disruption of the tear film.

With the increase in reports of dry eye symptoms, there was an increase in available treatments. Initial treatments consisted of basic lubricant tear drops designed to complement the aqueous layer of the tear film. Current treatments include lubricant drops composed of cellulose derivative products, glycerin-containing products, oil-based emulsion products, and polyethylene glycol products. Many of these modern treatments consist of some variation of hydrophilic lubricants encased in hydrophobic "cases." Other treatment methods such as gels, ointments, punctal plugs, surgery can be used to treat more severe dry eye symptoms, but they are beyond the scope of this design document (Schachet, 2008).

Environmental concerns related to the proposed solutions are negligible, as the designs do not introduce any additional non-biodegradable materials for CL wearers to use.

Candidate Solutions

Based on technical limitations and other design criteria set forth by this project, the best way to treat dry eye symptoms as a result of CL wear is to use nanoparticles loaded with an aqueous lubricant. Before going into further detail, it is important to acknowledge other potential solutions that this paper does not discuss.

Two current technologies used to treat dry eyes are gel goggles and overnight gel therapy lubricants. Both are effective methods of dry eye treatment, but they are typically used for conditions more severe than the ones that this design document aims to remedy. The gel treatments are more expensive than conventional lubricants such as polyethylene glycol. The overnight gel therapy lubricants cost approximately $30 for a 0.34 fl oz container whereas the polyethylene glycol eye drops cost approximately $10 for the same volume. Gel goggles cost approximately $50 and their gel inserts

can be reused 50 times. Each additional packet of gel costs approximately $25. Regardless of price, these solutions are not viable in the context of this document because of certain major drawbacks. Namely, the viscosity of the gel means that eyesight is significantly reduced when they are applied, and as such they are intended for nighttime use only. It is predicted that they would also be inconvenient to use on a daily basis, so buyers may not actually end up using the gel therapies as intended.

Current over-the-counter eye drops such as polyethylene glycol 400 (PEG 400) and hypromellose (HM) solutions have shown increased retention times relative to older hydroxypropyl methylcellulose (HPMC) and carboxymethylcellulose (CMC) drops. However, even PEG 400 and HM only have retention times with an upper limit of 90 minutes, meaning they must be applied several times a day. Therefore, they are effective short-term solutions, but their long-term efficacy is questionable. However, they can be repurposed to effectively address the design goals of this project. As mentioned earlier, the drug that is used to lubricate the eyes must be inert, isotonic with the eye, and it must maintain the same pH as the surrounding ocular environment. Despite its limitations, PEG 400 accomplishes these objectives more effectively than its competitors, HPMC and CMC. PEG 400, the current industry standard for artificial tears, will be used as the main lubricating agent for the proposed solution. The substance known as PEG 400 is actually a solution with the active ingredients polyethylene glycol (0.4%) and propylene glycol (0.3%). Inactive ingredients in PEG 400 serve to increase aqueous solubility and maintain pH. PEG 400 has been found to significantly improve tear osmolarity as compared to competitors such as HPMC and CMC (Undurraga, Iii, Schindelar, & Paugh, 2007). It will be the active drug in all three of the proposed solutions so that the effectiveness of the proposed solutions is maximized. Since the main point of comparison between the three proposals is delivery mechanism, PEG 400 will also serve as a constant so that the effectiveness of the mechanisms themselves can be compared rather than the activity of the drugs that they deliver.

Based on a review of the limitations of current treatment methods and the technologies available for ocular drug delivery, it was determined that the best way to treat eye dryness within the constraints of this project while meeting the goals is to encapsulate PEG 400 within nanoparticles. Nanoparticles in general have numerous advantages in drug delivery, including enhanced drug permeation, controlled release, improved targeting specificity, and high customizability. The solutions proposed in this design document all use a certain type of nanoparticle. The three types of nanoparticles that will be discussed are liposomes[6], microemulsions[7], and niosomes[8]. There are several other types of nanoparticles that can be used for ocular drug delivery, including nanosuspensions, dendrimers, and cyclodextrins, which could all contribute to viable solutions. However, a greater body of research exists for the three selected types of nanotechnology (Sahoo, Dilnawaz, & Krishnakumar, 2008).

