Targeting the Eye: Innovations in Ocular Drug Transport and Therapy

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***Abstract*—Many anatomical and physiological barriers affect how drugs are delivered to the eyes creating a bottleneck for ophthalmologists. The ocular barriers both static and dynamic limit the admission of xenobiotics and the absorption of therapeutic medicines. As a result, there are a number of drawbacks to using a typical ocular dose form to treat eye problems. The classification of ocular drug delivery methods and a general overview are covered in this review article along with examples of several traditional and modern formulations for ophthalmic drug delivery. Also included are constraints of traditional delivery with an eye towards finding cutting-edge methods including vesicular systems, nanotechnology, stem cell therapy as well as gene therapy oligonucleotide and aptamer therapy, protein and peptide delivery, and ribozyme therapy for treating various ocular illnesses. A high level of circulating drug would be necessary for systemic administration of a medicine to treat eye illness. Plasma to reach therapeutic concentrations.**

The duration of the medicine's activity can be noticeably extended and the frequency of drug administration can be decreased by adopting prolonged drug delivery. Designing formulations like microspheres, nanoparticles, and liposomes that function as effective ocular drug delivery systems can help achieve this type of drug delivery. The scientists can regulate and create secure drug delivery systems with the aid of an update of study development in ocular drug delivery. This review article provides current information on several methods for administering the medication to the ocular region.

***Index Terms*—Ocular drug delivery; S.O.D.I; insert; minidisc; DED; Insert.**

I. INTRODUCTION

Intracameral injection, which is frequently used to treat glaucoma, subretinal or suprachoroidal injections which are common approaches for gene and cell therapies and intravitreal (IVT) delivery which is a mainstay for the treatment of diseases affecting the back of the eye are just a few of the different ways that drugs can be administered into the eye. In general, periocular, systemic or topical treatments are available for posterior eye segment illnesses. Due to the blood-aqueous and blood-retinal barriers as well as the quick removal of drugs from the eye systemic drug distribution necessitates the administration of substantial doses. Additionally, large steroid doses can intensify negative side effects [01]. Eighty percent of the volume of the eye is made up of the vitreous humor a translucent, gel-like soft and ocular tissue that lies between the lens and the retina [02]. The anterior or posterior tissues of the eye contain anatomically distinct regions that serve as ocular medication targets. The disease state pharmacological characteristics and distribution to the target areas all affect how well a treatment works. Drug delivery is influenced by important pharmacokinetic factors including bioavailability drug removal from the target tissue dosing regimen and drug release or dissolution for each route of ocular drug administration [03]. The eye is a delicate and intricate organ in human physiology that is designed specifically for detecting and converting light impulses into information that is organised into various portions, particularly the anterior and posterior sections. Aqueous humour produced by the ciliary body fills the anterior chamber which is situated between the cornea and the iris [04].

Aqueous topical eye drops are most frequently used to treat ophthalmic disorders. However, these formulations raise both technical (such as solubility, stability, and preservation) and clinical (such as effectiveness, local toxicity, and compliance) difficulties. Advanced ocular therapy techniques are developed as a result, including particulate delivery systems that enhance the pharmacokinetic and pharmacodynamic characteristics of various drug molecules as well as novel controlled drug

delivery systems like dendrimers, microemulsions, muco-adhesive polymers, hydrogels, iontophoresis, collagen shields, and prodrug approaches [05]. For vision-threatening ocular disorders the ocular channel of administration's best treatment options cannot be achieved with the use of traditional drug delivery systems including eye drops, suspensions, and ointments [06].

Due to a number of variables, including reflexive blinking and tearing, nonproductive absorption, nasolacrimal drainage, metabolic decomposition, and the relatively impermeable corneal epithelial membrane these standard ophthalmic formulations typically exhibit low ocular bioavailability. Only a limited portion of an administered dose (1%–7%) is effectively absorbed as a result of these physiological and anatomical restrictions [07]. Top-down models and bottom-up simulations of ocular pharmacokinetics are crucial tools for forecasting and comprehending dosage form functionality in vivo. The simulations can help with pharmacokinetic comprehension by revealing connections between the administered dose, release rate, and measured concentrations in ocular tissues, tear fluid and plasma [08].

To make ocular medication delivery systems as effective as possible the following qualities are necessary. An effective corneal penetration. A protracted period of drug interaction with ocular tissue. Patient-friendly ease of installation and removal.

A form that is comfortable and non-irritating (the viscous solution shouldn't aggravate reflex flashes or lachrymation). Proper viscolyzer concentration and rheological properties [05].

II. PHARMACOKINETIC DYNAMICS IN OCULAR DRUG DELIVERY

The eye's medication pharmacokinetics take the following routes:

1] The anterior chamber can be reached through transcorneal permeation of lacrimal fluid.

2] Non-corneal drug penetration into the anterior uvea through the sclera and conjunctiva.

3] Blood-aqueous barrier-mediated drug delivery from the bloodstream into the anterior chamber.

4] Drug removal from the anterior chamber through the trabecular meshwork and Sclemm's canal after aqueous humour turnover.

5] Crossing the blood-aqueous barrier drugs are eliminated from the aqueous humour into the systemic circulation.

6] Drug diffusion across the blood-retina barrier into the posterior eye.

7] Administering medication intravitreally.

8] Drug removal from the vitreous through the blood-retina barrier via the posterior pathway. Drug removal from the vitreous through the anterior chamber and into the posterior chamber [09].

III. STRUCTURE AND FUNCTION OF THE EYE

The anterior and posterior portions of the eye can be substantially separated. The cornea, conjunctiva, iris, ciliary body, lens and aqueous humour make up the anterior segment whereas the sclera, choroid, retina and vitreous body make up the posterior section [10]. The eye is a spherical structure with a wall composed of three layers: the sclera on the outside, the choroid layer in the middle, the iris, the ciliary body and the retina on the inside [05].

Given that it makes vision possible the eye is the most important sense organ in the human body. It is a spherical object with a circumference of 69-85 mm and an anterior-posterior diameter of approximately 22-27 mm. [11].

Skeletal muscle in the eyelids allows them to close and protect the front of the eyeball. Dust is kept out of the eyes by the eyelashes that border each eyelid. Conjunctivitis an inflammation of this membrane that results in red, itchy and watery eyes can be brought on by allergies, certain bacteria or viruses [12]. The cornea also known as the transparent window at the front of the globe is present. After passing through the pupil light from the outside world enters the cornea and travels to the lens. To produce a crisp image the lens precisely directs light onto the retina [13].

