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Trends in the Therapeutic Drug Delivery System for the Management of Glaucoma: A Review

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Abstract:- Glaucoma is the most prevalent neurodegenerative disorder of the eye. It is often called "silent thief of vision" as the symptoms gradually develop and is identified in the later stage of disease that leads to serious irreparable vision impairment. Current trends in the treatment primarily aims at reducing the IOP through pharmacological agents, laser therapy and surgery. Less invasive topical regimens are the most preferred treatment option opted by the patients. Although, these topical therapies are highly preferred and efficacious the downsides of this traditional method involves poor patient compliance and low adherence to prescription. Novel ocular drug delivery platforms offer targeted drug delivery in addition to good therapeutic potential and is independent of patient administration. The role of the innovative drug delivery systems available should be emphasized. This review aims to highlight the recent trends and challenges in ocular drug delivery systems that are commercially available today and to be approved in the future overcoming the limitations of the customary traditional method. Multiple research works have shown sustained drug delivery system that are non-invasive, provide better patient compliance and can benefit the patient and physician alike.

Keywords:- *Glaucoma, Targeted Drug Delivery, Sustained Release, Compliance, Adherence.*

I. INTRODUCTION

Glaucoma is a disorder of the eye that causes significant damage to the optic nerve resulting in vision loss and bilateral blindness, predicted to affect 111.1 million of population by 2040(1). It is the primary cause of irreparable loss of vision globally. The patient clinically presents with raised ocular pressures that leads to optic neuropathy , giving rise to visual field loss(2) .The recent studies have concluded that the bilateral blindness in 9% of patients and unilateral blindness in 27% of the patients within the first 20 years of glaucomatous changes are precipitated by primary open angle glaucoma (POAG)(3). Evidences from randomised trials have depicted that reducing the IOP is effective in reduction in progression of disease and loss of vision, which has to be the main aim of the treatment in this condition(4). In general, the visual damage to the eyes in glaucoma is manifested as progressive and irreversible. Nevertheless, the progression of the visual field loss can be reduced by attaining the target intraocular pressure (IOP) within the normal range by using topical anti-glaucoma drugs. However, despite the readily available treatment options and well timed diagnosis of the condition, to manage the slowing down of the progression of vision loss has still been a challenge to the clinicians. The treatment options that are currently available involve medical therapy that includes both oral medications and topical drugs and is often considered as the first line treatment option. Other treatment options include filtering surgery, laser therapy and minimally invasive glaucoma surgery (MIGS)recent studies have pointed out that the factors such as rapid turnover of lacrimal secretion, increased nasolacrimal drainage, fast blinking reflex and human adherence factors such as poor compliance and persistence, lack of patient education on the timing, duration, effect of the pharmacotherapy, extent of the irreparable vision loss, complex dose regimens added to drug efficacy factors are the limitations contributing to the therapy(5-9). Various prevalence studies and interviews record that conditions like memory impairment, forgetfulness and mental issues of several other concerns like Alzheimer's are multiple other reasons that are accountable for decreased adherence to medical therapy as the condition is dependant on age. (10)Furthermore, the prevalence studies conducted on a sample of 41 adults with glaucoma along with other conditions such as depression, anxiety, cognitive impairment who are above 50 years of age concluded that 44% of the sample studied had impaired cognition. The studied also depicted that non compliance can also arise due to inability of the patient to instil the medicament into the eyes, specifically this can be noted in patients with arthritis(11). A survey done by Sleath et al on glaucoma patients revealed that 41% of the patients could not afford for the ocular hypotensive medications prescribed. Therefore, improper medication adherence can also be contributed by financial factors that can be a hindrance to life long treatment(12).

The recent advancements in the novel drug delivery systems are aimed at improving patient compliance and increased medication adherence with the aim of managing ocular hypertension and further preventing blindness.

This review is aimed at discussing the different novel drug delivery systems that are available currently and the techniques that are in different stages of development.

Ocular inserts

Ocular inserts are a significant advancement in the ocular drug delivery systems. They are multi-layered, drug-impregnated sterile devices that are placed in the conjunctival sac. They contain a polymeric support where

the drug is incorporated as a dispersion or solution and the drug is released over a prolonged duration. They can be classified into insoluble, soluble or bio erodible based on the chemical and physical properties(13).

