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OCCULAR DRUG DELIVERY SYSTEM: A RECENT CHALLENGES AND ADVANCES

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- **ABSTRACT**

Ocular drug delivery is one of the most fascinating and challenging tasks facing the Pharmaceutical researchers. One of the major barriers of ocular medication is to obtain and maintain a therapeutic level at the site of action for prolonged period of time. Ocular drug delivery is hampered by the barriers protecting the eye. The bioavailability of the active drug substance is often the major hurdle to overcome. Conventional ocular dosage form, including eye drops, is no longer sufficient to combat ocular diseases. This article reviews the constraints with conventional ocular therapy and explores various approaches like eye ointments, gel, viscosity enhancers, prodrug, penetration enhancers, microparticles, liposomes, niosomes, ocular inserts, implants, intravitreal injections, nanoparticles, nano suspension, microemulsion, in situ-forming gel, iontophoresis and periocular injections to improve the ocular bioavailability of drug and provide continuous and controlled release of the drug to the anterior and posterior chamber of the eye and selected pharmacological future challenges in ophthalmology. In near future, a great deal of attention will be paid to develop noninvasive sustained drug release for both anterior and posterior segment eye disorders. Current momentum in the invention of new drug delivery systems holds a promise toward much improved therapies for the treatment of vision-threatening disorders.

- **KEYWORDS:** Ocular drug delivery system.

- **INTRODUCTION**[1,2,3]

The eye is a complex organ with an unique anatomy and physiology. The structure of eye can be divided into two main parts: anterior segment and posterior segment. Anterior segment of the eye occupies approximately one-third while the remaining portion is occupied by the posterior segment. Tissues such as cornea, conjunctiva, aqueous humor, iris, ciliary body and lens make up the anterior portion. Back of the eye or posterior segment of the eye include sclera, choroid, retinal pigment epithelium, neural retina, optic nerve and vitreous humor. The anterior and posterior segment of eye is affected by various vision threatening diseases. Diseases affecting anterior segment include, but not limited to glaucoma, allergic conjunctivitis, anterior uveitis and cataract. While, age-related macular degeneration (AMD) and diabetic retinopathy are the most prevalent diseases affecting posterior segment of the eye. Topical instillation is the most widely preferred non-invasive route of drug administration to treat diseases affecting the anterior segment.

Conventional dosage forms such as eye drops account for 90% of the marketed ophthalmic formulations. The reason may be attributed to ease of administration and patient compliance. Nonetheless, the ocular bioavailability is very low with topical drop administration. Numerous anatomical and physiological constraints such as tear turnover, nasolachrymal drainage, reflex blinking, and ocular static and dynamic barriers pose a challenge and impede deeper ocular drug permeation. Hence, less than 5% of topically applied dose reaches to deeper ocular tissue. Also, it is difficult to achieve therapeutic drug concentration into posterior segment ocular tissues following topical eye drops instillation because of the above mentioned barriers.

The drug can be delivered to the posterior segment ocular tissues by different mode of administrations such as intra vitreal injections, periocular injections, and systemic administration. However, small volume of eye compared to whole body and presence of blood retinal barriers; makes systemic administration an impractical approach. Intra vitreal injection is the most common and widely recommended route of drug administration to treat posterior ocular diseases. Though, the need of repeated eye puncture with intra vitreal injections causes several side effects such as endophthalmitis, hemorrhage, retinal detachment and poor patient tolerance. The transscleral drug delivery with periocular administration route is evolved as an alternative mode of drug delivery to the posterior ocular tissues.

Although transscleral delivery is comparatively easy, less invasive and patient compliant, drug permeation is compromised by ocular static and dynamic barriers. Ocular barriers to transscleral drug delivery include: static barriers i.e., sclera, choroid and retinal pigment epithelium (RPE), and dynamic barriers, i.e., lymphatic flow in the conjunctiva and episclera, and the blood flow in conjunctiva and choroid.

