REVIEW ARTICLE

Revolutionizing Glaucoma Care: Innovative Latanoprost Drug Delivery Takes Aim at Vision Loss

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Abstract

Glaucoma remains one of the leading causes of irreversible blindness worldwide, presenting a significant public health challenge. Current glaucoma management primarily relies on eye drops, with prostaglandin analogs, such as latanoprost being a cornerstone of treatment. However, patient adherence, ocular side effects, and the need for consistent dosing pose substantial obstacles to effective care. This review paper introduces a groundbreaking approach to glaucoma management through innovative latanoprost drug delivery. By leveraging cutting-edge drug delivery technologies, including sustained-release systems and advanced ocular implants, this revolutionary approach aims to address the limitations of conventional eye drops and transform glaucoma care. In conclusion, the integration of innovative latanoprost drug delivery systems holds great promise for revolutionizing glaucoma care. These advancements offer the potential to significantly reduce the burden of vision loss associated with glaucoma and improve the quality of life for affected individuals. Further research and clinical trials are essential to validate the safety and efficacy of these new approaches and usher in a new era of glaucoma management.

Key words: Glaucoma, Implants, *In situ* gel, Latanoprost, Liposomes, Niosomes

INTRODUCTION

An optic neuropathy known as glaucoma is characterized by particular anatomical findings in the optic disc and particular functional deficiencies found by automated visual testing on the field. Although elevated intraocular pressure (IOP) is still acknowledged as a significant risk factor, the condition is not identified by this symptom.[1]

After cataracts, glaucoma is the second most common cause of blindness worldwide. According to estimates from 2010, 3.9 million persons worldwide are blind from angle-closure glaucoma, and 4.5 million are blind from open-angle glaucoma.

When compared to other studied prostaglandin (PG) analogs, latanoprost has been shown to have significant ocular hypotensive action with few side effects. Latanoprost is a PG F2-alpha isopropyl ester prodrug that is hydrolyzed by esterase into latanoprost acid to create the active form. This version stimulates PG receptor F activation as depicted in Figure 1. As a selective FP receptor agonist, latanoprost increases uveoscleral outflow to mediate its ocular hypotensive effect.[2]

GLAUCOMA

A common disorder of the eyes called glaucoma, if undetected and mistreated, can lead to blindness that is irreversible. Increased IOP causes glaucoma by harming the visual nerve and impairing vision.[3] The visual field contracts as retinal ganglion cell loss progresses in glaucoma, and there are noticeable changes to the neuroretinal rim tissue in the optic nerve head (ONH) as well.[4] Glaucoma is the primary cause of permanent blindness in the globe, affecting more than 70 million people globally, and 10% of whom are

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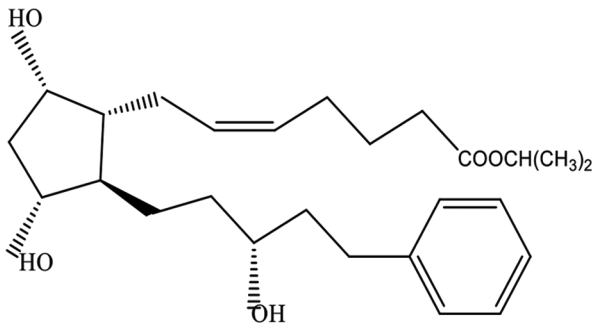

Figure 1: Structure of latanoprost

bilaterally blind. Since glaucoma can go undiagnosed until it is advanced, there is a good chance that more people have the condition than are now thought to have it. Only 10–50% of glaucoma sufferers, according to population-level surveys, are aware of their condition.[5]

Glaucoma risk factor

Population-based research is necessary to identify the risks for the development of glaucoma. The extent of the examination regimen used will determine the prevalence or incidence of glaucoma in a population study.[6]

Age, a strong family history of glaucoma, ocular trauma history, African American ancestry, vasospastic diseases, and reduced blood flow to the optic nerve are all risk factors for the development of open-angle glaucoma. However, glaucoma can also happen in infants and children. Even at low or normal levels of IOP, impaired blood flow to the optic nerve may make the nerve more vulnerable to injury.[3]

Angle-closure glaucoma is predisposed to aging, a significant family history of the disease, a history of eye trauma, Asian ancestry, and pseudoexfoliation.[3]

