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REVIEW ON OCULAR DRUG DELIVERY SYSTEM

Pravin Sanjay Jagtap*, Pranali Hatwar and Dr. Gajanan Sanap

Department of Pharmaceutics, LBYP College of Pharmacy, Pathri, Tq. Phulambri Dist. Ch. Sambhajinagar, Maharashtra, India.

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***Corresponding Author**
Pravin Sanjay Jagtap
Department of Pharmaceutics, LBYP College of Pharmacy, Pathri, Tq. Phulambri Dist. Ch. Sambhajinagar, Maharashtra, India.

ABSTRACT

Ocular drug delivery is the main issue facing formulation scientists and pharmacologists today. The most practical and patient-friendly method of administering medication is via topical eye drops, particularly when treating anterior segment disorders. Precorneal, dynamic, and static ocular barriers limit the delivery of drugs to the targeted ocular tissues. Furthermore, target tissues do not retain therapeutic drug levels for extended periods of time. Over the last twenty years, research on ocular drug delivery has made significant progress in creating innovative, safe, and patient-friendly drug delivery formulations and techniques that could potentially overcome these obstacles and sustain drug levels in tissues. The use of permeation and viscosity enhancers in conventional topical solutions has led to advancements in anterior segment drug delivery. It also entails creating custom topical formulations, like ointments, emulsions, and suspensions. Additionally, a number of Nano formulations for anterior segment ocular drug delivery have been introduced. The preferred method for treating ocular diseases is topical application due to the blood-ocular barrier. The most widely used traditional ophthalmic dosage forms consist of solutions, suspensions, and ointments; however, they are not very effective as therapeutic systems. The required amount of drug is not available for immediate therapeutic action because it binds to the surrounding extra orbital tissues. After administration, a significant portion of the topically applied drug is immediately diluted in the tear film, excess fluid spills over the lid margin, and the remaining portion is rapidly drained into the nasolacrimal duct Frequent topical administration is required to maintain adequate drug levels in light of these losses. To reach therapeutic levels when a medication is administered systemically to treat ocular diseases, there must be a significant amount of the

drug circulating in the plasma. The duration of the drug's action can be noticeably extended and the frequency of drug administration can be decreased by employing prolonged drug delivery. Creating formulations like liposomes, nanoparticles, and microspheres that can function as effective ocular drug delivery systems can help achieve this kind of drug delivery.

KEYWORDS: Ocular drug delivery systems, suspension, emulsion, ointments, Anatomy.

INTRODUCTION

The eye has an intricate physiology and is an extremely sensitive organ. It is made up of segments that are anterior and posterior. Generally, visual impairment resulting from different diseases has a significant impact on quality of life. Cataract is a clouding of the eye's lens and is the leading cause of blindness worldwide. About 40–60% of blindness worldwide is a result of cataract complications.[1]

Mutations in α, β, and γ crystalline and related genes cause early cataract development.[2] One well-known optic neuropathy condition associated with increased intraocular pressure (IOP) is glaucoma. In the later stage[3], it results in permanent blindness. Furthermore, aging, diabetes, and fungal infections are associated with visual impairment. Ocular diseases include retinoblastoma, fungal keratitis, diabetic retinopathy (DR), and age-related macular degeneration (AMD). According to a recent study, there are roughly 196 million AMD sufferers, 92.6 million DR patients, and 76 million glaucoma sufferers.

Many diseases, some of which are sight-threatening, can affect the eye. Because of the eye's distinct anatomy and physiology, treating these diseases has always presented a challenge for medical professionals and the pharmaceutical industry, particularly when it comes to the best way to administer drugs. When it comes to treating the anterior segment of the eye, topical eye drops are frequently used and the recommended form of treatment. But because new technologies are being developed, these medications typically do not reach the retina, vitreous, or choroid, for which there are other preferred drug administration routes.[4]

The most popular non-invasive medication delivery method for treating illnesses of the anterior segment is topical instillation. Ninety percent of the marketed ophthalmic formulations are in conventional dose forms, including eye drops. Patient compliance and convenience of administration might be the cause.[5,6]

An alternate method of medication delivery to the posterior ocular tissues of the eye gave rise to the trans scleral drug delivery with particular administration route. Despite the ease, minimal invasiveness, and patient compliance associated with trans scleral administration, ocular static and dynamic obstacles impede drug penetration. Ocular obstacles to trans scleral drug administration include: dynamic barriers, such as lymphatic movement in the conjunctiva and episclera and blood flow in the conjunctiva and choroid, and static barriers, such as the sclera, choroid, and retinal pigment epithelium (RPE).[7,8]

THE ANATOMY AND PHYSIOLOGY OF AN EYE[9]

The human eye is a vital sensory organ with a somewhat complex structure. The eye's three layers are the outermost fibrous layer, the middle vascular layer, and the inner neural layer. The eye can refract light, generate focus images, excite the nervous system, and allow vision. The cornea and sclera are the two primary structures found in the outer fiber layer. The sclera, or white part of the eye, comprises most of the outer layer.

The structure and different corridor of the Eye

Aqueous Humor: It's a jelly-like material found in the eye's anterior chamber.

Choroid: It absorbs unnecessary radiation and is located behind the retina.

Ciliary Muscle: This muscle, which resembles a ring, is joined to the iris. The ciliary muscle's capacity to contract and relax controls the iris's shape.