To overcome the ocular drug delivery barriers and improve ocular bioavailability, various conventional and novel drug delivery systems have been developed such as emulsion, ointments, suspensions, aqueous gels, nanomicelles, nanoparticles, liposomes, dendrimers, implants, contact lenses, nanosuspensions, microneedles, and in situ thermosensitive gels for the earlier mention ocular diseases. This review will provide an overview on various conventional and novel ophthalmic drug delivery systems developed to deliver drug to diseased ocular tissues for the treatment of ocular diseases.

- **Anatomy and Physiology of Eye[4,5]**

Eye is a spherical structure with a wall consists of three layers. Namely outer sclera, middle choroid layer, inner retina.

The schematic diagram of which is shown in fig. [1]. Sclera is a tough fibrous coating that protects the inner layers. It is white except for the transparent area at the front, the cornea, which allows the light to enter the eye.

The choroid layer, situated inside the sclera contains many blood vessels and is modified at the front of the eye as the pigmented iris. The biconvex lens is situated behind the pupil.

The chamber behind the lens is filled with vitreous humor, a gelatinous substance occupying 80% of the eyeball. At the back of the eye the light detecting retina.

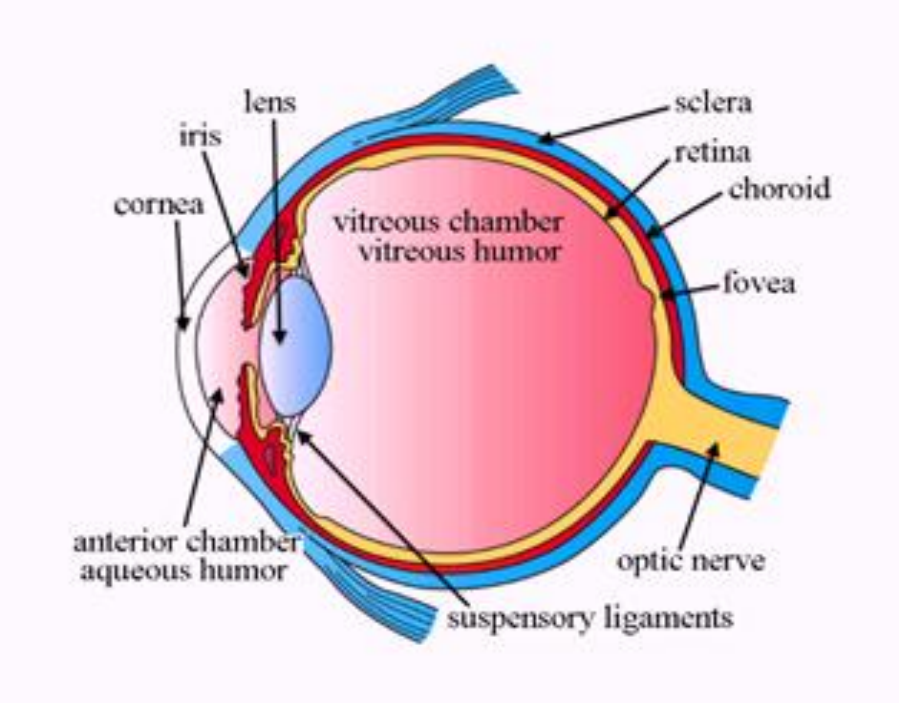


Figure 1: Anatomy of Human Eye.

a) ***Sclera***

The sclera is commonly known as "the white of the eye." It is the tough, opaque tissue that serves as the eye's protective outer coat. Six tiny muscles connect to it around the eye and control the eye's movements. The optic nerve is attached to the sclera at the very back of the eye. In children, the sclera is thinner and more translucent, allowing the underlying tissue to show through and giving it a bluish cast. As we age, the sclera tends to become more yellow.

