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# NOVEL APPROCHES FOR OPHTHALMIC DRUG DELIVERY SYSTEM

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## Abstract:

This review's goal is to provide readers with an up-to-date summary of what is currently known about ocular medication delivery. The unusual architecture and physiology of the eye have presented a significant barrier to drug delivery scientists. The rapid precorneal drug loss caused by nasolacrimal drainage, tear turnover, and drug dilution leading to low bioavailability is one of the main issues with conventional ocular dose forms. These efforts resulted in the creation of innovative drug delivery dosage forms such as mucoadhesive formulation, liposomes, occuserts, and nanoparticles. In terms of increasing medication bioavailability, lowering toxicity, and reducing dosing frequency, controlled drug delivery systems have significant benefits over conventional dosage forms. Drug delivery may be greatly enhanced in the future by developing non-invasive sustained drug delivery systems and examining the viability of topical application to deliver drugs to the posterior segment.

*Keywords* **—Anatomy and physiology, Cornea, Contact lens, Drug delivery, Eye, Emulsions, Formulations, Implants, Liposomes, Ointments, nanoparticle, occuserts**

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## I. INTRODUCTION

The structure and function of the eye are distinctive, making it a complex organ. There are two primary segments of the eye: the anterior segment and the posterior segment. The anterior segment makes up about one-third of the eye, with the posterior segment making up the remaining portion. The cornea, conjunctiva, aqueous fluid, iris, ciliary body, and lens are among the tissues that make up the anterior portion of the eye. The posterior segment of the eye is made up of the sclera, choroid, retinal pigment epithelium, neural retina, optic nerve, and vitreous humour. Several vision-threatening disorders affect the eye's anterior and posterior segments. Glaucoma, allergic conjunctivitis, anterior uveitis, and cataract are among the conditions that impact the anterior segment. Although age-related macular degeneration (AMD) and diabetic retinopathy are the conditions that affect the posterior portion of the eye the most frequently. [1]

The most popular non-invasive drug delivery method for treating illnesses of the anterior segment is topical instillation. 90% of the commercially available ophthalmic formulations are in conventional dosage forms like eye drops. The cause might be related to patient compliance and convenience of administration. However, topical drop delivery results in very limited ocular

  

absorption. Deeper ocular medication absorption is hampered by a variety of anatomical and physiological restrictions, including tear turnover, nasolacrimal drainage, reflex blinking, and ocular static and dynamic barriers. Less than 5% of the dose is administered topically so reaches deeper eye tissues. Due to the aforementioned barriers, it is also challenging to establish therapeutic medication concentration into posterior segment ocular tissues after topical eye drop application.[1]

By using several administration methods, including intravitreal injections, periocular injections, and systemic administration, the medication can be administered to the tissues of the posterior region of the eye. However, systemic administration is not a viable strategy due to the tiny volume of the eye in comparison to the rest of the body and the presence of blood-retinal barriers. The most popular and frequently advised method of administering medication to treat posterior ocular disorders is intravitreal injection. However, the requirement for frequent eye punctures to administer intravitreal injections results in several adverse reactions, including endophthalmitis, hemorrhage, retinal detachment, and low patient tolerance.[1]

Different traditional and novel drug delivery systems, including emulsions, ointments, suspensions, aqueous gels, nano micelles, nanoparticles, liposomes, dendrimers, implants, contact lenses, nanosuspensions, microneedles, and in situ thermosensitive gels, have been developed to overcome the barriers to ocular drug delivery and improve ocular bioavailability. To treat eye disorders, various traditional and cutting-edge ophthalmic drug delivery systems have been developed. This review will give an overview of these systems.[1]