Cornea: It's an epithelial membrane, clear and translucent. To get to the retina, light rays must go through the cornea. Light rays are refracted by the convex cornea, which helps to concentrate them on the retina.

Fovea: It is a tiny patch of the retina, measuring around 1.5 mm in diameter. It is the area of the retina where minute detail may be seen at great resolution.

Hyaloid: The vitreous humor and aqueous humor are separated by the hyaloids diaphragm.

Iris: The visible portion of the eye, the iris, lies in front of the lens and behind the cornea. It protrudes anteriorly from the ciliary body. Because the anterior and posterior chambers of the eye's anterior segment contain aqueous fluid generated by the ciliary body, the iris separates this region. Iris is supplied by both sympathetic and parasympathetic nerves. The pupil is contracted by parasympathetic stimulation and dilated by sympathetic activation.[10]

Lens: It is the lens of the eye, a flexible structure made up of many tissue layers protected by a hard capsule. It hangs from the ciliary muscle by means of the zonule filaments.

Optic Nerve: The second cranial nerve, the optic nerve, is in charge of vision. About a million fibers make up each neuron, which carries information from the retina's Rod and Cone cells.

Papilla: It is situated where the optic nerve exits the retina and is also referred to as the blind spot.

Pupil: It is the hole that allows light to enter the eye, allowing us to see and comprehend pictures. The iris creates this.

Retina: It is defined as the screen that forms an image as light enters the eye through the aqueous humor, pupil, lens, hyaloids, and vitreous humour, eventually arriving at the retina. The rod and cone photosensitive components found in the retina translate light into nerve impulses that go via the optic nerve to the brain.[11]

Sclera: The tough white sheath that encircles the exterior of the eyeball is called the sclera. It's made up of a membrane that keeps the eye's form and serves as the attachment point for the eye's extrinsic muscle.

Vitreous Humor: It resembles jelly and has a vitreous body.

AN INSIDE LOOKS AT EYE

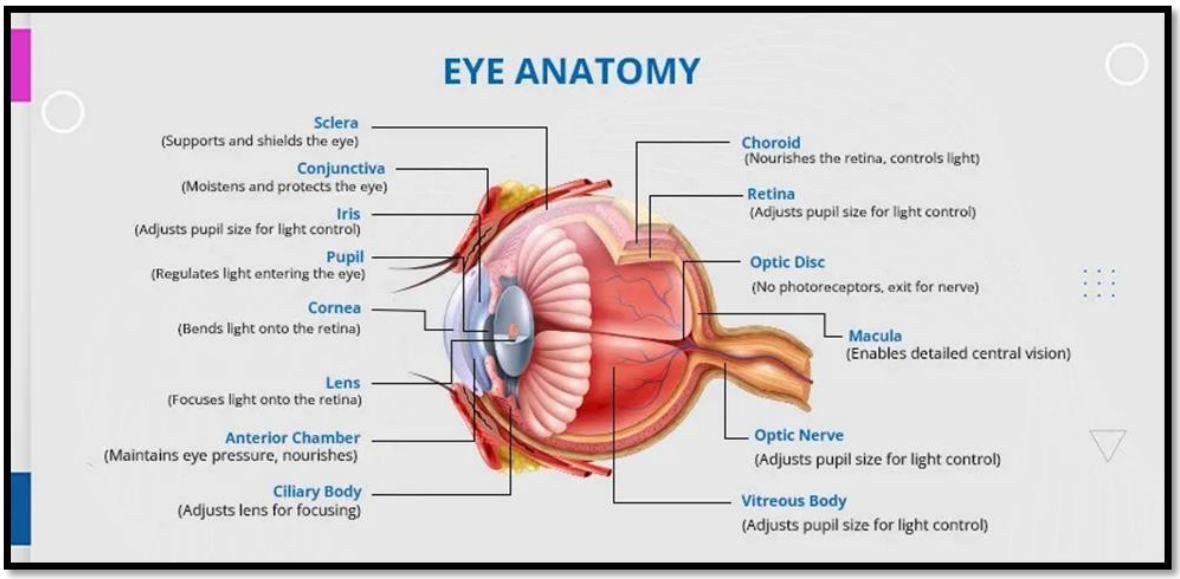

Fig. 1: Anatomy of an eye.

Advantages of ocular drug delivery system[12]

The following are ODDS's advantages.

- More precise dosage to mitigate the negative impacts of conventional systems' pulsed dosing.

- To distribute drugs in a regulated and continuous manner.
- To lengthen the corneal contact duration in order to enhance the drug's ocular bioavailability. Effective adhesion to the corneal face can negotiate this.
- To offer targeting inside the ocular globe to stop other ocular tissues from being lost.
- To go over obstacles such as lacrimation, drainage, and conjunctive absorption.
- To make the patient more comfortable, increase patient compliance, and enhance the medication's therapeutic effect.
- To improve the delivery system's housing.

Disadvantages[13,14]

The following list includes a number of drawbacks of the ocular medication delivery technology.

- The physiological limitation is the cornea's restricted permeability, which results in a poor absorption of eye medications.
- Because of the quick drug clearance through eye blinking and tear flow, the therapeutic action of the medicine is short-lived, necessitating frequent dosing.
- A significant amount of the provided dosage drains into the lacrimal duct, which may result in undesirable systemic side effects.

