Review Article

Advances in Ocular Drug Delivery System for Glaucoma Management – A Comprehensive Review

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ABSTRACT

In today's world delivery of ophthalmic drugs remains challenging despite easy accessibility via the ocular surface. Eye drops are easy and most widely used for drug delivery for treating ocular infections, particularly involving the internal segment having an additional benefit of avoiding first-pass metabolism there while passing through the systemic circulation. The challenges of drug administration through traditional methods involve improper patient education for drug installation techniques, compliance, adherence, and persistence. Different dynam ic and static ocular barriers involved only permit limited drug delivery to the target ocular tissues. In this review, we described the development of welltolerated drug delivery systems that helps to overcome the factors limiting adequate drug delivery t o the glaucomatous patients targeting infected tissues with traditional techniques.

Keywords: Drug delivery, Glaucomatous, Neuroprotection, Ocular surfaces, ophthalmic drugs

It is known that glaucoma is the second most common cause of blindness in the world. Patients with glaucoma present with high ocular pressures that can cause optic neuropathy precipitating in the corresponding visual field loss [1]. Recent studies showed there were about 60 million people having optic neuropathy secondary to glaucoma globally [2]. These studies have shown that primary openangle glaucoma (POAG) leads to bilateral blindness in 9% of patients and unilateral blindness in 27% of patients, within 20 years of the first glaucomatous changes [3]. During 2010, an estimated 4.5 and 3.9 million people were diagnosed with bilateral blindness due to open-angle glaucoma (OAG) and angle-closure glaucoma (ACG), respectively. The number increased to 5.9 and 5.3 million in the year 2020 of bilaterally blind people due to OAG and ACG [2].

Glaucoma is progressive and irreversible due to which visual field loss; however, attaining the normal range of the target intraocular pressure (IOP) within alleviates the progression of visual field loss. The initial management strategy for 'high-risk' glaucoma suspect or a patient diagnosed with OAG using topical anti-glaucoma drugs and lowering the IOP. Glaucoma is a slowly progressive pathology that can result in the loss of peripheral vision, decreased contrast sensitivity, and loss of visual acuity. Due to the asymptomatic nature of the early phases of the disease most patients experience undiagnosed loss of vision until the advanced stages of the disease have occurred. Thus the disease is known as the "silent thief of sight". This indolent optic neuropathy is characterized structurally by a loss of retinal ganglion cells and optic nerve axons. Glaucoma is the second leading cause of the world's blindness with nearly 70 million cases worldwide and accounting for 12% of all cases of preventable blindness. It is estimated that by 2020, close to 4 million Americans will have glaucoma with 50% undiagnosed and approximately 120,000 individuals developing blindness [4].In developing countries, where the access to adequate care and therapies is limited, people are going blind from a disease that can be successfully treated. Patients in these countries may not have the ability to get to their clinics routinely for refills and exams.

However, even in the US with ready access to medical care and pharmaceuticals, glaucoma continues to progress in many patients. Often poor IOP control is due to poor compliance and adherence to daily topical treatment regimens or inadequate, complex dosing regimens. Despite effective monotherapy agents, data has shown that upwards of 40% of OAG patients require combination therapy for IOP reduction with close to 75% of glaucoma patients requiring adjunctive therapy after five years. The complexity, cost, and administration issues with multiple medications further reduce patient compliance and adherence. Prescribing pharmacy claims data show the vast majority of patients do not take their

topical medications or renew their prescriptions, resulting in patients regularly missing doses. Retrospective population-based data suggests a minority of patients consistently adhere to their topical medication. A sustained mode of delivery where the patient's dependence on daily self-instillation is eliminated could dramatically improve these statistics [8]. Various studies have highlighted the shortcomings of treatment regimens, drug efficacy factors causing short precorneal residence time, reduced absorption, and rapid turnover of lacrimal fluid, extensive nasolacrimal drainage, rapid blinking reflex, human factors compliance, and persistence [5-7].

METHODS

For this review article we searched different electronic databases such as PubMed, Google Scholar. Studies were included from 1975 to 2020 available in the English language only.