Types of glaucoma

Glaucoma comes in a variety of forms, and they have traditionally been separated into two groups:[3]

Open-angle glaucoma

The disease usually has no symptoms in the early stages and progresses slowly. The diagnosis of open-angle glaucoma depends on three factors: The normal gonioscopic appearance of the anterior chamber, cupping and destruction of the glaucomatous optic disc, and loss of the peripheral vision field.[3]

Angle-closure glaucoma

When the pupil's ability to enable aqueous humor to enter the anterior chamber is blocked (pupillary block), angle-closure glaucoma occurs. The anterior chamber angle is blocked as a result of the iris's anterior bulge (iris bombé), which is brought on by the increased pressure behind the iris. IOP levels can be extremely high in people with acute angle-closure glaucoma. Because primary angle-closure glaucoma frequently affects both eyes, patients who have the condition in one eye are more likely to develop it in the other.[3]

Glaucoma symptoms

Although those with acute angle-closure glaucoma experience symptoms, those with other types of glaucoma typically do not (at least in the early stages), leading to the disease frequently being untreated with potential development.[7] The Glaucoma Symptom Scale (GSS) was created to evaluate the ocular symptoms that glaucoma patients experience.[8]

Ten ocular symptoms make up the GSS, six of which are not visible and four of which are redness, tearing, light sensitivity, and eyelid twitching and the perception of something in the eye are examples of non-visual symptoms. The symptoms of the eyes include "halos surrounding lights," "blurry/dim vision," "hard to see in daylight," and "hard to see in darkness.[7]"

Glaucoma diagnosis

When the condition is moderately advanced, glaucomatous neuropathy can easily be identified. The characteristic patterns of visual-field loss that is linked with diffuse with superimposed focal rim narrowing and retinal nerve fiber layer (RNFL) loss are simple to identify.[9]

However, due to ambiguous symptoms in the ONH, RNFL, or visual field, glaucoma diagnosis in its early stages can be difficult. To consistently detect early glaucomatous visual function loss, more sensitive tests have been developed. Imaging equipment has also been developed to detect the earliest symptoms of structural damage. A diagnosis of early glaucoma may be made by the physician with the help of other diagnostic tests.[9]

History and examination

Since glaucoma tends to run in families, it is more likely to be present if there is a family history of it.[9]

Quantitative tests and the diagnostic process

These include "selected" examinations of visual functions, such as optical coherence tomography and frequency doubling technology perimetry as well as standard automated perimetry (SAP) and short-wavelength automated perimetry.[9]

SAP

For glaucoma patients, visual field testing is crucial for determining the severity of vision loss and for tracking the disease's progression.[10]

Treatment of glaucoma

Lowering IOP is the primary proven way of treating glaucoma and is the main focus of management.[11]

Medical therapies

The initial line of treatment for OAG is typically topical medicine. A variety of drops, which may be categorized into five main groups: PGs analogs, beta-blockers, diuretics, cholinergic agonists, and alpha agonists, can be used to decrease IOP.[12]

PGs analogs decreased IOP greater than beta-blockers in numerous studies while posing fewer systemic side effects.[13]

RHO kinase inhibitors are a new family of glaucoma drugs that have recently come into existence. By directly affecting the contractile tone of the trabecular meshwork, they have been demonstrated to promote trabecular outflow.[12]

Laser therapies

Some patients continue to undergo optic nerve damage while receiving the maximal amount of medical therapy, and not all patients have their IOP reduced to the desired levels by medical care. Wise and Witter introduced argon laser trabeculoplasty as a therapy option for OAG.[14]

Although the mechanism is not fully understood, it is believed to be brought on by thermal energy directed at the trabecular meshwork, which results in focal scarring and thus creates space in nearby structures or by cytokine and phagocytosis inflammation, which results in structural changes with improved outflow.[15]

Surgical therapies

More invasive incisional techniques such as trabeculectomy, GDIs, non-penetrating glaucoma surgery, and microinvasive glaucoma surgery are advised when medication and laser therapy alone are unable to manage IOP.[12]

Prevention of glaucoma

Glaucoma cannot be prevented. However, you can reduce your risk of causing eye damage if you identify it quickly. These actions could aid in preserving your vision:

- Get yearly eye examinations
- Learn about your family's past
- Comply with your doctor's recommendations.