OCULAR DISEASES

Cataract

Globally, cataracts are the most common cause of visual loss. Roughly 40–60% of blindness worldwide is a result of cataract complications.[15] According to the National Programme for Control of Blindness and Visual Impairment[16], cataracts account for the majority of preventable blindness in India. The development of cloudiness or opacification in the eye lens is known as a cataract. Among the risk factors include smoking, genetic determinism, poor diet, 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 lenses.[17]

Glaucoma

One well-known optic neuropathy condition is glaucoma. Early symptoms include clouded vision, which in the later stages develops into permanent blindness. It causes the retinal ganglion cells to die and the optic nerve axon to slowly deteriorate, which results in blindness.[18] It is frequently linked to an increase in intraocular pressure (IOP) as a result of

abnormal aqueous fluid production or blockage.[19] Age, race, diabetes, genetics, myopia, migraines, and retinal vascular caliber are all risk factors. Women make up a larger proportion of the glaucoma population than males do, accounting for 59% of all cases of glaucoma in 2010, 70% of angle closure glaucoma, and 55% of open angle glaucoma.[15] Global incidence is predicted to reach 112 million by 2040 from an estimated 76 million in 2020.[20]

Age-Related Macular Degeneration (AMD)

One of the primary causes of visual loss in developed nations is AMD. It occurs more frequently in those over 50.[17] AMD is the cause of around 8.7% of blindness globally.[21] AMD affected around 196 million individuals in 2020, and by 2040, that figure is predicted to rise to 288 million.[22] The posterior region of the eye is involved in this multifactorial degenerative disease. Age, smoking, poor diet, high blood pressure, and immobility are risk factors. Although there is currently no cure for AMD, appropriate medicine may slow its development.[23]

Conjunctivitis

Generally speaking, conjunctivitis is the most common eye complaint. It is only the conjunctival tissue becoming inflamed. All ages, ethnicities, and genders are affected.[24] It may be classified as infectious or non-infectious depending on the etiology. Infectious conjunctivitis originates from microbial infection, while non-infectious conjunctivitis results from allergens and irritants.[24] Conjunctivitis is characterized by redness, pain, tears, and increased secretions from the eyes. About 40% of people worldwide have allergic conjunctivitis at some point in their lives.[25] Topical use of antimicrobial (infectious) or anti-inflammatory (non-infectious) medications is one way to treat conjunctivitis.

Fungal Keratitis

Since a healthy cornea would not let any fungal infection, fungal keratitis exclusively develops in corneal damage cases. It is brought on by several fungi, including Candida krusei, Candida albicans, Candida glabrata, Candida tropicalis, and Candida parapsilosis.[26] In third-world developing nations, 40% of infectious keratitis cases are caused by fungi.[15] Risk factors might be systemic (diabetes, HIV positive, and leprosy) or ocular (trauma, contact lenses, previous corneal surgery, and topical corticosteroids). Fungal keratitis causes corneal ulcers, stromal inflammatory infiltration, and poor wound healing. The expression of miRNA may change due to corneal inflammation.[27]

Retinoblastoma

A malignant tumor that affects the retina, retinalblastoma mostly affects children under the age of five. Retinoblastoma that if left untreated eventually results in blindness and death (99%). Approximately 1 in 20,000 live newborns experience it.[28] It occurs at the same rate in both genders. The tumor suppressor gene RB1, which codes for the retinoblastoma protein, is mutated, and this is the reason. Bilateral (40%) or unilateral (60%) can apply.[15] Options for treating retinoblastoma include surgery, systemic chemotherapy, cryotherapy, and radiation. According to recent research, the formation of angiogenic blood vessels and the release of compensatory proangiogenic factors are essential stages in the treatment of retinoblastoma.[29]

Routes of ocular drug delivery

Topical, intra-vitreal, intracameral, periocular, suprachoroidal, and subconjunctival are the typical routes for ocular medication administration.[30]

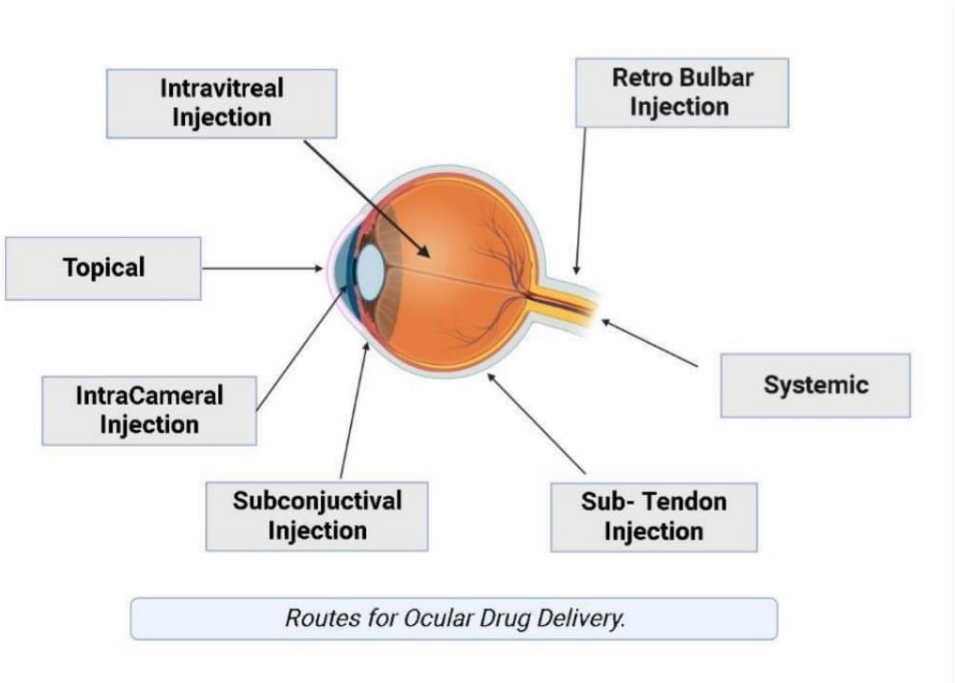

Fig. 2: Different routes of ocular drug administration.