Ocular Inserts- For the release of therapeutic drugs over a prolonged duration ocular inserts are sterile drugimpregnated microdevices placed in or around the eye. Based on their physical and chemical properties, the inserts are classified into insoluble, soluble, or bioerodible [9]. The contact time of the drug to a few days increased the ocular surface after insertion, thereby increasing manifold bioavailability due to reduce washout by tears.

Pilocarpine Ocular Inserts- In 1976, Bensinger *et al.* demonstrated the use of a synthetic biosoluble matrix in the conjunctival cul-de-sac to increase the contact time of pilocarpine with the corneal tear film for intraocular pressure (IOP) control. Different doses ranging from 0.5 to 2 mg, 32 h post-insertion recorded with a significant reduction in the IOP [10]. The IOP had the maximum lowering of 6.25 ± 2.48 mmHg on the placement of 0.5 mg pilocarpine inset. While, a higher dose of 1.5 mg pilocarpine reduced the IOP by 8.14 ± 0.96, 5 h post-placement. A significant reduction in the IOP was noted at 32 hours after insertion of the 1 mg pilocarpine.

Soluble Ophthalmic Drug Inserts- As the soluble ocular drug insert (SODI) is an oval-shaped ocular insert made up of a copolymer of polyacrylamide, ethyl acrylate, and vinylpyrrolidone. Maichuk [11] first reported and used to administer drugs including pilocarpine through the inferior cul-de-sac. The drug insert converts into a viscous polymer solution after 10 to 15-sec contact with the tear film followed by conversion to a polymer solution within 60–90 min of administration.

Ocusert- Ocusert was one of the earliest models of ocular inserts developed by Armaly and Rao [12], made commercially available by Alza Corporation Inc. Ocusert releases the drug at a constant rate of 20 or 40 µg/h for an extended period of 7 days. Pilocarpine was loaded in a polymer membrane system consisting of an inner layer of pilocarpine in alginate gel di-(Ethylhexyl) phthalate for a release enhancer sandwiched between two outer layers of ethylene-vinyl acetate (EVA) designed to release the drug at a predetermined constant rate. Zimmerman *et al.* studied Pilocarpine delivery in 40 patients for Ocusert with a target release rate of 20 µg/h. Initially, the mean IOP was recorded to be 25.6 ± 5.6 mmHg. IOP was reduced to 19.9 ± 3.9 mmHg by using pilocarpine-loaded Ocusert. The study reported that the patients do not prefer the pilocarpine drops over the Ocusert system. No side effects from the Ocusert were noted [13]. Pavan-Langston *et al.* studied 29 patients who showed that pilocarpine-loaded Ocuserts releasing either 20 or 40 µg/h of pilocarpine a satisfactory control of the IOP. The Ocuserts side effects were minimal or absent [14]. Ocusert did not become a widely accepted method of drug delivery, although the clinical studies showed positive outcomes. This is because of the difficulty of device insertion, failure in satisfactorily controlling IOP in many patients, ejection of the device from the eye, irritation during insertion, and the difficulty of device insertion [15].

Poly (Vinyl Methyl Ether-Maleic Anhydride) Anhydride (PVMMA) Ocular Inserts- PVMMA and its alkyl monoesters are bioerodible polymers used for controlled timolol release in animals. The systemic effect of timolol is reduced by the polymer-assisted drug release. Finne *et al.* [16] found a lower steady-state concentration (1.0 ± 0.1 ng/ml) in plasma three hours after administration and a peak concentration of timolol in tear fluid (64 ± 9 µg/ml). They also reported a 1.6-fold increase in timolol concentration in tears (104 ± 8 µg/ml) on the addition of disodium phosphate as a buffer.