Pilocarpine Ocular inserts

The usage of a synthetic bio soluble matrix in the conjunctival sac was demonstrated in 1976 by Bensinger and colleagues. This was performed to increase the corneal tear film for IOP. At 32 hours post insertion , the IOP was recorded for different doses extending from 0.5-2 mg and a considerable reduction in IOP was seen. The Pilocarpine inserts that were loaded with 1mg Pilocarpine showed a considerable decrease in the IOP at 32 hours of placement Whereas, on placement of 0.5 mg Pilocarpine insert, a decrease of 6.25+/-2.48 mmHg was seen and at a higher dose of 1.5mg Pilocarpine insert, the IOP reduced by 8.14+/-0.96 mmHg 5 hours after placement(14-15).

Soluble ophthalmic drug inserts

Soluble ophthalmic drug inserts (SODI) are ocular inserts that constitutes a copolymer of polyacrylamide, ethyl acrylate and vinyl pyrrolidone and are generally ovally shaped(16).The drug insert after 10-15 seconds of contact with the tear film softens and transforms into a viscous polymer. Further, within 60-90 minutes of administration, it gets converted into a polymer solution. The drug gets released by dissolution due to changes in the state of the SODI on insertion in the conjunctival sac. As per reports from the recent studies, it could be a beneficial once a day treatment for glaucoma because SODI loaded with 2.7mg pilocarpine showed the same effect as 4-12 eye drop instillations or 3-6 ointment applications (17).

Ocuserts

They are ocular inserts developed by Armaly and Rao. Ocuserts are one of the earliest models that provides a constant rate of drug release of 20 or 40 µg/ hr for a time duration of 7 days. They can be inserted in the upper or lower cul-de-sac and weekly replacement of the insert is required. The polymer membrane system was loaded with pilocarpine that has an inner layer of pilocarpine in alginate gel between two layers of ethylene-vinyl acetate (EVA). This setup causes the release of drug at a constant rate. The pilocarpine released from the ocusert show targeted drug delivery and acts at specific sites such as iris, ciliary body and trabecular network. Zimmerman and colleagues used ocuserts in 40 patients for the pilocarpine delivery at the rate of 20 µg/hr. The mean IOP was recorded to be 25.6+/-5.6 mmHg. The IOP decreased by 19.9+/-3.9 mmHg with the usage of pilocarpine loaded ocusert. The study also reported that the ocusert system was found to be more favourable than the pilocarpine drops, and no side effects from the usage of ocusert were noted(18). Another study that reported the side effects of ocuserts to be minimal was done by Pavan-Langstan and team with group of 29 patients. The pilocarpine loaded ocuserts was designed to release drug at either 20 or 40µg /hr and a fine control of the IOP was recorded(19). However, in spite of the positive result from the clinical studies, ocuserts are still not preferred choice of drug delivery due to certain limitations such as irritation at the site of insertion, ejection of the device from the eye, difficulty to insert the device in the eye. (20)

Collagen Shields

The collagen shields were initially used as a postoperative corneal bandage(21). The drug delivery model for the collagen shields was developed by Bloomfield and colleagues. Wafer-shaped collagen inserts infused with gentamicin was inserted into the rabbits eye. A higher level of gentamicin in the tear film and tissues were found when compared to the dosage forms such as eye drops, ointment or subconjuctival injections(21). In this system of drug delivery, hydrophilic drugs are loaded in the collagen matrix. A dry shield is soaked in the aqueous solution of the drug. The hydrophobic drugs are directly added to the shield during the manufacturing process(22). The recent study of collagen shields undergoing animal trials by Agban and group is the cross-linked collagen shields consisting of nanoparticles, titanium oxide (TiO2), Zinc oxide (ZnO), and polyvinylpyrrolidone (PVP) capped zinc oxide (ZnO/PVP). They are designed for providing a controlled delivery of pilocarpine hydrochloride over a prolonged duration in glaucoma patients. The report from the study group showed that pilocarpine hydrochloride when cross linked with ZnO/PVP nanoparticles exhibited a sustained release for a period of two weeks(23).