Table 1: Summary of Routes of Administration, Benefits, and Challenges in Ocular Delivery.

Route	Benefits	Challenges	Application in the treatment of disease
Topical	Excellent patient compliance that is noninvasive and self-managed.	Greater rate of tear dilution and turnover, barrier function of the cornea, efflux pumps, and BA <5%.	blepharitis, scleritis, episcleritis, conjunctivitis, keratitis, and uveitis
Oral/Systemic	Patient compliant and noninvasive route of administration	BAB, BRB, high dosing causes toxicity, BA <2%	Scleritis, episcleritis, CMV retinitis, PU
Intravitreal	Direct delivery to vitreous and retina, sustains drug levels, evades BRB	Retinal detachment, hemorrhage, cataract, endophthalmitis, patient incompliance	AMD, PU, BRVO, CRVO, DME, CME, UME, CMV retinitis
Intracameral	Decreases the systemic and corneal adverse effects associated with topical steroid treatment, increases medication levels in the anterior chamber, and does away with the need for topical drops.	TASS, TECDS	Anesthesia, prevention of endophthalmitis, inflammation and pupil dilation
Subconjunctival	Delivery to the front and rear segments, the depot formulation location	Conjunctival and choroidal circulation	Glaucoma, CMV retinitis, AMD, PU
Subtenon	In contrast to intravitreal administration, high vitreal drug levels, relative noninvasiveness, and fewer problems	RPE, chemosis, subconjunctival hemorrhage	DME, AMD, RVO, uveitis
Retrobulbar	Give large local anesthetic dosages; these are more effective than peribulbar, and they have less effect on IOP.	Retro bulbar hemorrhage, globe perforation, respiratory arrest	Anesthesia
Posterior juxtascleral	Safe for depot formulation distribution, maintains medication levels in the macula for up to six months, and reduces the risk of endophthalmitis and intraocular damage	Requires surgery and RPE acts as barrier	AMD

Drug Delivery Systems for Ocular Route

Drop instillation is a well-known technique for administering a medication to a patient while ensuring their compliance. It involves using a topical route to deliver the medication to the lower precorneal portion of the eye. However, due to the reflux phenomenon that occurs during eye blinking; only around 20% of the initial dosage is retained in the precorneal portion of the eye. The concentration of medication accessible in the precorneal Pharmaceutics 2019, 11, 460 3 of 29 sites is a major factor influencing the drug's diffusion throughout the corneal tissues. However, a longer retention period in the corneal tissue and increased corneal permeability are required in order to obtain an efficient ocular dispersion of the medication utilizing eyedrops.[31,32] Drug development must consider how novel drug compounds and drug delivery methods interact with certain transporters as ocular drug transporters have the potential to change a medicine's effectiveness.[33] The solute carrier (SLC) family and the ATP-binding cassette (ABC) family are the two main groups of these ocular transporters. SLC transporters move their substrates across the cell membrane via enhanced diffusion, coupling an ion or electrochemical gradient, or both. Adenosine triphosphate (ATP) serves as the energy supply for ABC transporters.[33]

Table 2: Types of ocular drug delivery systems.

Topical dosage forms	Conjunctiva Inserts
	Contact Lenses
	Gels
	Nanoparticles
	Mucoadhesive Polymers
	Ointments
	Solutions
	Suspensions
Intraocular dosage forms	Implants
	Nanoparticles
	Inserts

Conventional Topical Formulation

EYE DROP

Eye drop formulations contain a range of elements that make them a commonly recommended form. They are non-invasive, safe, act right away when applied, have a high patient compliance rate, and are appropriate for the product. When eye drops are applied, the supported drug is absorbed through a pulsatile mechanism that happens after the drops are applied topically. The drug concentration then quickly declines as a result of a kinetic profile

that roughly corresponds to a first order elimination process. Consequently, a number of modifiers, such as cyclodextrins, enhancers of viscosity and permeability, are strong enough to be used in eye drop formulations in order to increase the duration of drug contact, the permeability capacity, and the critical bioavailability of the desired molecule(s).[34,35,36,37]

Fig. 3: Eye drop.

The chemicals should be selected based on how well they can sensitize the eye globe, not just on how well they can work as penetration enhancers. These findings indicate that research has been done in recent decades to produce alternative chemicals with better qualities and no negative effects on the targeted eye components. In order to improve properties like the bioavailability of the encapsulated medications, the length of time they spend in the precorneal tissues, and the solubility values, emulsions, ointments, and suspensions were investigated.[38,39] Even with the most advanced industrial and state-of-the-art manufacturing processes for creating new goods based on nanotechnology, conventional formulas continue to be heavily promoted.However, the use of the earlier formulations was linked to significant adverse effects, including inflammation, ocular tissue irritation, uneven stability, and impaired vision. In order to achieve superior performances in an in vivo organic environment while avoiding major undesired consequences, the latest study has mostly focused on increasing the important aspects that have been outlined and lowering the side effects attributed to these formulations. Many attempts are being made to try to use common formulations to get the required medications to the posterior tissues of the eye. The specific advancements made in each formulation up to this point and the general outlook for the next several years regarding formulation advancement are discussed in the sections that follow.

