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OCULAR DRUG DELIVERY SYSTEM

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ABSTRACT
The human eye is a sophisticated organ with distinctive anatomy and physiology that hinders the passage of drugs into targeted ophthalmic sites. Effective topical administration is an interest of scientists for many decades. Their difficult mission is to prolong drug residence time and guarantee an appropriate ocular permeation. Several ocular obstacles oppose effective drug delivery such as precorneal, corneal, and blood-corneal barriers. Routes for ocular delivery include topical, intravitreal, intraocular, juxtascleral, subconjunctival, intracameral, and retrobulbar. More than 95% of marketed products exists in liquid state. However, other products could be in semi-solid (ointments and gels), solid state (powder, insert and lens), or mixed (*in situ* gel). Nowadays, attractiveness to nanotechnology-based carries is resulted from their capabilities to entrap both hydrophilic and lipophilic drugs, enhance ocular permeability, sustain residence time, improve drug stability, and augment bioavailability. This review aims to clarify anatomy of the eye, various ocular diseases, and obstacles to ocular delivery.

KEYWORDS: Ocular drug delivery, Anatomy, Drug delivery, Bioavailability, Barriers, Novel system.

1. INTRODUCTION

Eye is a very sensitive organ with a sophisticated physiology. It is composed of anterior and posterior segments.[1] Anterior segment of the eye occupies approximately one-third while the remaining portion is occupied by the posterior segment. Tissues such as cornea, conjunctiva, aqueous humor, iris, ciliary body and lens make up the anterior portion. Back of the eye or posterior segment of the eye include sclera, choroid, retinal pigment epithelium, neural retina, optic nerve and vitreous humor. The anterior and posterior segment of eye is affected by various vision threatening diseases. Diseases affecting anterior segment include, but not limited to glaucoma, allergic conjunctivitis, anterior uveitis and cataract. While, age-related macular degeneration (AMD) and diabetic retinopathy are the most prevalent diseases affecting posterior segment of the eye.[2] Topical application of drugs to the eye is the most popular and well-accepted route of administration for the treatment of various eye disorders.

1.1 Advantages of ocular drug delivery systems

- Increased accurate dosing. To overcome the side effects of pulsed dosing produced by conventional systems.
- To provide sustained and controlled drug delivery.
- To increase the ocular bioavailability of drug by increasing the corneal contact time. This can be achieved by effective adherence to corneal surface.
- To provide targeting within the ocular globe so as to prevent the loss to other ocular tissues.
- To provide comfort, better compliance to the patient and to improve therapeutic performance of drug.
- To provide better housing of delivery system.

1.2 Disadvantages of ocular drug delivery system

- The drug solution is the stays a very small period on the eye surface.
- They can interfere with the vision.
- They should generally rapid elimination of the drug through the eye blinking and tear flow results in a short duration of the therapeutic effect resulting in the frequent dosing regimen.
- The major portion of the dose administered drains into the lacrimal duct and causes unwanted systemic side effects.
- The physiological restriction is the limited permeability of the cornea resulting in low absorption of ophthalmic drug formulation.

1.3 Limitations of ophthalmic drug delivery

- Dosage form cannot be terminated during emergency.
- Interference with vision.

- Difficulty in placement and removal.
- Occasional loss during sleep or while rubbing eyes.

Despite these limitations, significant improvements in ocular drug delivery have been made. The improvements have been with objective of maintaining the drug in the bio-phase for an extended period. The anatomy, physiology and biochemistry of the eye render this organ impervious to foreign substances.[3]

1.4 Anatomy And Function of Eye

The eye is basically a globe suspended in the ocular orbit that is designed to concentrate, transmit, and detect incoming light. This arrangement of tissues gives the eye its specific role for vision.

It is a spherical structure with a wall consisting of three layers:

- Outer sclera
- Middle choroids layer
- The inner retina[4]

The sclera is tough fibrous coating that protects the inner layers. It is white except for the transparent area at the front, the cornea which allow light to enter the eye. The choroid layer, situated inside the sclera, contains many blood vessels and is modified at the front of the eye as pigmented iris. The iris is the coloured part of the eye (in shades of blue, green, brown, hazel, or grey).

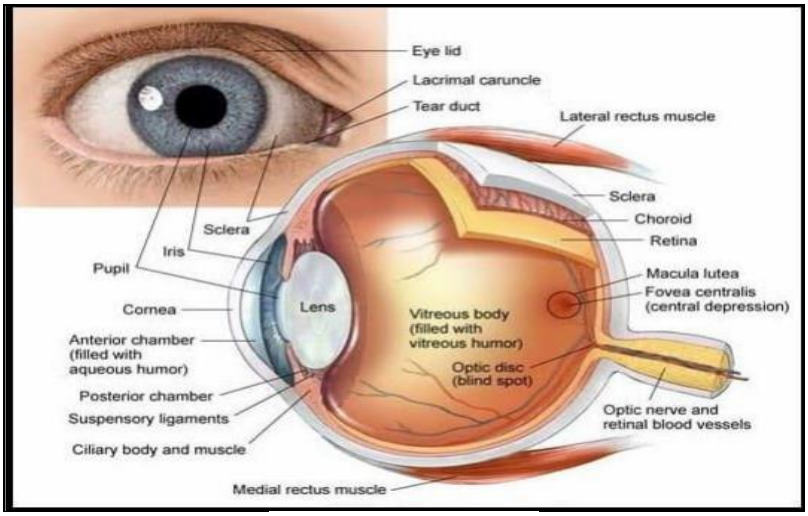

Fig. 1: Anatomy of Eye.

