Ocular Drug Delivery System – A Review

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Abstract- One of the difficult methods in new medication delivery systems is ocular drug delivery. Although the eye is a vital organ of the human body, it occasionally experiences diseases or problems for a variety of reasons. Ocular medication delivery systems (with a suitable dosage form) are used to treat eye diseases and disorders, depending on the nature and severity of the medical problem. Only some parts of the surface of ocular medication distribution are constrained and therefore require a smaller dose than systemic circulation. Ocular problems are treated with medication applied topically because of blood flow obstacles in the eye. For this reason, it is important to understand anatomy and physiology as the drug is administered in several ways. Conclusion: This review discusses the challenges and obstacles in the paths of proposing a novel ocular drug delivery targeting rug along with their possible remedies. Various ocular delivery barriers, such as the ocular surface barrier, and lacrimal fluid eye barrier along with the blood ocular barrier have been discussed that need to be overcome for designing new ocular drug delivery.

Keywords: Ocular drug delivery system, eye, ocular diseases, nanoparticles, dendrimers, retrobulbar.

INTRODUCTION

The eye is a unique organ with distinct functions and a complex anatomical and physiological structure. It is challenging to develop pharmaceutical delivery systems for it because of its wide range of structural variations. The main problem with eye drops used in normal ocular medicine administration is that they are quickly and fully clear from the eye, resulting in significant drug loss. [1][2].only a small portion of the medication used in an eye drop penetrates the corneal layer and into the eye's inner tissues. [3][4]. A broad taxonomy is the source of the two methods of ocular medication administration that target the anterior and posterior segments. The use of conventional pharmaceutical delivery methods including eye drops, suspensions, and ointments is unsatisfactory for the treatment of ocular illnesses that seriously impair vision. [5]. Diabetic In most industrialized nations, retinal diseases such as retinopathy, age-related macular degeneration (AMD), and retinal vascular disorders are the leading causes of declining eyesight. [6]. Devices for delivering intraocular medications to the eyes have undergone a number of advances. In clinical trials for neovascular AMD, the drawbacks of intra-vitreal injections have been proven to reduce the socioeconomic treatment load on the intraocular dose rise. [7][8]. Tissue engineering has recently been used to study hydrogels, micro-needles, microbots and nanoparticles, iontophoresis, dendrimers, in-situ gels, and pro-drug approaches. These surface conjugation-modified drug delivery techniques improve the efficiency of drug administration and lengthen intravitreal half-lives due to the prolonged drug release, increased biocompatibility, and decrease in biological drug degradation. [9][10]There have been studies into several periocular drug administration methods that are thought to be less enveloping than vitreal injections. [11][12]

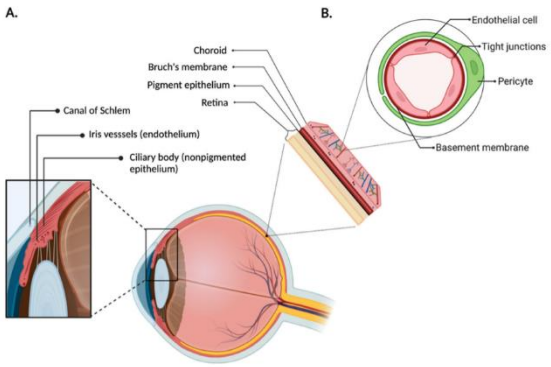

Figure 1. Anatomical barriers of the eye. (A) In the anterior of the eye, the blood-aqueous barrier, consisting of the iris/ciliary blood vessels and non pigmented ciliary epithelium, limits access to the anterior of the eye and prevents therapeutic entry to the intraocular environment. (B) In the posterior of the eye, the blood-retinal barrier, comprised of the retinal capillary endothelial cells and retinal pigment epithelium cells, prevents therapeutics from entering the posterior segment from the bloodstream.[45]