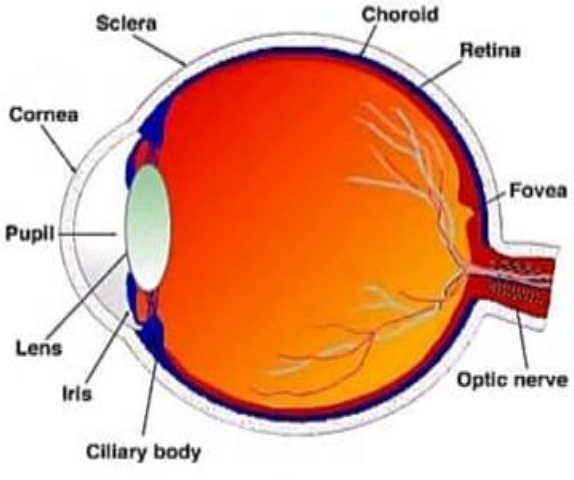


Fig.1: Cross section of the eye [05]

Cornea: The cornea is a potent refracting surface that contributes significantly to the eye's focusing ability. The hydrophobic corneal epithelium serves as the main impediment to drug penetration and is made up of the outer epithelium, middle stroma and inner endothelium [14]. The epithelium consists of 5–7 cell layers with annular tight connections that reduce hydrophilic drug paracellular penetration [15]. A highly specialised tissue called the cornea acts as a mechanical barrier to keep pathogens out of the eye [16].

Retina: The retina is the eye's deepest layer. Images are transformed into electrical impulses which are then transmitted to the brain via the optic nerve and processed there [14]. Only at these two spots are the ora serrata and the optic disc connected making up the posterior section of the retina [17].

Choroid: The choroid is a vascular layer that runs from the ora serrata (area of the anterior edge of the retina) to the optic nerve and is situated between the sclera and Bruch's membrane (BM) [17].

Iris: The component of the eye that gives it colour called the iris [14]. The iris is a spherical, skeletal, contractile structure that faces the lens all the way back to the cornea [18].

Lens: The lens is a biconvex transparent structure that is covered in a thin layer of transparent material. Incoming light is refracted and focused onto the retina by the lens [14].

Conjunctiva: To lubricate the eye the conjunctiva is a mucous membrane that starts at the edge of the cornea and lines the inner surface of the eyelids and sclera [14]. This area's substantia propria is thicker because it has two layers: a superficial lymphoid layer with connective tissue made up of lymphocytes, mast cells, plasma cells and neutrophils and a deeper fibrous layer containing nerves, blood vessels and the Krause glands. The rear of the eyelids is where the palpebral conjunctiva is found [16].

Sclera: The "white of the eye" or sclera the protective outer layer of the eye keeps the form of the eye [14]. The outer covering of the eyeball which is white and resembles an opaque, rigid sheath is known as the sclera [18].

Macula: The macula can be found in the centre of the retina at the rear of the eye. The best vision is produced in this region [14]. The retina's macula which is where the vast majority of photoreceptor cells are found is where light is converted into nerve signals. Near the centre of the retina, the macula has a noval structure a pigmented area with different ganglion cells and about 200 million of them [18].

Aqueous Humar: Aqueous humour, which is a transparent substance that resembles water is found in the front, smaller part [14]. The anterior chamber of the human eye is filled with aqueous humour which has a capacity of about 300µl. The ciliary processes secrete aqueous humour which exits the anterior chamber at a rate of about 1% every minute [19].

The aqueous humour transports neurotransmitter molecules to the cornea, trabecular meshwork and lens removes metabolic waste products and helps to maintain a healthy intraocular pressure (IOP) [17]. The rear and anterior regions of the eye are filled with a nonvascular, translucent, clear fluid. It delivers vital nutrients such sodium, chloride ions and ascorbate salt as well as removes waste from nonvascular tissue and delivers it to the cornea [18].

IV. STRATEGIC ADVANTAGES

1) They improve dosage rate accuracy and consistency. It is possible to prevent pulsed dosing in conventional systems.
2) It is possible to establish a regulated, sustained release of medication.
3) They improve medication bioavailability in the eye by lengthening corneal contact duration which is made possible by the drug's efficient adhesion to the corneal surface.
4) Targeting within the ocular globe is necessary to prevent the loss of ocular tissues.
5) They avoid the conjunctival absorption, drainage, and lacrimation, which serve as protective ophthalmic barriers.
6) Additionally, they increase patient compliance, provide comfort and boost the effectiveness of medicinal drugs.
7) Better housing for delivery systems is provided by them.
8) They enable drug self-administration.
9) There are fewer systemic and ocular side effects and absorption is quicker.[20]
10) To offer a regulated and sustained medication delivery.

11) In order to prevent damage to other ocular tissues, it is necessary to provide targeting within the ocular globe.
12) To enhance patient comfort, patient compliance and drug therapeutic effectiveness [09].

V. DRAWBACKS

The following are the main issues with ophthalmic medication delivery systems:

1) The medication solution's brief contact time with the eye's surface.
2) Inadequate bioavailability.
3) Drugs that dissolve unstable.
4) Preservative use [20].

VI. PHYSIOLOGICAL AND ANATOMICAL BARRIERS TO OCULAR DRUG DELIVERY

The architecture and physiology of the eye have ocular barriers that are extremely effective at protecting its inner components from outside substances [21]. These ocular barriers, which regulate liquid absorption, comprise the blood-ocular barrier, tear film, conjunctiva, cornea, blood-aqueous barrier and blood-retina barrier. Conjunctiva, sclera, cornea, retina-blood-aqueous barrier and blood-retinal barrier are examples of anatomical barriers. Second, there are active physiological cleaning systems that guard all of the ocular mechanisms. The systems include the blink reflex, conjunctival blood flow, efflux transport, and choroid, which protect the eye from harmful medication effects as well as nasolacrimal drainage and pre-corneal tear production for the removal of irritants [04].

The majority of systemic absorption occurs after the fluid has flowed into the nasal cavity or is transmitted through the conjunctival sac to the nearby blood capillaries [20]. Following instillation, the lacrimal fluid flow clears the eye's surface of the substances that were injected. The excess volume of the injected fluid is flown to the nasolacrimal duct swiftly in a matter of minutes, despite the fact that the lacrimal turnover rate is only about 1 l/min [09]. Systemic absorption can happen either after the fluid has flowed into the nasal cavity or straight from the conjunctival sac via nearby blood capillaries. Systemic absorption of the medicine as opposed to ocular absorption is another cause of ineffective drug clearance.

However, the majority of the dose of a small-molecular-weight medication is quickly absorbed into the systemic circulation rather than ocular absorption is another cause of ineffective drug elimination.

But the majority of the dose of a small-molecular-weight medication is quickly absorbed into the bloodstream [05].