1.4.1 Sclera

Collagen fibers and proteoglycans are embedded in an extracellular matrix, specifically in the sclera. Scleral permeability is dependent on the molecular radius and kind of goes away as the molecular radius increases. In contrast to the anterior sclera, the posterior sclera has a looser weave of collagen fibers. The human selera is especially thick around the limbus (0.53 + 0.14 mm), thin on the equator (0.39 + 0.17 mm), and significantly thicker near the optic nerve (0.9-1.0 mm). The increase in hydrophobic/lipophilic human capsules suggests that selera permeability has decreased. The sclera, or white portion of the eye, is the firm white sheath that forms the ball's outer coat. The focus is maintained in the same manner due of the globe shape. In addition, hydrophilic capsules may more easily diffuse than lipophilic capsules through the aqueous medium of proteoglycans in fiber matrix pores. The medication molecule's permeability through the sclera may also be influenced by its cost. Because positively charged capsules connect to the negatively charged proteoglycan matrix, they may also exhibit extremely poor permeability.

1.4.2 Conjunctiva

The conjunctiva is responsible for maintaining and repairing the preconeal tear film in addition to shielding the eyes. The thin, visible membrane known as the conjunctiva is located on the inner surface of the eyelids and is visible on the outside of the globe. The substantia propria, which is highly vascularized, submucosa, and epithelium are the building blocks of the conjunctiva. The bulbar epithelium is composed of five to seven movable layers. The form now resembles a pallisade rather than a pavement due to the tight connections between the corneal epithelial cells, which make the conjunctiva extremely impermeable. While the cornea is limited to molecules larger than 5000 Da, molecules as large as 20,000 Da have the ability to move the conjunctiva. It has also been suggested that drug clearance is mostly influenced by the absence of drug through the human conjunctiva, which is capable of absorbing between two and thirty times as much medication as the cornea. The existence of 1.5 million globlet mobileular varied with age dependent on several intersubject variability and age is responsible for the maximal density of conjunctiva. The primary cause of both vernal and atopic kerato conjunctivitis is a minor

variation in goblet mobileular density, which manifests itself mostly in the concentration of tear mucin.

1.4.3 Choroid

The choroid layer, which is situated behind the retina, feeds the outer regions of the retina and absorbs excess radiation. This thin, somewhat vascular membrane is made up of blood vessels. Its hue is dark brown, and its pigment composition is as follows: © 2022 IJRTI | Volume 7, Issue 11 | ISSN: 2456-3315 IJRTI2211039 Blurred vision (caused by an excessive amount of mild at the retina) is prevented by International Journal for Research Trends and Innovation (www.ijrti.org) 237, which absorbs excess mild. The choroid has one of the body's greatest blood flow rates. Through the lamina fusa, the choroid is a weakly attached structure to the interior floor of the sclera.

1.4.4 Retina

The human retina is located behind the eye. The "display" that an image is formed on due to light that has gone through the cornea, aqueous humor, pupil, lens, and vitreous humor before reaching the retina is known as the retina. Retinal function extends beyond just being a display onto which an image may be created; it also collects the information contained in that image and sends it to the brain in a format that the body can use. As such, the retinal "display" is a slightly sensitive form that lines the inside of the eye. It is made up of photosensitive cells called rods and cones, as well as the nerve fibers that connect them. These cells translate light into nerve impulses, which are then transmitted to the brain via the optic nerve.

1.4.5 Iris

It's a colored portion of the attention that lets you change how much light comes in. Positioned in the rear of the cornea but in front of the lens is the iris, a thin, circular contractile curtain. The ability of the iris to control the pupil's scale allows it to change the amount of light that is let into the attention.

1.4.6 Lens

The lens is a transparent form contained in a conspicuous, thin capsule. It is positioned behind the attention-deficit student and encompassed by the cillary muscles. Light passing through the attention is helped to refract (first refracted through the cornea). At the retina, the lens concentrates light into an image. Lodging is the term for the form-adjusting process of the lens, which is accomplished by contracting and relaxing the ciliary muscles.

1.4.7 Optic nerve

Nerve signals are transmitted from the attention to the brain by the optic nerve, a bundle of more than a million nerve fibers. These nerve markers consist of information on a picture that the brain can process. The optic disk is the portion of the optic nerve visible at the retina that is located on the front floor.

1.4.8 Pupil

The amount of light that is allowed into the attention is controlled by a black orifice located inside the iris. The pupil is typically perceived as the darker "centre" of attention, but it may actually be more accurately defined as the circular opening in the iris's center through which light enters the attention.

1.4.9 Cornea

The clear, noticeable protrusion in the cornea at the front of the attention that sends images back to the scared system. The adult cornea has a radius of roughly 7-8 mm, which makes up about one-sixth of the entire floor area of the attention ball. This area may be made up of vascular tissue, to which nutrients and oxygen are supplied through lachrymal fluid, aqueous humour, and blood vessels at the junction of the cornea and sclera (fig. 1). The epithelium, Bowman's layer, stroma, Descemet's membrane, and endothelium are the five layers that make up the cornea. This is a crucial route for drugs to enter the eye. The epithelium is composed of five layers, or 10^-6 cells. Within the cornea, the thickness ranges from 0.5 to 0.7 mm. The corneal epithelium is a significant barrier to drug absorption into the attention; it is highly impermeable in comparison to many distinct epithelial tissues (intestinal, nasal, bronchial, and tracheal). The epithelium is composed of five to six layers of squamous stratified cells, with a thickness ranging from around 50 to 100 um and a daily turnover of about one mobile layer. The stroma, also known as substania propria, makes up around 90% of the cornea's thickness and is primarily made of 200–250 collagenous lamellae and 85% water. The lamellae provide the body with energy while maintaining the membrane's visual transparency. The open nature of the stroma allows the hydrophilic solutes to diffuse. Nestled between the stroma and the endothelium, the descemet's membrane is secreted with the help of the endothelium.