OCULAR DISEASES

Over 500 different types of eye conditions are currently recognized, including glaucoma, macular degeneration, diabetic retinopathy, dry eye disease (DED), etc. Due to shifting eye usage habits and an older population, ocular disorders are becoming more commonplace. These conditions have a significant negative influence on people's health and quality of life, highlighting the urgent need for successful interventions. Unquestionably, drug therapy is essential in the management of many eye disorders. Glaucoma The second greatest cause of blindness globally, behind cataracts, is glaucoma, an eye condition marked by progressive vision loss. [13]. It is estimated that the number of glaucoma patients will increase to 111.8 million by 2040. High intraocular pressure (IOP) is an essential feature of glaucoma. The loss of corneal endothelial cells can be caused by increased intraocular pressure [14]. Additionally, excessive intraocular pressure can constrict the blood vessels in the retina, harming the retinal ganglion cells and the optic nerve.Despite the fact that glaucoma is a complex disease, the primary goal of current treatment is to lower intraocular pressure in order to delay or minimize further vision loss.Most treatments start with topical Anti-glaucoma drugs,Due to substantial precorneal loss and minimal corneal penetration, topical treatment has a bioavailability of less than 5%. However, repeated ocular delivery reduces patient compliance. [15]To properly distribute medications, increase bioavailability, and maintain the efficacy of anti-glaucoma medications, nanotechnology must be used. Age-related macular degeneration AMD is the third most common cause of severe, permanent vision loss worldwide, and by 2040, there will be almost 300 million AMD sufferers.Clinically, it can be separated into early AMD and late AMD. Medium-sized stone fruit and retinal pigment changes are two examples of early AMD clinical symptoms. Late AMD is categorized as either neovascular (also known as wet or exudative) or non-neovascular (also known as atrophic, dry, or non-exudative), which may result in central vision loss and legal blindness. [16]. Antioxidant vitamin supplements and high zinc dosages can decrease the spread of disease from the early to the advanced stages. [17]. Intravitreal injection (IVT) of anti-vascular endothelial growth factors (VEGF) (such as bevacizumab (Bev), aflibercept, etc.) effectively treats neovascular AMD, but it’s still invasive. Therefore, exploiting new drug delivery systems for personalized drug delivery is particularly important. Diabetic retinopathy Diabetic retinopathy is a chronic complication of diabetes and the leading cause of vision loss and blindness globally. In severe cases, retinal detachment can gradually manifest as blurred vision, ocular floaters, distorted vision, and even partial or complete vision loss [18]. Clinically, if laser treatment is performed in time, retinal circulation can be improved, avoiding vitreous hemorrhage and retinal neovascularization. However, for patients with macular edema, it is usually necessary to inject anti-VEGF to treat macular edema and improve vision. Unfortunately, regular intravitreal injections may cause damage to the ocular tissue, and not all patients respond optimally. Vitrectomy is needed in case of fundus hemorrhage or proliferative vitreoretinalopathy [19]. Given the low bioavailability of drugs, potential adverse effects, and inevitable risks in major surgery, novel drug delivery methods are required to bring new ideas for the therapy of DR. Dry eye disease Dry eye disease, known as dry keratoconjunctivitis, is a multifactorial ocular surface disease. It is characterized by tear film instability, hypertonicity, inflammation, ocular surface damage, and nerve paresthesia. Five to fifty percent of people get dry eye globally [20]. Ocular irritability, pain, soreness, a feeling of a foreign body, and impaired vision are some of the signs and symptoms of DED. DED has a significant negative impact on patients' quality of life, induces psychological worry, and places a tremendous financial burden on society. To date, the pathogenesis of DED has not been fully elucidated, and most researchers perceive that inflammation is the core of its pathogenesis. The diagnosis and treatment of DED can be divided into two main categories: dehydration type and evaporation type. Artificial tears, local secretagogues, corticosteroids, and immunosuppressants are common medication therapies; nevertheless, they can have adverse consequences such as glaucoma, low patient compliance, eye pain, and raised intraocular pressure. Exploiting new drug delivery methods to overcome ocular barriers and improve drug bioavailability is particularly critical.