Ocufit SR

This device is designed for controlled release of drug over a long period of time. It is a flexible rod shaped silicon device that has been designed for holding the medicament in the conjunctiva for a long time. There are different models available that vary between 25 and 30 mm in length and a maximum of 1.9mm in diameter(24). This device was found to have more favourable properties like sustained release and increased duration of retention in the eye. It was reported that these placebo devices retained for a duration of two weeks when inserted in the upper fornix in more than 70% of the study sample(24).

Mini-disc

The mini discs, also known as Ocular Therapeutic System (OTS) is a miniature contact lens developed by Bawa and Colleagues. It is a polymer that constitutes hydroxyethyl methacrylate and ethylene glycol methacrylate. The size and shape of the mini disc is such that it enables the easy instillation of the device in the upper or lower eyelid, without any impact on the eyes. It has a diameter of 4-5mm with a concave and convex face. The concave is such that it is conformed to the sclera of the eye. It does not exhibit any irritation to the eye such as deformity in vision, reduced permeability of oxygen, and foreign body sensation(25).

New Ophthalmic Delivery Systems

New ophthalmic Delivery System(NODS) are manufactured water soluble films such as polyvinyl alcohol (PVA) film and are placed at the lower conjunctival sac for delivering precise amounts of drug and has a radiolabelled flag that is loaded with pilocarpine nitrate. The pilocarpine NODS showed eight times better precorneal bioavailability

and higher compliance when compared to 2% w/v pilocarpine nitrate solution(26).

Punctal Plugs

They are drug delivery system that are currently used to treat post-operative inflammation and can be a beneficial option in the drug delivery for glaucoma. They usually function by reducing tear drainage and increasing the amount of tears on the ocular surface by blocking the punctum and canaliculus. They can also be used by infusing the plug with a medicament that will be gradually released over a specific time period. Dexamethasone at a dose of 0.5mg is a hydrogel intracanalicular plug and is currently used for the treatment of pain and post operative inflammation (27). This system was found to be more favourable and preferred over topical therapy(28). They cats as sustained release drug delivery platform for the therapy of glaucoma. The recent development is the punctal plug delivery system(PPDS) that uses a L-shaped plug with a latanoprost core that is non biodegradable and is instilled at the slit lamp (29). The L-PPDs showed adverse events such as mild tearing and discomfort that are often also associated with the commercial punctal plug designs. Travoprost, a prostaglandin analogue was also incorporated with a punctal plug delivery device. These punctal plugs constitutes a hydrogel rod which can swell thereby fills the canalicular space and gradually releases the travoprost from the microsphere matrix (30). In the recent times punctal plug systems are used in the treatment of a wide variety of ocular conditions. This method of drug delivery systems have certain disadvantages such as localized pain at the site of instillation, sensation of foreign particles, retention in the tear film. Although it is a non-invasive and flexible approach certain complications such as infection of the lacrimal drainage system, ocular irritation have been reported.

Therapeutic Contact lenses

The development of contact lenses have become a beneficial alternative compared to the topical administration of the medicament due to their site-specific action. Moreover, it has a wide range of application to patients for vision correction. In a study that was conducted to evaluate the reception of the sustained release preparation, it was noted that 56% of the patients accepted the usage of contact lenses from a sample size of 150 patients(31). This makes them an ideal drug delivery due to easy availability and the ease of administration. They provide more than 50% bioavailability compared to the eye drop formulations due to property such as extended wear. Hence, they can provide regulated and sustained ocular drug delivery (32,33). There are water soluble polymeric hydrogels that are cross linked to form network called as soft contact lenses. The water soluble drugs such as timolol and dorzolamide can elute rapidly through the hydrated polymer networks. Regardless of this, they are a widely used drug delivery system(34). In 1974, the delivery of antiglaucoma drugs through soft contact lenses was demonstrated by Hillman. It was performed by using a polymer of vinyl pyrrollidone that was soaked in 1% pilocarpine. At the end of the study, he concluded the soft contact lenses to be as beneficial as the topical administration of 4% pilocarpine eye drops(35). The recent developments in this drug delivery system has enabled improved sustained drug release and monitoring of IOP. The usage and testing of drug eluting contact lenses was done almost 50 years ago but their usefulness was restricted by the rate of drug delivery(36).

