Latanoprost and Timolol in Hydrogel Soft Drug-Dispensing Contact Lenses: A Comparative Analysis

Abstract:

Currently, glaucoma patients only have the option of instilling glaucoma eye drops into their eyes. This method results in 1-7% absorption of the medication, and the effects of the medication taper quickly. Additionally, surveys show that glaucoma patients frequently forget to insert their eye drops, and also have difficulty in administering their eye drops daily. Researchers at the Massachusetts Eye and Ear Infirmary have recently developed latanoprost drug-dispensing hydrogel soft contact lenses with a polymer film that dispense the drug, latanoprost, into the eye to help facilitate the process for glaucoma patients to take their medication. However, some glaucoma patients do not respond to latanoprost because they have uveitic glaucoma or they do not want to experience latanoprost’s ocular side effects such as change in iris color and lengthening of eyelashes. Glaucoma patients need alternative drugs to latanoprost which can be inserted into drug-dispensing contact lenses if they become available on the market. Another commonly used glaucoma drug to reduce intraocular pressure levels is timolol. This could be an option for patients who do not respond to latanoprost. While, timolol has fewer ocular side effects than latanoprost, timolol presents more systematic adverse effects. Timolol is also less expensive to buy compared to latanoprost. Timolol has comparable, extended drug release rates like those of latanoprost which leads to lower intraocular pressure levels in the eye. This
alternative to latanoprost would let glaucoma patients who do not respond well to latanoprost an opportunity to try timolol-dispensing contact lenses once they become available to consumers.

**Introduction:**

Glaucoma is an ocular disease in which there are increased intraocular pressure levels within the eye causing eventual damage to the optic nerve and loss of vision. The intraocular pressure level is set by a balance between production of the aqueous humor fluid in the eye and its outflow through the trabecular and uveoscleral pathways. According to the Glaucoma Research Foundation, glaucoma is the leading cause of irreversible blindness world-wide with no cure available as of now. The only option patients have to treat glaucoma is instilling prescribed glaucoma medications like eye drops into their eyes to reduce the intraocular pressure levels. This concludes in a small amount of the medication absorbed, and the effects of the medication are not prevalent. Likewise, case studies show that glaucoma patients regularly forget to insert their eye drops, and also have difficulty in administering their eye drops daily. Drug-dispensing contact lenses have the potential to become the next revolutionary medical innovation because of their ability to elute a drug from the polymer film within which increases bioavailability, hence reducing drug wastage. With this, glaucoma patients will have lower patient non-adherence rates and the lenses as a whole will help decrease the progression of the glaucoma disease. Lenses in development have latanoprost in them, but another widely used drug, timolol, might be an effective option for glaucoma patients who do not respond to latanoprost because they have uveitic glaucoma or they don’t want to experience any of latanoprost’s ocular side effects such as change in iris color and lengthening of eyelashes. While, timolol has fewer ocular side effects than latanoprost, timolol presents more systematic adverse effects which occur in patients occasionally. Additionally, timolol is less expensive to buy compared to latanoprost. Moreover,
timolol has comparable, extended drug release rates which leads to lower intraocular pressure level reductions like those of latanoprost.

**Systemic Adverse and Ocular Side Effects**

**Subclaim:** Two of the most popular drugs that glaucoma patients take are latanoprost and timolol. Timolol has systematic adverse side effects such as cardiac arrhythmias and severe bronchospasms, syncopes, cerebrovascular events, heart failure, depression, states of confusion, and impotence. On the other hand, latanoprost has ocular side effects such as increased iris pigmentation, growth of eyelashes, change in iris color, stinging, blurred vision, eye redness, itching, and burning. Many people who use timolol do not experience its more serious side effects while latanoprost’s ocular side effects are more likely to occur in glaucoma patients. If they do experience timolol’s more serious side effects, it is most likely due to drug interactions with other drugs patients are taking at the same time.