TRADITIONAL ROUTES OF DRUG ADMINISTRATION

Topical administration, conjunctival and scleral administration, intracameral administration, intravitreal injection, retrobulbar injection, systemic

routes, and others are among the classic modes of delivery. Depending on the routes of administration, a medicine must get through one or more ocular barriers in order to reach the intended site.

TOPICAL ADMINISTRATION

The most popular and simple method of administering drugs to the eyes is topically [21]. Comparatively speaking, it has the benefits of being generally non-invasive, minimizing systemic pharmacological adverse effects, and being reasonably simple for patients to administer. Since solutions make up 95% of the commercially available products in the global market for ophthalmic drugs, they are the primary choice for treating many eye illnesses. [22]. However, due to the unique physiological and anatomical structure of the eye, drug delivery in the eye is limited, and bioavailability is usually less than 5%. To increase the effectiveness of medication delivery through the local route, high drug concentrations and repeated instillations are frequently required, which may result in poor patient compliance and a variety of side effects.After topical treatment, there are two basic ways to increase ocular bioavailability: Enhance the permeability of medicines administered to the cornea, sclera, or conjunctiva, and (a) lengthen the pre-corneal retention duration. [23]Prodrugs, mucus osmotic particles, enhancers, collagen corneal shields, and therapeutic contact lenses are just a few of the methods that have been suggested to extend drug residence duration following topical delivery. [24]. In addition, nanocarriers also open up new windows for liquid and semi-solid formulations to increase drug availability.

SUBCONJUNCTIVAL AND TRANSSCLERAL ADMINISTRATION

A less invasive and efficient method of delivering medications to the front or posterior eye chamber is subconjunctival administration. This method avoids the corneal and blood-aqueous barriers, potential side effects, and first-pass metabolism of some systemic medicines.[25]However, because of blood and lymphatic drainage through the conjunctiva, the subconjunctival route may result in drug loss Similar to that, transscleral delivery is a quick, minimally invasive, and better for patients procedure. This path can go around barriers in the eye's front portion. [26]. At the same time, the large surface area of the sclera (about 95% of the total surface area of the eye) offers the chance to deliver antioxidants, neuroprotective agents, or anti-angiogenic agents to targeted sites in the retina [27]. It has been shown that molecules as large as 70 kDa can easily pass through the sclera, but molecules as small as 1 kDacan pass through the cornea. The intraocular bioavailability of this approach is, however, lower than that of direct intravitreal injection because of the dynamic barriers.

INTRACAMERAL ADMINISTRATION

Drugs are injected intracamerally right into the anterior chamber of the eye [28]. With some systemic medicines, this local delivery strategy avoids their negative effects and first-pass metabolism. Additionally, it stays away from the cornea, conjunctiva, and BAB.Thus, intracameral injections allow relatively easy and efficient drug delivery to the anterior segment of the eye.Currently, prophylactic antibiotics or anesthetics related to eye procedures are administered via intracameral injections [29]. Drugs cannot, however, be administered through the anterior chamber to the eye's posterior chamber. Drugs in the anterior chamber typically need to be reorganized, diluted, sterilized, prepared in unique ways without preservatives, and administered in the right concentrations and doses. Corneal endothelial cell toxicity and toxic anterior segment syndrome may occur if incorrect doses and preparations are used.

INTRAVITREAL INJECTION

To treat ophthalmic illnesses of the eyeball, intravitreal injection is a favored way of medication administration in the posterior region of the eye. Free medicines can be eliminated fast following IVT injections due to vitreous fluid turnover [30]. To get good treatment results, frequent IVTs are needed, which could have negative side effects such as retinal detachment, eye infection, endophthalmitis, and increased intraocular pressure [31]. As a result, the best treatment method for IVT is a single injection of the medication with the eyelids closed and without retracting the needle. Recent research has concentrated on preserving therapeutic effects, lengthening treatment intervals, and safeguarding healthy ocular tissues. As safer and more effective alternatives to treat ocular illnesses, NPs, intravitreal implants, hydrogels, combinatorial systems, and minimally invasive procedures are now being studied in preclinical and clinical settings [32].