Vitamin E loaded contact lenses.

The method of using Vitamin E as a transport barrier for timolol was developed by the study performed by Chauhan and team. During the course of the study, it was found that by increasing the loading concentration of Vitamin E from 10%-40% in the lenses, there was a notable increase in the rate of drug release (37). The rate of timolol increased by a factor of 5 and 400 which is a quadratic increase in drug release with the loading of 10% and 40% Vitamin E. Even so, the loading of Vitamin E in the lenses caused increase in size of the lens, reduced diffusion of oxygen, and ion permeability was also found to be reduced(37).

Film impregnation in contact lenses.

They are latanoprost eluting contact lenses for the drug delivery in glaucoma. They are manufactured by enclosing the drug film in a methafilion lenses. When the experiment was performed on glaucomatous monkeys, they showed sustained release for a duration of one month. The amount of drug present in the monkeys eye was more than that could be delivered by topical drops. These contact lenses are made with a polymer drug film that is 40-45mm thickness. On administration, there was an initial burst of latanoprost in aqueous humour and thereby achieving a steady concentration. The concentration achieved was similar to the average steady state concentration of any commercially latanoprost solution. It was reported that there was a reduction in the mean IOP at ranges of 2.9+/-1.0 to 6.6+/-1.3mmHg with topical latanoprost, 4.0+/-1.1 to 7.8+/-3.8mmHg in 97g contact lenses. From the study it was concluded that the latanoprost eluting contact lens was as effective as topical eye drops and there was a steady lowering of the IOP(38).

Enzyme-triggered timolol release

This system of contact lens was designed by Kim and team and constitutes of implanting Nano diamonds (NDs) with timolol. The ND-Nano gel embedded in the lens function to bring about enzyme trigger that causes the release of timolol. The sustained drug release is caused by the chitosan degradation from the activation of the lysozyme. The steady drug release at 24Hr of administration was found to be 9.41 µg. However, this method has reported certain limitations that restrict its clinical applications are decreased oxygen permeability, protein adherence, infection at the site of application(39).

Intraocular implants

This drug delivery system has been designed to release the medicament over a prolonged duration of time. Although implants a feasible option in the treatment for long-term drug delivery, they are not a commending option, due to the surgical procedures involved during the process.

OZURDEX, produced by Allergan is an intravitreal implant that constitutes degradable dexamethasone, has been used for the therapy of certain conditions like macular edema and non infectious uveitis. After implantation, the device degrades itself while delivering the medicament(dexamethasone). Currently, studies are conducted for the management of atrophy due to macular degeneration associated with age, by designing implants loaded with brimonidone tartarate in polylactic co-glycolic acid (PLGA) intravitreal polymer matrix. At present, they are used for its neuroprotective effect and reducing the IOP. These NOVADUR PLGA system is a beneficial option in the management of glaucoma when approved(40).

Microelectromechanical system

The micromechanical system (MEMS) is designed to mechanically push the drug from the reservoir by bubble generation that occurs on electrolysis. The drug can be filled as per the needs any number of times. This system allows the ophthalmologists for easy administration of the medicament into the eyes without any surgical procedures. The system is primarily based on electrolysis. It is connected to a check valve and drug refill port to monitor the rate of drug delivery. This MEMS pumping mechanism was elucidated by Saati and team. A major advantage is that a single instillation of the drug notably lasts for a duration of 3-4 months. The rate of drug release can be controlled by the rate if electrolysis. With certain alterations, this system can also be used to deliver multiple drugs in the intravitreal delivery. The MEMS system can be a good possible option of drug delivery and the only associated drawback is the invasive procedures for instilling the device into the eye that can be linked to certain long and short term risks and complications(41).