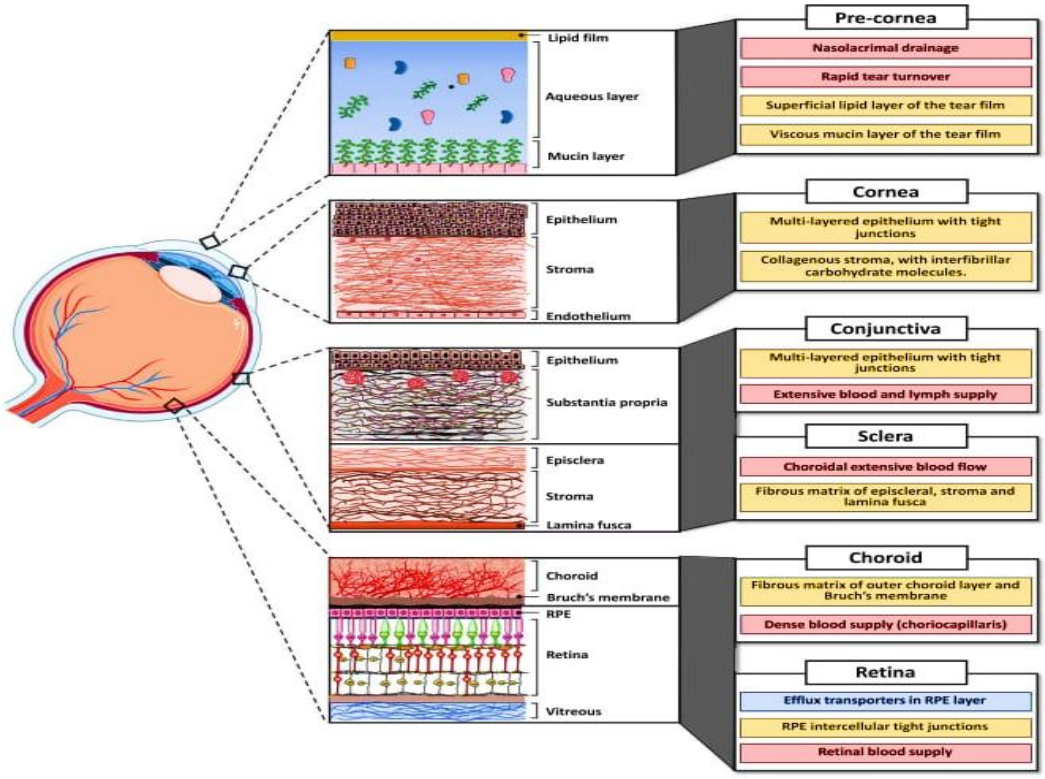


Fig.2. Schematic representation of the most significant barrier structures of the eye. The pink, yellow and blue background highlights significant dynamic, structural or metabolic barrier properties, respectively. The layers are arranged starting with the ocular surface, assuming the drug is topically applied and is moving towards the vitreous. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.) [22]

Lacrimal Fluid Eye Barrier:

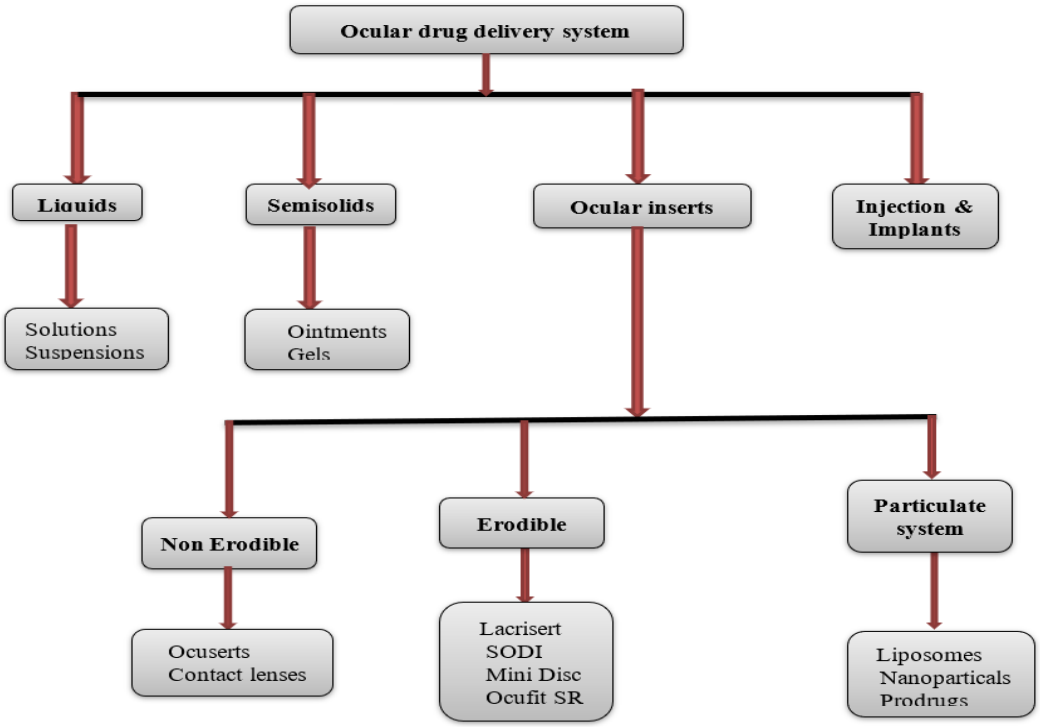
Drug absorption from the lacrimal fluid can be restricted by the corneal epithelium in the eye. The penetration of the medication paracellularly is restricted by tight junctions made of corneal epithelial cells. Compared to hydrophilic medicines, lipophilic medications exhibit greater corneal permeability [20]. Drug absorption from the lacrimal fluid into the eye is constrained by the corneal epithelium [09]. The conjunctiva has a surface area that is about 20 times higher than that of the cornea and is often a leakier epithelium than the cornea [06]. Therefore, compared to hydrophilic medicines, lipophilic medications often have corneal permeability that is at least an order of magnitude higher. Transcorneal permeation is the primary method of medication entry from the lacrimal fluid to the aqueous humour despite the cornea's strong epithelial layer [05].

Blood Ocular Barrier:

The bloodstream contains blood ocular barriers, which protect the eye from xenobiotics. Blood-retina and blood-aqueous barriers make up its two components [20]. Endothelial cells in the uvea make up the anterior blood-eye barrier. This barrier restricts the entry of hydrophilic medicines from plasma into the aqueous humour as well as the access of plasma albumin. The integrity of this barrier may be compromised by inflammation, allowing unrestricted medication delivery to the anterior chamber. In actuality, this barrier's permeability has not been well described. Retinal pigment epithelium (RPE) and the tightly packed walls of retinal capillaries make up the posterior barrier separating the blood supply from the eye [09]. The lining of the microvasculature that supplies the neural retina is made up of retinal endothelial cells (inner BRB). The lack of fenestrations and the expression of certain intercellular junction proteins are characteristics of the retinal microvascular endothelium [22].

This barrier restricts the penetration of hydrophilic medicines from plasma into the aqueous humour and hinders the entry of plasma albumin [06]. Only 1% to 2% of an administered medicine can reach the retina and vitreous region due to the outer BRB, which is made up of tight connections between RPE cells and separates the choroid and Bruch's membrane from the inner retina [23].