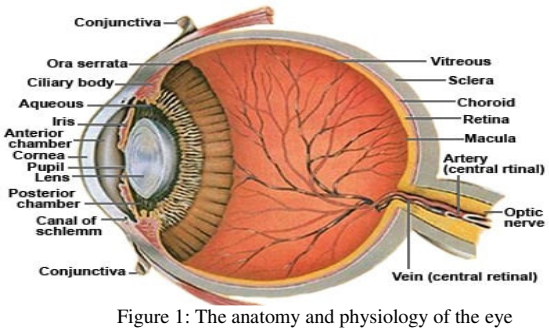


Figure 1: The anatomy and physiology of the eye

## II. STRUCTURE OF THE EYE

**The eye is made up of 3 main parts**: [2]

Eyeball, Orbit (eye socket), Accessory (adnexal) structures

The eyeball is the primary component of the eye. The diameter of each of the sphere-shaped eyes is approximately 2.5 cm (1 inch) 6. The majority of the vitreous humor, a clear, jelly-like fluid, fills the interior of the eyeball. It aids in maintaining the eye's shape and supporting the inside tissues. It is divided into three layers. (Or tunics): **Outer layer**: The outermost layer or covering of the eye **Sclera**: The sclera is the tough, white connective tissue that covers the outside of the eyeball serves as the protective covering **Cornea**: The cornea is the transparent, dome-shaped layer on the front of the eye that allows light to pass through. Cornea types. Epithelium, stroma, Endothelium.**Middle Layer**: The term "vascular tunic" refers to the middle layer of the eye's wall. This has 3 main parts: **Iris**: The iris is the eye's slender, musculoskeletal, and coloured portion. It is situated halfway between the lens and the cornea. To alter the amount of light entering the eye, the iris dilates and dilates the pupil. **Choroid**: The choroid supplies oxygen and nutrients to the retina. It containspigment-producing cells called melanocytes, which help absorb light and minimize reflections. **Ciliary body**: present behind the iris, it is the muscular ring of tissue that changes the shape of the lens so it helps in focus **Inner Layer**: The innermost layer of the wall of the eye is made up of the retina or neural tunic. **retina**: is the thin layer of cells at the back of the eyeball

  

and works like the film of a camera. **Lens:** The lens is a transparent structure that lies directly behind the cornea and iris. The lens changes shape to allow the eye to focus on objects.**Orbit:** The orbit (eye socket) is a bowl-shaped cavity that contains the eyeball. The bone and connective tissues cushion and protect the eye. **Eyelids:** The eyelids are folds of skin that cover and protect the eye. It contains glands, that produce an oily secretion that covers the tear layer and prevents the tear from evaporating and the eyelids from sticking together.

## III. MERITS OF OCULAR DRUG DELIVERY SYSTEM[3]

The advantages of ocular drug delivery systems include: Summarized below.

increased dosing accuracy. to avoid the negative effects of conventional systems' pulsed dosing.

to deliver drugs in a controlled and sustained manner.

to prolong corneal contact duration in order to maximize the drug's ocular bioavailability. Effective adhesion to the corneal surface can accomplish this.

To provide targeting inside the eyeball so as to limit damage to adjacent ocular structures.

To circumvent the protective barriers like drainage, lacrimation, and conjunctival absorption to provide comfort, and better compliance to the patient, and to improve the therapeutic performance of the drug.

To provide better housing for the delivery system

They can easily be administered by the patient himself.

They have quick absorption and fewer visual and systemic side effects.

## IV. DEMERITS OF OCULAR DRUG DELIVERY SYSTEM[3]

The drug solution only remains on the eye's surface for a brief period of time.

It shows inadequate availability.

Shows instability of the dissolved drug.

There is a need to use preservatives.

## V. BARRIRESTO DRUGPERMEATION[4]

### V.IPhysiological barriers

The tear film is the eye's main line of protection. Precorneal variables include solution drainage, tear dilution, tear turnover, and enhanced lacrimation further limit the bioavailability of medications that are applied topically. An isotonic aqueous solution of proteins, including lysozyme, and lipids make up the lacrimal fluid.Lowering drug concentration isseen leading to diminished drug absorption. Rapid clearance from the precorneal area by lacrimation & through nasolacrimal drainage & spillage further reduces contact time between the tissue & drug molecules. This in turn lowers the exact time for absorption and reduced bioavailability.

### V.IIAnatomical Barriers:

There are two possible entrance points for dose forms when applied topically: either through the cornea or a non-corneal route. The epithelium is a tightly packed, stratified tissue made up mostly of five parts. It serves as a significant impediment to the transfer of hydrophilic drugs via intercellular gaps. The non-corneal pathway moves over the conjunctiva and sclera while avoiding the cornea. This pathway is crucial, particularly for big, hydrophilic compounds like peptides and proteins. Because tight junction proteins are expressed far less often in the conjunctiva than in the corneal epithelium, the conjunctiva is more permeable than the cornea, particularly for hydrophilic molecules.