EMULSIONS

It is advantageous to use an emulsion-based formulation technique to increase a drug's solubility and bioavailability. Oil in water (o/w) and water in oil (w/o) emulsion systems are the two forms of emulsions that are commercially used as delivery methods for active pharmaceutical ingredients.[40] O/w emulsion is a widespread and generally favored method of ocular medication administration over w/o system. Less discomfort and improved ocular tolerance of the o/w emulsion are among the causes. Currently available ocular emulsions in the US include RestasiseTM, Refresh Endura® (a non-medicated emulsion for eye lubrication), and AzaSite®. Emulsions have been shown in several investigations to be effective in prolonging drug release, increasing ocular bioavailability, and boosting precorneal residence time and drug corneal permeability.[41]

A recent research by Tajika et al.[42] showed that using an emulsion as a carrier, a prednisolone derivative at 0.05% [3H] difluprednate had better anti-inflammatory action. The results showed that, after a single or several topical drop instillations, an emulsion may transport a medication to the anterior ocular tissues in the rabbit eye, with a tiny quantity of drug reaching the posterior tissues. The cornea had the maximum radioactivity in both single and multiple topical drop instillation trials. It was followed by the iris-ciliary body, retina-choroid, conjunctiva, sclera, aqueous humor, lens, and vitreous humor. Tmax was 1 hour for retina-choroid and 0.5 hours for cornea, conjunctiva, lens, iris-ciliary body, aqueous humor, and vitreous humor following single drop treatment. The quantity of medication in systemic circulation was quite little. Tmax for the lens and retina-choroid with repeated dosage instillation was 8 and 0.5 hours, respectively. Urine and feces eliminated around 99.5% of the entire dosage of radioactivity after 168 hours. This study supports difluprednate emulsion as a viable treatment option for inflammations of the anterior eye.

To improve ocular performance and absorption, emulsions including lipid additions such stearylamine and soyabean lecithin were tested as azithromycin carrier systems.[43] The parameters of tear elimination were compared between azithromycin solution and emulsion at three, five, and ten mg/mL azithromycin dosages. In vivo experiments using topical drop delivery were carried out on rabbits.Emulsion was shown to function as a carrier for azithromycin while simultaneously slowing the drug's release, enhancing its chemical stability, and extending its precorneal residence duration. Furthermore, compared to aqueous solutions, azithromycin's chemical stability (t1/2) at pH 5.0 and 7.0 was enhanced by

emulsion formulation. Overall, the findings point to lipid emulsion as a potential delivery system for drugs into the eyes.

SUSPENSIONS

Another type of non-invasive topical medication carrier method for the eyes is suspensions. A appropriate suspending and dispersing agent is combined with an aqueous solvent to create suspension, which is defined as finely split insoluble API suspended in the solvent. Stated otherwise, the saturated solution of API represents the carrier solvent system. In comparison to medication solution, suspension particles prolong drug contact time and duration of action by remaining in the precorneal pocket. Particle size affects how long a medicine acts in suspension. The medication absorbed into the ocular tissues from the precorneal pocket is replenished by smaller size particles. Larger particle sizes, on the other hand, aid in prolonging particle retention and delaying drug dissolution.[44] Therefore, it is anticipated that the best pharmacological activity will come from the ideal particle size. Numerous suspension formulations are available for treatment of bacterial infections in the eyes around the globe. One of the commercial medications that is highly suggested for people responding to steroid treatment is TobraDex® suspension. TobraDex® is a combination medicine containing 0.1% steroid and 0.3% antibiotic tobramycin. This commercial product's excessive viscosity is its main flaw. As of late, Scoperetal.[45]

Made an effort to enhance TobraDex®'s antibacterial efficacy and in vivo pharmacokinetics while lowering its viscosity. The goal of creating this formulation was to enhance the qualities, tear film dynamics, and tissue penetration of the suspension formulation. The new solution, called TobraDex ST®, contains the steroid dexamethasone (0.05%) and tobramycin (0.3%). The novel formulation displayed very low settling over 24 hours (3%) compared to commercially available Tobra-Dex® (66%), according to suspension settling trials. Ocular distribution tests revealed that rabbits treated with TobraDex ST® compared to Tobra-Dex® had greater tissue concentrations of tobramycin and dexamethasone. It was discovered that the new suspension formulation outperformed TobraDex® in terms of effectiveness against Pseudomonas aeruginosa and Staphylococcus aureus. Higher than TobraDex® amounts of dexamethasone were found in the aqueous humor in clinical trials involving human volunteers.

These findings point to a potential replacement for commercial suspensions in the form of a novel suspension formulation. This is because compared to the commercially available

TobraDex® suspension, the new suspension has improved pharmacokinetics, bactericidal properties, and patient compliance.