There are not a great number of non-engineering solutions to dry eyes resulting from CL wear. The obvious option is to discontinue CL wear, but that defeats the purpose. Millions of people rely on CLs, with many of them having reasons beyond simple cosmetics. For example, semi-professional and professional athletes with vision problems rely almost exclusively on CL wear. Discontinuation of CL wear is not a reasonable option for mild cases of eye dryness.

Considering the above information, these three potential solutions were formulated:

- Hydrogel contact lenses with PEG 400-loaded liposome suspension
- PEG 400-loaded microemulsions applied as eye drops

- PEG 400-loaded niosomes applied as eye drops

In the remainder of this section, the advantages and disadvantages of the three delivery mechanisms will be compared, and one mechanism will be selected as the primary design proposal. The design challenges of that mechanism and the implications of the success of this project will then be explained in greater detail.

Hydrogel Contact Lenses with PEG 400-Loaded Liposome Suspension

Liposomes are vesicle nanoparticles with a lipid bilayer structure. The amphipathic properties of the bilayer give liposomes a unique ability to deliver either hydrophobic or hydrophilic drugs. In this design, PEG 400 – a hydrophilic substance – will be encapsulated in the aqueous core of the liposome. The primary advantage of using a liposomal drug delivery mechanism is the high residence time of drug-delivering particles in the tear film. By altering the composition of the phospholipid bilayer of a liposome, the liposome can be engineered to have a positive charge. Since the surface of the eye has a slightly negative charge, positively charged phospholipids, such as phosphatidylcholine, can electrostatically bind to the eye surface. The result is an increased ocular bioavailability[4] of the drug within the liposome. The specific liposome design that would be recommended for this project is known as dimyristoyl phosphatidylcholine (DMPC), which is useful for delivering hydrophilic drugs. The lens design is a hydrogel formulation known as poly-2-hydroxyethyl methacrylate (p-HEMA). P-HEMA is a common contact lens material partially due to its excellent potential for drug delivery. The lenses would have a thickness between 0.1 and 1 mm, depending on the synthesis method and conditions. A potential PEG 400 loading formulation would be approximately 1.5 mg to 5 mg of a PEG 400 solution per gram of dry hydrogel. To accommodate for the size of the particles in a PEG 400 solution and the size of the liposome bilayer itself, liposomes with a diameter of roughly 20 nm would have to be used (Gulsen, Li, & Chauhan, 2005).

Based on related studies, this formulation would have an estimated therapeutic residence time of seven days. Over those seven days, 65-75% of the loaded drug would be delivered to the eye surface via diffusion. In the first few hours after application, 15-30% of the loaded drug would be delivered. The remainder of the (average) 70% would then be delivered over the course of the next 6 days, after which the drug would reach equilibrium between the lens and the eye surface. Because of the exceptional therapeutic residence time of the drugs in this lens design compared to eye drop drugs, the interval at which old lenses are discarded and replaced with new ones could be fine-tuned to find a balance between pharmacokinetics and lens cost. Also worthy of note is that the 6 day drug delivery time period is associated with the lens itself. Liposomes can release drugs for upwards of 24 hours (Henriksen et al., 1995), so the effects of the liposome-loaded lens should be therapeutic for approximately 7 days (Gulsen et al., 2005). Considering existing research on the effect of PEG 400 on eye dryness, users of this lens treatment can expect a decrease of more than 11 mOsmol/L in tear osmolarity after 30 days of daily lens wear. Research suggests that osmolarity can be further decreased with continued lens wear over several months (Benelli et al., 2010).