According to Li, Abrahamson, Kapoor, and Chauhan, in “Timolol Transport from Microemulsions Trapped in HEMA Gels,” “It is known that systemic absorption of beta-blockers such as timolol causes a number of side effects, such as cardiac arrhythmias and severe bronchospasms, syncopes, cerebrovascular events, heart failure, depression, states of confusion, and impotence” (298). Li et al. contend that more systematic adverse effects are observed in patients treated with timolol than latanoprost and that the risk for cardiac disorder is higher in timolol (7). Consequently, as a result of these systematic adverse side effects timolol is known to have Schuman argue that

The elderly, who are most likely to have glaucoma and to be using topical betaadrenergic receptor antagonists, are particularly vulnerable to developing clinically important drug interactions. Because the incidence of disease increases
with age, this patient group is likely to have multiple coexisting conditions for which it may be using numerous medications. (178)

Timolol was one of the first glaucoma drugs doctors prescribed to glaucoma patients beginning in the 1978. Topical beta adrenoceptor blockers, also commonly known as beta-blockers, is the class of drugs timolol falls under. Timolol is a nonselective beta-blocker that prevents the stimulation of the adrenergic receptors used for increased cardiac action. Timolol lowers the intraocular pressure within the eye by inhibiting the production of the aqueous humor. Timolol should be applied into drug-dispensing contact lenses despite the wide array of side effects that occur since in most patients these systematic adverse side effects are less likely to produce an occurrence. Timolol causes less ocular side effects, such as eye irritation, than latanoprost and can even be prescribed to patients who have cataracts as well as patients who have glaucoma. If these severe side effects do occur, they are most likely due to the drug interactions the patient is experiencing since they are taking multiple medications at once which can complicate timolol in the process. Most glaucoma patients are elderly, so they have preexisting conditions that conflict with the glaucoma drug timolol in the process of ingestion which results in multiple systematic adverse side effects.

In agreement with Li et al. Schuman argues, in “Antiglaucoma Medications: A Review of Safety and Tolerability Issues Related to Their Use,” “Given the effects of systemically absorbed topical beta-adrenergic-receptor antagonists on the cardiovascular system, the potential for a serious drug interaction in a patient receiving other drugs that exert effects on the cardiovascular system is high” (177).

The drug interaction that results from taking the topical beta-adrenergic-receptor antagonist, timolol, and other drugs the glaucoma patients is taking affecting the cardiovascular
system causes the severe systematic adverse side effects to happen. Timolol’s side effects are not due to the composition of the drug itself; moreover, the systematic adverse side effects are happening from the drug interactions. In addition, pharmaceutical companies have to list timolol’s severe systematic adverse side effects since most patients that have glaucoma are elderly and are in clinical trials that confirm that they are taking other medications at the same time as timolol and have shown these effects. However, most patients using timolol do not experience these more serious side effects from timolol, so timolol should be included in drug-dispensing contact lenses for glaucoma patients who do not respond to latanoprost.

Furthermore, Patel and Spencer explain that “Latanoprost... unlike timolol, is not associated with systemic adverse effects. However, 3 to 10% of patients treated with latanoprost 0.005% have shown increased iris pigmentation after 3 to 4.5 months’ treatment” (364). Schuman is in accord with this and explains that, “This is the most common side effect of latanoprost therapy, occurring in 6.6% of eyes within 3 months of beginning therapy and increasing in incidence over time such that after 2 years of therapy, changed iris pigmentation occurred in >18% of eyes in clinical studies” (184). Schuman also confirms that, “Changed iris pigmentation and discontinuations of therapy because of the possibility of changed iris color, are major reasons for withdrawal from latanoprost therapy” (184).