OINTMENTS

Another class of carrier systems designed for topical application is ophthalmic ointments. The ingredients of ocular ointment are a combination of solid and semisolid hydrocarbons, namely paraffin, which melts at the physiological temperature of the eyes, which is 34 °C. The biocompatibility of a hydrocarbon determines its choice. Ointments support and enhance the drug's sustained release and ocular bioavailability.[46]

Methicillin and cephem-resistant Staphylococcus aureus (MRSA) as well as aerobic and anaerobic gram positive bacteria are all effectively combatted by the glycopeptide antibiotic vancomycinHCl (VCM). Despite VCM's increased activity, there was no suitable topical formulation on the market. Although improved ocular tissue permeability of VCM was not anticipated in a healthy eye, there have been some documented clinical effects of VCM solution in the treatment of ocular diseases. The disruption of the ocular barrier was thought to be the cause of the observed effects, potentially leading to enhanced drug penetration. et al. Fukuda[47] examined the intraocular dynamics of ophthalmic ointments containing vancomycin hydrochloride in rabbits. Consequently, the authors attempted to illustrate the ocular dynamics of VCM ophthalmic ointment (TN-011) with indications restricted to MRSA infections outside of the eye. It was discovered that 1.56 μg/g is the minimal growth inhibitory concentration needed to treat MRSA bacterial infections. Rabbits were used in in vivo experiments (normal vs. Bacillus subtilis (BS) group). The central parenchyma was injected with BS solution to create the BS group in the cornea. Topical ocular ointment (1% VCM) was administered to the rabbit eyes of the normal and BS groups as treatment. After 15 minutes, the normal group's cornea had a VCM concentration of 12.04 ± 4.73 μg/g .was reached after 30 minutes, and at 120 minutes, it had dropped to 0.49 ± 0.97 μg/g. Conversely, after 15 minutes and 240 minutes of administration, the VCM concentrations in the cornea of the BS group were 25.60 ± 11.01 μg/g and 3.68 ± 1.38 μg/g, respectively. Since the MRSA infection-induced BS group's VCM concentrations were kept above MIC levels, it is anticipated that TN-011 will provide significant benefits to the patients.

IN SITU GEL

The environmental sensitivity of the polymers used in ophthalmic in-situ gelling causes minor structural changes in response to variations in temperature, ionic strength, and pH.

When injected into the eye, in-situ forming gels are liquids that quickly gel in the cul-de-sac of the eye to generate viscoelastic gels that adapt to changes in the surrounding environment. Lastly, under physiological circumstances, gradually release the medication.[48] This will result in a prolonged residence duration of the gel generated in-situ and a sustained release of the medication, both of which increase patient compliance by maximizing bioavailability, minimizing systemic absorption, and reducing the frequency of dosing schedule.[49] Additionally, in-situ gelling devices have demonstrated a number of additional potential benefits, including a straightforward manufacturing process, simplicity of administration, and the delivery of precise dosages.[50]

Fig. 4: In situ Gel.

CONTACT LENSES COATED WITH DRUG

Water-soluble chemicals that are released from this medication form's surface after it has been applied to the eyeball for a prolonged amount of time might be absorbed. In order to produce lenses, the earliest and most often utilized polymer was cross-linked poly(2-hydroxyethyl methacrylate) with a little quantity of ethylene glycol dimethylacrylate. Utilizing silicon-based lenses has been the subject of research in recent years. The number of publications about contact lens use that have been published in recent years has increased, indicating that interest in these lenses is continually growing. Research has been done on the pharmaceutical availability of lenses for timolol, ciprofloxacin, dexamethasone, and cyclosporine, among other medications.

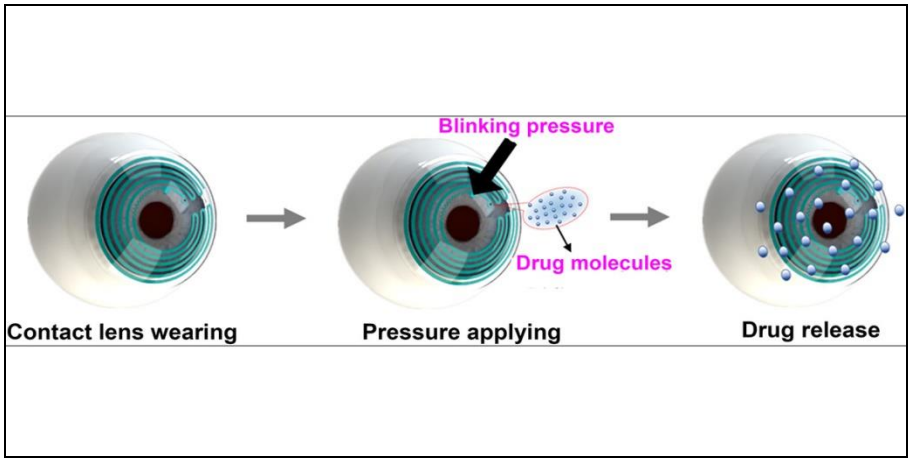

Fig. 5: Contact lenses.

LIPOSOMES

Phosphatidylcholine, stearylamine, lecithin, and a-L-dipalmitoylphosphatidylcholine are the common components of liposomes, which are phospholipid drug carriers. These carriers have several benefits, including relative intoxicity, biodegradability, biocompatibility, and amphiphilic qualities. It is also highlighted that their volume of drug containment is restricted and that their stability is lower than that of therapeutic systems based on polymers. Furthermore, the large-scale manufacture of them is highly technologically challenging and costly. Their use in ocular medicine formulations improves the administered substance's bioavailability and shields it from the enzymes found on the corneal epithelium's surface. It is important to note that a variety of parameters, including as the efficiency of liposome encapsulation, liposome size and charge, liposome stability in the conjunctival sac, and liposome affinity for the corneal surface, affect how well liposomes carry the active component. Positively charged liposomes have a greater attraction for negatively charged corneal surfaces and conjunctivalmucoglycoproteins than do negatively and neutrally charged ones. As a result, they slow down the removal of the active component from the application site. It has been suggested that liposome suspensions added to mucoadhesive gels or coated with mucoadhesive polymers promote the adherence of negatively and neutrally charged liposomes to the corneal or conjunctival surface. Liposomal ophthalmic medication formulations were being developed for the following active ingredients: ciprofloxacin, acetazolamide, pilocarpine, acyclovir, and chloramphenicol.