LATANOPROST

Elevated IOP is one of the main risk factors for the onset and progression of glaucoma (IOP). Therefore, one important glaucoma therapy option is topical prostaglandins (PGs), which have a potent ocular hypotensive impact (mostly due to an increase in uveoscleral outflow).

The European Glaucoma Society has authorized PGs/prostamides as the primary glaucoma treatment.[4] The effectiveness of these medications in decreasing IOP, the absence of significant systemic adverse effects, the need for only once-daily dosing, and their generally favorable tolerability profile all played major roles in the decision.

The use of latanoprost, an ester prodrug of prostaglandin F2 (PGF2), in the treatment of glaucoma is the main topic of this article. Due to its excellent efficacy-tolerability profile, latanoprost continues to be prescribed the most frequently among the topical PGF2 analogs currently on the market for the treatment of glaucoma.

Problems associated with latanoprost delivery

Latanoprost is now available as a 0.005% (50g/mL) clear solution and the suggested dose is 1.5 g (one drop) in the afflicted eye once a day. If a dose is missed, the course of treatment should still be followed as usual. However, latanoprost's inability to dissolve in water is one of its main drawbacks. Thus, a solubilizing step must be added to the manufacturing process to increase solubility, or the concentration of the preservative employed, such as benzalkonium chloride, can be increased, but doing so can have negative side effects.[17]

Presently accessible latanoprost delivery techniques

Sterile ophthalmic solutions containing antibacterial agents

Pfizer created the 1st version of latanoprost, called Xalatan®. It was provided as an isotonic, buffered aqueous solution that was sterile, with a pH of 6.7 and an osmolality of roughly 267 mOsmol/kg. Latanoprost weighs 50 g per milliliter of Xalatan. Benzalkonium chloride, a preservative, is added at 0.02%. Sodium chloride, sodium dihydrogen phosphate monohydrate, sodium hydrogen phosphate, and water for injection are added as an excipients to maintain the pH and stability of the formulation. Bottles that have not been opened should be refrigerated at a temperature of about 50 C to protect the formulation from light. For fewer than 8 days during shipping, a bottle may be stored at 400 C. Bottles that have been opened may be kept at room temperature for up to 6 weeks at 250 C. There have been concerns raised about the use of benzalkonium chloride because of its harmful effects.[16,17]

Sterile ophthalmic solution without an antimicrobial agent

The first latanoprost formulation without preservatives to be sold was by the laboratories. Clear sterile ophthalmic drops contain

50 g of latanoprost per mL of eye drop solution, or 0.005%, at a dosage of 0.05 mL per day. To prevent contamination, they are offered in 0.2 mL polyethylene containers.[18]

Importance of Novel Delivery

One of the primary problems with eye drops is that little of the drug really penetrates the cornea and into the tissue, where some of it is lost due to the blinking reflex and nasolacrimal drainage. Moreover, medication that is not absorbed by the cornea travels down the nasolacrimal duct and into the circulation, causing adverse reactions.[19]

Because the active form of latanoprost acid is more hydrophilic and penetrates the cornea's endothelium and epithelium, its bioavailability declines.[19] Therefore, there is a critical need for innovative delivery techniques due to:

- Difficult dosage regimen
- Low drug permeability across the tissue
- Significant drug waste

NOVEL DELIVERY SYSTEM OF LATANOPROST

Latanoprost-loaded biodegradable nanosheet[20]

LBNS may be a treatment option for glaucoma because it frees patients from having to administer antiglaucoma eye drops every day. This substance is offered as a thin film and has highly distinctive proportions. In contrast to other nanomaterials, its thickness is of the nanometer order, while its width and length are of the centimeter order. If necessary, its proportions can be adjusted to any length, width, or even thickness as shown in Figure 2.[20]

They employed sodium alginate and chitosan in their investigation. A cationic polymer with advantageous biological properties is chitosan. An anionic polymer with a large application in medicine is sodium alginate. Lipophilic and hydrophilic chemicals can be loaded onto the multilayered nanosheet employing polycations and polyanions without the requirement for any chemical alterations.[20]

An adhesive treatment for the cornea is called LBNS. Latanoprost acid produced by LBNS was found in aqueous humor up to 6 days following application, according to the study.[20]

Biodegradable nanoparticles of latanoprost[21]