Latanoprost associates with ocular side effects like iris pigmentation and lengthening of the eyelashes. Latanoprost’s ocular side effects happen more frequently in patients compared to timolol’s systemic adverse side effects. Glaucoma patients who do not want to experience such effects do not take this drug and need an alternative to latanoprost-dispensing contact lenses if they were to become available on the market. Patient non-adherence rates are high since glaucoma patients make the decision to discontinue their latanoprost medication due to these
ocular side effects. Glaucoma patients should not be discontinuing their medication based on side effects and if they do discontinue their medications, they should inform their doctor so they can take another glaucoma medication. Patient non-adherence rates can lower by having a timolol-dispensing contact lenses available for glaucoma patients who do not want to have latanoprost’s ocular side effects.

Schuman notes that, “The color changes occur most frequently in green-brown eyes (48% of treated patients), followed by yellow-brown (29%) and blue- or gray-brown eyes (15%) and can range from darkening of the peripheral iris stroma to a remarkable color change” (184). Further, according to the Animated Dissection of Anatomy for Medicine, Inc. which is accredited by URAC, which is also known as the American Accreditation HealthCare Commission, prostaglandins such as Xalatan “…appear to be safe for people with asthma. Side effects include itching, redness, and burning…muscle and joint pain may also occur…may permanently change eye color from blue or green to brown” (1).

One of latanoprost’s most significant ocular side effect is the change in iris color. However, if a glaucoma patients has a light eye color such as blue or green it then changes to brown whereas glaucoma patients who already have brown eyes do not experience the significant change in iris color. Latanoprost is better for patients who have asthma since there are no side effects affecting the respiratory system. Conversely, people who experience arthritis or fibromyalgia should be taking a different glaucoma medication such as timolol due to the possible side effects of joint and muscle pain. In addition to glaucoma patients who do not respond to latanoprost since they have uveitic glaucoma or they do not want to experience the ocular side effects such as change in iris color and lengthening of eyelashes, glaucoma patients who have arthritis or fibromyalgia should also be taking timolol. These glaucoma patients who
experience these disorders need an alternative to latanoprost-eluting contact lenses. Therefore, timolol should be an option to be inserted into drug-dispensing contact lenses so that more glaucoma patients with different preliminary conditions can still use these contact lenses once they become available on the market.

On a different note, according to Digiuni, Fogagnolo, and Rossetti, in “A Review of the Use of Latanoprost for Glaucoma Since its Launch,” “there have been case reports of herpetic keratitis in patients under treatment with latanoprost” (735). Digiuni, Fogagnolo, and Rossetti acknowledge that, “the use of prostaglandin F2a...may lead to a deepening of the upper eyelid sulcus (DUES) in the long term” (736). According to Sakata et al., in “Incidence of Deepening of the Upper Eyelid Sulcus in Prostaglandin-Associated Periorbitopathy with a Latanoprost Ophthalmic Solution,” “the development of DUES in one patient (right eye) that appeared 2 months after starting LAT” (1448). Digiuni, Fogagnolo, and Rossetti argue that, “the development of dendritiform epitheliopathy has been observed in four patients with glaucoma following latanoprost therapy” (736). Digiuni, Fogagnolo, and Rossetti observe that, “herpetic dermatitis of the periocular skin associated with latanoprost therapy has also been reported in two patients aged 79 and 84 years” (736).

There are patient cases in which latanoprost produces more severe side effects than its usual ocular side effects which pertain to change in iris color, lengthening of eyelashes, itching, burning, and redness. These more serious side effects latanoprost creates eye conditions that can affect the patient detrimentally and may not be able to get cured. For example, herpetic keratitis has no cure because once the herpetic simplex virus is in the body, there is no way to get rid of it. Patients can only prevent recurring outbreaks from occurring. The viral infection of the eye is a very severe side effect to consider that patients need to take into consideration of whether to take
latanoprost or not. For patients who do not wish to endure the risk of developing this viral infection of the eye, timolol may be the better glaucoma medication to take and to make this drug available in drug-dispensing contact lenses form would benefit these patients. Deepening of the upper eyelid sulcus is another adverse cosmetic side effect along with change in iris color and lengthening of eyelashes that glaucoma patients do not want to encounter while taking this drug. Herpetic dermatitis is an autoimmune disorder that consists of a chronic, itchy rash. This disorder links to people developing certain cancers of the intestines which can be deleterious to the human body. Glaucoma patients not willing to take this risk of developing this chronic autoimmune disorder should take a different intraocular pressure lowering drug such as timolol that does not result in such patient cases.