With proper synthetic procedures and composition, the lens suspension can have a pH of 6.5, which is considered safe for ocular drug delivery. pH is maintained by buffers in the PEG 400 solution as well as other components of the liposome's phospholipid bilayer. In accordance with existing research, a lens with a liposome suspension is predicted to have a transmittance of 80%,

which is 10% lower than a pure p-HEMA hydrogel lens. However, this is still well within the acceptable percent transmittance for a CL. It should also be noted that the 10% difference was found between 1 mm thick lenses, and thinner lenses should have a smaller difference between transmittance of pure and liposome-loaded lenses (Gulsen et al., 2005).

Despite the extensive utility of liposomes in drug delivery, adoption of liposome-based drug delivery systems is limited because of a few notable drawbacks. Liposomes have a short shelf life and a relatively low drug capacity. Significant fluctuations in ambient temperature can alter the permeability of the lipid bilayer. Additionally, they are difficult to synthesize and sterilize (Sahoo et al., 2008).

The retail price of liposome-loaded contact lenses is difficult to predict. Disposable, soft contact lenses typically retail for $25 for a pack of 6 lenses. If the lenses are replaced every two weeks, the annual cost would be between $500 and $700 . It is safe to assume that liposome-loaded contact lenses would retail for significantly more if they were to be commercialized. Furthermore, the drug delivery mechanism is only functional for one week, so the yearly cost of the lenses would be roughly double the cost of the normal lenses. For the purposes of this design document, an annual cost of $1200 will be assumed (Heiting, n.d.b). It is important to note that the $1200 price includes the price of the contacts themselves, so the *additional* yearly cost for someone who already wears contacts would be $600.

PEG 400-Loaded Microemulsions Applied as Eye Drops

A microemulsion is a type of vesicle that is similar to a liposome in that it has an amphipathic nature that can be used to deliver both hydrophilic and hydrophobic drugs. Microemulsions are composed of a single layer of surfactants[10] instead of a phospholipid bilayer. The surfactant serves to stabilize the interface between the microemulsions and the surrounding environment by decreasing the surface tension of the surrounding solution. Non-ionic surfactant vesicles are preferred because ionic surfactant vesicles are toxic to the eye. According to Vandamme (2002), the most common surfactants used in microemulsions for ocular drug delivery are “the poloxamers, polysorbates, polyethylene glycol and tyloxapol.” A suspension of PEG 400-containing microemulsions applied to the eye surface in the form of an eye drop could be a viable candidate solution for treating eye dryness. Compared to liposomes, microemulsions have a much smaller droplet size and much lower viscosity, partially due to their smaller size. They are also more easily prepared, more easily sterilized, and more thermodynamically stable than liposomes (Sahoo et al., 2008). Microemulsion eye drops are exceptionally clear, with transmittance values of 98-100% (Nair et al., 2011).

Compared to conventional eye drops, microemulsion suspensions have a much greater bioavailability, or time period over which a drug can be released and have an effect. Conventional drops have a bioavailability of 1-10%, whereas microemulsion suspensions have been shown to have a bioavailability over twice that amount. In comparisons of drug delivery kinetics between the two methods, the microemulsion drug delivery period after application was approximately 2-6 times greater than its conventional competitor (depending on the specific substances tested). That figure translates to a drug residence time of approximately 6-8 hours per application. Based on this figure, microemulsion-loaded eye drops would have to be administered around twice a day to have constant drug delivery during waking hours. Since normal eye drops often need to be applied four times a

day or more for constant lubrication, this is certainly an improvement on current standards (Vandamme, 2002). Compared to the liposomal delivery mechanism described in the previous section, the residence time of a microemulsion suspension would be shorter because the microemulsion solutions wears away until it is reapplied. Therefore, the effect of microemulsion drops on tear osmolarity is expected to be slightly lower in magnitude than the effect of liposome-loaded contact lenses on tear osmolarity. Therefore, users can expect an estimated decrease of up to 10 mOsmol/L in tear osmolarity after 30 days of applying the microemulsion-loaded eye drops twice a day.