In light of this, the objective of this research was to develop a novel LA delivery system based on nanotechnology that was appropriate for subconjunctival injection and to evaluate its basic *in vitro* and *in vivo* features. To achieve this, the physicochemical and releasing characteristics of nanoparticles with LA encapsulated were investigated shown in Figure 3. These nanoparticles were made of biocompatible and biodegradable poly (lactide)-poly (ethylene glycol) (PLA-PEG) copolymers.[22]

The effectiveness of the suggested delivery strategy for decreasing IOP was assessed in normotensive albino rabbits following subconjunctival injection. LA-loaded nanoparticles dramatically reduced IOP, and the IOP lowering effect persisted for 8 days. In addition, during the course of the trial, IOP in the nanoparticle group was substantially lower than those in the other three study groups (free drug, NPs that are blank, and the control group).[21]

Liposomal gel of latanoprost[23]

To maintain and boost latanoprost's ocular delivery, they had created liposomal gels that were filled with the drugas shown in Figure 4. The vesicles had minimal to no agglomeration and were spherical in form. By carefully adjusting the drug/lipid and cholesterol/lipid ratios, it was possible to

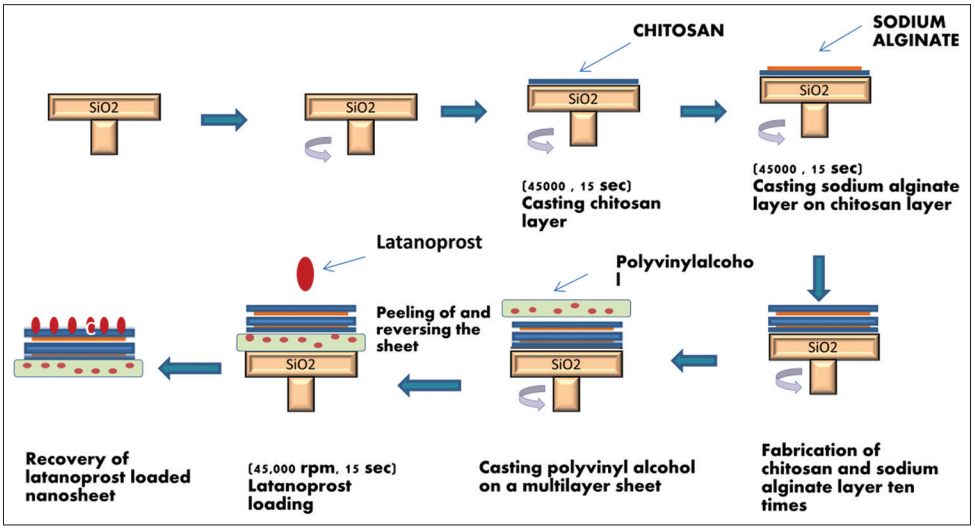

Figure 2: Scheme for creating biodegradable nanosheets that are loaded with latanoprost

regulate the drug encapsulation effectiveness and loading capacity. The effectiveness of drug encapsulation was 90%, while the drug loading capacity was 16%. The drug-loaded vesicles were incorporated into Pluornic® gels to produce a sustained drug release.

These gels' promise as an efficient ocular delivery route for latanoprost where no irritation potential was detected was confirmed by *in vivo* experiments in rabbit eyes. In addition, drug-loaded liposomal Pluornic® gels significantly outlasted commercial latanoprost eye drops by achieving extended and better IOP reduction for up to 72 h. The total treatment result and patient compliance could both be improved by these new formulations, which could lower the frequency of drug delivery.[23]

Implantation of a latanoprost-embedded disk intrascleral[23]

This work proposes a novel intrascleral implantable latanoprost-imbedded disc material for the management of glaucoma. The drug release for the disc material using the intrascleral approach has been demonstrated to be at least 84 days based on the data obtained as shown in Figure 5.