Collagen shield- Collagen shields as postoperative corneal bandages developed by Dr. Svyatoslav Fyodorov [17]. Bloomfield *et al.* developed the drug delivery model for the collagen shields. A higher level of gentamicin in the tear film, tissues in rabbit eyes using wafer-shaped collagen inserts impregnated with gentamicin as compared with ointment, eye drops, and subconjunctival injection demostrated by Bloomfield *et al.* [18]. Collagen shields, were loaded with hydrophilic drugs in the collagen matrix by soaking a dry shield in the aqueous solution of the drug. The water-insoluble drugs are directly added to the shield during the manufacturing process. Agban *et al.* [19] developed cross-linked collagen shields consisting of nanoparticles of titanium dioxide (TiO2), zinc oxide (ZnO), polyvinyl pyrrolidone (PVP), and capped zinc oxide (ZnO/PVP) for controlled delivery of pilocarpine hydrochloride in glaucoma patients over a prolonged duration that undergoing animal trials. The results from the group show a sustained release of pilocarpine hydrochloride when cross-linked with ZnO/PVP nanoparticles for 14 days.

Ocufit SR- Developed by Escalon Ophthalmics Inc. is a flexible rod-shaped silicon elastomer device designed for

retention in the conjunctival fornix for controlled release of drugs over long periods. The different models are a maximum of 1.9 mm in diameter and range between 25 and 30 mm in length. Katz and Blackman [20] later reported that expulsion of rod-shaped devices was significantly less frequent than that of oval, flat inserts. The insoluble Ocufit had favorable properties of both long retention and sustained drug release. In 70% of the cases, the upper fornix placebo device was retained for two weeks or more.

Minidisc- Bawa *et al.* [21] developed the Minidisc or Ocular Therapeutic System (OTS) the miniature contact lens with a diameter of 4–5 mm with a convex and a concave face latter conforming substantially to the sclera of the eye. The minidisc is a polymer of hydroxyethyl methacrylate and ethylene glycol methacrylate. The size and shape of the OTS allow easy placement of the device under either upper or lower lid without any foreign body sensation, distortion in vision, or decreased oxygen permeability.

New Ophthalmic Delivery System (NODS) - NODS is used for delivering drugs in precise amounts to the eye through the lower conjunctival sac using a water-soluble film loaded with the drug [22]. The device consists of 20µm-thick, 4 × 6 mm2 medicated flag, attached to a 0.7-mmlong paper-covered handle and a 3- to the 4-µm-thick membrane. NODS is manufactured using water-soluble polyvinyl alcohol (PVA). Greaves *et al.* [23] used radiolabeled NODS loaded with pilocarpine nitrate to evaluate the pharmacokinetics and bioavailability in human subjects.

Topical bimatoprost ocular insert- A bimatoprost-loaded insert consisting of a silicone matrix with a polypropylene backbone for sustained delivery to treat glaucoma underwent randomized phase II clinical trial [24]. The diameter of the insert ranged from 24 to 29 mm and was placed between the upper and lower fornices. The bimatoprost ocular insert elutes the drug at a variable rate for six months, depending on the polymer-drug matrix properties. In 2016, De Souza and colleagues developed an ocular insert with mucoadhesive properties developed from polymers of chitosan. The data from the in vitro studies showed sustained release of brimonidine tartrate. Moreover, the authors highlighted the adherent properties of the chitosan-based polymer on the conjunctiva. They also confirmed the rate of constant release for a prolonged period of 30 days without an initial burst. The insert had biocompatibility with the surrounding ocular tissues [25]. Patient education continues to be a significant challenge when it comes to the successful use of the inserts as it requires fine manual techniques to manipulate and place the insert. It was seen that the level of education and age continue to be the factors that govern the success of these devices when used for glaucoma [26]. Hitoshi *et al.* studied the efficacy of ophthalmic inserts of timolol based on poly (2-hydroxypropyl methacrylate) and poly (2-hydroxyethyl methacrylate) polymers. The results from the study indicated that the prepared inserts resulted in a controlled release and an improved ocular bioavailability of timolol [27].

Soak and Release- Waltman and Kaufman [31] first demonstrated the potential use of hydrophilic polymers of 2-hydroxyethyl methacrylate (HEMA) for drug delivery using fluorescein stain. In 1974, Hillman demonstrated the delivery of antiglaucoma drugs through soft contact lenses. He used polymers of vinylpyrrolidone soaked in 1% pilocarpine for drug delivery. He reported the system to be as efficacious as 4% pilocarpine topical eye drops [32].