**Cost Comparisons and the Effect of Socioeconomic Status on Glaucoma**

**Subclaim:** Timolol is less expensive to buy compared to latanoprost since beta-blockers, a class of drugs that timolol falls under, are generally inexpensive unlike prostaglandins, a class of drugs that latanoprost falls under. The difference in price, however, does not undermine timolol’s ability as an efficient glaucoma drug because people living at a lower socioeconomic class have higher rates of glaucoma and need access to an intraocular pressure lowering drug like timolol.

According to Rylander and Void, in “Cost Analysis of Glaucoma Medications,” “The most inexpensive brand name glaucoma medication was Timoptic 0.5% (Merck & Co, 10.0 ml), with a yearly cost of $203.47 at twice daily dosing” (107). Rylander and Void also observe that, “The most inexpensive overall medications were the generics timolol maleate 0.5% (Falcon, 15.0 ml) at $150.81” (107). Rylander and Void note, “Beta-blockers were the least expensive glaucoma medications. The costs varied widely amongst the brand name beta-blockers, ranging
between $203.47 (Timoptic 0.5%, 10.0 ml) and $657.24 (Betoptic S, 2.5 ml)” (107). According to Table 2: Glaucoma Medication Average Wholesale Price Trends, in 2006, the average wholesale price of timoptic was $22.10 and the percent change from 2002 to 2006 was 0.00 for 5.0 ml (110). This same economic trend correlates in Italy. In agreement with the same monetary trends of timolol, according to Costagliola, Parmeggiani, and Sebastiani, in “Assesting the Cost-Effectiveness of Switching from a Beta-Blocker to Latanoprost in the Treatment of Ocular Hypertension,” In Italy, they point out that, “The timolol 0.5% solution, the one most commonly prescribed, is the product with a very similar cost/day among the various manufacturers, with no significant differences between generic and brand ophthalmic solutions (from €0.04 to 0.05). The cost/year supported by patients varies from €14.60 to 18.25” (1781).

Rylander and Void compare the yearly cost of taking a beta-blocker for glaucoma to prostaglandins and comment that the, “Yearly cost of the prostaglandin analogue products ranged from $427.69 (Travatan, 5.0 ml) to $577.62 (Lumigan, 7.5 ml)” (107). In a table of volumetric and economic data for glaucoma medications, Rylander and Void illustrate that the yearly cost for taking Xalatan was $463.40 at twice daily dosing. (108). According to Table 2: Glaucoma Medication Average Wholesale Price Trends, in 2006, the average wholesale price of Xalatan was $58.84 and the percent change from 2002 to 2006 was 11.02 for 2.5 ml (110). Additionally, according to Costagliola, Parmeggiani, and Sebastiani, in “Assesting the Cost-Effectiveness of Switching from a Beta-Blocker to Latanoprost in the Treatment of Ocular Hypertension,” In Italy, they observe that “Patients under l latanoprost 0.005% (Xalatan®, Pharmacia & Upjohn) sustain a daily cost of €0.27, which for a 1-year treatment period, becomes €98.55” (1782). Further, according to Peeters et al., in “Latanoprost versus Timolol as First Choice Therapy in Patients with Ocular Hypertension,” “The costs are lower for strategy ‘start
with timolol’ than for strategy ‘start with latanoprost’, namely €5,456 against €6,794 per patient (€3,514 against €4,397 when discounted)” (151).