RETROBULBAR INJECTION

Drugs are delivered to the retrobulbar space using the retrobulbar method by inserting needles through the eyelid and orbital fascia [33]. Triamcinolone acetonide is injected retrobulbarly to treat macular edema brought on by retinal vein occlusion. Amphotericin B administered retrobulbarly has a stronger antifungal effect than administered intravenously. Chlorpromazine is injected retrobulbarly to alleviate painful blindness. [34]

ADVANCED DRUG DELIVERY SYSTEM TO EYE

Various methods have been employed in recent years to cure eye diseases. Nanotechnology-based optical formulations are one of the strategies being studied right now for both anterior and posterior segment medication administration. The correct particle size can be used to create a system based on nanotechnology that ensures minimal irritancy, adequate bioavailability, and compatibility with ocular tissue. Numerous nanocarriers, such as nanoparticles, nanosuspensions, liposomes, nano-micelles, contact lenses, microneedles, in situ thermosensitive gels, dendrimers, and nano-wafers have been developed for the administration of ocular medications. A few of them have led to findings that are hopeful for improving ocular bioavailability. [35]. Nanoparticles: Solid, uniform particles that are fewer than microns in size, preferably less than 500 nm, and can be polymers. Depending on the preparation techniques used, nanoparticles can be formed as either nanospheres or nano-capsules. Nanoparticles come in a wide variety of forms, such as magnetic, bio-adhesive, gold, silver, solid lipid, and self-aggregating ones. Nanoparticles' ability to mix with biological molecules and their in vivo biodistribution can both be changed. If the nanoparticles are coated with a muco-adhesive or charged polymer, they may spend longer amounts of time on the ocular surface. It has been discovered that a range of pharmaceuticals, including eye treatments, can be latently supplied to the eye utilizing liposomes. Depending on their size and construction [36]. There are numerous preparation methods, but they can be divided into two categories: those that use polymerization of monomers and those that use precipitation of polymers. Nanosuspension: According to some articles, less than 600 nm-sized water-insoluble particles are colloidally disseminated in water as nanosuspensions. These systems need a surfactant, polymer, or both to remain stable [37]. Following instillation, the tiny particles adhere to the ocular tissues and create a depot where the medication will eventually be released. The larger surface area of the nanoparticles also enables an appropriate rate of drug release and preserves a constant drug concentration in order to achieve the required bioavailability. Additionally, hydrogels and ocular implants contain nanosuspension for a specified amount of time for sustained action [38]. In the year of 2017 research done on the Econazole and the result of this study is When compared to the suspension formulation's 4-hour drug release, the nanosuspension formulation performed better, releasing the drug over a period of 7-8 hours [39]. Liposomes: Due to their high biocompatibility and cell-like membrane comprised of phospholipids from natural sources, liposomes are a promising technique for giving medications to the eyes. Liposomes can bind to the hydrophobic corneal epithelium when applied topically, improving pharmacokinetics and minimizing negative side effects. The rabbit keratitis models received fluconazole-loaded liposomes; fluconazole solution served as the standard. Results after 21 days of monitoring revealed that liposomal fluconazole medication was more effective than the control treatment at curing infection. Positively charged liposomes have been demonstrated to have a higher affinity for attaching to the corneal surface than neutral or negatively charged vesicles. Nano-micelles: Topical drops based on nonmicellar technology are gaining interest as a noninvasive drug delivery method due to their smaller size, hydrophilic corona, ability to stay in the systemic circulation for a longer period of time, and ability to accumulate in sick tissues through the EPR effect. The selection of surfactant and polymer for this nonmicellar technology should be appropriate for facilitating drug distribution to both the front and posterior portions of the eye. Contact lenses: The newest method of administering ocular medication is contact lenses. In this system, contact lenses are placed in the eye while still containing drugs. The drug is released from these lenses over a very lengthy period of time. Contact lenses with hydrophilia are widely used. The material [water soluble medications] was absorbed after they drank drug solvent. Bionite lenses, which contain the hydrophilic polymer 2-hydroxy ethyl methylacrylate, deliver fluorescein to the human eye. They accelerate the rate of medication