2. Barriers to Effective Ocular Drug Delivery

2.1. Barriers in the Anterior Segment

2.1.1. Tear Film

Tear film is one of the precorneal barriers that lowers the effective concentration of the medications administered because of drug molecule binding to the tear proteins, faster clearance, and dilution by the tear turnover (about 1 µL/min). Furthermore, the instillation dosage typically ranges from 20 to 50 µL, while the cul-de-sac has a smaller amount of 7 to 10 µL. The extra volume may leave through the nasolacrimal duct or overflow onto the cheek.[5]

2.1.2 Cornea

As a mechanical and chemical barrier, the cornea, which is made up of five layers: the epithelium, stroma, Descemet's membrane, endothelium, and Bowman's membrane, restricts the entry of external substances into the eye and shields intraocular tissues. The basal and wing cells have gap junctions, whereas the surface epithelial cells have tight junction complexes. The inner

endothelial cells, which contain macula adherents, are covered by the stroma and Descemet's membrane, which also permits the transverse movement of materials.

The semi-permeable membrane of the cornea passively permits material movement between its cells. Only relatively small molecules (average diameter of 2.0 nm) can pass through the holes due to the tight junctions, or zonulae occludens, on the surface of the corneal epithelium that block the passage of hydrophilic and macromolecular molecules. The stroma is more hydrophilic and impedes the transverse wave of lipophilic molecules because to its high content of hydrated collagen. Additionally, charged molecules' ability to interact with ions is hindered by the negatively charged pores at physiological pH. Factors like the drug's degree of ionization, charge, lipophilicity, and molecular weight all affect the transcorneal transfer. Drugs may occasionally not reach the posterior regions of the eye at therapeutic concentrations because of decreased diffusion across the vitreous humor, even though they have successfully diffused into the aqueous humor via transcorneal transport.[6]

2.1.3. Blood–Aqueous Barrier

The blood-aqueous barrier (BAB) is composed of endothelial cells in the iris vasculature, the inner wall endothelium of Schlemm's canal, and tight junctions in the non-pigmented epithelium of the ciliary process. The passage of ions and other tiny materials between neighboring cells is governed by the tight junctions, which control paracellular transport. The BAB acts as a specific doorway for regulated molecular transport rather than being totally impenetrable.[7]

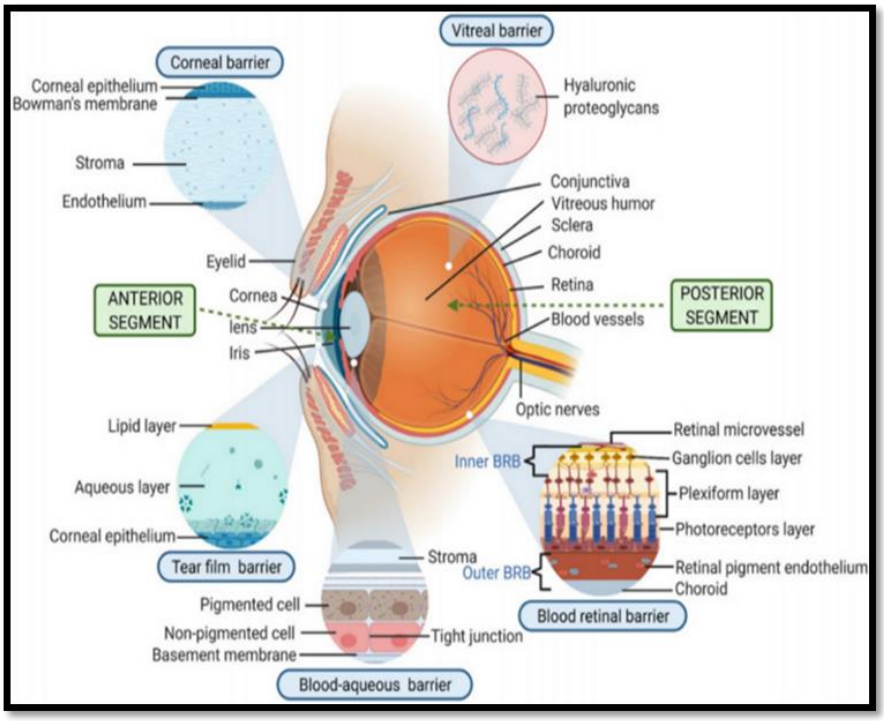

Fig. 2: Barriers in the Anterior and Posterior Segment.

2.2. Barriers in the Posterior Segment

2.2.1 Vitreous Humor

The aqueous humor, which fills the anterior part of the eye, is a low viscosity, mildly alkaline fluid situated between the cornea and iris. It has an approximate volume of 300 µl. The ciliary epithelium secretes 2-3 microliters of aqueous humor each minute into the posterior chamber of the anterior portion of the eye. After passing through the pupil and around the lens, the fluid enters the anterior chamber. Finally, the aqueous humor exits the eye by the episcleral veins, Schlemm's canal, and the trabecular meshwork. Merely 3% or less of the medication administered topically reaches the aqueous humor via penetrating the cornea. This is further diminished by the quick turnover of aqueous humor, which further lowers the gradient of drug concentration. Another dynamic barrier is the direction in which the aqueous humor flows from the ciliary body via the trabecular meshwork, which is opposite to the direction necessary for molecular mobility. A medication comes into contact with the iris, pupil, and lens as it gradually travels from the aqueous humor towards the posterior segment. The provided data is insufficient to assess the barrier nature of these structures. Drug penetration is further hampered by indications of active drug transporter expression in the iris and ciliary body. Additionally, the amount of medication that reaches the posterior segment may be decreased by drug binding to melanin pigment in the iris and ciliary body.[8]