The histopathologic evaluation, which looked at the tissues from the eyes' microscopic changes, revealed no signs of aberrant edema, neovascularization, fat infiltration, necrosis, fibrosis, or inflammation [Figure 6]. These results suggest that there was no tissue toxicity in the primary eye compartments or the tissue surrounding the surgically altered area.[23]

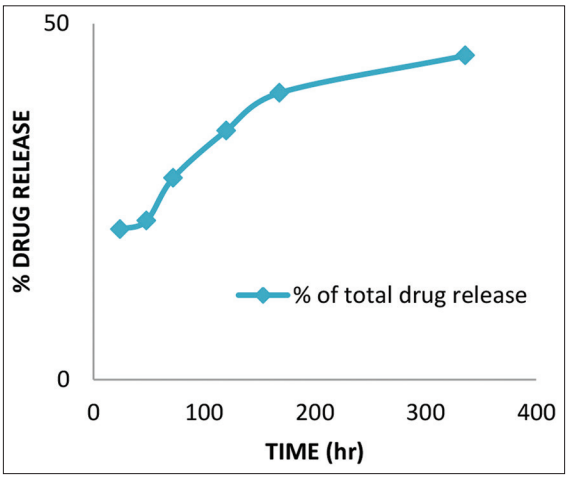

Figure 3: % of total drug release with time

In situ gel of latanoprost[24]

The *in situ* gelling technology promises to reduce administration frequency, resulting in improved patient compliance. This newly created latanoprost thermosensitive *in situ* gel may offer a minimally invasive substitute for the common glaucoma eye drop.

The *in situ* gel formulation's anti-glaucoma effectiveness was 2.9 times greater than that of an eye drop. In comparison to the conventional eye drop, which showed a gradual decline in IOP that lasted for just 3 h, it also exhibited a quick fall in IOP within 30 min of administration that lasted for 8 h. The latanoprost-loaded *in situ* gelling approach is more stable across a range of temperatures than the traditional eye drop. A minimally invasive alternative to the prevalent eye condition glaucoma may be provided by the recently developed latanoprost thermosensitive *in situ* gel.[24]

Latanoprost niosomes as a sustained release ODDS[25]

Traditional glaucoma eye drops require frequent administration, which reduces patient adherence and results in a less-than-ideal therapeutic outcome depicted in Figure 7. It was added to niosomal gels to get over these restrictions and prolong the anti-glaucoma action of latanoprost. More than 88% drug encapsulation efficiency was attained.

In vivo, certain latanoprost niosomes included in PL gel exhibited sustained drug release without irritating rabbit eyes. Furthermore, for 3 days, this gel decreased IOP in rabbits with normal blood pressure. This effect lasted considerably longer than that seen with Xalatan® eye drops, which needed to be applied multiple times every 24 h. The study's findings support the idea that latanoprost niosomal PL gel has the ability to increase patient compliance, decrease the frequency of drug administration, and extend drug release.[25]

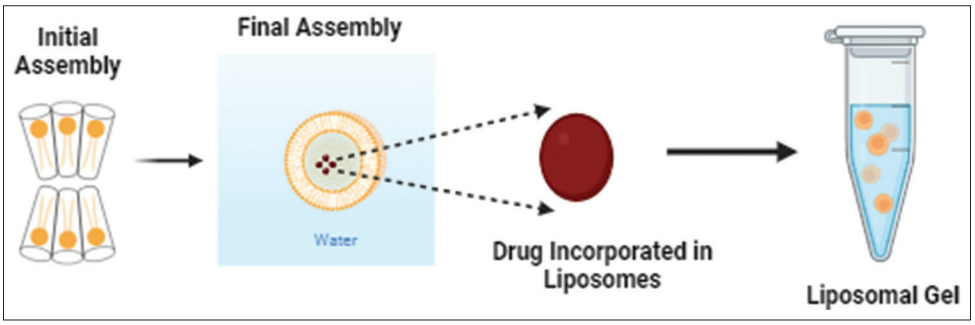

Figure 4: Liposomal gel of latanoprost

Latanoprost loaded phytantriol cubosomes[26]

The antiglaucoma medication latanoprost was produced in this study as a new drug carrier system using nanosized cubic liquid crystals (cubosomes) as shown in Figure 8. Cubosomes (CubLnp) containing phytantriol and latanoprost were created top-down. The formulations' latanoprost concentrations ranged from 0.00125% to 0.02% w/v. The average size of all cubosomes was 200 nm, the polydispersity index was 0.1, the zeta potential was approximately −25 mV, and the encapsulation effectiveness was over 90%.