### V.III Blood Retinal Barriers (BRB)

The BRB consists of inner and outer components, inner BRB (RB), and outer BRB (oBRB).The BRB regulates fluids and molecular movement between the ocular vascular beds and retinal tissues and prevents leakage into the retina of macromolecules and other potentially harmful agents.The iBRB is

  

established by the tight junctions between neighboring retinal endothelial cells. These specialized TJ restrict the diffusional permeability of the retinal endothelial layer.The OBB is established by the TJ between neighboring retinal pigment epithelial cells (RPE). The RPE is composed of a single layer of retinal pigment epithelial cells that are joined laterally toward their apices by TJ between adjacent lateral cell walls.The RPE plays a fundamental role in regulating. access of nutrients from the blood to the photoreceptors as well as eliminating waste products and maintaining retinal adhesion.

## VI. APPROACHES TO OVERCOME BARRIERS

VI.IBioavailability improvement

**Viscosity enhancer**: viscosity-increasing polymers are usually added to ophthalmic drug solution which leads to an increase in viscosity.Ex: PVP, HPMC, HPC, PVA methylcellulose[5]

**Eye ointment**: ointment is usually formulated using mixtures of semisolid and solid hydrocarbons.Upon installation, in the eye, the ointment breaks up into small droplets and remains as a depot of the drug in a cul-de-sac for an extended period.Hence useful in improvising drug bioavailability and sustaining drug release. [6]

**GEL**: Ophthalmic gels consist of mucus-binding polymers that provide local delivery of the active ingredient into the eye. Such a polymer has a property known as bio adhesion, that is, attaching a drug carrier to a specific biological tissue. Ex. HPMC,PVP HPC[7]

**PRODRUG**: The principle of prodrugs is to improve the permeability of the cornea to drugs by modifying the hydrophilic or (lipophilic) properties of the drug. After penetrating the cornea, the prodrug is enzymatically or chemically converted to the active parent compound. The ideal prodrug must not only have increased lipophilicity and a high partitioning coefficient but also have a high enzyme sensitivity. Ex. acyclovir, ganciclovir[8]

**PENETRATION ENHANCER**: the transport characteristics across the cornea can be maximized by increasing the permeability of the corneal epithelial membrane. It has the main disadvantage of ocular irritation and toxicity Ex: parabens, tween 20, saponins, and cetylpyridinium chloride.[9,10]

## VII. NOVEL APPROACHES FOR OCULAR DRUG DELIVERY SYSTEM

### Liposomes

Liposomes are defined as microscopic vesicles consisting of one or more concentric lipid bilayer, which separates through water or aqueous buffer compartments. Liposomes are widely used in eye drop formulations due to Their properties have intimate contact with eyeball surfaces, mainly cornea, and conjunctiva, so the drug absorbed through the eye can be increased [11]. Liposomal formulations can be developed by the use of phosphatidylcholine, stearyl amine, and varying amounts of cholesterol or lecithin and -L-dipalmitoyl-phosphatidylcholine [12-13]. The main advantages of this type of distribution system are due to their properties i.e., biocompatibility, biodegradability, amphoteric properties, and relative toxicity [12, 14, 16]. Drug delivery to a target site or site specificity and sustained drug release is also favorable. Liposomes are often prepared for drugs with low absorption, lower partition coefficient, and low solubility, and have medium to high molecular weight [17]. The surface load of liposomes should be considered when formulating an eye distribution system; if the liposomes are positively charged, it is observed that they are preferably imaged by the negatively charged corneal surface, while neutral or negatively charged liposomes are not absorbed by the cornea face. According to the number of reported searches, the property pharmaceutical ingredients used in liposomal ophthalmology the formula is acyclovir, pilocarpine, acetazolamide, chloramphenicol, and ciprofloxacin [15, 13].

### Niosomes

  

Niosomes are chemically stable bilayer nanocarriers consisting of nonionic surfactants and are used as carriers for hydrophilic and hydrophobic drugs. They don't have the same disadvantages as liposomes chemically unstable, prone to oxidation, and including highly unstable phospholipids as well as expensive [12, 14, 18, 19]. Thus, niosomes have many advantages, especially because they are biodegradable, biocompatible, and non-immunizing, causing them to increase the contact time between the drug and the cornea, thereby increasing the bioavailability of medicine. A modified form of the noisome, the disco some, also acts as an eye drop carrier. The size of the discosomes is from 12 to 16m. This gives him the advantage of not allowing him in Its general circulation and disc shape allow for a better fit in the conjunctival sac [14]. The size of the disc distinguishes them from niosomes because the first is composed of nonionic surfactants and SolulanC[21], a lanolin derivative and a mixture of cholesterol (ether of cholesterol and polyethylene glycol) and ethoxylated fatty alcohols (ethers of cetyl alcohols and polyethylene glycol). The use of liposomal carriers as a drug delivery system has been reported on ganciclovir [20], cyclopentolate, or timolol [14]