In different parts of the world, such as the United States and Italy, the price of timolol is generally less expensive compared to latanoprost by a significant price gap. Patients taking timolol on a yearly basis spend about half of what patients do taking latanoprost. The price difference occurs because the class of drugs that timolol classifies under, which is beta-blockers, is less expensive to purchase than the class of drugs that latanoprost classifies under which is prostaglandin analogues. Beta-blockers have been around on the market longer than prostaglandin analogues thus making them less new. Beta blockers are also in use for conditions other than glaucoma such as hypertension and migraines making them versatile drugs unlike latanoprost which is specifically used to treat glaucoma. Timolol also has not been through a notable increase in price in recent years in comparison with latanoprost. Despite the prominent price gap of the two commonly used glaucoma medications, latanoprost and timolol, the effectiveness of timolol is not undermined as it is still is an effective drug to use to lower intraocular pressure levels in the eye. Timolol is a viable option for people living in developing countries, like India, who cannot afford to buy expensive drugs to treat themselves or for people at low socioeconomic levels in developed countries, such as the United States. Timolol has been around for 37 years, considerably longer than latanoprost, because of its ability to reduce the intraocular pressure level and its capability to be at a low price lets it become a better option for people living at low socioeconomic levels.

According to Yip et al., in “Socioeconomic Status, Systolic Blood pressure and Intraocular Pressure: The Tanjong Pagar Study,”
Lower education and income levels were associated with higher IOP. People who had tertiary level education had the lowest mean IOP of 13.4 mm Hg, whereas participants who had no formal education and those who had only primary level education had the highest mean IOP of 14.7 and 14.8 mm Hg, respectively. Similarly, those who earned the most (.2000SGD) also had the lowest mean IOP of 13.8 mm Hg. (57)

Additionally, Yip et al. argue that “People who had a university level education had a mean IOP that was 0.8 mm Hg lower (95% confidence interval (CI) 21.66 to 0.10 right eye; 21.82 to 0.15 left eye) than those without any formal schooling” (58). Similarly Shweik et al. report in “Measures of Socioeconomic Status and Self-Reported Glaucoma in the UK Biobank Cohort,” “As household income decreases, individuals are significantly more likely to report a diagnosis of glaucoma. Rates of glaucoma were highest among those of lowest annual income, of £18,000 (2.4%), and decreased as income increased, with the lowest rates among those with an income of £100,000/year” (1362). Also Buys and Jin observe in “Socioeconomic Status as a Risk Factor for Late Presentation of Glaucoma in Canada” “The presentation of late stage of glaucoma was 35.48% in the highest income quintile compared with 55.32% in the lowest income quintile” (85). Yip et al. note that the, “The Baltimore Eye Survey has shown that African Americans have a higher prevalence of glaucoma…and it is well recognized that African Americans experience poorer health than Americans with European heritage” (58).

People living at lower socioeconomic levels mostly come from lower educational backgrounds and lower income levels. There is a correlation between people living at lower socioeconomic levels and having a higher intraocular pressure level. This trend contrasts of how people living at higher socioeconomic levels with more education attainment have lower
intraocular pressure levels and occurs in the United States, Canada, and the UK. Hence, people living at lower socioeconomic levels need a reasonably priced drug they can afford to lower their high intraocular pressure levels otherwise the progression of glaucoma will occur which results in blindness. Similarly, according to *The State of Working America*, African Americans have the highest poverty rate in the United States. African Americans in the United States are at a disadvantage in terms of socioeconomic level and this connects with why they have a higher incidence of glaucoma. Living in a low socioeconomic level relates to having a high intraocular pressure level which results in glaucoma, and this is what most African Americans are experiencing. Timolol is an efficient option for those living at lower economic levels, such as African Americans, since it produces comparable results like that of latanoprost and is at a reasonable price compared to other glaucoma drugs such as latanoprost. Timolol is half as expensive as latanoprost and corresponds to equivalent drug release rates which effectively lowers the intraocular pressure level.

**Drug Release Rates Comparison**

**Subclaim:** Timolol has comparable, extended drug release rates like those of latanoprost which leads to lower intraocular pressure levels in the eye. The lower intraocular pressure levels in the eye contribute to a slower progression of the glaucoma disease in the eye. For glaucoma patients who cannot take latanoprost because they have uveitic glaucoma or they don’t want to experience any of latanoprost’s ocular side effects such as change in iris color and lengthening of eyelashes, this is an effective choice since its drug release rates are like those of latanoprost.