A comparable emulsion-based eye drop called Cationorm retails for approximately $17 per 0.34 fl oz, which is more expensive than the $10 price of the same volume of normal PEG 400 eye drops (Cationorm, n.d.). For the sake of comparison, if a user applied the microemulsion drops twice a day to each eye for a year, the cost would amount to $125. Unlike the price of the liposomal treatment, however, this price does not include the cost of the contact lenses that the user would presumably be wearing throughout the year. The shelf life for microemulsions is difficult to determine because estimates vary wildly between several months and a few weeks. However, the American Academy of Ophthalmology recommends that any eye drop solution should be discarded 3 months after opening (2015).

PEG 400-Loaded Niosomes Applied as Eye Drops

A niosome is another nanoscale vesicle that has high potential for ocular drug delivery. Niosomes are composed of a non-ionic surfactant bilayer that has characteristics of both liposomes and microemulsions (Sahoo et al., 2008). Like the other two candidate solutions, niosomes can theoretically be loaded with PEG 400 and be applied as an eye drop to treat chronic eye dryness in CL wearers.

As described by Karim et al. (2010), there are many similarities between niosomes and liposomes. For example, the pH and solubility of a niosome can be altered by modifying the surfactant composition so that it can be optimized for ocular drug delivery. However, the differences between the two are prominent enough that they can be treated as separate candidate solutions. The following is a summary of the differences between niosomes and liposomes (Karim et al., 2010):

Table 1. Comparison of Liposomes and Niosomes

	Liposomes	**Niosomes**
Composition	Neutral or charged double chain phospholipids	Single chain non-ionic surfactant
Cholesterol Concentration	Greater concentration	Lower concentration (allows better drug entrapment)
Cost	Comparatively expensive	Inexpensive
Stability	Phospholipids prone to oxidative degradation	Surfactants are stable
Storage	Requires special conditions	No special requirement

Toxicity	Oxidative degradation makes liposomes toxic to eye	Less toxic

A niosome suspension applied as an eye drop would have an estimated bioavailability similar to that of microemulsions (about 20%), and could release therapeutic levels of a drug for 12 hours (Patidar & Jain, 2012). At that rate, niosome drops would only have to be applied twice per day or less. Since the structure of niosomes is more similar to that of liposomes than microemulsions, niosomes are more viscous than niosomes. As a result, the percent transmittance of a niosome eye drop solution would likely be less than 98%, but more than the 80% afforded by liposome-loaded contact lenses. Because of its relatively recent development, data for the effect of a niosome-based eye drop on tear osmolarity is not explicitly available at this point in time. However, based on its similarity of the microemulsion eye drop mechanism, users can expect an estimated decrease of up to 10 mOsmol/L in tear osmolarity after 30 days of applying the niosome-loaded eye drops twice a day. Likewise, the price of a niosome-based eye drop is not explicitly available. According to Karim et al. (2010), niosomes are cheaper than liposomes, and liposomes are more expensive than microemulsions, so the price of a niosome-based eye drop would presumably be between the two.

Compared to liposomes and microemulsions, niosomes present a novel solution, but, as implied by the above paragraph, one of the major challenges of a niosome-based drug delivery mechanism is the relative lack of available information. Much of the data concerning niosomes is qualitative in nature, rather than quantitative. Regardless, some of the advantages that niosomes can offer are too great to ignore.