b) Choroid layer

The choroid lies between the retina and sclera. It is composed of layers of blood vessels that nourish the back of the eye. The choroid connects with the ciliary body toward the front of the eye and is attached to edges of the optic nerve at the back of the eye. It is situated inside the sclera, contains many blood vessels and is modified at the front of eye as the pigmented iris. The biconvex lens is situated just behind the pupil. The chamber behind the lens is filled with the vitreous humor, a gelatinous substance occupying 80% of the eye ball. The anterior and posterior chambers are situated between the cornea and iris, and iris and lens, respectively and filled with aqueous humor. At the back of the eye is the light detecting retina.

c) The Cornea

The cornea is the transparent, domeshaped window covering the front of the eye. It is a powerful refracting surface, providing 2/3 of the eye's focusing power. Like the crystal on a watch, it gives us a clear window to look through. Because there are no blood vessels in the cornea, it is normally clear and has a shiny surface. The adult cornea is only about 1/2 millimeter thick and is comprised of 5 layers: epithelium, Bowman's membrane, stroma, Descemet's membrane and the endothelium. The cornea is an optically transparent tissue that conveys images to the back of the eye and covers about one-sixth of the total surface area of the eye ball. The cornea is considered to be the main pathway for the permeation of drugs into occupying 80% of the eye ball. The anterior and posterior chambers are situated between the cornea and iris, and iris and lens, respectively and filled with aqueous humor. At the back of the eye is the light detecting retina.

d) The Conjunctiva

It is basically involved in the formation and maintenance of the pre-corneal tear film and in the protection of the eye. It is thin, vascularised mucous membrane that lines in the posterior surface of the eyelids and basement membrane of the epithelium and the stroma.

e) The stroma or Substantia Propria

Located behind the epithelium, the stroma comprises about 90 percent of the cornea. It consists primarily of water (78 percent); layered protein fibers (16 percent) that give the cornea its strength, elasticity, and form; and cells that nourish it. The unique shape, arrangement, and spacing of the protein fibers are essential in producing the cornea's lightconducting transparency.

f) The Descemet's Membrane

This is secreted by the endothelium, lies between the stroma and the endothelium. V. The Corneal Endothelium: This single layer of cells is located between the stroma and the aqueous humor. Because the stroma tends to absorb water, the endothelium's primary task is to pump excess water out of the stroma. Without this pumping action, the stroma would swell with water, become hazy, and ultimately opaque. outer regions of the cornea. The human conjunctiva is 2 to 30 times more permeable to the drugs than the cornea and it has been proposed that loss by this route is a major path for drug clearance.

g) The nasolacrymal drainage system

It consists of three parts. Secretory system, distributive system and excretory system. The secretory system consists of basic secretors that are stimulated by blinking and temperature. Change due to evaporation and reflex sectors that have an efferent parasympathetic nerve supply and secrete in response to physical or emotional stimulations. The distributive system consists of the eye lids and the tear meniscus around the lid edges of the open eye. The excretory part of nasolacrymal system consists of the lachrymal puncta; the superior, inferior and common canaliculi, the lachrymal sac and the nasolacrymal duct.