According to Ciolino et al., in “*In Vivo* Performance of a Drug-Eluting Contact Lens to Treat Glaucoma for a Month,” “All lenses demonstrated an initial burst release followed by slower release during the 4-week study period. In the CL 65:35, 20 group, 90% of the total
amount of drug was released during the first 3 days” (434). Similarly in “Extended Latanoprost Release from Commercial Contact Lenses: In Vitro Studies Using Corneal Models,” Mohammadi et al. contend that “In the no-cells model, release was first measured in KSFM to allow for comparisons between all in vitro models… an initial burst in the first 6 hours was observed, followed by saturation, when no more drug was released, despite the available drug in the contact lens material” (4).

Mohammadi et al. realize that

Performing the contact lens release experiments in the presence of corneal epithelial cells resulted in significant changes…the amount of latanoprost released from senofilcon A was dependent on the presence of cells in the in vitro models; a significantly higher amount of latanoprost was released in the monolayer and multilayer models when compared to the no-cell model. (4)

Furthermore, Mohammadi et al. observe that

With latanoprost free-acid, contrary to what was observed with the ester form of the drug, a significantly lower release occurred in the presence of cells when compared to no-cells. Table 3 presents the release of latanoprost free-acid from tested commercial contact lenses after 24 hours for each of the in vitro models. When comparing the amount of drug release at 24 hours in the monolayer model, the latanoprost free-acid results show a significant decrease (approximately 30%) in the amounts of the drug that has been released from galyfilcon A and senofilcon A silicone hydrogels (Table 2). (4)

Latanoprost displays an initial burst which then subsides in the next period of time depending on the type of contact lens it is in. For drug-dispensing contact lenses, latanoprost’s effects can go up to a month while in commercial contact lenses it has a shorter duration since
there is no polymer film within the contact lenses. Timolol has similar drug release rates which compare to those of latanoprost and prove to be as notable, so that glaucoma patients can use timolol if they do not respond well to latanoprost. *In vitro*, senofilcon A, non-ionic contact lenses, releases a significantly larger amount of latanoprost models with layers which associates to what would happen *in vivo* since the human eye makes up multiple layers. However, when the control of the study uses latanoprost free-acid, since when there are no cells latanoprost cannot metabolize to its free-acid form, there was a decrease in the drug release rate which suggests that patients that decreased layers of cells in their eye need to switch to a different glaucoma drug like timolol. Since latanoprost is relatively new compared to timolol, its drug release rates are pointedly high and since it is considered lipophilic and better penetrate the cornea and hydrolyze completely. Nonetheless, timolol has been around for many years that proves its durability as a glaucoma drug to compete against latanoprost. Timolol’s drug release rates are as effective and can be implemented into drug-dispensing contact lenses for patients who need to use timolol than latanoprost.

Moreover, Mohammadi et al. analyze and suggest that,

the limited amount of drug that was released in our fixed volume model is likely the result of the high partition ratios of the latanoprost between the contact lens material and the aqueous solutions. Furthermore, our results from the no-cells model suggest that latanoprost has a lower affinity toward PBS compared to KSFM. The better solubility of latanoprost in KSFM compared to PBS is likely due to the difference in composition, such as the presence of growth factors and other ionic compounds in the culture medium which are absent in the buffered saline solution. (7)
The similar drug release trend is observed in timolol. In “Drug Delivery by Contact Lens in Spontaneously Glaucomatous Dogs,” Peng et al. observe that

At room temperature, pure NIGHT & DAY released 80% of loaded timolol to PBS in the first 30 min, and released the remaining drug in 2 hours. For NIGHT & DAY lens with 25% vitamin E loading, it took more than 12 hours to release 75% of the included drugs inside the lens, while the total duration of drug release was extended to about 100 hours. (207)

In agreement with Peng et al., according to Guidi et al., in “Modification of Timolol Release from Silicone Hydrogel Model Contact Lens Materials Using Hyaluronic Acid,” “Incorporating low concentrations of HA into the polymer network resulted in the release of higher amounts of timolol compared with lenses that did not contain HA” (275). Similarly, Guidi et al. observe that “Timolol release was sustained for a duration of approximately 2 days, and the dose of drug was shown to be controlled by both HA–drug interactions and molecular imprinting within the silicone hydrogels” (269).