Table 2. Summary and Comparison of Candidate Solutions

	Liposome-Loaded Contact Lenses	**Microemulsion Eye Drop Solution**	**Niosome Eye Drop Solution**
Proposed Lubricant	Polyethylene Glycol 400	Polyethylene Glycol 400	Polyethylene Glycol 400
Bioavailability of Drug	>>20%	20%	20%
Therapeutic Drug Release Period After Application (hours)	168	6-8	12
Decrease in Tear Osmolarity After 30 Days of Use	10	10	10
Clarity of Vision During Treatment (% Transmittance)	80-90	98-100	90-98
Annual Cost	$1200	$125	$125 < *x* << $1200
Miscellaneous Concerns	Liposomes have short shelf life; difficult to	N/A	Small body of academia

	synthesize; can be toxic if oxidized		concerning niosomes

Proposed Solution

The general criteria set forth in the Overall Analysis and Objectives section were that the proposed solution must be safe, comfortable, easy to use, long-lasting, and cost-effective. Based on these objectives, the best candidate solution may be a combination of two candidates.

The proposed lubricant is the same for all solutions, so it serves as a control for the comparison of the various drug delivery methods. Liposome-loaded contact lenses have the greatest bioavailability of any of the solutions since the lens itself contributes to the controlled release of drugs. The other two solutions are applied as eye drops, so – despite the nanoparticles' increased retention time – there is no slow diffusion of the drug over time. The therapeutic drug release period and ease of use also heavily favor the liposome-loaded contact lenses. In order to apply the lens treatment, a user need only wear the prescribed contact lenses daily as they would normally wear lenses. For the other two candidate solutions, the eye drops would have to be applied twice daily. The lenses provide a constant flux of liposome-encased lubricant while eye drop residence times in the eyes steadily fall until the eye drops are reapplied. Because of these drug delivery kinetics, it is predicted that liposome-loaded contact lenses would cause a decrease in tear osmolarity greater than or equal to 10 mOsmol/L over a 30 day period. Over the same period, the effect other two candidates would be slightly lower in magnitude, simply because the drug-loaded lenses offer continuous drug release and higher bioavailability. The microemulsion and niosome eye drop candidates hold an advantage when it comes to vision clarity during treatment, with percent transmittances of 98-100% and 90-98%, respectively. Because of the viscosity of liposomes, the liposome-loaded contact lenses only offer 80-90% transmittance, but that is well within the acceptable range of transmittance. Furthermore, the clarity can be improved by using thinner lenses or fewer liposomes per lens.

The two candidates that are applied as eye drops also have a significant advantage in annual cost for a user. The $1200 annual cost of the liposomal treatment includes the cost of contact lenses, which users of the other two candidate solutions also wear. The best way to compare the cost of the solutions may be to compare the total price of the treatment and the contact lenses. When the contact lenses are taken into account, a year of the liposomal treatment costs $1200, a year of the microemulsion treatment costs $725, and a year of the niosomal treatment costs between $725 and $1200 (although it is likely closer to $725 than it is to $1200). Between the most expensive solution and the least expensive solution, there is a $475 annual difference.

Lastly, there are miscellaneous concerns to consider for the liposomal and niosomal treatments. The concerns regarding niosomes mainly center around the relatively small body of knowledge that exists for them. Because of the limited resources available, it may be more difficult to formulate a niosome solution that works as intended. For liposomes, the concerns are more serious. Although it is difficult to find an exact number, academic sources say with near unanimity that liposomes are difficult to synthesize and that they have short shelf lives. Furthermore, liposomes are prone to oxidative degradation, which makes them toxic to an ocular environment.

Contact lenses loaded with nanoparticles are the most therapeutically promising of the three candidates. The main drawbacks for the contact lens candidate solution are the high price and the issues associated with the stability and synthesis of liposomes. One way to mitigate the negative

effects of liposome-loaded contact lenses is to load the lenses with niosomes instead of liposomes. Niosomes have many of the same therapeutic characteristics as liposomes, but they are more economical, easier to synthesize, easier to store, and safer for the ocular environment (See Table 1). Therefore, the proposed solution is the use of a hydrogel contact lens with a PEG 400-loaded niosome suspension (henceforth abbreviated NCL).