penetration with fluorescein. [40]. Microneedles: The development of microneedles and the use of the tools to treat glaucoma are both related to microvascular injection. It is made out of a blunt needle attached to a flexible, tapered tube that has a microneedle or micropipette at the end for inserting into small blood arteries. The sclera or the small region between the sclera and choroid known as the "suprachoroidal space" can both be treated with these needles to deposit a medication or carrier system [SCS] .In situ thermosensitive gels are simply injected as solutions into the conjunctival sac, where they change into gels with their preferred residence times. The chemical and physical changes brought on by the physiological environment result in the sol-gel transition. This type of gel combines the advantages of a patient-friendly solution with a gel with a favourable residence time for improving ocular bioavailability [41]. Several adaptable polymers have a variety of gelling properties. A combination of these polymers might lead to better results than using just one polymer. But for the present investigation, a solution of sodium alginate and HPMC was prepared for use as an ocular in situ gel-forming method Alginate is a natural polymer made from brown sea algae. The material generates stable hydrogels when certain divalent cations, such as Ca2+, Sr2+, and Ba2+, which are present in modest levels in tear secretion. Drug delivery uses sodium alginate, a polymer that is very hydrophilic and biocompatible. It experiences osmotically induced gelation, where a change in ionic strength causes the fluid injection to gel. [42]. Dendrimers: The macromolecules known as "dendrimers" are made up of a network of branches and a central core. They are a suitable solution carrier for the delivery of ocular medications due to its nanotechnology, simplicity in manufacture, functionality, and capacity to affix multiple surface groups. Drugs for the eye are routinely administered with PAMAM dendrimers. In order to avoid the development of scar tissue during glaucoma filtration surgery, modified PAMAM dendrimer conjugates containing glucosamine [DG] and glucosamine 6-sulfate [DGS] were developed. These compounds exhibit anti-angiogenic and immunomodulatory properties, respectively. Following glaucoma filtration surgery, these modified conjugates were subconjunctivally administered into rabbits. This drastically reduced pro-inflammatory and pro-angiogenic responses, which consequently reduced the production of scar tissue. The results of the experiment indicated that clinical application of DG and DGS to the eyes would be effective and safe in avoiding the development of scar tissue after glaucoma filtration surgery [43]. Nano-wafers: As shown in Figure 5, which are tiny circular discs or rectangular membranes holding a range of drug-filled Nano-reservoirs, the ocular surface is coated with nano-wafers. They prolong the duration of drug release, which increases therapeutic efficacy. During the medicine release procedure, the nano-wafers melt and vanish.The effects of Axi-5-NW on the corneal wound healing process were investigated using corneal fluorescein staining. The Axi-5-NW treatment had no impact on the corneal wound healing, and a usual healing pattern was seen, according to the investigation's findings. By the ninth day, the corneal surface had fully healed, and both the Axi-5-NW and Axe-eye drop treatment groups saw roughly a similar rate of epithelial closure of the corneal surface [44].

CONCLUSION

- This review discusses the challenges and obstacles in the paths of proposing a novel ocular drug delivery targeting rug along with their possible remedies. Various ocular delivery barriers, such as the ocular surface barrier, and lacrimal fluid eye barrier along with the blood ocular barrier has been discussed that need to be overcome for designing new ocular drug delivery.
- The distribution problems to the anterior and posterior regions have been highlighted as a delivery system challenge for ocular medications. In order to improve the delivery mechanism for ocular membranes, new developments in dendrimers, in situ forming gel, iontophoresis, microneedles, micro-robotics, microparticles, and nanoparticles were discussed.
- These cutting-edge technologies and/or formulations also preserve drug release, enhance therapeutic drug bioavailability in the eye, and have a high precorneal residence time, no/minimal irritation.
- A review of recent research developments in ocular drug delivery is necessary and beneficial for drug delivery experts to modify their thought processes and create innovative and secure drug delivery methods.

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