**Nanoparticle/ nanosphere**

These are polymeric colloidal particles, ranging in size from 10 nm to 1 nm, where the drug is dissolved, carried, encapsulated, or adsorbed [22]. It includes several substances that are biodegradable, such as natural substances or Synthetic polymers, lipids, phospholipids, and metals. Okay nanoparticles, drugs can be formulated in many ways such as by being integrated into the matrix or attached to the surface of Biodegradable polymers used for the preparation. Nanoparticles used in drug delivery to eye tissues are polylactide (PLA), polycyanoacrylate, poly (D,L-lactide), and natural polymers such as chitosan, gelatin, sodium alginate, and albumin. In the last 10 years, nanoparticles have been used as carriers in drug delivery for eye disorders and yielded promising results. A specific type of Nanoparticles can be classified as small capsules with a central cavity surrounded by a polymeric membrane and solid spheres, known in the form of nanocapsules and nanospheres, respectively. Marchal et al. (1993) reported that the nanocapsules exhibited better efficacy than nanoparticles, because drugs (betaxolol, carteolol) are present in a fused form in the oil core, diffusing at a higher rate than in the cornea [23]. Some authors have reported that nanocapsules have many effects due to the presence of a mucus-sticking property that shows an increased residence time and biological response [24]. So these things can improve the bioavailability of the drug at the ocular site and also reduces quantification frequency. Alonso et al. (1995) reported in their study that poly-e-caprolactone-based nanoparticles have cyclosporine has better corneal absorption than oily solution [25]

**Nano-suspension and nano-dispersion**

Nano-suspension is created for drugs that are difficult to dissolve in water suspended at the nanometer scale in a suitable dispersion medium. Here technology that can be used appropriately for the drug fraction formed high-energy crystals, so they are insoluble in organic (lipophilic) or hydrophilic medium. polymer nanoparticle suspensions are constructed using inert polymer resins and could be used as an important drug delivery vehicle, potentially increasing drug release and improving bioavailability. The A carrier with such properties can be used as an inert carrier used for eye drops, as they are not irritating to the cornea, iris, or conjunctiva. An example of such support is polymer suspension of nanoparticles containing the active ingredient flurbiprofen (FLU) composition and eudragit RS 1001 and RL 1001 are the polymers used. Production of nano-dispersed chitosan alginate for drug prolongation delivery and improved transcorneal permeability have been reported by Morsi et al. (2015) [26, 27].

**Microemulsion**

Stable dispersion of water in oil, facilitated by the addition of surfactants and co-surfactant combined to reduce surface tension, is called microemulsion. Microemulsions lead to a reduction in dosing

  

frequency and improve the ocular bioavailability of the drug. The main advantage of this form of the galaxy is its high thermodynamics stability, smaller droplet size, i.e., 100 nm (approx.), and clear appearance. Ansar et al. (2008) reported a microemulsion formulation, which is an oil-in-water system consisting of pilocarpine as a drug, lecithin, propylene glycol, PEG 200 as surfactant/co-surfactant and isopropyl myristate to form the oil phase [28].

**Dendrimer**

Dendrimers are symmetric structures made up of repeating units of branched molecules surrounding a central nucleus, recently proposed as local drug delivery systems [29]. Often used the dendrimers introduced into the ocular system are poly-(amidoamine) (PAMAM), PLL, polypropyleneimines (PPI), and phosphorus dendrimers. They are used as carriers to deliver nucleic acids drugs, mainly in the ocular delivery system [30], but sometimes used for low molecular weight drugs can be hydrophilic (antibiotics) or lipophilic (anti-glaucoma) drugs [31,36]. According to the reported methods, it is found that the transporter performance can be increased by modifying the surface using methods such as PEGylation or acetylation, which help reduce their toxic factors [32, 33, 37]. Thus, the advantage to use dendrimer as a drug carrier for topical applications is improve drug residence time in the anterior corneal region, increase drug bioavailability, and prolonged therapeutic effect [31, 34, 35, 36]

**in situ-forming gel**:

the droppable gels are liquid upon instillation and they undergo a phase transition in the ocular cul-de-sac to form a Visco elastic gel and this provides a response to the environmental changes. it prolongs the residence time and improves the ocular bioavailability of the drug. Parameters that can change and trigger the phase transaction ofdroppable gels include PH, change CAP latex, and cross-linked polyacrylic acid.[38]