Major Design and Implementation Challenges

The following list summarizes the general design and implementation challenges associated with engineering an NCL treatment:

- Choosing which type of niosome to use for the treatment
- Choosing a method by which to synthesize niosomes
- Finding the right balance of hydrophilic and lipophilic drugs in the niosome's surfactant bilayer
- Finding the precise composition of the lubricant required to ensure therapeutic effect and safety
- Engineering the drug delivery kinetics of both the hydrogel lens and the niosomes
- Finding the optimal storage methods and conditions for NCLs.

One of the first decisions that would have to be made in the design process would be choosing which type of niosome is used for the treatment. According to Karim et al. (2010), the three main types of niosomes are "small unilamellar vesicles (SUV, size = 0.025-0.05 μm), multilamellar vesicles (MLV, size = >0.05 μm), and large unilamellar vesicles (LUV, size = >0.10 μm)." The size of the vesicles would determine the amount of drug that the vesicles can encapsulate as well as the rate at which the vesicles diffuse from the CL and onto the eye surface. Next, the synthesis method must be decided upon. Popular niosome synthesis methods include micro fluidization and reverse phase evaporation. Micro fluidization involves interaction between two fluid streams at very high velocity in micro channels. The channels are engineered to encourage SUV formation with great reproducibility. Reverse phase evaporation can be used to synthesize LUVs. In reverse phase evaporation, a clear gel is formed by sonicating a mixture of cholesterol, surfactant, ether, chloroform, and aqueous-phase containing drug. Subsequent steps, including the addition of phosphate-buffered saline and heating, yield niosomes.

The next design challenge is determining the composition of the niosome's non-ionic surfactant bilayer and the balance of lipophilic and hydrophilic substances in the bilayer. One basic requirement for the surfactant is that it must have a hydrophilic head and a lipophilic tail. The surfactant must have the same pH as the ocular surface (6.5). The rigidity, potential leakage, and drug delivery kinetics of the niosome are also determined by the composition of the surfactant bilayer. Notably, the drug release rate of a niosome varies inversely with the cholesterol content of the surfactant bilayer. Table 3 compares various types of non-ionic surfactants (Karim et al., 2010).

Table 3. "Different types of non-ionic surfactants"

Type of non-ionic surfactant	**Examples**
Fatty alcohol	Cetyl alcohol, searyl alcohol, cetostearyl alcohol, oleyl alcohol
Ethers	Brij, decyl glucoside, lauryl glucoside, octyl glucoside, Triton X-100, nonoxynol-9
Esters	Glyceryl laurate, polysorbates, spans

Block copolymers	Poloxamers

Another design challenge is determining the exact composition of the lubricant. It has been mentioned earlier that PEG 400 is a popular lubricant, but commercial PEG 400 eye drops are actually solutions of PEG, propylene glycol, polyvinyl alcohol, and other substances designed to increase ocular solubility, maintain pH, and sterilize the solution (Undurraga et al., 2007). The physical and chemical properties of the lubricant can also affect niosome membrane rigidity and drug release kinetics. Table 4 summarizes the effect of drug natures on niosome formation (Karim et al., 2010).

Table 4. "Effect of the nature of drug on the formation of niosomes"

Nature of Drug	Leakage from Vesicle	Stability	Other Properties
Hydrophobic	Decreased	Increased	Improved trans-dermal delivery
Hydrophilic	Increased	Decreased	~
Amphiphilic	Decreased	~	Increased encapsulation, altered electrophoretic mobility
Macromolecule	Decreased	Increased	~

The last major design consideration that needs to be made is the method by which the niosomes are stored. At room temperature, niosome encapsulation has been shown to be stable for about 6 months before significant drug leakage occurs and the surfactant bilayer becomes rigid (Bragagni, Mennini, Ghelardini, & Mura, 2012). This relatively short expiration date means that users cannot buy a year's worth of supply in one bulk order and that manufacturing companies cannot mass produce it without being reasonably sure that it will sell. That is, unless a more effective storage method can be implemented. As more research is carried out, long-term storage methods are likely to arise.