Microemulsion Loaded Lenses- The microemulsions for drug dispersal were favored due to the thermodynamic stability, high drug-loading capacity, ease of preparation, increased wettability, and easy tailoring of the drug release pattern. Multiple groups have developed drug-loaded microemulsion-incorporating contact lenses [48]. Gulsen and Chauhan encapsulated timolol in microemulsion stabilized within a silica shell using octadecyltrimethoxysilane (OTMS), followed by dispersion in a hydrogel lens. This model has shown sustained release of up to 8 days without affecting the transparency of the lens [33]. Li *et al.* [34] developed contact lenses loaded with timolol, with oil-in-water-type microemulsions using a combination of ethyl butyrate, and Pluronic F127. The group fabricated the microemulsion-laden gels, ethyl butyrate/water microemulsions stabilized by Pluronic F127 surfactant, and subsequently polymerized after the addition of HEMA.

Vitamin E–loaded Lenses- Chauhan *et al.* developed the technique using Vitamin E as an in-situ transport barrier for timolol. The drug release was significantly increased by elevating the loading concentration of Vitamin E from 10% to 40% in contact lenses [28]. The group demonstrated a quadratic increase in drug release duration in Vitamin E loading. Loadings of 10% and 40% Vitamin E increased the release time of timolol by a factor of about 5 and 400, respectively. However, Vitamin E loading in the lens led to an increase in lens sizes, a reduction in oxygen diffusion, and a significant decreament in ion permeability.

Film Impregnation in Contact Lens- Ciolino *et al.* [35] designed a latanoprost-eluting contact lens for treating glaucoma, manufactured by encapsulating the drug film enclosed in methafilcon lenses. These lenses have shown sustained release for up to 1 month in glaucomatous monkeys. The amount of drug delivered to the eye exceeded or was comparable to the delivered topical drops. Contact lenses with polymer-drug films (40–45 mm in thickness) demonstrated an initial burst of latanoprost in the aqueous humor, a steady concentration was similar to the average hourly concentration

delivered from a drop of commercially available latanoprost solution [52].

Enzyme-triggered Timolol Release- Kim *et al.* [36] embedded nanodiamonds (NDs) loaded with timolol in contact lenses. The ND–nanogel embedded contact lens acts as an enzyme trigger for the delivery of timolol. The nanogels sequester timolol before activating the lysozyme that causes chitosan degradation and subsequently allows sustained drug release. After 24-h treatment with lysozyme, the total steady drug release from the lens was 9.41 μg.

Intraocular Implants

Intravitreal Implants- Intravitreal implants are devices capable of delivering drugs for a prolonged duration in the eye. Although surgical implants present a viable option for long-term drug delivery, the invasive nature of the initial and subsequent surgical procedures to remove the implants does not make them a favorable choice for drug delivery. OZURDEX is a degradable dexamethasone intravitreal implant produced by Allergan, which was used to treat macular edema and noninfectious uveitis [53]. The device slowly degrades after implantation in the vitreous while delivering dexamethasone. The manufacturer conducts clinical trials of the implants loaded with brimonidine tartrate in the proprietary NOVADUR poly (lactic-coglycolic acid) (PLGA) intravitreal polymer matrix platform for the management of geographic atrophy due to agerelated macular degeneration. Topical daily ophthalmic brimonidine tartrate drops were prescribed for IOP reduction and neuroprotective effect. If the NOVADUR PLGA platform implants with brimonidine tartrate are approved, they can also be adapted for use in glaucoma patients [37].

Subconjunctival Inserts-The subconjunctival inserts were used as implants as a replacement for viscoelastic depot delivery injections. The VS101 ocular insert was one such insert developed by ViSci Inc. in 2014 and later underwent a phase I/II multicentric randomized control study to evaluate the safety and effectiveness of subconjunctival latanoprost insert in subjects with ocular hypertension or OAG [38].

PCL-PEG Inserts-Ng and colleagues used biodegradable microfilm synthesized by a combination of poly (lactide)/poly (ε-caprolactone) (PLC) and poly (εcaprolactone)/poly (ethylene glycol) (PLC/PCL-PEG). The polymer was loaded with timolol maleate and inserted by conjunctival dissection [39]. The authors reported a decrease of 50.1% ± 8.5% in IOP from baseline in primates with ocular hypertension, which was sustained for 140 days.