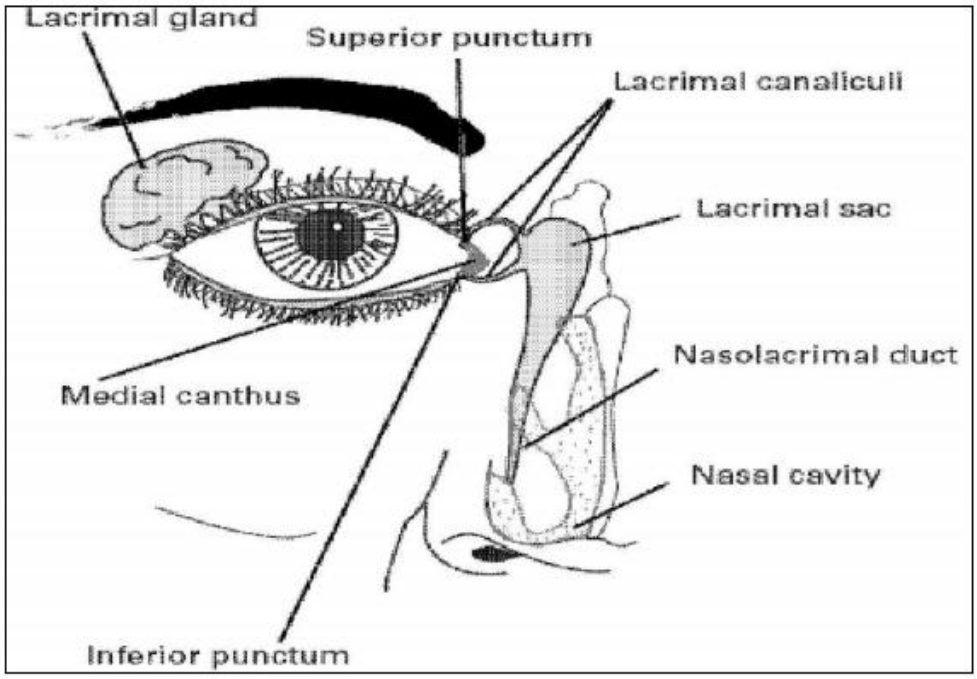


Figure 2: The Naso-lachrymal system.

- **Need for The Improvement In Ocular Drug Delivery Systems[6]**

Eye is the most accessible site for topical administration of a medication. Drugs are commonly applied to the eye for localized action on the surface or in the inferior eye. A major problem in ocular therapeutics is the attainment of an optimal drug concentration at the site of action poor bioavailability of drugs of drugs from ocular dosage forms is mainly due to precorneal loss factors. Which includes tear dynamics, nonproductive absorption, transient residence time in cul-de-sac, and relative impermeability of the corneal epithelial membrane? Due to these constraints only a small fraction of drug. effectively 1% or even less of the instilled dose is ocularly absorbed. Normal dropper used with conventional ophthalmic solution delivers 50- 75µl per drop and portion of these drops quickly drain until the eye is

back to normal resident volume of 7µl. because of this drug loss in front of eye, very little drug is available to enter in to the eye. Actual corneal permeability of drug is quite low and very small corneal contact time of about 1-2min in humans for instilled solution commonly less than 10% 10-12 consequently very small amount actually penetrates the cornea and teaches intraocular tissue 13,14. Ideal ophthalmic drug delivery must be able to sustain the drug release and remain in the vicinity of the front of the eye for prolong period of time consequently it is imperative to optimize ophthalmic drug delivery, one of the way to do so is by addition of polymers of various grades, development of viscous gels, development of colloidal suspension or using erodible/non-erodible insert to prolong the pre-corneal drug retention. Cornea offers more resistant to negatively than positively charged compounds.

- **Characteristics To Optimize Ocular Drug Delivery System[7]**

✓ Good corneal penetration.
✓ Prolong contact time with corneal tissue.
✓ Simplicity of instillation for the patient.
✓ Non irritant and comfortable form. (Viscous solution should not provoke lachrymal secretion & reflux blinking.)
✓ Appropriate rheological properties & concentration of the viscous system.

- **Advantages of Controlled Ocular Drug Delivery Systems[7]**

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

- **Eye Conditions**[8]

→ *Age-related macular degeneration:* A loss of central vision.

→ *Amblyopia (lazy eye):* One eye sees better than the other as a result of not using the other eye during childhood. The weaker eye may or may not "wander." The weaker eye is called the "lazy eye."

→ *Astigmatism:* A defect that causes an inability to properly focus light onto the retina. Astigmatism causes blurry vision that can be corrected with glasses, contact lenses, or, in some cases, surgery.

→ *Black eye:* Swelling and discoloration (bruise) around the eye as a result of injury to the face.

→ *Blepharitis:* Inflammation of the eyelids near the eyelashes. Blepharitis is a common cause of itching or a feeling of grit in the eyes.