2.2.2 Sclera and Bruch's–Choroid Complex

The choroid is a highly vascularized membrane that lies between the sclera and the retinal pigment epithelium (RPE). It has a thickness of about 200 µm and is

composed of five different layers: the suprachoroidal layer, two vascular layers, Bruch's membrane, and the choriocapillaris layer. Hydrophilic substances are repelled by the choroid, but positively charged lipophilic medications can form slow-release depots by binding to the tissue. The sizes of medication molecules also affect how well they diffuse into the posterior eye segment. The primary components of Bruch's membrane, which is between 2-4 μm thick, are collagen and elastin fibers. Larger molecules can flow through the heavily fenestrated capillaries in the choriocapillaris layer because their holes range in size from 6 to 12 nm.

The sclera, which is the opaque outer layer of the eye, is composed mainly of collagen fibers, glycoproteins, and proteoglycans. Its usual thickness ranges from 0.5 to 1 mm. Drug permeability across the sclera is dependent on a number of parameters, including lipophilicity, molecular weight, size, and charge. Hydrophilic substances, like as methazolamide, have the ability to pass through the sclera. Under normal pH circumstances, the proteoglycan matrix in the sclera bears a negative charge, which facilitates the transport of negatively charged solutes past this barrier.[9]

2.2.3. Blood-Retinal Barrier

The BRB, which consists of retinal pigment epithelium cells (RPEs) as the outer blood-retinal barrier and retinal capillaries as the inner blood-retinal barrier, respectively, further blocks drug entrance from the blood into the posterior chamber. Measuring drug permeability through RPEs is simpler, whereas measuring permeability through retinal capillaries is more difficult. Furthermore, a key element in the drug's ability to pass through retinal capillaries is particle size.[10]

3. Ocular drug delivery routes

There are several possible routes of drug delivery into the ocular tissues. The selection of the route of administration depends primarily on the target tissue.

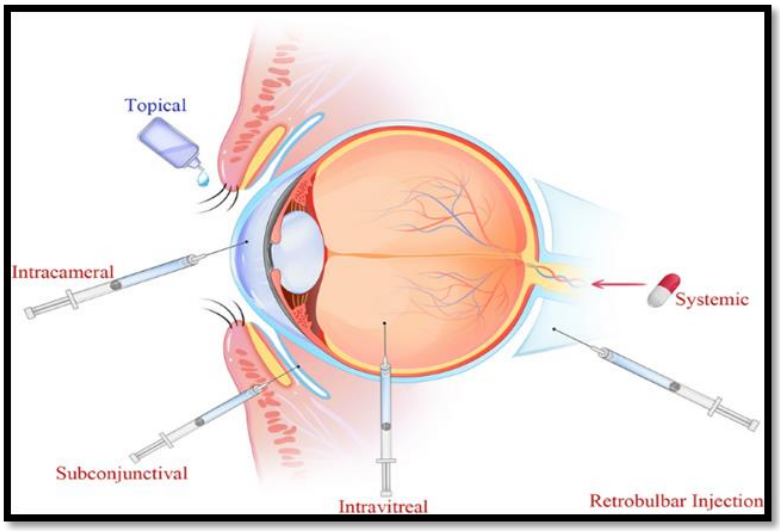

Fig. 3: Different Routes of Drug Administration.

3.1 Topical Administration

Topical distribution accounts for more than 95% of marketed ocular drugs, making it the most widely used route of ocular drug delivery. Despite being a non-invasive technique, its bioavailability is restricted (<5%) due to its short residence length and insufficient corneal penetration. Moreover, bioavailability is decreased by blinking, tears, and nasolacrimal entrance into the systemic circulation. When applied topically, high dose concentrations can have unfavorable side effects. A patient's compliance may also be impacted by frequent dosing.[11] After topical treatment, there are two primary methods to increase ocular bioavailability: both (a) lengthen the pre-corneal retention period and (b) improve the permeability of medications applied to the cornea, scleral, or conjunctiva. Many strategies, such as prodrugs, mucus osmotic particles, enhancers, collagen corneal shields, and therapeutic contact lenses, have been put forth to extend the duration of drug residence following topical delivery.[12]

3.2 Periocular and Intraocular Injections

While intraocular injections are typically administered via intracameral and intravitreal injection, periocular injection delivery techniques include subconjunctival, subtenon, peribulbar, retrobulbar, and subretinal administration. In clinical practice, medication administration to the posterior portion of the eye remains a significant issue due to the intricacy of the ocular anatomy and physiology. In an effort to address the inadequacy of topical and systemic administration in providing therapeutic drug concentrations to the posterior segment, the periocular and intraocular routes of administration are now being utilized. The most popular and generally advised method of administering medication for posterior ocular illnesses is intravitreal injection, which can also be a useful means of delivering

high therapeutic doses. However, it can result in low patient compliance and an increased risk of problems such endophthalmitis, ocular hypertension, cataracts, vitreous hemorrhage, and even retinal detachment because of the frequent requirement for very intrusive injections to maintain therapeutic levels.[13]