Implications of Project Success

If this design is successful, it will have several implications for individuals as well as the contact lens and ocular drug delivery market at large. For individuals with dry eye symptoms because of extended CL wear, the obvious implication is that they will be able to receive a convenient and effective treatment for a reasonable price.

If this project is a success, it would be hugely beneficial for our startup company. Aside from the immediate benefits of this design, it would pave the way for additional projects and encourage investors to fund those projects. In the future, this company may further specialize in novel drug delivery mechanisms for treating other ocular diseases such as glaucoma.

For the overall market, the success of this treatment would lead to an increased interest in niosomes and CL-based drug delivery mechanisms. In turn, this would lead to an increase in niosome-based and CL-based treatment methods. Other pharmaceutical companies may try to develop competing solutions, and those methods may be difficult to compete against with the limited

resources of our startup. Alternatively, larger corporations may seek to acquire our company, assuming our projects are successful enough. Sales of conventional eye drops may decrease among CL wearers.

The success of this project is not expected to have a significant socioeconomic or political impact. The treatment methods proposed are already being researched and used. Repurposing those methods to treat dry eye symptoms should not have any form of societal impact, other than an increase in properly lubricated eyes.

References

Agarwal, A. (2006). Dry eye: A practical guide to ocular surface disorders and stem cell surgery. Thorofare, NJ: SLACK.

American Optometric Association (AOA), 2003. Facts and stats.

Benelli, U., Nardi, M., Posarelli, C., & Albert, T. G. (2010). Tear osmolarity measurement using the TearLab™ Osmolarity System in the assessment of dry eye treatment effectiveness. *Contact Lens and Anterior Eye, 33*(2), 61-67. doi:10.1016/j.clae.2010.01.003

Bragagni, M., Mennini, N., Ghelardini, C., & Mura, P. (2012). Development and characterization of niosomal formulations of doxorubicin aimed at brain targeting. *Journal of Pharmacy & Pharmaceutical Sciences, 15*(1), 184. doi:10.18433/j3230m

Cationorm Md sine Augentropfen. (n.d.). Retrieved December 10, 2016, from http://www.versandapo.de/en/10096/9617765/CATIONORM-MD-sine-Augentropfen.htm

Doughty, M. J., Fonn, D., Richter, D., Simpson, T., Caffery, B., & Gordon, K. (1997). A patient questionnaire approach to estimating the prevalence of dry eye symptoms in patients presenting to optometric practices across Canada. *Optometry and Vision Science, 74*(8), 624-631. doi:10.1097/00006324-199708000-00023

Gulsen, D., Li, C., & Chauhan, A. (2005). Dispersion of DMPC liposomes in contact lenses for ophthalmic drug delivery. *Current Eye Research, 30*(12), 1071-1080. doi:10.1080/02713680500346633

Heiting, G. (n.d.)a. When were contact lenses invented? Retrieved December 06, 2016, from http://www.allaboutvision.com/contacts/faq/when-invented.htm

Heiting, G. (n.d.)b. How much do contacts cost? Retrieved December 08, 2016, from http://www.allaboutvision.com/contacts/faq/contact-cost.htm

Henriksen, I., Sande, S. A., Smistad, G., Ågren, T., & Karlsen, J. (1995). In vitro evaluation of drug release kinetics from liposomes by fractional dialysis. *International Journal of Pharmaceutics, 119*(2), 231-238. doi:10.1016/0378-5173(94)00403-r

Holly FJ. Formation and stability of the tear film. *Int Ophthalmol Clin* 1973 Spring;13(1)73-96.