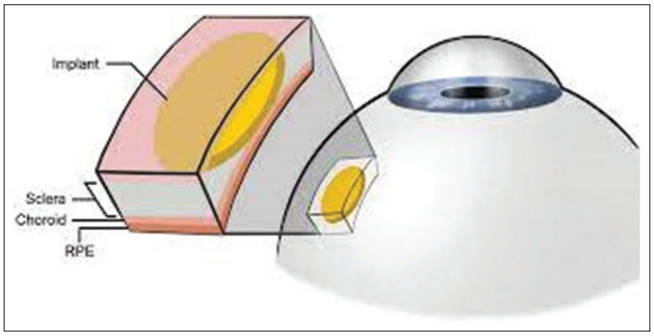

Figure 5: Latanoprost-imbedded disk implant material located in the suprascleral plane

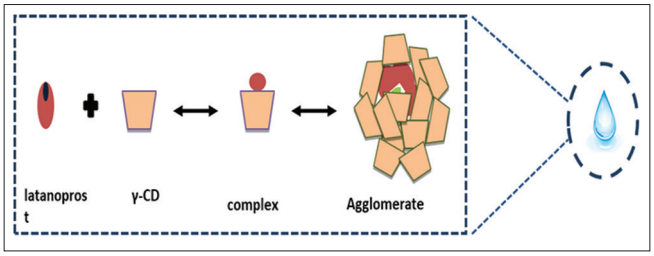

Figure 6: Improved stability of latanoprost

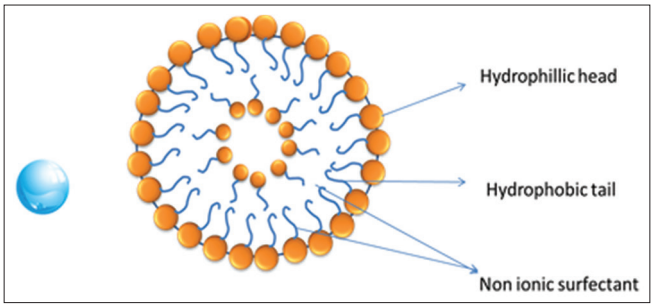

Figure 7: A typical structure of niosome

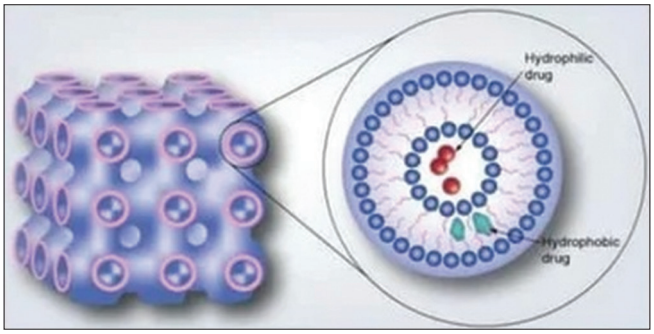

Figure 8: A typical structure of cubosomes

Latanoprost release from cubosomes remained uniform throughout time, according to *in vitro* studies, indicating a sustained release profile. The subconjunctival injection of CubLnp to normotensive rabbits was employed to evaluate the *in vivo* hypotensive intraocular impact based on this behavior. They obtained positive outcomes in contrast to a commercially available latanoprost formulation (0.005% w/v).[26]

Latanoprost-loaded cyclodextrin (CD) microaggregate suspension[27]

A naturally occurring cyclic oligosaccharide produced by bacteria when starch is digested is CD. The following three factors are the main ways that CD aggregates facilitate medication absorption in the eye: (1) The aggregates make the medication more soluble in tears. (2) Because the aggregates are sticky to the mucous membrane, they can prolong the retention of the medication on the ocular surface and allow for continuous drug release. (3) The aggregates serve as a vehicle to help the medicine penetrate the hydrophilic layer and directly contact the cornea's surface [Figure 6].

LAT/CD suspension ocular drops were successfully created in this investigation. LAT/CD suspension eye drops revealed clear sustained release characteristics, according to an *in vitro* release study. LAT/CD eye drops displayed increased cell permeability and no discernible cytotoxicity, according to an *in vitro* corneal permeation investigation. *In vivo* experiments on rabbits demonstrated that LAT/CD eye drops effectively prolonged precorneal retention and displayed better bioavailability in the anterior part of the eye when compared to commercial eye drops.[27]

Iontophoretic ocular delivery of latonoprost-loaded nanoparticles[28]

Iontophoresis is regarded as a non-invasive method of administering medication to the eye. When utilized within the proper range of electric current (5 mA), the iontophoresis approach can improve the penetration of charged medication molecules into the target eye tissues without causing permanent tissue damage.