Classification of ocular drug delivery systems [14]



Liposomes:

Liposomes are tiny lipid vesicles that are intended to contain pharmaceuticals. Natural lipid-based liposomes are weakly immunogenic, biodegradable, biologically inert, create no antigenic responses and have low inherent toxicity. Therefore, it is anticipated that medications contained in liposomes will be delivered to receivers with little to no negative effects and without rapid poly (lactide-co-glycolide) breakdown [12]. Phospholipids, lipid conjugated polymers and cholesterol are all components of liposomes. The size and presence of multiple phospholipid layers determine the classification of a liposome, which includes small unilamellar vesicles between 10 and 100 nm, large unilamellar vesicles between 100 and 300 nm, and multilamellar vesicles made up of more than one phospholipid bilayer [24]. In a mouse model, the C6-ceramide liposomal formulation significantly reduced ocular inflammation. This suggests that ceramide-loaded liposomes are effective in treating anterior segment ocular inflammation [25]. Acyclovir was organised in liposomes with cationic and anionic shielding. To achieve this, the roles of cationic and anionic inducers respectively, were assigned to dicetylphosphate and stearylamine. The cationic liposomes had a higher concentration in the cornea tissues than anionic liposomes or acyclovir alone when the concentrations of acyclovir were tested 2.5 hours after topical treatment to the rabbits' eyes. Even more quickly absorbed throughout the corneal tissues were the cationic liposomes. These findings suggest that the cornea's surface is negatively charged and that positively charged formulations that interact electrostatically with the ocular structure have the strongest ability to attach to those structures [26].

Niosome:

Niosomes, which are primary bilayer vesicles made of non-ionic surfactants have the unusual capacity to bind to both hydrophilic (in vesicular bilayer membranes) and lipophilic (in aqueous compartments) substances [24]. Niosomal delivery for ocular use was created to get around some of the drawbacks of liposomal administration including cost, phospholipid purity and oxidative degradation. Noisome are chemically stable and both hydrophilic and lipophilic drug trapping is possible. It is a sizable, bilayered vesicle made up of non-ionic surfactant, measuring 12–16 m in size [27].

Nanoparticles:

To efficiently get past ocular barriers and deliver the medicine to the ocular tissue either by passive or active transport, drug-loaded nanoparticles can range in size from 50 to 500 nm. In the cul-de-sac, a solution of nanoparticles (NPs) can be placed to achieve continuous drug administration over an extended period of time. The NPs' surface charge significantly affects how well they absorb light in the eyes [25]. The diminutive size of nanoparticles is a very positive trait for their potential to reduce irritation in ocular tissue and to sustain drug delivery without needing repeated doses both of which are important for therapeutic compliance. These hydrophilic formulations might however be quickly removed from the precorneal compartment. In support of this mucoadhesive nanoparticles with the intention of topical administration were created with an improved time of residence in the precorneal compartment as a result. Some substances such as chitosan, hyaluronic acid or polyethylene glycol (PEG) are currently used to extend the time that nanoparticles remain in the previously mentioned compartment [26]. The nano-spheres were characterised for particle size and size distribution by dynamic light scattering, zeta-potential, drug content and encapsulation efficiency and in vitro drug release profile (phosphate buffer pH 7.4, 50 ml) were also studied. The created nanospheres have a pH 7.4 zeta potential range of 21–36 mV and an average particle size of 318–556 nm (polydispersity range of 0.325–0.489) [12].

Nanostructured Lipid Carrier (NLC):

The second generation of nano lipid carriers is known as NLC. They are made up of a mixture of medicines, surfactants and biocompatible lipids. NLC is a better choice than SLN because of their biocompatibility behaviour and stability. NLC was created to address the issues of drug escape via the matrix during storage as well as to improve the efficiency of drug loading. For example, cold homogenization, hot-emulsification ultrasonication and hot homogenization are some of the techniques utilised to prepare NLC [24].

Solutions:

Topical eye drop solutions are patient-compliant, noninvasive, immediate-acting drug for mulations. When eye drop solution are injected into the cul-de-sac, the corneal and conjunctival tissue quickly absorb them on first order. An increase in drug perme ation and drug bioavailability can be attained by modifying the drug properties or properties of the drug-delivery system [25].

Emulsion:
The encapsulated medications' bioavailability and solubility are both goals of formulations with an emulsion nature. This design's main formulative method relies on two different emulsions: oil-in-water (O/W) and water-in-oil (W/O). The O/W emulsion is preferred over the W/O emulsion for use in the administration of medications to ocular tissues because it has more advantageous properties such reduced irritation of the target tissues and improved eye tolerance [26]. A biphasic system made up of two immiscible phases is an emulsion. Ophthalmic emulsions may be beneficial for increasing the bioavailability and solubility of previously water-insoluble medications [25]. Emulsions have a reputation for enhancing the medicine they are delivering's bioavailability, penetration and residence duration [28].

Suspension:
Chemically speaking, these pharmaceutical forms are characterised as drug dispersions made with a hydrophilic solvent that contains a dispersion agent or suspension to produce a saturated final solution. Additionally, this kind of formulation will be appropriate once it doesn't need an invasive application technique. The precorneal tissue absorbs the particles that make up the suspension, extending the time that the drug is in touch with the tissues and the amount of time it is therapeutically active. One of these systems' unique characteristics is that the formulation's required well-designed particle size has a direct bearing on how long a drug's action lasts [26].
Insoluble medication particles that have been finely split and suspended in an aqueous media with solubilizing and dispersing agents are called ocular suspensions. The precorneal cavity keeps drug particles suspended, extending the duration that the drug is in contact with the body [25].

Nanosuspension:
Another nano-controlled release system utilised in the treatment of several eye diseases is nanosuspension. These are the het erogenous colloidal discrete system, which are stabilized by surfactant [29]. They are able to get through obstacles in ocular drug delivery because of their size range of 10 to 1000 nm [24]. some of these effects were also examined in the context of enhanced glucocorticoid solubilization for ocular use utilising nanosuspensions. The glucocorticoids dexamethasone, hydrocortisone and prednisone are the preferred medications to treat pathological diseases when a varied degree of inflammation is present and disrupting the anterior area of the ocular tissues. Today's therapy approach involves using the prior pharmacological drugs in repeated high doses; however, this has the unintended side effect of causing cataract, optic nerve damage and even glaucoma. In support of this, the formulation of the glucocorticoids was done in the form of nanosuspensions to boost the bioavailability of the medications specified in the formulation in the eye [26].

Ointments:
Ointments are employed as medication delivery systems and fall under the category of topical preparations. Due to the fact that these systems are typically composed of a mix of solid and semisolid hydrocarbon molecules, their typical melting points are close to the human eye's operating temperature of 34 °C. But which hydrocarbon should we pick for a specific objective? This small distinction makes a significant difference in a formulation's biocompatibility because the substance must not be rejected by the body in order to avoid further organic side effects and even to guarantee the effectiveness of the formulation's goals of increasing drug bioavailability and maintaining the delivery process [26]. What hydrocarbon is chosen for usage in the ointment is mostly determined by its biocompatibility [28].