3.3 Systemic administration

Systemic administration is a drug delivery technique that reaches the posterior eye segment through the choroidal capillaries, primarily by oral and intravenous methods. However, the drug molecules are impeded from penetrating by the blood-aqueous barrier (BAB) and blood-retinal barrier (BRB). As a result, a far higher dose is needed for the medication to be effective, which increases the drug's toxicity. Systemic administration is advised in certain conditions, primarily those that are systemic (such as rheumatologic disorders) or life-threatening (such as endophthalmitis). But it is preferable to postpone systemic delivery if a patient only has a single eye issue. The systemic approach has unavoidable side effects, even with its high oral and intravenous bioavailability. For the reasons listed above, systemic administration is not a recommended procedure, and there are numerous obstacles associated with using this drug delivery method to administer the medication to the posterior section.[14]

3.4 Subconjuctival route

A minimally invasive method for administering medication to the posterior region of the eye is the subconjunctival route. Injecting drugs or placing implants in the subconjunctival space allows for greater permeability across the retina/choroidal area, avoiding the conjunctival and corneal barriers. Thus, the subconjunctival methods are promising due to the decreased likelihood of hazards associated with intravitreal injections, such as endophthalmitis, intraocular inflammation, retinal toxicity, and retinal detachment. However, limited retinal bioavailability is caused by scleral barriers to the choroid, clearance in the blood, and lymphatic flow in the subconjunctival area. Approximately 80–90% of small molecules injected in the subconjunctival region were quickly absorbed into the blood and lymphatic flow of the systemic circulation in earlier experiments. The conjunctiva's abundant and dynamic network of lymphatic networks is important to the drug clearance process. Due to the drug's regulated release and efficiency, the subconjunctival route has been deemed limited.[15]

4. Ocular Diseases

4.1 Cataract

Globally, cataracts are the most common cause of vision loss. Roughly 40–60% of blindness worldwide is a result of cataract complications. Cataract (62.6%) is the primary cause of preventable blindness in India, according to the National Programme for Control of Blindness and Visual Impairment. The development of cloudiness or opacification in the eye lens is known as a cataract. Among the risk factors include smoking, genetic determinism, poor nutrition, diabetes, and UV radiation exposure. Three forms of cataracts can be distinguished: cortical, nuclear, or posterior subcapsular. The crystallin protein controls the transparency and clarity of the lens. The early development of cataracts is caused by mutations in the α, β, and γ crystallin genes. Glycation, oxidative stress, and exposure to lipophilic substances raise the calcium level in the lens and cause crystallin buildup, which are the three main causes of cataracts. Hydroxyl radicals and hyperglycemia act as mediators of oxidative stress. These days, the option for treating opaque lenses is surgical removal. On the other hand, early anti-cataract medication use may reduce the need for surgery. Anti-cataract agents are antioxidants that have multiple functions, including radical hunting and chelation. Metformin, lanosterol, resveratrol, and curcumin are a few anti-cataract medicines.[16]

4.2 Conjunctivitis

The inflammation or swelling of the conjunctiva is known as conjunctivitis, or pink eye. It is among the most prevalent eye conditions, although if caught early enough, it is rarely serious and unlikely to impair vision. Allergens, diseases, or chemicals can induce conjunctivitis. People who already have seasonal allergies are more likely to develop allergic conjunctivitis. People who wear contact lenses are more likely to get allergic conjunctivitis, particularly if they don't replace their lenses often. Most common cold-causing bacteria, viruses, and streptococci are the main causes of infectious conjunctivitis. If treatment for ophthalmia neonatorum, an infectious conjunctivitis that develops in the first month of life, is delayed, it can become severe and result in irreversible visual impairment. More than 40% of instances of ophthalmia neonatorum are caused by chlamydial conjunctivitis, which is passed on during childbirth from moms carrying a chlamydia trachomatis infection. Exposure to dangerous substances in the environment might result in chemical conjunctivitis. Depending on the underlying reason, conjunctivitis can be treated with topical antihistamines, non-steroidal anti-inflammatory medications, steroids, and antibiotics.[17]

4.3 Age-related macular degeneration

Globally, AMD is the third most common cause of severe permanent vision loss, and by 2040, there will likely be close to 300 million AMD sufferers. Early AMD and late AMD are the two clinical subtypes. Early AMD is characterized by medium-sized stone fruit and changes in retinal pigmentation; late AMD is categorized as either non-neovascular (also known as atrophic, dry, or non-exudative) or neovascular (also known as wet or exudative), which can result in central vision loss and legal blindness.

Antioxidant vitamin supplements and high-dose zinc can prevent the progression of disease from its early stages to its advanced stages. Neovascular AMD is successfully

treated with intravitreal injection (IVT) of anti-vascular endothelial growth factors (VEGF) (e.g., aflibercept, bevacizumab (Bev), etc.); nonetheless, this is still an invasive procedure. Thus, it is especially crucial to take advantage of novel drug delivery methods for customized drug delivery.[18]

4.4 Dry eye disease

The preocular tear film condition known as dry eye syndrome (DES) damages the ocular surface and is linked to sensations of discomfort in the eyes. Other names for DES include xerophthalmia, keratitis sicca, sicca syndrome, keratoconjunctivitis sicca (KCS), ocular surface disease (OSD), dysfunctional tear syndrome (DTS), and dry eyes. The literal translation of the Latin term keratoconjunctivitis sicca is "dryness of the cornea and conjunctiva." The fact that the English term "desiccate" includes the word "sicca" may be useful to you. Sjögren's syndrome is another name for the dry eye condition in which the eyes do not produce enough tears.[19] ../../../../../win/Downloads/.Phadatare, S.P., Momin, M., Nighojkar, P., Askarkar, S. and Singh, K.K., 2015. A comprehensive review on dry eye disease: diagnosis, medical management, recent developments, and future challenges. Advances in Pharmaceutics, 2015The most popular option for treating DES has been cyclosporine, which works by preventing the activation of inflammatory immune cells and the creation of cytokines. The commercial eye drops that provide cyclosporine to treat DES are called Restasis® and Cequa®.[20]