Liposomes

The liposomes are vesicular lipid systems that are neutrally charged. They form encapsulated complex with the lipophilic drug and is delivered as an eye drop solution. In order to avail better permeability and enhanced residence time of the drug they can be injected subconjuctivally. Experiments done by Natarajan and group used latanoprost-loaded egg-phosphatidylcholine liposomes for delivery. In storage at 4°C, the liposomes were stable for a time period of 6 months, and at 25°C they were found to be stable for a duration of 1 month. In about 60% of the subjects, a slow and sustained release of latanoprost was reached by 2 weeks *in vitro*. Compared with the daily instillation of topical latanoprost(25+/-0.9mmHg) a noticeable sustained IOP lowering was observed in liposome treated animals(4.8+/-1.5mmHg) for a duration of more than 3 months(42)(43). Further, for delivering pilocarpine Monem and team used multilamellar vesicles (MLVs) as vehicle. It was reported from their experiment that increased efficacy in reduction of IOP was exhibited by MLVs encapsulating pilocarpine HCl. It was also reported that a considerably shorter duration of drug action was exhibited by negatively charged MLVs encapsulating pilocarpine HCl and free pilocarpine HCl. Further the team also theorized that in humans the frequency lf drug instillation would turn down to half with utilizing the MLV vehicle and thereby achieve increased patient compliance(44).

Polymeric nanoparticles

Nanoparticles are particles having very small molecular size. This can benefit in efficient drug delivery to the anterior as well as posterior chamber through the body fluid-blood(aqueous and retina barrier)(45). On the basis of the origin of monomers, they are classified into various types. Electrospraying and electrospinning methods that are used for packing the drug in the nanoparticles should be given importance. An *in vitro* study was conducted by Mehta and team that used a single-needle electrohydrodynamic process for inserting a stable nanocoating to the contact lens with timolol maleate. The study reported the biphasic release of drug, initially there was rapid release that was gradually followed by sustained release (46).

Chitosan-based polymeric nanoparticles

Chitosan is a 2-amino-2-deoxy-beta-D-glucan, it is being broadly tested for the manufacture of nanoparticles for drug delivery. They are an appropriate choice for the delivery of antiglaucoma drugs due to the biocompatible, biodegradable and mucoadhesive properties of chitosan(47). Chitosan nanoparticles that are loaded with a beta-adrenergic agent like betaxolol, that has been prescribed for lowering the IOP has been developed by Li and group. As per the data published from the reports, there was 1.75 times higher value compared to the topical eye drops(48). Nanoparticles from glycosylated polymer are loaded with timolol maleate for ocular drug delivery have been developed by Zhao and team. Due to high lipid solubility, an increased transcorneal penetration was reported(49). Mehta and team adopted the technique of electrohydrodynamic atomization of timolol maleate-loaded PVP and poly(N-isopropylacrylamide). This methodology was used by the researchers for the sustained release of timolol maleate using the combination of chitosan and borneol. It was concluded from the experiments that it showed biphasic and triphasic release and was dependent on the composition (50).

Gelatin nanoparticles

Gelatin is an easily available and highly biocompatible substance. Hence, they can be used as a polymeric vehicle for the delivery of antiglaucoma drugs to the eye. In a study done by Shokry and team, it was found that there was increased mucoadhesion and transcorneal permeability when the gelatin nanoparticles where used for the release of timolol maleate. This is due to the attraction of the positively charged particles to the negatively charged lipid layer in the cornea (51). The *in vivo* studies that was performed in the albino rabbits reported a sustained lowering of IOP over a prolonged duration of time. Also, the *in vitro* studies showed a rapid secretion of timolol initially followed by a sustained release over a prolonged duration of time. In another study that was performed by Liao and group, they used mesoporous nanoparticles that were silica-based for pilocarpine delivery with a coating of gelatin. The *in vivo* IOP lowering was efficacious for a duration of 21 days. Whereas, the *in vitro* studies done with the gelatin-

coated mesoporous nanoparticles showed a sustained release for a duration of 36 days (52).