**Nanomicelles**[6]

Nanomicelles can deliver medications that are poorly soluble in water and protect molecules like proteins or peptides because they have an internal hydrophobic fatty acyl chain and an outer hydrophilic polar head. These structures are amphiphilic and have the potential to have an inherent ability to be surfactants or polymers [39, 40]. Cholkar et alrecent .'s review studies showed the crucial limitations in the use of these systems for achieving the goal of medication delivery for the treatment of ocular tissues. The major benefits of this kind of formulation include their ease of preparation, final small size, and incredible capability to encapsulate large amounts of pharmaceuticals. The formulations with such morphology thus permit enhanced Drug bioavailability with enhanced clinical outcomes after subsequent acquisition [41, 42]. The formulation format of nanomicelles was employed in several clinical studies with various medications. An objective copolymer of poly hydroxyethyl aspartame (PHEAC) and its corresponding pegylated molecule was used in a study by Civiale et al. to create nano micelles packed with dexamethasone and deliver the formulation to the eye's anterior segment globes of rabbits The aqueous humor was extracted and analyzed to determine the drug concentrations. The results showed that dexamethasone encapsulated in PHEAC nano micelles had increased values for bioavailability compared to the drug's typical suspensions, with an overall quantity value 40% higher than the control suspension formulation. The outcomes indicated that it might be beneficial to use these nanomicelle formulations to topically deliver small compounds to the ocular region [43]. The ocular globe underwent gene therapy using nanomicellar devices. Another investigation, this one conducted by Liaw and colleagues, attempted to deliver certain genes by topical application to the ocular tissues. It was stated that a copolymeric lattice made of poly(ethylene oxide), poly(propylene oxide), and poly(ethylene oxide) might be used as a delivery system In this scenario, LacZ was transfected into mouse and rabbit ocular

  

tissues. Selected genes were integrated into plasmids containing the DNA of interest fused with the reporter gene. After obtaining the results, it became evident that these technologies offered a sizable opportunity to convey genetic data. The tissue-specific promoters keratocan and keratin 12 were used in further studies with additional genomic data. The activity of a different reporter gene, which is translated into the active -Gal enzyme that transforms a reagent into a color-identifiable molecule, was used to measure the overall expression of the genes of interest. After six days of continuous dosing, three times per day, of pK12-Lac Z-PM, an eye drop formulation, administered to the corneal tissues of mice and rabbits, the distinguishable color was seen. Additionally, the endocytic route in conjunction with the relative size of the acquired particles by paracellular transference was the most likely mechanism responsible for the transfection process [44]. CEQUA is one of the newest ocular products to use nanomicelles. The purpose of this medication, a cyclosporine ophthalmic solution at 0.09%, is to stimulate tear production in individuals with keratoconjunctivitis sicca (dry eye) [45].

## VIII. APPROACHES FOR CONTROLLED AND CONTINUOUS OCULAR DRUG DELIVERY

The following ophthalmic drug delivery systems have been reported for control and continuous drug release

### microparticles

The microparticles are isotropic, transparent, translucent, and Thermodynamic stability systems of oil, surfactant, and water The size of droplets varies between 20 and 200 nm [46]. Microparticles are defined as polymer particles with the size of microns Which drug in the polymer matrix is suspended in the liquid medium? The drug is evenly dispersed in the polymer matrix or covalently bonded to the polymer backbone [47]. Transparent applied topically to the eye, the particles enter the lacrimal sac in the eye, and the drug is released from that sac by several processes. such as diffusion, chemical reaction, or polymer degradation. The microparticles increase the residence time in front of the cornea, allowing continuous and prolonged drug release. This eventually leads to an increase in the ocular bioavailability of the drug and reducesthe frequency of quantification, but microparticle preparations are often Do not use for eyes as they irritate due to high concentrations of particle size. Microparticles have properties such as biodegradation, bio-adhesion, and biocompatibility, making them suitable for manufacturing with polymers.

### Ocular inserts

Ophthalmic inserts are solid patches that, when placed in the conjunctiva, slow the rate of drug release. Eye insertion also overcomes the problem of frequent dosing by effectively maintaining the concentration of the drug and giving rise to controlled, sustained, and continuous medication use. Insert eyes also has various benefits such as improved absorption of drugs due to increase exposure time and minimize dosage and application frequency. The main disadvantage of these inserts is the patient's non-compliance with the feeling of frequent foreign body penetration in the eyes, the feeling of difficulty in self-insertion, and the feeling of loss of eye plug. Eye insertion is done using different techniques that make them soluble, susceptible to erosion, and in hydrogel form [48].