4.5 Glaucoma

Glaucoma, a set of eye illnesses that can cause vision loss by injuring the optic nerve, is the leading cause of permanent blindness worldwide. It is a neurodegenerative disease that damages retinal ganglion cells and their axons. One of the main risk factors for optic neuropathy is elevated intraocular pressure (IOP). Globally, 111.8 million individuals are expected to be affected with glaucoma by the year 2040. The current standard of care for glaucoma involves reducing the intraocular pressure (IOP) through surgery or daily eye drops, although there are several mechanisms involved in the disease's development and progression. Because the frequency of the eye drops must be closely adhered to in order to achieve effective management of the IOP, patient compliance with topical drop instillation is infamously low.[21]

5. Conventional ocular drug delivery system

Nowadays, there are several types of ocular drug delivery system in the market including ophthalmic eye drops which are highly used by patients. Others are emulsion, suspension, ointment and polymeric gel preparation.

5.1 Eye Drops

Of all topical eye preparations, topical eye drops are the most practical, non-invasive, and patient-friendly. When it comes to treatments, eye drops face a few obstacles. According to the study, a significant portion of patients had trouble injecting the drops. In addition, the solution may be lost or diluted due to tear drainage, which rises with the amount of eye drops used. Apart from that, the eye pocket's small capacity makes it impossible to determine the amount of medicine absorbed into the ocular tissue. Commonly used as a preservative, benzoalkonium chloride can also lead to a number of issues, including the peeling away of corneal epithelium cells at their borders, which stops the cells from growing and causes the intercellular gaps in the superficial corneal cells to expand. The usage of cyclodextrin as a hydrophobic molecule carrier to boost the topical eye drop's bioavailability, permeation enhancer to increase the active ingredient's uptake, and viscosity enhancer to lengthen the duration of contact.

5.2 Emulsion

The use of submicron emulsion (ranging from 0.1µm to 0.3µm) in conjunction with non-ionic surfactant to boost stability has revived interest in emulsion usage in the past. The ocular medication solubility and bioavailability may be improved via emulsion-based formulation. Emulsions that are now on the market as vehicles for active pharmacological components are primarily classified into two categories: water in oil (w/o) and oil in water (o/w). Of these two emulsions, the (o/w) kind is better since it has a higher ocular tolerance and causes less ocular irritation. In terms of ocular formulation, the emulsion-based formulation can be advantageous in that it can increase the drug's bioavailability, improve corneal permeability, improve precorneal residence time, and provide sustained-release qualities. Emulsion containing chitosan as a surface coating can potentially increase precorneal residence duration. Examining the eyes of male albino rabbits with chitosan-coated emulsion versus uncoated emulsion. The outcomes demonstrated improvements in the half-life (1.8 times) and mean residence time (1.5 times) of the Drugs in comparison to non coated emulsion.

Ophthalmic emulsions do have certain restrictions, though. They are unstable and prone to a number of instability events, including creaming, flocculation, and coalescence. When the dispersed phase emerges from the suspension and produces flakes, this process is known as flocculation. Another unstable mechanism that causes the scattered droplets in the suspension to continually join to generate larger droplets is called coalescence. A distinct layer between the two phases known as creaming is created when one of the emulsion's phases migrates to the top or bottom based on their respective densities. As a result, the study recommended using surfactants to raise the emulsion products' kinetic stability.

5.3 Suspension

A suspension is a finely insoluble active medicinal component that has been dispersed in a solvent. Stated differently, it can be described as a concentrated mixture of active pharmacological components. Compared to ophthalmic drops, this kind of ocular drug delivery system offers a number of advantages. The primary advantage lies in its potential to enhance the drug's duration of action and contact time since the insoluble suspension stays in the precorneal pocket rather than being diluted or washed away by the tear. The varied particle sizes of the suspended particles also contribute to the enhancement in the duration of the drug's action. The large particles will be held in the precorneal pocket and dissolve slowly, while the little particles will refill the medication that has been absorbed. When it comes to crossing the cornea and reducing ocular irritation, prednisolone acetate suspension works better than prednisolone phosphate solution. Additionally, 1% and 2% repabimide suspension was the subject of a four-week randomized, double-blind, multicentre phase II clinical investigation conducted in comparison to a placebo. When compared to a placebo, this trial showed that both treatments are safe and effective in treating dry eye. Furthermore, it was discovered that a suspension with a higher concentration worked better than one with a lower concentration. Suspension has a number of disadvantages in addition to its advantages.

For instance, experiments were conducted to lower the high viscosity of TobraDex® and enhance its pharmacokinetics and bactericidal efficacy. As a result, TobraDex ST®, a novel suspension formulation, was created and shown improved pharmacokinetics, bactericidal properties, and patient compliance. The fact that the suspension formulation must be shaken in order to achieve the necessary dosage level is another disadvantage. As a result, the dosage of the medication given to the eye will change and patient compliance may decline. The efficacy of ocular drugs is limited by patient compliance, as efficacy increases with frequency of administration. Low patient compliance may also have an impact on the suspension's effectiveness.

5.4 Ointment

Ointment is a combination of solid and semisolid hydrocarbons, such paraffin, that melts at body temperature and doesn't irritate the eyes. Generally speaking, ointments come in two varieties: compound-based ointments, which are composed of a two-phase system similar to an emulsion, and simple-based ointments, which are composed of a single continuous phase. The ointment will fragment into tiny droplets when administered to the eye, staying in the conjunctival sac for an extended amount of time. This process results in the main benefit of ointment: it acts as a drug depot in the conjunctival sac, enhancing and extending the absorption of the medication. The development of an ointment should have a number of desirable qualities, such as being uniform, non-irritating to the eye, easily made, and not producing an excessive amount of obscured vision. Ophthalmic ointment has a significant disadvantage that may lessen its effectiveness, despite the fact that it can improve and extend medication absorption. Low patient compliance can arise from ointment application-related vision impairment and sporadic discomfort. It is typically used at night before going to bed as a result.