When timolol is in commercial contact lenses, the rate at which the drug releases is equivalent to latanoprost. According to Ciolino et al., the drug release latanoprost produces is 3 days while timolol approximates to four days in Peng et al.’s study which is similar. Accordingly, in Guidi et al.’s study the timolol release estimates to be about 2 days which is analogous to latanoprost in Ciolino et al.’s study. The addition of hyaluronic acid at a low concentration that enables high amounts of timolol release to assimilate into drug-dispensing contact lenses, so that glaucoma patients that use timolol have a higher amount of timolol that delivers to their eyes to lower the intraocular pressure. The drug interactions with hyaluronic acid did not create any negative effects in glaucoma patients in the study, so it is safe to assume
that it can be inserted into drug-dispensing contact lenses. Hyaluronic acid is a good option to increase timolol release since hyaluronic acid is a viscous fluid carbohydrate present in humors of the eye, connective tissue, and synovial fluid. Glaucoma patients who take timolol would achieve similar drug release rates like those of latanoprost which affirms that timolol needs to be inserted into drug-dispensing contact lenses.

Further, according to Jung et al., in “Glaucoma Therapy by Extended Release of Timolol from Nanoparticle Loaded Silicone-Hydrogel Contact Lenses,”

The particle loaded gels released timolol for an extended duration ranging from about a month at room temperature to about a day at 80 °C. Contact lenses loaded with the particles could retain the drug during packaging in refrigerated conditions and provide extended release after insertion in the eyes.... (83)

Jung et al. explain that,

The particle loaded Acuvue Oasys lenses release timolol for about 2 weeks with an average release rate of 6 μg/day. The lenses packaged in a refrigerator for 2 weeks release drug at significantly reduced rates, but without any initial burst. The absence of the initial burst suggests that timolol was not released from the PGT particle matrix and thus the reduction in the drug loading during packaging is due to diffusion of the timolol–PGT particles into the packaging medium. (88)

In one trials of Jung et al.’s study, timolol proves to have a parallel drug release rate like that of latanoprost at a specified temperature. In addition the duration of the timolol drug release rate is approximately the same as the duration of the latanoprost drug release rate in Ciolino et al.’s experiment. In Jung et al.’s study, they did not use drug-dispensing contact lenses like Ciolino et al. and instead use the method of particle loading for the contact lenses. The method
they utilize is ineffective as there is no initial burst which shows that the timolol does not release initially. The particle loading technique is not an efficient way for timolol to release at an extended time. If Jung et al. did this study with drug-dispensing contact lenses with a polymer film like Ciolino et al. did, the timolol would have an initial burst since it releases through the polymer film and does not require refrigeration. On the other hand, if Jung et al. can improve this procedure by finding a solution to stop the diffusion of the timolol-PGT particles into the packaging. The solution lets timolol have an initial burst to extend its drug release further.

Nevertheless, the drug release rates Jung et al. achieve in the first trial show that timolol is as efficient as latanoprost and can be a potential option for glaucoma patients willing to use it due to complaints with latanoprost, patients that have medical conditions like uveitic glaucoma, or glaucoma patients who need a more affordable drug choice.