They suggest a novel method for the iontophoretic delivery of drug-loaded nanoparticles into the eye. Their method involves applying the drug-loaded nanoparticles topically, then using skin-attached electrodes to perform non-invasive iontophoresis to allow them to penetrate the eye tissues. This prolonged drug exposure even with a single treatment because the nanoparticles remained in the eye for a longer duration and released the drug steadily during that time.[28]

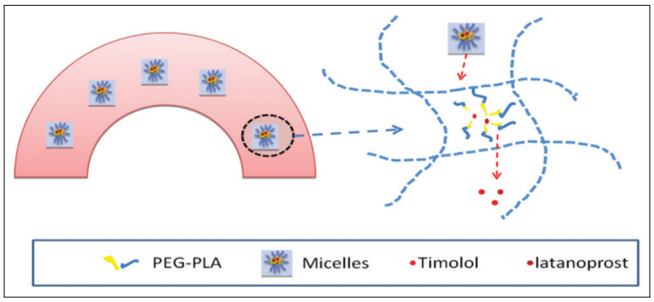

Figure 9: Drug release mechanism from micelles-laden CLs

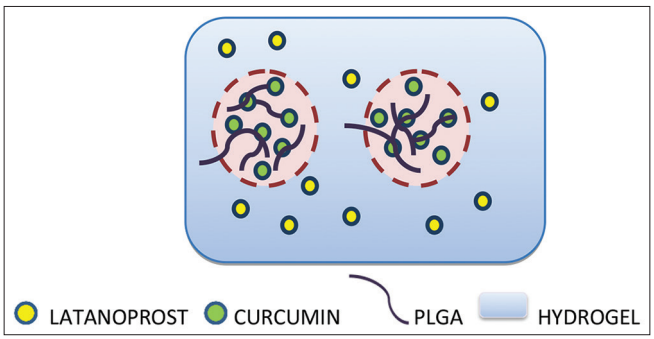

Figure 10: Latanoprost and curcumin-loaded nanoparticles

DUAL DRUG DELIVERY

Latanoprost and timolol co-delivery from micelles-laden contact lenses[29]

To promote patient compliance and accomplish the intended IOP-lowering effect, micelles-laden contact lenses (CLs-M) were developed in the current study. These lenses were designed to administer a beta-blocker (timolol) and a PGs F2 analog (latanoprost) simultaneously. Thin-film hydration was used to create the latanoprost and timolol-loaded mPEG-PLA micelles, which were then incorporated into the CLs matrix through HEMA photopolymerization [Figure 9].

Timolol and latanoprost had sustained drug release in the tear fluid for over 120 h and 96 h, respectively, according to an *in vivo* PK investigation, indicating an improvement in drug residence time and greater bioavailability of both medications administered through CLs-M10.

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Latanoprost and curcumin-loaded nanoparticle-containing thermosensitive chitosan gelatin hydrogel[30]

The study designed and characterized a dual-drug delivery system using a topical eye drop formulation of CUR-NPs and a hydrogel filled with latanoprost as shown in [Figure 10].

A mixture of chitosan and gelatin was created. An autoclave was then used to sanitize the solution. Using a 0.22 m filter, a 44.4% (w/v) glycerol 2-phosphate disodium salt hydrate (GP) solution was sterilized. The chitosan/gelatin solution was then stirred while a GP solution was added dropwise. The chitosan/gelatin/GP solution was used as a controlled release mechanism and stored at 4°C. The chitosan/gelatin/GP solution was stirred after latanoprost and CUR-NPs were added, and the mixture was then chilled in an ice-water bath for 30 minutes.

Both latanoprost and curcumin-loaded NPs released from the designed hydrogel indicated the prolong release profile for 7 days, according to *in vitro* drug release investigations.

CONCLUSION

The currently available technologies, including sterile ophthalmic solutions, have a number of limitations; hence, innovative systems, such as coated ocular films, biodegradable nanoparticles, drug-eluting contact lenses, and *in situ* intravitreal implants were briefly explored. From the aforementioned ideas, coated ocular films designed to be inserted in the eye's "cul-de-sac" have proven effective at overcoming fundamental issues such as low patient compliance and bioavailability. Furthermore, more research should be done to identify a promising candidate for a mucoadhesive polymer as well as a degrading polymer for sustained release. To give latanoprost, thin polymeric films that have been differently coated are a viable option.

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