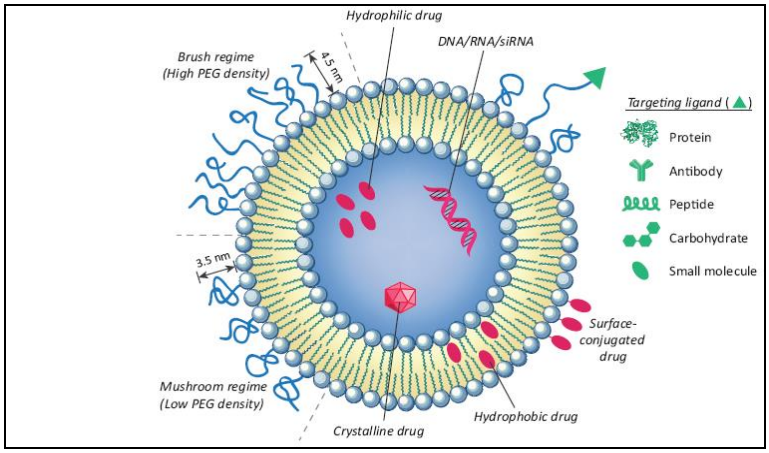

Fig. 6: Liposomes.

NIOSOMES AND DISCOSOMES

Niosomes are two-layered carriers for both hydrophilic and hydrophobic particles that are chemically stable and free of the drawbacks of liposomes, such as oxidative phospholipid breakdown and the high cost of natural phospholipids. Niosomes are constructed of nonionic surfactants. Additionally, the duration of drug-to-cornea contact is prolonged by these biodegradable, biocompatible, and non-immunogenic carriers, increasing the drug's bioavailability. Modified niosomes, or discosomes, have the potential to transport eye medications. They range in size from 12 to 160 meters. The addition of nonionic surfactants, such as Solulan C24, a lanolin derivative made of a combination of ethoxylated fatty alcohols (ether of cetyl alcohol and polyethylene glycol) and ethoxylated cholesterol (ether of cholesterol and polyethylene glycol), distinguishes discosomes from niosomes. One of discosomes' advantages is their small; it prevents them from entering the broader circulation. Additionally, the disc shape guarantees a more secure fit of this form within the conjunctival sac. A significant amount of study has previously been done on niosomal medication formulations for timolol, cyclopentolate, and ganciclovir.

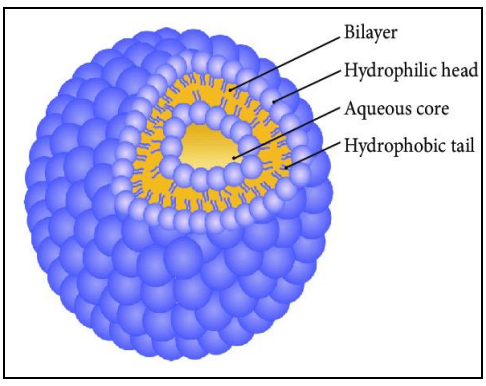

Fig. 7: Neosomes.

OCUSERTS

In order to deliver the drug at a nearly constant rate based on difusional mechanisms, queserts, also known as ocular inserts, are sterile preparations with a thin, multilayered, solid or semisolid consistency that are placed into the cul-de-sac or conjunctival sac. Their size and shape are specifically designed for ophthalmic application. These inserts are inserted into the cornea or lower fornix, and less commonly, they are inserted into the upper fornix. They typically consist of a polymeric drug delivery system. Ocuserts improve bioavailability, lengthen the duration of action, lower the frequency of administration, and enhance corneal contact time—all of which contribute to improved patient compliance. The first product in this category that Alza Incorporated USA is marketing is the Ocusert, pilocarpine ocular treatment system.

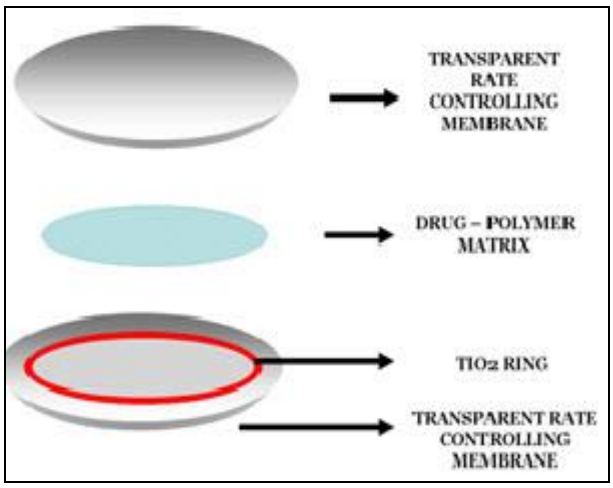

Fig. 8: Ocuserts.