Karim, K., Mandal, A., Biswas, N., Guha, A., Chatterjee, S., Behera, M., & Kuotsu, K. (2010). Niosome: A future of targeted drug delivery systems. *Journal of Advanced Pharmaceutical Technology & Research, 1*(4), 374. doi:10.4103/0110-5558.76435

Lemp, M. A., Bron, A. J., Baudouin, C., Castillo, J. M., Geffen, D., Tauber, J., . . . Sullivan, B. D. (2011). Tear osmolarity in the diagnosis and management of dry eye disease. *American Journal of Ophthalmology, 151*(5). doi:10.1016/j.ajo.2010.10.032

Muselier-Mathieu, A., Bron, A. M., Mathieu, B., Souchier, M., Brignole-Baudouin, F., Acar, N., . . . Creuzot-Garcher, C. (2013). Ocular surface assessment in soft contact lens wearers; the contribution of tear osmolarity among other tests. *Acta Ophthalmologica, 92*(4), 364-369. doi:10.1111/aos.12103

Nair, R., Badivaddin, M., Sevukarajan, M., Sakeena parveen, S., & Jeyachitra, B. (2011, June). Development and characterization of ofloxacin microemulsions for ocular application. *International Journal of Chemical and Pharmaceutical Sciences, 2*(2), 43-49. Retrieved December 10, 2016.

Narayanan, S. (2011, February 07). Osmolarity: A diagnostic test for dry eye. Retrieved December 07, 2016, from https://www.reviewofoptometry.com/article/osmolarity-a-diagnostic-test-for-dry-eye

Nichols, J. J., Willcox, M. D., Bron, A. J., Belmonte, C., Ciolino, J. B., Craig, J. P., . . . Sullivan, D. A. (2013). The TFOS international workshop on contact lens discomfort: Executive summary. Investigative Opthalmology & Visual Science Invest. *Ophthalmol. Vis. Sci., 54*(11). doi:10.1167/iovs.13-13212

Patidar, S., & Jain, S. (2012). Non-ionic surfactant based vesicles (niosomes) containing flupirtine maleate as an ocular drug delivery system. *Journal of Chemical and Pharmaceutical Research, 4*(10), 4495-4500. Retrieved December 10, 2016.

Pritchard, N., Fonn, D., & Brazeau, D. (1999, November 26). Discontinuation of contact lens wear: A survey. *International Contact Lens Clinic, 26*(6), 157-162. doi:10.1016/s0892-8967(01)00040-2

Sahoo, S., Dilnawaz, F., & Krishnakumar, S. (2008). Nanotechnology in ocular drug delivery. *Drug Discovery Today, 13*(3-4), 144-151. doi:10.1016/j.drudis.2007.10.021

Schachet, J. L. (2008, November). The golden age of dry eye management. Retrieved December 06, 2016, from https://www.reviewofoptometry.com/ce/the-golden-age-of-dry-eye-management

Shelf-life of Eye Drops. (2015). Retrieved December 10, 2016, from https://www.aao.org/eye-health/ask-ophthalmologist-q/eye-drop-shelf-life

Tiffany, J. M. (2003). Tears in health and disease. *Eye, 17*(8), 923-926. doi:10.1038/sj.eye.6700566

Tseng SC, Tsubota K. Important concepts for treating ocular surface and tear disorders. *Am J Ophthalmol* 1997 Dec;124(6):825-35.

Undurraga, M. I., Iii, G. O., Schindelar, M., & Paugh, J. (2007). Ocular surface retention time and extensions of TFBUT of a lubricating eye drop. *Acta Ophthalmologica Scandinavica, 85*, 0-0. doi:10.1111/j.1600-0420.2007.01062_3208.x

Vandamme, T. (2002). Microemulsions as ocular drug delivery systems: Recent developments and future challenges. *Progress in Retinal and Eye Research, 21*(1), 15-34. doi:10.1016/s1350-9462(01)00017-9

Wolff E. The muco-cutaneous junction of the lid margin and distribution of the tear fluid. *Trans Ophthalmol Soc* UK 1946;66:291-308.