Gel:
Where more synthetic ointments are used ocular gels have become more popular as a replacement. The viscosity enhancers may be used in some circumstances to increase viscosity, which results in a longer precorneal residence period for the formulation on the ocular surface. At high water concentrations the viscosity enhancers create a thick gel. The benefits of utilising ophthalmic gels over ointments include comfort, reduced systemic exposure, less frequent dosage and less clouded vision. Even though ophthalmic gels are more viscous they only have a little amount of bioavailability. The greater viscosity of ophthalmic gels causes vision blurring and eyelid mating which decreases patient acceptance [27].

Injection:
In 1895, the first intravitreal injections (IVIs) were created to treat vitreous haemorrhage and retinal detachment. However, since it was discovered that IVIs could circumvent the blood-retina barrier in the 1970s, the number of IVIs has skyrocketed. Antibiotics, steroids, gases and other substances are now routinely injected. IVI is a technique used to get the highest medication

concentrations possible in the vitreous and retina. Typically, a 30–32-gauge filter needle is used for the injection, which is directed towards the inferotemporal quadrant in order to avoid the visual axis. With the exception of gas-based treatments, it is thought that injecting more than 100 L is dangerous.

A cotton-tipped applicator is placed over the injection site for injections greater than 0.05 ml after the needle has been removed from the body to reduce reflux. Antibiotic use varies a bit from group to group, with some preferring to forgo preoperative administration. Antibiotics aid in the prevention of problems like endophthalmitis, however there is some evidence that there are specific situations when they may not be necessary. Ocular discomfort, subconjunctival haemorrhage and increased intraocular pressure (IOP) are the most typical IVI consequences. Endophthalmitis is the most serious complication, with a risk range of 0.14% to 0.87% per injection and it most frequently happens when antiviral drugs are given and least frequently when gases are injected [28].

Microspheres:

The following are the main benefits of this formulation made by dispersing PLGA microspheres that have been drug-loaded: Administration is simple. Degradability and biocompatibility. Modification of the type of microspheres used in the dispersion to affect the pace and duration of medication release. Little movement of particles in vitreous. Regular re-administrations are possible without removing older implants.

These polymers come in a wide range of molecular weights and ratios of lactide to glycolide. Drug delivery using PLGA polymer microspheres has become highly popular. The pharmaceutical industry has recently grown interested in custom-developing a sustained release formulation to provide the desired duration of medication activity in varied pathological conditions [12].

Hydrogel:

Bound networks of synthetic and/or biological hydrophilic polymers that absorb aqueous fluids make up hydrogels. Numerous hydrogels are available expressly for intra- and extra-ocular uses, including contact lenses and vitreous replacements. Hydrogels have also been tested for use with optic nerve stabilization, medication delivery and/or cell encapsulation [30].

Cross-linked, water-based polymeric assemblies are what are known as hydrogels. Because of the hydrophilic functional group in their structure, hydrogels have a special capacity to absorb water. There are natural and synthetic polymers that can be used to make hydrogels [24]. These hydrogels continuously produced vancomycin at detectable quantities for over three weeks [28].

Table 1: Comparative description of nanocarriers with their benefits and disadvantages [10].

Drug delivery system	Benefits	Disadvantages
Nanosuspensions	Colloidal dispersion system of hydrophobic drugs in dispersion medium which is stabilized by surfactant and polymer with size range of 10 nm to 1000 nm Increases solubility, thus enhancing the bioavailability of ocular drugs Enhances the residence time in the cul-de-sac and prolongs drug release owing to its ability to enhance the inherent solubility of poorly water-soluble drugs in lacrimal fluid	Physical-stability, sedimentation
Liposomes	Liposomes size range is of 0.08 to 10.00 mm Encapsulate both hydrophilic and lipophilic drugs Biocompatible and non-toxic Leakage of encapsulated drug Improves corneal permeability Decreases dosing frequency	Lack of scalability potential owing to its low stability Production costs are very high
Niosomes	Niosomes are 10 to 1000 nm in size Less toxic, biodegradable, biocompatible, and mucoadhesive because they are composed of nonionic surfactants Controlled drug release and targeted delivery to ocular tissues, hence enhanced bioavailability of drug	Inefficient drug loading Leaching of encapsulated drug

VII. TECHNIQUES FOR DELIVERING DRUGS TO THE EYE

The following is a description of the numerous potential pathways for ocular medication delivery:

Topical ocular:
Eye drops are typically used to administer topical ocular medications, although they only have a brief contact period with the eye surface. Designing the formulation (e.g., gels, formulations that gelify, ointments, and inserts) might lengthen the duration of contact, consequently and the duration of drug action [09].
To keep the medication concentration on the ocular surface, eye drops must be used frequently. Ointments can prolong their stay on the ocular surface, although patient compliance is impaired by obscured vision. Increased lacrimal production during inflammation causes the medicine to be supplied to the location to be diluted and quickly removed. Additionally, there are numerous alternative ways to absorb drugs such as nasolacrimal drainage, in which the nasal mucosa is responsible for absorbing 80% of the drug [10]. Because topical treatment is a non-invasive administration approach, it is still the recommended option for treating ocular problems. Over 90% of the ophthalmic products available now come from it [31].

Sub-conjunctival administration:
By using this technique, the medication is given to the mucus membrane, which includes the inner surface of the eyelids and the region inside the eyeball [20]. Drugs have traditionally been administered to the uvea through subconjunctival injections at higher concentrations. For a number of reasons, this method of medicine delivery is currently gaining popularity. The development of controlled release formulations to distribute medications to the posterior segment and to direct the healing process following surgery (such as glaucoma surgery) has opened up new, intriguing possibilities because to advancements in pharmaceutical formulation and materials science [06].

Intravitreal injection:
This method involves injecting the drug into the vitreous humour of the eye. Several eye problems are treated with this mode of administration; distribution through this ocular route[20]. The vitreous and retina are more easily accessible when drugs are administered directly into the vitreous. However, it should be emphasised that the RPE barrier's obstruction makes distribution from the vitreous to the choroid more challenging. Small molecules can diffuse quickly in the vitreous, whereas bigger molecules, especially those that are positively charged, have limited mobility [06].

Systemic Route:
The blood-aqueous barrier (BAB) and blood-retinal barrier (BRB), which are present in the anterior and posterior portions of the eye, respectively are frequent obstacles to the systemic administration of ophthalmic medications[20]. When considering systemic administration strategies for ocular drug delivery, parenteral and oral doses are taken into account. The eye has a poor blood supply compared to the rest of the body and only 1% to 2% of a medicine injected reaches the retina and vitreous region due to tight connections of the retinal pigment epithelium cells, necessitating frequent drug delivery to achieve the desired therapeutic effect[10]. More significantly, the BOB limits the medicines' access to the tissues around the eyes. As previously established, BAB limits the amount of drugs that can enter the anterior portion of the eye from the systemic circulation, whereas both inner and outer BRB permit very little drug delivery [31].
This mode of administration has the potential to result in systemic cytotoxicity and non-specific drug binding to various tissues[12].