5.5 Polymeric Gel

Another dosage type for topically administering medication to the eye is ocular gel. Mucoadhesive polymers, one of the components that make up gels, are crucial for the localized distribution of active substances. Ophthalmic gels have been made more effective by using mucoadhesive polymers. This polymer allows the drug carrier to adhere to biological tissue, improving ocular bioavailability and extending the duration of contact. Ophthalmic gels come in two varieties: preformed gel and in-situ forming gel. Because ophthalmic premade gel is present as a gel substance at room temperature, it is not as desirable as other dosage forms. This property's application in ocular drug delivery is limited due to the low accuracy and repeatability of drug administration, which frequently results in crusty eyelids, lachrymation, and blurred vision. Because in situgels offer the benefits of both solution and gel, they have become a focal point in gelling systems. A viscous liquid preparation known as "in situforming gel" will transition to a gel phase by any one of these three mechanisms: pH triggered, temperature triggered or ion activated.[22]

6. Nanotechnology based ocular drug delivery

Many methods have been used in the last few decades to cure illnesses of the eyes. One strategy being investigated for drug distribution to the front and posterior segments of the eye is the use of nanotechnology in ocular formulations. It is possible to create nanotechnology-based solutions with the right particle size to guarantee minimal eye tissue irritation, sufficient bioavailability, and compatibility. For the purpose of delivering drugs to the eyes, several nanocarriers have been created, including liposomes, nanoparticles, nanosuspensions, nanomicelles, and dendrimers. In terms of enhancing ocular bioavailability, a few of them have demonstrated encouraging outcomes.[23]

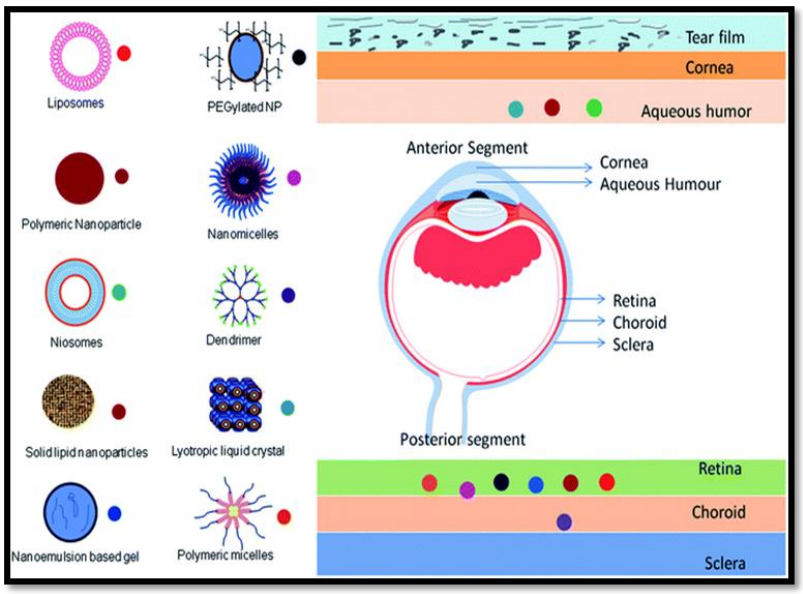

Fig. 4: Nanotechnology Based Ocular Drug Delivery System.

6.1 Liposomes

Liposomes are spherical, lipid-based vesicles that range in size from 0.08 to 10.00 mm and are made up of cholesterol and phospholipids. They are biocompatible, biodegradable, flexible, and have the ability to contain both hydrophilic and hydrophobic medications in one system at the same time. Liposomes have been used in numerous attempts to increase their stability, focused activity, bioavailability, and corneal penetration. Liposomes have been studied for targeted drug delivery and extended drug release. Using a thin-film hydration technique, Fahmy et al. created liposomes containing latanoprost and thymoquinone, which were then injected subconjunctivally to cure glaucoma. The drug-loaded liposomes had an 88% encapsulation efficiency and a particle size of less than 0.2 mm. Studies on the release of drugs in vivo and in vitro demonstrated that drug-loaded liposomes significantly decreased intraocular pressure up to 84hr compared to test formulations.[24]

6.2 Nanoparticles

Nanoparticles are colloidal particles that range in size from 10 to 1000 nm. When it comes to ocular delivery, nanoparticles are typically made of proteins, lipids, and natural or synthetic polymers including poly (lactide-co-glycolide) (PLGA), polylactic acid (PLA), albumin, sodium alginate, and chitosan. Drug-loaded nanoparticles can take the form of nanospheres or nanocapsules. In nanospheres, the drug is evenly dispersed throughout the polymeric matrix 41, but in nanocapsules, the drug is contained inside the polymeric shell. Over the last few decades, there has been an increased interest in using nanoparticles for the transport of drugs into the eyes. Several researchers have worked to create drug-loaded nanoparticles that can reach the tissues in the front and posterior parts of the eyes.[25]