AP-PCL Inserts-Alkoxylphenacyl-based polycarbonate polymers in combination with polycaprolactone (AP-PCL) were used by Manickavasagam *et al.* [40] for sustaining delivery of brimonidine tartrate for three months. The major drawback attributed to the subconjunctival inserts is the requirement of a surgically invasive procedure which creates a small opening in the conjunctiva with a possibility of subconjunctival migration, infection in need of an Operating Room procedure for insertion/removal of the device.

Micro Electro-mechanical System-The system termed as micro electro mechanical system (MEMS) works on the principle of bubble generation by electrolysis to mechanically push the loaded drug out of the reservoir. The device, currently in a preclinical development phase, also allows loading the drug multiple times [41]. Saati *et al.* demonstrated the use of the MEMS pumping mechanism was based on electrolysis connected to a drug refill port a check valve to control delivery. The procedure is similar to the implantation of a glaucoma aqueous drainage device.

Liposome- The liposome-encapsulated drug was delivered as a solution as an eye drop. Natarajan and colleagues used latanoprost-loaded egg-phosphatidylcholine liposomes for delivery. The liposomes remained stable for at least six months on storage at 4°C and at least one month at 25°C. A sustained release of 60% of latanoprost was achieved by two weeks in vitro. A high sustained IOP-lowering effect was recorded in liposome-treated animals (4.8 ± 1.5 mmHg) compared with daily administration of topical latanoprost (2.5 ± 0.9 mmHg) beyond 90 days [42]. Monem and colleagues used multilamellar vesicles (MLVs) as a vehicle for delivering pilocarpine. They reported neutral MLVs encapsulating pilocarpine HCl exhibited the most prolonged efficacy in the reduction of IOP. They also reported negatively charged MLVs encapsulating pilocarpine HCl exhibited a significantly shorter period of drug action [43]. The group speculated that the frequency of administration of drug administration in humans would be reduced to half with the usage of MLV vehicles, thus promoting better compliance.

Polymeric Nanoparticles- Due to their molecular-scale size, nanoparticles efficaciously deliver drugs in the anterior chamber in the posterior compartment via the bloodaqueous and the blood-retina barrier, respectively [44]. Different types of nanoparticles were classified based on the origin of the constituent monomers and its emphasis was laid on effective drug loading on the nanoparticles through the process such as electrospraying and electrospinning. Mehta *et al.* demonstrated a single-needle electrohydrodynamic process for adding a stable nanocoating to the contact lenses with timolol maleate. The in vitro studies showed biphasic release of the drug, with an initial burst release followed by sustained release [45].

Chitosan-based Polymeric Nanoparticles- Chitosan, a 2amino-2-deoxy-beta-D-glucan, is being widely tested for

synthesizing nanoparticles for drug delivery [46]. The biodegradable, biocompatible, and mucoadhesive properties of chitosan make it highly suitable for delivering antiglaucoma drugs. Li and colleagues [47] developed chitosan nanoparticles loaded with beta-adrenergic agent betaxolol, prescribed for lower IOP. The ex vivo data published by the authors show a 1.75 times higher value compared with the topical eye drops. Zhao and colleagues [49] have developed timolol maleate–loaded nanoparticles from glycosylated polymers of chitosan for ocular delivery. The authors reported an augmented transcorneal penetration due to high lipid solubility. The authors reported that the data from the in vivo experiments showed a sustained release over a significantly longer duration of time. Mehta *et al.* used electrohydrodynamic atomization of timolol maleate–loaded PVP and poly (N-isopropyl acrylamide). The authors used the formulation approach for sustained timolol maleate release used the combination of chitosan, borneol and reported the biphasic and triphasic release, depending on composition [49].

Poly (Lactic-co-glycolic Acid) Nanoparticles- PLGA is a copolymer of cyclic dimers (1, 4-dioxane-2, 5-diones) of glycolic acid and lactic acid [50]. Salama and colleagues [51] used PLGA nanoparticles for the delivery of brinzolamide subconjunctivally and reported the release of the drug was prolonged for a period of up to 10 days after a single dosage. Khan and colleagues used PLGA-based nanoparticles for the delivery of forskolin, a natural extract with potent noradrenergic stimulatory action on adenylate cyclase [52, 53]. The authors reported a steady release of the drug from the PLGA polymer, with 90% release over 72 h compared with eye drops (96.6% release in 12 h).