Suprachoroidal Route:
This administration route targets the supra choroid region of the eye. Suprachoroidal space refers to the area between the sclera and the choroid[20].

Parilocular Route: In this route of administration, the medication is given around the eye. It can be accounted for by percutaneous ocular steroid injection, which involves injecting steroids near the eye to treat intraocular edoema or inflammation[20].

Intracameral Route:
In this mode of administration, a medicine acts in either the anterior or posterior chambers of the eye. Anaesthetic fluid can be injected into the eye's anterior chamber, typically during surgery to illustrate it[20].

Route of administration ophthalmic drugs [32].

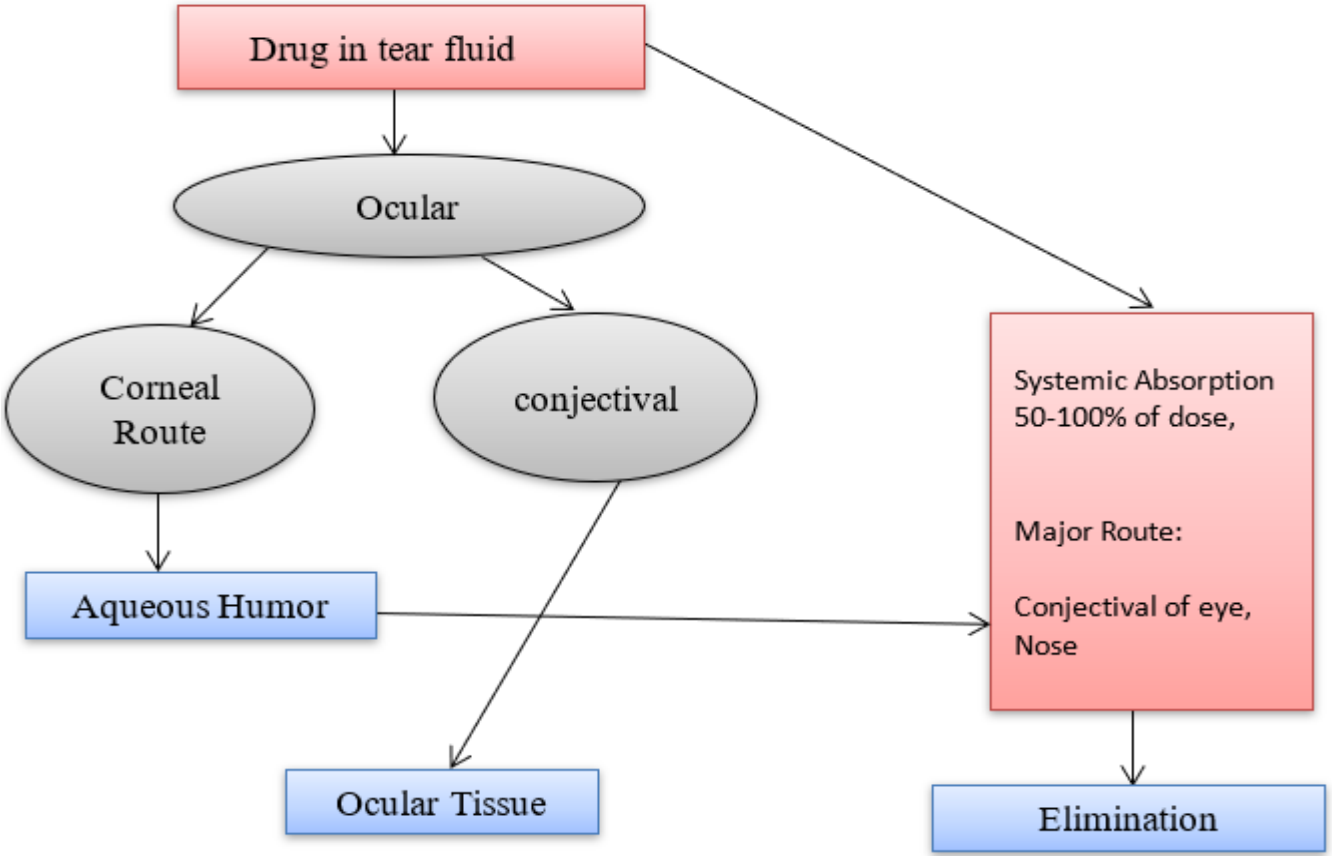


Table 2: Comparison of various routes of ocular drug administration: benefits and obstacles [33].

Route	Benefits	Obstacles	Diseases/Disorders Treated
Topical	Patient compliance is high; self-administration and noninvasive nature	Corneal barrier difficult to penetrate; dilution and efflux via tears is high	Conjunctivitis, keratitis, uveitis, episcleritis, scleritis, blepharitis
Intravitreal	Direct delivery to retinal and vitreal structures; drug has high bioavailability	Patient compliance low; riskof retinal detachment, hemorrhage,development of endophthalmitis or cataracts	AMD, BRVO, CRVO, DME, CMV retinitis
Sub-Tenton	Relatively noninvasive, decreased risk of comorbidity compared with intravitreal delivery, maintains high vitreal drug levels	Retinal pigment epithelium is a barrier; subconjunctival hemorrhage, chemosis	DME, AMD, RVO, uveitis
Posterior juxtascleral	Advantageous for drug depository; avoids intraocular damage, and macula can sustain drug level for 6 mo	Retinal pigment epithelium barrier, and surgical procedure required;	AMD, risk of endophthalmitis
Systemic/Oral	Promotes patient compliance, noninvasive mode of delivery	Retinal and blood-aqueous barriers; low bioavailability leading to systemic toxicity	Scleritis, episcleritis, CMV retinitis, posterior uveitis
Intracameral	Reduces systemic and corneal side effects vs. topical steroid use; high anterior chamber drug concentration	Toxic endothelial cell destruction syndrome and toxic anterior segment syndrome pose major risks to patients	Anesthesia, prevention of endophthalmitis, inflammation, pupil dilation
Subconjuctival	Anterior and posterior delivery method, ideal for depot formation	Choroidal and conjunctival circulation of therapies increases toxicity	Glaucoma, CMV retinitis, AMD
Retrobulbar	Minimal IOP involvement, ideal for high local anesthetic administration	Respiratory arrest, retrobulbar hemorrhage, globe perforation	Anesthesia

BRVO, branched retinal vein occlusion; CMV retinitis, cytomegalovirus retinitis; CRVO, central retinal vein occlusion; IOP, intraocular pressure

Ocular DDS:

Although less efficient, commercially available ophthalmic medication formulations are useful in managing DED. The most popular drug delivery method, particularly for treating anterior segment illnesses like DED is ocular instillation. The targeted ocular tissues, the anterior segment, are subject to local therapies that have low bioavailability due to significant obstacles posed by physiological eye defences such tear production, nasolacrimal duct drainage and complicated eye anatomy. As a result, therapeutic medication levels in target tissues are not maintained over time. Nanomedicines, as delivery vehicles, have greatly advanced in ophthalmology due to DED's multifactorial nature and multiple underlying diseases. By overcoming ocular physiological barriers with the help of mucoadhesive properties, they boost the bioavailability of ocular medications with the goal of delivering drugs to the target site at the right concentration. Additionally, they administer medications in a preplanned sustained release manner.