In accord with Jung et al., in “Timolol Transport from Microemulsions Trapped in HEMA Gels,” Li et al. observe that

The data shows a very slow release with about 1% of the drug diffusing out each day. The release rates are almost linear for the first 40 days and then increase significantly in an almost exponential manner. Finally, the rates level off when a majority of the drug loaded in the gel is released. The cumulative drug release profiles are thus sigmoidal in shape. This behavior is interesting because typically in a diffusive system, the release rates decrease with time because of the reductions in concentration. (300)

Li et al. observe that in the gel loaded with meA as a function of time,

The results show that the gel releases drug for about 25 days, during which about 55% of the drug has diffused out. The type meA gel (gel loaded with meA) loses about 17.5% of the drug in the extraction step. Thus, the total drug release amounts to about 75% of
the drug loading. A fraction of the loaded drug may be irreversibly trapped in the gel, and additionally, a fraction of the drug may be lost in the process of extracting the timolol base into the oil phase. (301)

In addition, Li et al. discern that in pluronic microemulsion-laden gels, “90% of the drug diffused out during the extraction phase, and the remaining amount is released in the first 1.5 h of the drug release experiments” (302). Li et al. suggest to do equilibrium experiments on gel A and found that, “These gels lost 17.5% of the entrapped drug during the extraction phase. The results of drug release experiments show that about 8% of the entrapped drug diffuses out in a period of about 10 days” (302).

The application of HEMA gels for timolol transport is a somewhat effective method to release timolol. The initial release is slow, but increases at an increasing rate as the duration of time goes on. For about a month, timolol’s drug release rate is associates well to Ciolino et al.’s monthly latanoprost-dispensing contact lenses. The timolol loss needs be resolved in order for the HEMA gels to release the entirety of the drug. HEMA gels can an alternative to soft silicone hydrogels in the manufacturing of contact lenses, but most contact lenses use soft silicone hydrogels. Clinical trials using latanoprost and timolol in HEMA gels and soft silicone hydrogels should be performed to see which composition of the contact lenses help release more of the glaucoma drug at a faster rate. Conversely, with soft silicone hydrogels a polymer film aids the drug-dispensing contact lenses to dispense the drug. Timolol again verifies its ability to be in drug-dispensing contact lenses model since it can release the drug at a steady monthly rate which relates to Ciolino et al.’s latanoprost-eluting contact lenses.

Conclusion:
According to the Glaucoma Research Foundation’s website, 20% of patients have uveitic glaucoma. These patients cannot use latanoprost as their glaucoma medication because they do not respond to it with their specific type of glaucoma. While we know that timolol in contact lenses models such as drug-soaking, *in vitro* and *in vivo*, and nanoparticle loading have comparable drug release rates like that of latanoprost, we can correlate that timolol will have similar rates in drug-dispensing contact lenses. We need experimental drug trials on whether timolol has equivalent drug release rates like latanoprost specifically in a drug-dispensing contact lenses model. In addition, after the trials are complete and if timolol does have analogous drug release rates, drug-dispensing contact lenses need to have timolol inserted inside. Also in general drug-dispensing contact lenses need to go into clinical trials so the Federal Drug and Food Administration can approve them for eyewear and glaucoma patients can have a convenient way to obtain their medication on a daily basis. Other types of glaucoma such as open-angle, angle-closure, normal-tension, and congenital need to be analyzed on which glaucoma drug works best for each one. If they involve a drug other than timolol and latanoprost, other glaucoma medications such as alpha agonists and carbonic anhydrase inhibitors need to be inserted into drug-dispensing contact lenses to help these patients. On a similar note, research needs to be done on how combined glaucoma medications of for example, timolol and latanoprost, work in drug-dispensing contact lenses and how those drug release rates compare. On the other hand, drug-dispensing contact lenses can work for applications other than glaucoma such as people who have to take other medications on a daily basis and wear contact lenses. Drug-dispensing contact lenses are a fairly recent development as the latanoprost-eluting lenses were developed in 2013. However, drug-dispensing contact lenses with glaucoma medications should become
available on the market soon to help glaucoma patients facilitate the medication process to lower patient non-adherence rates and slow the progression of the glaucoma disease in the eye.
Works Cited