Gelatin Nanoparticles- The ease of availability and high biocompatibility make gelatin a favorable polymeric vehicle for the delivery of antiglaucoma drugs to the eye. Recently, Shokry and colleagues reported the use of gelatin nanoparticles for delivering timolol maleate and reported increased mucoadhesion and transcorneal permeability due to its positive charge attracted to negatively charged lipid layers in the cornea [54]. The in vitro release studies showed a burst effect of timolol release followed by a sustained profile over a prolonged duration. The in vivo studies in the albino rabbits showed a sustained and higher efficacy in IOP lowering. In another study, Liao *et al.* [55] used silica-based mesoporous nanoparticles for pilocarpine with gelatin coating. The in vitro data showed a 36-day release profile of the gelatin-coated mesoporous nanoparticles with an efficacious in vivo IOP-lowering effect for 21 days.

Propoxylated Glyceryl Triacylate Nanoparticles- Jung *et al.* [56] developed a contact lens based on the principle of dispersing timolol-loaded propoxylated glyceryl triacylate (PGT) nanoparticles within the lens. Timolol–PGT particles release the drug for an extended period (>30 days at room temperature) by hydrolysis of the ester bond. The bioavailability of timolol delivered through the contact lens showed 50% bioavailability as compared with only 1–2% through eye drops.

PGT–ethylene Glycol Dimethacrylate Nanoparticles- Jung and Chauhan [57] also developed a lens with highly cross-linked particles consisting of monomeric units with multi vinyl functionalities such as PGT and ethylene glycol dimethacrylate (EGDMA). The 3.5-nm nanoparticles encapsulated 48–66% of the drugs. The rate constant of ester hydrolysis was significantly less than those of the previous models developed by the same group, possibly due to steric effects and the low water content of the highly cross-linked hydrophobic particles. The nanoparticles dispersing timolol were encapsulated with linked nanoparticles enclosed within contact lenses, which increases the duration of drug release from 1 to 2 h to about four weeks. The drug-dispensing particles were dispersed in hydroxymethyl methacrylate (HEMA) gels that were commonly used for manufacturing contact lenses. Xu and colleagues [58] developed micelles that could be loaded on the contact lenses for sustained release of timolol and latanoprost simultaneously for management of glaucoma. The micelles were synthesized by free radical polymerization of the HEMA monomer with timolol and latanoprost. The lenses released timolol and latanoprost in tear fluid for 144 and 120 h, respectively. The in vivo data showed sustained timolol and latanoprost release for 120 and 96 h in tear fluid, respectively.

Nanospheres /Microspheres- The penetration of drugs loaded on the nanosphere depends on the size, charge, architecture, and surface of the carrier nanoparticle systems [59, 60]. The architecture of the nanospheres consists of a di-block copolymer that is a hydrophobic block [polycaprolactone (PCL)], a hydrophilic component [polyethylene glycol (PEG)]. The unique structure of nanospheres allows a longer residence time on the surface of the cornea to provide the drug with a carrier followed by fusion with the corneal epithelial membrane, hence reducing the dosing frequency [61]. Chiang *et al.* [62] initially reported 6 mmHg with brimonidine polylactic acid (PLA) microspheres that results in reduced IOP for one month in normotensive rabbit eyes. The in vitro analysis of the brimonidine microspheres showed a sustained release of the drug for 35 days.

OHR1031- It is a macromolecular drug for glaucoma management that incorporates into microparticles using a dissolvable hydrogel template technology [63]. The drug is dissolved into a PLGA polymer-solvent mixture, and the microparticles are formed using the dissolvable template technology. The median size of drug-loaded particles is 60 μm. The authors reported that the OHR1031 content in the microparticles was 57%-100% incorporation efficiency. The

drug release rate was nearly zero-order for over three months with virtually no initial burst.