Pharmaceutical formulators notably strive to provide safer formulations free of preservatives for DED [34]. The most common ocular drug delivered is eye drops, however they have insufficient contact with epithelial cells and are difficult to keep in the tear film for extended periods of time. Superoxide dismutase (SOD) a medication used to treat a number of oxidative stress-related ocular illnesses has already undergone significant research when combined with different chemical carriers [35].

The most popular non-invasive method of administering actives for a variety of anterior and posterior segment illnesses including glaucoma, uveitis, cataract and age-related macular degeneration is topical instillation in the eye. Due to its ease of administration and patient-friendliness it is well-liked. However, the eye's natural anatomical barriers restrict medication absorption via this pathway. The medication is promptly removed from the ocular area by the lacrimal fluid [36].

Table 3: Ocular drug inserts device [09].

Name	Description
Soluble ocular drug insert	Small oval wafer, composed of soluble copolymers consisting of actylamide, N-venyl pyrrolidone and ethyl acetate, soften on insertion
New ophthalmic drug delivery system	Medicated solid polyvinyl alcohol flag that is attached to a paper- covered with handle. On application, the flag detaches and gradually dissolves, releasing the drugs
Collagen shields	Erodible disc consists of cross-link porcine scleral collagen
Ocusert	Flat, flexible elliptical insoluble device consisting of two layers, enclosing a areservior, use commercially to deliver Pilocarpine for 7 days
Minidisc or ocular therapeutic	system 4-5 mm diameter contoured either hydrophilic or hydrophobic disc
Lacrisert	Rose-shape device made from Hydroxy propyl cellulose use for the eye syndrome as an alternative to tears
Bioadhesive ophthalmic eye insets	Adhesive rods based on a mixture of Hydroxy propyl cellulose, ethyl cellulose, Poly acrylic acid cellulosephthalate
Dry drops	A preservative free of hydrophilic polymer solution that is freeze dried on the tip of a soft hydrophobic carrier strip, immediately hydrate in tear strip
Gelfoam	Slabs of Gelfoam impregnated with a mixture of drug and cetyl ester wax in chloroform

Insert:

Inserts are cul-de-sac-shaped solid and/or semisolid dosage forms that are thin, aseptic, drug-loaded, multilayered and built with specialised ocular application in mind. It can also overcome the barrier present in conventional ocular administration systems [27]. As a result, a wide variety of ocular drug delivery methods were created in order to increase the drug's bioavailability. Numerous solid devices placed in the eye's cul-de-sac, such as microspheres, nanoparticles, liposomes and ocular inserts, are included in the formulations of in-situ gelling polymers. Although the benefit of a precise, regulated rate of administration has been realised, there are a number of drawbacks, such as patient comfort, insert placement and removal that could accidentally cause the system to be lost from the eye. Smaller devices store information better than larger ones, while rod-shaped devices retain information better than oval ones [32]. The mechanisms of diffusion, osmosis and bio-erosion control the amount of drug released from the ocular inserts. The inserts can totally disintegrate after 24 hours. The kind and amount of polymer used greatly affects how easily the inserts erode. The physiological parameters

of each person influence the pattern of medication release from the ocular inserts. The reservoir or matrix structure in the non-erodible inserts aids in sustaining the medication release [37].

Implant:

Alternatives to the monthly or biweekly bolus IVI injection are required for the recurring delivery of many of the medications used to treat posterior illnesses. Intravitreal implants have been considered as an alternative to reduce problems even further, get around high clearance rates and increase the bioavailability of common medications. These implants typically consist of a polymeric container and can be either biodegradable or semipermanent. Additionally, compound systems nano, micro or liposomes enclosed in a polymeric housing are widely employed. Infections of the vitreous and retina caused by bacteria and viruses can currently be effectively treated using intravitreal implants. The vitreous acts as a particularly efficient vehicle for the transfer of medications to nearby areas of the eye since it is a largely acellular, highly hydrated substance. Drugs administered through the vitreous also have less access to the systemic circulation, which lowers the possibility of non-ocular side effects from therapies like corticosteroids [28]. Intraocular implants are used specifically to deliver the medicine in a regulated manner over an extended period of time. Intraocular injections and the related complications can be avoided with the use of an ocular implant. Implants are made intravitreally at the pars plana, which is anterior to the retina and posterior to the lens, for the administration of drugs to the posterior tissue [27].

VIII. CONCLUSION

Ocular inserts, collagen shields, ocular films, disposable contact lenses and other novel drug delivery devices like hiosomes are all parts of the new ophthalmic delivery system. Nanoparticles and 20 Combining medication delivery systems is a more recent approach that aims to boost a drug's therapeutic response. A better dose form for topical ophthalmic administration may result from this. Only a few of these drug delivery systems' products have reached the market. An ideal system would have minimal systemic effects and prolonged effective medication concentration at the target tissue.

The creation of novel therapies was prompted by the complexity of eye physiology and the factors that limited the effectiveness of conventional methods. As a result, in Diverse therapies have been adopted in order to effectively transport the therapeutic agents to the ocular surface while overcoming the challenges and barriers that impact the existing treatments. Numerous efforts have been made in ocular research to create novel drug delivery methods that are secure and accepted by patients. As stated in this article, various studies have been conducted recently that are used to treat both the front and posterior portions of the eye.

REFERANCES

[1] Annuryanti F, Dominguez-Robles J, Kurnia AQ, Adrianto MF, Larraneta E, Thakur RRS. Fabrication and characterisation of 3D-printed triamcinolone acetonide-loaded polycaprolactone-based ocular implants. Pharmaceutics. 2023;15:243.

[2] Luo RH, Nguyen KT, Parekh AM, Puri R, Reilly MA, Swindle-Reilly KE. The roles of vitreous biomechanics in ocular disease, biomolecule transport, and pharmacokinetics. Curr Eye Res. 2023;48(2):195-207.

[3] Subrizi A, del Amo EM, Korzhikov-Vlakh V, Tennikova T, Ruponen M, Urtti A. Design principles of ocular drug delivery systems: importance of drug payload, release rate, and material properties. Drug Discov Today. 2019;24(8):1769-1776.