6.3 Dendrimers

Organic polymers called dendrimers have a central core from which 'branches' radiate outward to take the form of a sphere. Because of their high loading capacity, flexible exterior functional motif, and regulated drug release, these particles are beneficial for ocular medication delivery. By adding hydrophilic groups to the outer branches of dendrimers, which subsequently interact with water, it is possible to make them water soluble, just like liposomes. Hydrophilic medicines can be conjugated to a variety of functional groups present at the ends of these polymeric branches. Because they are commercially available, dendrimers with poly(amidoamine) (PAMAM) as their structural motif are increasingly being employed for ocular gene therapy. The capacity of dendrimers to avert endosomal acidification sets them apart. They have a large buffering capacity as well as the ability to encourage the osmotically driven rupture of endosomes, which improves theefficiency of gene transfer. The safety, tolerability, and pharmacokinetics of D-4517.2, a hydroxyl dendrimer that subcutaneously administers a VEGFR tyrosine kinaseinhibitor to healthy volunteers, are now being assessed in a phase 1 clinical trial (NCT05105607). This and other recently developed medication delivery methods.[26]

6.4 Niosomes

Another type of self-assembling, nonionic carrier system is niosomes, which are bilayered structured nanovesicles made of lipid-based nanocarriers that can encapsulate both hydrophilic and lipophilic compounds. They increase the drug's ocular bioavailability by releasing it regardless of pH. The effectiveness of niosomes as carriers for protein transport to ocular tissues is still being studied, despite the fact that they are biodegradable, biocompatible, nontoxic, nonimmunogenic, and have good chemical stability, much like liposomes.[27] Niosomes' small size provides a

crucial ability to get around the ocular drainage process and improve drug retention on the surface of the eye. Gugleva et al. found that sorbitan monostearate (span60) and cholesterol formulation resulted in niosomes with a high encapsulation efficiency of doxycycline hyclate. This delayed drug-release rate was well tolerated in mice's eyes.[28]

6.5 Solid lipid nanoparticles and nanostructured lipid carriers

Solid lipid nanoparticles (SLNs) are colloidal carrier systems with a particle size range of 10 nm to 500 nm that are composed of lipids distributed in an aqueous surfactant environment. They work well when delivering hydrophobic medications. It has been demonstrated that SLNs have better retinal penetration and longer-lasting sustained drug release at the ocular location. They can lessen the toxicity brought on by often giving a large amount. To treat retinal illnesses intravitreally, Ahmed et al. synthesized etoposide-loaded SLNs using the melt emulsification and ultrasonication techniques. The synthesized SLNs had an entrapment effectiveness of 80.96 ± 2.21% and a particle size of 239.43 ± 2.35 nm. The produced formulation demonstrated a seven-day sustained release of the medication in the vitreous area, following an initial burst release. Limitations of SLN-based nanocarriers include low loading capacity, drug ejection due to lipid crystallization, and alpha to beta confirmation conversion during storage. As a next-generation lipid nanocarrier that can offer better drug loading and stability, nanostructured lipid carriers, or NLCs, have been studied. Solid and liquid lipids are combined in a nanocarrier system to create NLCs. Because of the asymmetric nature of NLCs, drug release is rather sluggish and is prevented from being expelled. Because of their lipid nature, effective drug-loading capability, and good durability, NLCs are a perfect drug delivery mechanism for the back of the eye.[29]

6.6 Nanosuspension

Nanosuspensions are colloidal systems stabilized by the addition of polymers or surfactants, in which drug particles smaller than a micron are scattered. Nanosuspensions present a viable delivery method for hydrophobic medicines. When used to deliver medication to the eye, nanosuspensions have a number of benefits, including longer retention times in the precorneal tissues, higher bioavailability for medications that are insoluble in tear fluid in the ocular space, less irritation in the ocular tissues, ease of formulation into drops for ophthalmic use, and sterilization.

Pignatello et al. created a nanosuspension method that uses Eudragit RS100® to deliver ibuprofen (IBU) to the eyes. Their formulation demonstrated regulated release and had a mean particle size with a positive charge. Miosis-induced rabbit eye in vivo investigations demonstrated its suppression. However, a large concentration of the free medication did not enter the conjunctival sac from the system following the injection of the nanosuspension. After the formulation was applied, the concentration of IBU in the aqueous humor of the eye increased, but there was no sign of toxicity or irritation.[30]

7. CONCLUSION

For many years, ocular scientists have faced a significant obstacle in the form of drug delivery to specific ocular tissues. Using traditional formulations of medication solutions as topical drops had some disadvantages that led to the development of alternative carrier systems for ocular delivery. A great deal of work is being done in the field of ocular research to create innovative drug delivery systems that are safe and acceptable to patients. Researchers are working very hard right now to enhance traditional formulations' in vivo performance. On the other hand, ocular scientists are becoming increasingly interested in the novel methods, tools, and uses of nanotechnology in medication administration. Drug molecules are administered by invasive, non-invasive, or minimally invasive methods by being encased in nanoscale carrier systems or devices. Numerous nanotechnology-based carrier systems, including liposomes, nanoparticles, nanomicelles, nanosuspensions, and dendrimers, are being produced and extensively researched. Only a small number of them are used in clinical settings and are produced on a huge commercial basis. The body of the patient benefits from nanotechnology by experiencing less drug-induced toxicities and visual loss. Additionally, when targeting moieties are employed, these nanocarriers/devices improve specificity, prolong drug release, and assist in lowering dose frequency. However, after a non-invasive method of medication administration, a carrier system that could reach targeted ocular tissue—including the tissues in the rear of the eye—still has to be developed. The current rate of ocular research and development is anticipated to produce topical drop formulations that avoid non-specific drug tissue accumulation, deliver therapeutic drug levels into targeted ocular tissue (both anterior and posterior), and maintain high precorneal residence times. Soon, this delivery method might take the place of intrusive techniques like intravitreal and periocular injections for administering drugs to the back of the eye.[31]

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