The ophthalmic insertsare classified based on their solubility behaviour.

1. Insoluble ophthalmic inserts, 2. Soluble ophthalmic inserts,3. Bio-erodible ophthalmic inserts

#### 1. Insoluble ophthalmic inserts

The insoluble inserts are sub-classified into three groups.

a. Diffusional inserts

b. Osmotic inserts

c. Contact lenses

  

**Diffusional Inserts**: A innovative medication delivery method based on a porous membrane is called the Ocuserts system. A diffusional release mechanism underlies the drug release from diffusional inserts. The core drug reservoir of the diffusional inserts is encased in a specially created semi-permeable/microporous membrane, allowing the medication to diffuse from the reservoir at a carefully controlled pace.The lachrymal fluid penetrates through the membrane until sufficient internal pressure is reached which controls the drug release from such a system.

**Osmotic Inserts**:In general, the osmotic inserts/ocuserts contain two separate osmotic solutes. Separate compartments are used for the drug and the osmotic solute, with the drug reservoir being enclosed by an elastic impermeable membrane and the osmotic solute reservoir being enclosed by a semi-permeable membrane.The tear's diffusion into the osmotic compartment inducing on osmotic pressure due to drug diffusion.

**Contact Lenses:**Contact lenses are a covalently cross-linked hydrophilic or hydrophobic polymer that forms a three-dimensional network which able of retaining aqueous drug solution or solid components. Contact lenses are structures shaped and initially used for vision correction. Contact lenses are widely used as a potential drug delivery device by pre-soaking them in drug solutions. The main advantage of this system is increasing the possibility of correct vision and drug release at the same time.

### 2. Soluble Ophthalmic Inserts

Soluble ophthalmic inserts represent the oldest class of ophthalmic inserts These soluble inserts offer the advantage of being completely soluble so that they do not need to be removed from their site of application thus, limiting the interference to insertiononly.The therapeutic agents are preferably absorbed by soaking the insert in a solution containing the drug, drying and rehydrating it before use on the eye. The amount of drug loaded will depend upon the amount of binding agent, the concentration of drug solution in which the composite is soaked as well as the duration of soaking.The release of drug from this type of insert/ocuserts due to permeation of tear fluid into the inserts increases the high release rate of the drug through diffusion and forms a gel layer around the core of the insert.

### 3. Bio-Erodible Inserts

The bio-erodible inserts/ocuserts are consists of a material homogenous dispersion of drug included or not into a hydrophobic coating which is substantially impermeable.The bio-erodible inserts/ocusert consist of bio-erodible poly (e.g. cross-linked gelatin derivatives, polyester derivative) which undergo hydrolysis of the chemical bond and hence dissolution.The ability to alter the final structure of these bio-erodible polymers during synthesis and the inclusion of anionic or cationic surfactants allows for the change of their erosion rate.When a device comes into touch with tear fluid, it causes a brief diversion of the matrix, which leads to the release of the medication from the system.

### Implant

The goal of intraocular implant design is to prolong the operation of the drug, as well as its controlled release using polymers or polymer systems. An injectable drug delivery system, such as liposomes and nanoparticles, is easy to administer, but the drawback is that after inserting, it becomes hard to retract particles in any complications, such as toxic reactions. So it is It is beneficial to use an implant to balance the drug and time ratio Release. Eye implant removal is easy and can be removed by surgical intervention. Implants can be classified into two types depending on the characteristics of the polymer(s) used.

## IX. APPROACHES FOR POSTERIOR SEGMENT DRUG DELIVERY

### Intraocular injection

Research reports reveal that intravitreal injection for the posterior region became popular all over the world as a medical system in recent years. Injections are made directly into the following