SoliDrop- SoliDrop by Otero Therapeutics consists of a thermoresponsive hydrogel carrier and drug-loaded polymer microspheres. On administering a single brimonidine-loaded gel/microsphere drop, the IOPlowering efficacy (reduced by 30% of baseline IOP) was comparable to that of rabbits receiving twice-daily, standard brimonidine drops for 28 days. The gel drops were retained in the fornix during the entire period of the study [64].

ENV 515/Travoprost XR- ENV515 PGA/travoprost XR therapy is a particle replication in a nonwetting templatebased biodegradable polymer drug delivery system. The implant is rod-shaped and fits the anatomy of the iridocorneal angle in the anterior chamber, allowing its administration via an acceptably sized needle. The result from the phase II clinical trial reported that a single low dose of ENV515 decreases the mean IOP by 6.7 ± 3.7 mmHg over eleven months. The mean IOP after a single low dose of ENV515 was 19.5 mmHg over the 11 months [68].

Bimatoprost SR- Bimatoprost SR is a biodegradable implant for the decrement of IOP with a 4-month sustained release period [69]. In the first phase III clinical study, Bimatoprost SR reduced IOP by 30% over the 12-week primary efficacy period. The results showed no requirement of supplementary treatment for IOP lowering for one year after the last implant insertion. The magnitude of IOPlowering efficacy with Bimatoprost SR observed in this study is similar to that observed with daily topical prostaglandin analogs. Bimatoprost SR was well tolerated in the majority of patients.

Graybug- Graybug is a drug-encapsulated microparticle formulation to provide continuous IOP lowering that is administrated by the treating physician every 3 –6 months using a subconjunctival injection. GB-203 is a preclinical stage dual mode of action, single molecular entity agent that can hydrolyze into an active agent that has the potential to lower IOP and a second active agent that can provide longterm neuroprotection [70]. Another pilot polymer depot formulation of GB-6249-103 developed on the Graybug platform safely has been shown to deliver its payload in a sustained manner both in vitro and in vivo [71]. A significant reduction in IOP was observed within the first week following injection of the formulation in rabbits. The results recorded a sustained maximum IOP lowering of ~20% over two months.

OTX-TP- The OTX-TP (Ocular Therapeutix) delivered travoprost to the ocular surface via an intracanalicular punctal plug for up to three months, resorbs, and drains through the nasolacrimal system [72]. It consists of PEGbased hydrogel with embedded travoprost–loaded PLA microspheres. These microspheres slowly degrade and show a sustained drug release over 30 days. Perera *et al.* [73] in a study reported a 100% retention rate of the plugs, ten days post-implantation, and a reduction in IOP by 5.4–7.5 mmHg. It is minimally invasive, contains fluorescein to monitor any retention, and clears from the body through absorption. The studies have shown an enhanced therapeutic benefit for 90 days with a consistent 90% retention rate. The phase II trial did not find any serious adverse effects and showed only slightly less hypotensive effects as compared with timolol.

Latanoprost Punctal Plug Delivery System- Goldberg and Williams [74] used the Latanoprost Punctal Plug Delivery System (L-PPDS) for lowering IOP in OAG patients. The data reported by the authors showed a reduction in mean IOP by 5.7 mmHg. They also reported that 60% of subjects in the study showed at least 5 mmHg or higher IOP reduction, and 47% of the subjects showed a reduction of at least 6 mmHg. A statistically significant 22.3% mean change in IOP was recorded in the subjects with L-PPDS when compared with controls.

Evolute- Evolute, a punctal plug delivery system developed by Mati Therapeutics has been tested with latanoprost in patients with OAG or ocular hypertension [75]. The plug consists of a drug core, which allows unidirectional sustained drug elution into the tear film. In phase II clinical trial, an overall punctal plug retention rate of 96% was reported at 12 weeks. In the second phase, the retention rate of plugs was 92% in the 12th week. The punctal plugs loaded with travoprost reduced the pressure by 7 mm compared with a 5-mmHg decreased pressure with latanoprost.