Mechanism of Drug release of ocular drug delivery system[51]:- The following is the mechanism of controlled drug release into the eye.

Diffusion

Typically, the drug is released into tear fluid through the membrane at a controlled rate and continuously in this diffusion mechanism. The process of diffusing from one area with a higher drug concentration across a concentration grade is how the drug is released. If their inserts are inserted, a solid, inedible body with pores and distributed medication is created. Diffusion through the pores is typically how the medication is released. The gradual dissolution of the solid drug dispersed in this matrix as a result of the aqueous solution's inward diffusion can further regulate this controlled release. Since these glassy polymers are

practically drug-impermeable, no diffusion through the dry matrix occurs in this soluble device, and true dissolution primarily occurs through the polymer swelling.

1. Osmosis

Transverse impermeable elastic membranes are typically used as inserts in this osmosis mechanism, allowing the inserts to pass from the first to the second compartment. The impermeable material and its elastic membrane surround the first compartment, which is bounded by a semi-permeable membrane leading to an impermeable elastic membrane. This is a drug aperture located in the inserts' impermeable wall. A solute that is impervious to the semipermeable membrane is present in the first compartment. The medication, which is once more in the liquid or gel form, is stored in the second compartment.is positioned in the aqueous environment of the eye in these inserts. In order to force the drug through the drug release aperture, diffuse water is introduced into the first compartment, and the elastic membrane is stretched to expand in that compartment and contract in the second.

2. Bio-erosion

The insert's body is made of a bio erodible material in this bio-erosion mechanism, which allows for controlled, sustained drug release through matrix bio-erosion upon the insert's contact with tear fluid. Although the drug may be evenly distributed throughout the matrix, it is generally thought that when the drug is superficially concentrated in the drug matrix, a more controlled release occurs.

Factors limiting ocular bioavailability of drugs[52]

1. Tears

− Usually, the lachrymal gland secretes these tears.

−The maintenance of proper eye function is greatly aided by tears.

−Tears in healthy individuals contain lipids, proteins, carbohydrates, water, electrolytes, and mucins.

−Other elements, such as cytokines, antigens, and inflammatory mediators, can be present in various illness situations.

−Reducing the amount of time the medication may enter the ocular tissues as a result.

2. Conjunctiva

−Mucous tissue typically makes up the conjunctiva.

−The conjunctiva produces mucus and antimicrobial peptides that help lubricate and protect the eye.

− This conjunctiva has a lot of vascularization.

−They are crucial in serving as the ocular surface's protective barrier.

−The application of the posterior section is impeded by the systemic absorption.

−Because of this, administering medication through the sub conjunctiva is a more effective technique to improve the effectiveness of topical drug application.

3. Cornea

−The layer in front of the eye is called the cornea.

−It is distinguished by a high water content, which prevents lipophilic molecules from passing through the corneal layer.

−They are typically the corneal epithelium and its surrounding tissue; the stoma is the barrier that prevents macromolecules from penetrating.

−Because of their hydrophilic and lipophilic characteristics, molecules should seem to have an amphiphilic nature in order to penetrate across the three layers.

− In addition to shielding the ocular tissue, the cornea also has the ability to refract light.

4. Sclera

− In order to support the extra ocular muscle, the sclera keeps the form of the eye globe resistant to both internal and external forces.

−Glycoproteins and collagen fibrils make up the majority of these sclera.

− It has been claimed that the drug molecules' charge, shape, and molecular radius all influence how well they penetrate the sclera layer.

− According to reports, this sclera is more porous and harder to trap tiny molecules of negatively charged glycoproteins.

CONCLUSION

For scientists working in the sector, developing effective treatments for eye illnesses is a daunting task. They contain collagen shields, disposable contact lenses, ocular films, and other formulations in a novel ophthalmic delivery system. Utilizing a mix of drug delivery methods to enhance the therapeutic impact or therapeutic response of an effective medicine is a more recent trend in these ocular delivery systems. An ocular formulation's residence period on the corneal surface might be extended to improve medication absorption and decrease delivery frequency. Common pharmacological formulations used for this purpose, such as

medications given as eye drops, have drawbacks that necessitated the use of unique carriers intended for the ocular administration route. For many years, ocular scientists faced a significant barrier in getting drugs to the targeted ocular tissues. Numerous problems with using traditional formulations of medication solutions as topical drops led to the creation of several carrier systems for ocular administration. The ocular implant is a successful improvement in the treatment of eye diseases. By lowering the frequency of dose, offering prolonged and regulated drug administration, and lowering the frequency of dosing, this focuser offers several benefits to enhance patient compliance while also lowering the negative effects of the medication. Thus, it makes sense to take into account unconventional methods including iontophoresis, liposomes, nanotechnology, microspheres, and in situ forming gel for efficient distribution, which will improve ocular absorption and minimize adverse effects. Therefore, the creation of innovative noninvasive drug delivery methods that can get past ocular obstacles, maintain drug release, and keep effective drug levels at the back of the eye will be critically needed.

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30. Anish Menon1 and NehaMathur* 1Amity Institute of Pharmacy, Lucknow, Amity University Uttar Pradesh, Sector 125, Noida, 201313, India. *Amity Institute of Pharmacy, Lucknow, Amity University Uttar Pradesh, Sector 125, Noida, 201313, India. Address for correspondence:Dr. NehaMathur, Associate Professor, Amity Institute of Pharmacy, AmityUniversity Uttar Pradesh, Lucknow campus.
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