  

passage through pars plana to transport the drug to pass all barriers. Several studies have been conducted to find out the pharmacokinetic parameters of antiviral drugs, such as ganciclovir [49], foscarnet [49], and cidofovir [50], antibiotics: Cefazolin [51], amikacin, moxifloxacin [52], ceftizoxime, ceftriaxone ceftazidime [53], clindamycin [54] and gentamicin [55], steroids: dexamethasone [56], triamcinolone acetonide [57] and monoclonal antibodies, such as rituximab [58], bevacizumab [58] after intraocular injection. If the molecular weight of the drug is very high, the vitreous retention time also seems to be higher. Molecule larger, i.e. linear >40 kDa and spherical molecules >70 kDa seems to have a long retention time due to the presence of barriers around the lens humor [59, 60]. So this route is more for drugs with higher molecular weight (>500 Da) and also with a longer half-life. The first-order velocity kinematics is mainly responsible for removing residues from the vitreous humorous [61]. Even the use of drugs by intravitreal injection can be achieved by increasing the concentration of the drug in the neural retina; side effects such as retinal detachment due to repeated injections retinal hemorrhage, endophthalmitis, and other toxicity retinopathy occur due to higher concentrations in bolus. doses management can lead to patient non-compliance [62-65]. Ausayakhun et al. (2005), found in their study that cytomegalovirus (CMV) retinitis can be controlled using ganciclovir in vitreous (2 mg in 0.1 ml each) and reported data showed 60% of treated eyes remained stable, 13D44 showed improvement and 26% showed reduction visual acuity [66]. However, retinal detachment has been noticed in 6%, intraocular bleeding was observed in 1% and endophthalmitis was observed in 1% of treated eyes. Hence we can observe from research that problems related to endosperm injection should be considered [66]. Some Other studies have also been done with similar results, which say intravitreal injection is helpful, but not good for diseases of the latter [67-68]. Evolving in the design of drug delivery systems and surgical procedures has led to the development of endothelial implants glass chambers for a longer time. the difference between vitreous injections and vitreous implants istheir administrative time. The injections can be given 2 or 3 times a week and at best can be changed monthly, respectively.

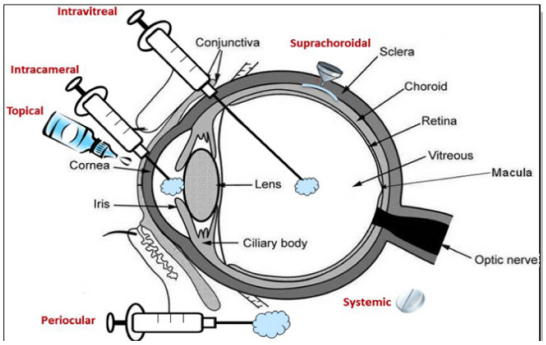


Figure 2:Routes of administration ocular drug delivery

## Ionic electrophoresis

Ocular ion electrophoresis is one of the rapidly growing areas of research Its non-invasive nature is to deliver drugs to both anteriorly and posterior parts of the eye. Iontophoresis is defined as a non-invasive method of low-efficient membrane transport of ionized drugs current [69, 70]. Drugs can pass through the membranesthrough two pathways, migration and electroosmosis. Eye ion electrophoresis, classified as the transcranial, sclera, or transscleral [69], is considered one of the most attractive options. The OcuPhor™ system is designed using an applicator, Dispersion electrode, and dose controller for transdural ion electrophoresis [71]. The device works because it releases the active ingredient half in the retina-choroid. Another similar device is in production called Visulex™, which allows for specific transport molecules to be ionized across the membrane. Antibiotics, that are successfully used are gentamicin, tobramycin, and ciprofloxacin, but not vancomycin, due to its high molecular weight [72]. Successful Birth results have been seen with drugs such as dexamethasone and antisense ODN [73].

  

## X. LIST OF OCUSERTS OF DIFFERENT OPHTHALMIC DRUGS AVAILABLE IN MARKET[74]

TABLE I- OPTHALMIC DRUG AVAILABLE IN MARKET

| SR NO | DRUG | CATEGORY OF DRUG | POLYMER/BASE |
|---|---|---|---|
| 1 | CIPROFLOXACIN | Anti-infective agent | HPMC, PVP MC and EC |
| 2 | OFLOXACIN | Antibacterial agent | Polyethylene oxide and EUD L 100 |
| 3 | PEFLOXACIN | Antibiotic agent | EUD RS100, EUD RL100 and PVP K-30 |
| 4 | ACYCLOVIR | Antiviral agent | MC, HPMC, HPC, and starch |
| 5 | BRIMONIDINE TARTRATE | Intraocular pressure lowering agent | PVA, EC, and PVP K-30 |
| 6 | FLUCONAZOLE | Antifungal agent | HPMC, PVP and PVA |
| 7 | ACECLOFENAC | The non-steroidal anti-inflammatory agent | EUD L100, EUD RL100,HPMC and EC |
| 8 | LEVOBUNOLOL | Beta-blocker agent | MC, PVP and HPMC |
| 9 | DICLOFENAC SODIUM | Non-steroidal anti-inflammatory drug | HPMA and EUD L100 |
| 10 | TIMOLOL MALEATE | Anti- glaucoma agent | MC, HPC, EUD RS100 EUD RL100, EC and PVP |