Propoxylated glyceryl triacylate nanoparticles

This contact lens system was developed by Jung and team by diffusing the lens with timolol-loaded propoxylated glyceryl triacylate (PGT) nanoparticles. At room temperature, the initial timolol PGT particles released the drug for a long duration of more than 30 days. This release of drug is caused by the constant hydrolysis of the ester bond. The bioavailability of this drug delivery system was found to be 50% in contrast to the eye drops which has only 1-2% of bioavailability. There was a significantly reduction in the IOP for a duration of almost 5 days. One of the major drawback of this system of drug delivery is that ion and oxygen permeability was significantly reduced (53).

Nanospheres/Microspheres

The release of the medicament into the eye by the microsphere system is dependant on factors such as size, charge and surface chemistry of the nanoparticle system (54). The framework of this system includes a diblock copolymer, which is a hydrophobic block [Polycaprolactone (PCL)] and hydrophilic component[Polyethylene glycol(PEG)]. This framework of nanosphere system causes elevated duration of the drug on the corneal surface and thereby fusion of the drug with a carrier on the corneal epithelial membrane. This mechanism is beneficial for reducing the dosage frequency(55). Chiang and team performed experiments in normotensive rabbits eye and noted a significant reduction in IOP for 1 month by 66mmHg with the usage of brimonidine polylactic acid(PLA) microspheres. The *in vitro* analysis of this system reported a sustained release of the drug for a duration of 35 days(56).

Injectable systems

They are passive drug delivery systems that provide target specific release of the medicament over an extended period of time. This method is a minimally invasive procedure and are implanted at the target site preferably by an ophthalmologist. These injectable systems can provide a prolonged duration delivery approximately for about a month by using the polymer delivery vehicle. There are degradable as well as non-degradable polymers that can be used in injectables for the delivery of drug into the eye(57). Degradable PLGAs are most often preferred for this system whereas, non-degradable polymers such as ethylene-co-vinyl acetate can trigger an immune response due to the presence of a foreign agent over an extended duration(58). The rate of distribution of the medicament from the injectable is variable. There is an initial rapid release of the drug causing an upsurge in the release. A limitation that is associated with this system is the poor interaction of the hydrophilic drugs with the degradable polymers since they are hydrophobic in nature. Hence, the efficacy of the system can be compromised(59).

Graybug

Graybug is a microparticle formulation in which the drug is encapsulated. This system can provide lowering of IOP and is administered by a physician using a subconjuctival injection at a time gap of 3-6 months. GB-203 is a molecular agent that undergoes hydrolysis and gets converted into two active forms. The first active form significantly lowers the IOP and the second active form aids in neuroprotection(60).

Microneedles

Microneedles are individual or arrays of micrometre-sized needles manufactured using metals or polymers. The dimension of the needles makes them the instillation of this system less invasive and can also provide more site specific drug delivery. Jiang and team used this method for the delivery of pilocarpine into the anterior chamber through the intrascleral route, using 500-750 µm stainless steel micro needles. At the end of the study, there was 45 times increase in the absorption of drug in contrast to the conventional eye drops(61).

II. CONCLUSION

In the treatment of glaucoma, factors such as patient adherence, patient compliance and regular follow up of the therapy have a huge impact on the effective management of this condition. Numerous research works and studies that are conducted on the various innovative methods of ocular drug delivery have reported a significant lowering of IOP and neuroprotection. The topical method of drug delivery which is less invasive, is still the preferred choice of treatment by the patients. This traditional method of drug delivery has certain limitations such as increased systemic absorption , less patient compliance and adherence, inadequate bioavailability, first pass metabolism. Hence, additional studies should be done with patient and provider perspective for the adoption of these innovative systems.

This review was done to emphasize the recent trends and challenges in developing an effective drug delivery system in the management of glaucoma. Some of the devices mentioned are still in various stages of development. Therefore, they cannot be widely generalizable. The impact of these methods can only be determined by large scale human based studies to understand the best fitting therapeutic option. There is a high prevalence of ocular surface disease in patients instilling the commercially available antiglaucoma drugs with added preservatives. These innovative drug delivery systems could overcome these challenges faced.

As the studies and developments continue to evolve, additional therapeutic options that could benefit the patient and provide a better quality of life can be implemented.

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