[4] Akulo KA, Adali T, George MT, Bodamyali T. Intravitreal injectable hydrogels for sustained drug delivery in glaucoma treatment and therapy. Polymers (Basel). 2022;14:2359.

[5] Shivhare R, Pathak A, Shrivastava N, Singh C, Tiwari G, Goyal R. An update review on novel advanced ocular drug delivery system. World J Pharm Pharm Sci. 2013;1(2):545-568.

[6] Dhanapal R, Vijaya RJ. Ocular drug delivery system: a review. Int J Innov Drug Discov. 2012;2(1):4-15.

[7] Guzman-Aranguez A, Colligris B, Pintor J. Contact lenses: promising devices for ocular drug delivery. J Pharmacol Ther. 2012;136:1-12.

[8] Balla A, Ruponen M, Valtari A, Toropainen E, Tuomainen M, Alvarez-Lorenzo C, et al. Understanding dexamethasone kinetics in rabbit tear fluid. Eur J Pharm Biopharm. 2022;172:53-60.

[9] Tangri P, Khurana S. Basics of ocular drug delivery systems. Int J Res Pharm Biomed Sci. 2011;2(4):1541-1552.

[10] Gorantla S, Rapalli VK, Waghule T, Singh PP, Dubey SK, Saha RN, et al. Nanocarriers for ocular drug delivery: current status and translation opportunity. Nanoscale Adv. 2020;2:27835-27855.

[11] Adrianto MF, Annuryanti F, Wilson CG, Sheshala R, Thakur RRS. In vitro dissolution testing models of ocular implants for posterior segment drug delivery. Drug Deliv Transl Res. 2022;12:1355-1375.

[12] Palani S, Joseph NM, Goda CC, Zachariah A, Ayenew Z. Ocular drug delivery. Int J Pharm Sci Res. 2010;1(3):1-15.

[13] Habibi M, Mobasseri S, Zare A, Souriaee V. Drug delivery with therapeutic lens for glaucoma treatment: a numerical simulation. Biomed Eng Adv. 2022;3:100032.

[14] Hajare A, Mali S, Salunkhe S, Nadaf S, Bhatia N, Bagal P, et al. A rational approach to ocular drug delivery systems: an overview. World J Pharm Res. 2014;3(2):3324-3348.

[15] Agarwal P, Rupenthal ID. Non-aqueous formulations in topical ocular drug delivery – a paradigm shift? Adv Drug Deliv Rev. 2023;198:114867.

[16] Dosmar E, Walsh J, Doyel M, Bussett K, Oladipupo A, Amer S, Goebel K. Targeting ocular drug delivery: an examination of local anatomy and current approaches. Bioengineering (Basel). 2022;9:41.

[17] Moiseev RV, Morrison PWJ, Steel F, Khutoryanskiy VV. Penetration enhancers in ocular drug delivery. Pharmaceutics. 2019;11:321.

[18] Akhter MH, Ahmad I, Alshahrani MY, Al-Harbi AI, Khalilullah H, Afzal O, et al. Drug delivery challenges and current progress in nanocarrier-based ocular therapeutic systems. Gels. 2022;8:82.

[19] Rathore SK, Nema RK, Sisodia SS. An overview and advancement in ocular drug delivery systems. Int J Pharm Sci Res. 2010;1(10):11-23.

[20] Raj VK, Mazumder R, Madhra M. Ocular drug delivery system: challenges and approaches. Int J Appl Pharm. 2020;12(5):1-10.

[21] Polat HK, Unal S. Development of besifloxacin HCl loaded ocular in situ gels: in vitro characterization study. J Fac Pharm Ankara. 2018;47(1):39-50.

[22] Alshaikh RA, Waeber C, Ryan KB. Polymer-based sustained drug delivery to the ocular posterior segment. Adv Drug Deliv Rev. 2022;187:114342.

[23] Han H, Li S, Xu M, Zhong Y, Fan W, Xu J, et al. Polymer- and lipid-based nanocarriers for ocular drug delivery. Adv Drug Deliv Rev. 2023;196:114770.

[24] Qamar Z, Qizilbash FF, Iqubal MK, Ali A, Narang JK, Ali J, Baboota S. Nano-based drug delivery systems for ocular diseases. Recent Pat Drug Deliv Formul. 2019;13(4):246-254.

[25] Gote V, Sikder S, Sicotte J, Pal D. Ocular drug delivery: present innovations and future challenges. J Pharmacol Exp Ther. 2019;370:602-624.

[26] Souto EB, Ferreira JD, Machado AL, Ettcheto M, Cano A, Camins A, et al. Advanced formulation approaches for ocular drug delivery. Pharmaceutics. 2019;11:460.

[27] Mythili L, Ganesh GNK, Monisha C, Kayalvizhi R. Ocular drug delivery system – an update review. Res J Pharm Technol. 2019;12(5):2500-2506.

[28] Sharabati MA, Sabouni R, Husseini GA. Biomedical applications of metal–organic frameworks. Nanomaterials (Basel). 2022;12:277.

[29] Allyn MM, Luo RH, Hellwarth EB, Swindle-Reilly KE. Considerations for polymers used in ocular drug delivery. Front Med (Lausanne). 2022;8:787644.

[30] Kumaran KSGA, Karthika K, Padmapreetha J. Comparative review on conventional and advanced ocular drug delivery formulations. Int J Pharm Pharm Sci. 2010;2(4):1-10.

[31] Mohamed HB, El-Hamid BN, Fathalla D, Fouad EA. Current trends in pharmaceutical treatment of dry eye disease. Eur J Pharm Sci. 2022;175:106206.

[32] Huang Y, Cao L, Paeakhonskiy BV, Skirtach AG. Hard, soft and hybrid drug delivery carriers based on $CaCO_3$ and alginate. Pharmaceutics. 2022;14:909.

[33] Abourehab MAS, Rajendran RR, Singh A, Pramanik S, Shrivastav P, Ansari MJ, et al. Alginate as a promising biopolymer in drug delivery and wound healing. Int J Mol Sci. 2022;23:9035.

[34] Narayana S, Ahmed MG, Jaswanth BHG, Shetty PK, Nasrine A, Thriveni M, et al. Recent advances in ocular drug delivery systems and VEGF targeting. Future J Pharm Sci. 2021;7:186.

[35] Cantarelli MA, Pellerano RG, Marchevsky EJ, Camina JM. Multivariate optimization of an analytical method for pharmaceutical analysis. Anal Sci. 2011;27(1):73-78.

[36] Dosmar E, Walsh J, Doyel M, Bussett K, Oladipupo A, Amer S, Goebel K. Targeting ocular drug delivery: anatomy-based approaches. Bioengineering (Basel). 2022;9:41.

[37] Han H, Li S, Xu M, Zhong Y, Fan W, Xu J, et al. Nanocarriers for ocular drug delivery: current perspectives. Adv Drug Deliv Rev. 2023;196:114770.