## XI. FUTURE ASPECTS

Medication to the eye has been around for decades and remained a difficult task due to related issues It has bioavailability. Special study of area Drug delivery to the eye has led to the development of new a drug delivery system for delivering a drug to the eye; which set a new standard for the effective prevention and treatment of eye diseases. much research has not yet been done It can further improve existing dosage forms, overcome bioavailability issues, and extend the shelf life of new formulations. It has a noticeable and improved release profile. But the immediate need is to develop formulations that do more than just target the entire eye. But the novelty should also have improved properties Site-specific within the eye, enabling therapy Both anterior and posterior segments can be given correctly. Care must also be taken in procedures Development of new techniques for ocular drug delivery. be technology-compatible patients too. The text of the draft, Therefore, contains the optimal amount of therapeutic agent A single dose should be sufficient for treatment. there may be rapid development in the eye area Only dispense drugs if researchers know each other well Proper anatomy and physiology of the eye in normal and diseased conditions, the nature of all barriers therein, and the dynamics of the various compartments in your eyes. This trend of recent innovations is in the shape of innovative drug delivery systems and Levels of compliance with higher brands. As the complex nature of various diseases and barriers Provided through the eyes, always prevents effective management of eye diseases, Therapeutic concentrations at the site of infection can be overcome over an extended period with a single application of such an obstacle.

Drug delivery ininvasive modes is not safe, effective, and patient-compliant. In these cases, the periocular route of drug administration appears to provide sustained drug levels in a variety of ocular pathologies affecting the anterior and posterior portions of the eye. Also, liposomal drug delivery approaches may be a promising strategy for some drug molecules with poor absorption across the ocular barrier. This colloidal drug delivery system could significantly improve the current therapeutic state and serve as an alternative after periocular administration. Traditional delivery systems such as eye drops, suspensions, and ointments are suboptimal. However, more than 90% of the ophthalmic preparations marketed for the treatment of eye diseases are eye drops. Advances in nanotechnology science and non-invasive techniques for drug and gene delivery will continue to be at the forefront of the design and development of new ocular drug delivery systems. Of particular note is non-invasive sustained drug delivery for conditions affecting both the anterior and posterior

  

segments of the eye. A transparent understanding of the complexities associated with normal and disease states, various physiological barriers, and pharmacokinetics will greatly accelerate further developments in the field of drug delivery to the eye.

## XII. CONCLUSION

For decades, there has certainly been one mechanism for specific drug delivery to the ocular environment.Challenge Usual pharmaceutical formulations are used as medicines for this purposeB. Eye drops had drawbacks and had to use a different carrierIntended for the ocular route of administration. To overcome such limitations, we need to make deep investmentsIt is being implemented in the field of ophthalmic research to create a safe system that allows for higher cure rates.Improved efficacy and patient compliance. Today scientists are working hard to achieve thisAdvances in vivo models will enable the further application of future innovations to clinical trials. next to,the dawn of the nanotechnology era with future production methods and emerging technologiesInterest is growing due to the potential for additional applications in ophthalmic application systemsThe scientific community is active in this field. A new method of drug encapsulation was carried out to build these nano-systems and then managed according.Invasive, non-invasive, or slightly invasive techniques. Fresh in parallel with these advancesSystems - dendrimers, liposomes, nano cells, nanostructured lipid carriers (NLC), solids, etc.Lipid nanoparticles (SLNs) – have been extensively studied, but there are few commercially available options.The preclinical safety of lipid nanoparticles (SLNs, NLCs) has already been reported in many studies.Applications include use as an ocular drug delivery system. The development of thisNanotechnology approach opens up new therapeutic possibilities by reducing side effects that can often be caused by the inherent toxicity of drug molecules to the patient's organism including blindness. Innovative technology has other benefitsTreatment outcomes such as the ability to be more specific to certain tissues with certain surfacesMolecules that help reduce dosing frequency, and also pharmacokineticsdrug profile. However, there remains a need for vectorized systems for observing tissues.A requirement especially for tissues located behind the eye, which should also be avoidedInvasive procedures. Therefore, delivery systems will certainly be commercialized shortly.Outperform current invasive techniques.

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