Pentablock copolymer gels- The pentablock copolymer gels were used as a vehicle for topical and intraocular delivery of glaucoma drugs like bimatoprost. The Food and Drug Administration (FDA) has approved five different pentablock copolymers for use in the eye. These include polyglycolic acid (PGA), PCL, PEG, PLA, and PLGA [76]. The drug was introduced as an eye drop, then changes physical characteristics based on body temperature at contact. The change in viscosity gives the vehicle copolymer gel-like characteristics gets accumulated under the lower palpebra, releasing the drug over a longer period.

Microneedles- Microneedles are drug delivery devices manufactured using metals or polymers with dimensions between 10 and 200 μm. The ultra-dimensions of these devices make the drug delivery less invasive and more targeted to the sites of drug action. Jiang *et al.* used 500 to 750 μm long-coated stainless-steel microneedles delivering pilocarpine into the anterior chamber via the intrascleral route. The authors reported a 45-fold increase in drug absorption compared with conventional eye drops [77, 78].

DISCUSSION

In this review article, we described the development of welltolerated drug delivery systems that helps to overcome the factors limiting adequate drug delivery to the glaucomatous patients targeting infected tissues with traditional techniques. Ocusert did not become a widely accepted method of drug delivery although the clinical studies showed positive outcomes the difficulty of device insertion, failure in satisfactorily controlling IOP in many patients, ejection of the device from the eye, irritation during insertion, and the difficulty in device insertion [14]. The ease of availability and application of Therapeutic contact lenses make them an ideal drug delivery system. The therapeutic contact lenses help in sustained and regulated ocular drug delivery due to their unique properties like extended wear and more than 50% bioavailability comparison with eye drop formulations [27, 28]. Soft contact lenses are water-soluble polymeric hydrogels crosslinked to form networks. These hydrogel lenses are widely used for drug delivery, even though the delivery of watersoluble drugs, such as timolol and dorzolamide, elutes from the highly hydrated polymer networks rapidly [29].

In comparison, the soft contact lenses manufactured by polymerization N, N-diethyl acrylamide methacrylic acid deliver timolol over a prolonged period [30]. Injectable systems are passive delivery systems capable of delivering medications to the target tissues for an extended period. The injectable systems are typically implanted at the site of drug release through a minimally invasive procedure, usually in an outpatient setting. The injectable systems use a polymer delivery vehicle to prolong delivery up to a few months around the surrounding tissue. Both degradable and non-degradable polymers have been developed used as injectable systems for drug delivery in the eye [65]. Degradable PLGAs are materials of choice for developing such a system. The non-degradable alternative such as the polymer of ethylene-co-vinyl acetate may lead to an immune response due to the prolonged presence of a foreign body [66]. The rate of dispersion of drugs from these systems is variable, with an initially more massive quantity release. The water solubility of the drug affects the efficacy because hydrophilic drugs interact poorly with degradable polymers as they are hydrophobic [67].

Several methods of treatment of glaucoma in the patient's eye were discussed in this review and also, we discussed the development of the well-tolerated drug delivery systems that helps to overcome the limiting factor of adequate drug delivery systems. In the past, many studies have emphasized the importance of adherence, compliance, and persistence for the management of glaucoma. We know the available drugs are efficacious in lowering IOP and neuroprotection, the traditional methods of topical drug delivery have been not satisfactory due to poor target bioavailability, increased systemic absorption, and poor patient compliance.

CONCLUSION

This review described the direction and ongoing innovation/research to address the challenges of safer and more effective drug delivery challenges associated with the previous one. The majority of the devices studied in this article are currently in various stages of development and are not commercially available. The impact of these devices on the patients can only be gauged once they are available for clinical use and extensive clinical data are available for scrutiny. Notwithstanding the lack of data, the critical role of these devices in glaucoma management shortly needs to be emphasized.

The potential of increasing patient compliance and persistence for optimum outcomes with the help of these devices is unprecedented. Eye drop installation has always been a challenge, especially in the geriatric and pediatric age group patients. Effective localized delivery will prevent drug loss due to systemic absorption and firstpass metabolism thereby, minimizing drug wastage. The prevalence of ocular surface disease in patients installing antiglaucoma drugs with added preservatives may be overcome with the newer devices. The most significant advantage of these devices was the improved quality of life of the patients who adhere to a strict regime of repeatedly putting eye drops throughout the day.

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