→ *Cataract:* A clouding of the natural internal lens of the eye, which can cause blurred vision.

→ *Chalazion:* An oil-making gland gets blocked and swells into a bump.

→ *Conjunctivitis:* Also known as "pinkeye," conjunctivitis is an infection or inflammation of the conjunctiva, the clear layer that covers the front of the eye. It is usually caused by allergies, a virus, or a bacterial infection.

→ *Corneal abrasion:* A scratch on the clear part of the front of the eye. Pain, light sensitivity, or a feeling of grit in the eye is the usual symptoms.

→ *Diabetic retinopathy:* High blood sugar damages blood vessels in the eye. Eventually, weakened blood vessels may start leaking or overgrow the retina, threatening vision.

→ *Diplopia (double vision):* Seeing double can be caused by many serious conditions. Diplopia requires immediate medical attention.

→ *Dry eye:* Either the eyes don't produce enough tears, or the tears are of poor quality. Dry eye can be caused by medical problems such as lupus, scleroderma, and Sjogren's syndrome.

→ *Glaucoma:* Progressive loss of vision usually associated with increased pressure inside the eye. Peripheral vision is lost first, often going undetected for years.

→ *Hyperopia (farsightedness):* Inability to see near objects clearly. The eye is "too short" for the lens, or certain eye muscles have weakened with age.

→ *Hyphema:* Bleeding into the front of the eye, between the cornea and the iris. Hyphema is usually caused by trauma.

→ *Keratitis:* Inflammation or infection of the cornea. Keratitis typically occurs after germs enter a corneal abrasion.

→ *Myopia (nearsightedness):* Inability to see clearly at a distance. The eye is "too long" for the lens, so light isn't focused properly on the retina.

→ *Optic neuritis:* The optic nerve becomes inflamed, usually from an overactive immune system. Painful vision loss in one eye typically results.

→ *Pterygium:* A thickened conjunctival mass usually on the inner part of the eyeball. It may cover a part of the cornea, causing vision problems.

→ *Retinal detachment:* The retina comes loose from the back of the eye. Trauma and diabetes are common causes of this problem, which often requires urgent surgical repair.

→ *Retinitis:* Inflammation or infection of the retina. Retinitis may be a long-term genetic condition or result from an infection.

→ *Scotoma:* A blind or dark spot in the visual field.

→ *Strabismus:* The eyes do not point in the same direction. The brain may then favor one eye, causing decreased vision (amblyopia) in the other eye.

→ *Stye:* Bacteria infect the skin on the edge of the eyelid, creating a tender red bump.

→ *Uveitis (iritis):* The colored part of the eye becomes inflamed or infected. An overactive immune system, bacteria, or viruses can be responsible.

- **Eye Tests**[8]

→ *Tonometry:* A test that measures pressure in the eye, called intraocular pressure. Tonometry is used to check for glaucoma.

→ *Slit lamp examination:* A physician or optometrist shines a vertical slit of light across your eye while examining through a microscope. This general exam can detect many eye problems.

→ *Fundoscopic exam:* Dilating drops first widen the pupil. By shining bright light in the back of the eye, the examiner can view the retina.

→ *Refraction:* If vision is impaired, a series of lenses are placed before the eyes to determine the right corrective lens prescription.

→ *Visual acuity test:* Reading ever-smaller-sized letters across the room identifies distance vision problems. Reading up-close can identify problems with near vision.

→ *Fluorescein angiography:* A fluorescent dye is used to take a sequence of retinal images.

→ *Regular adult eye exam:* This collection of tests may include the ones mentioned above plus others, such as eye movement.

- **Eye Treatments**[8]

→ *Contact lenses and glasses:* Glasses or contact lenses correct refractive errors such as nearsightedness, farsightedness, and astigmatism.

→ *LASIK (laser assisted in situ keratomileusis):* A doctor creates a thin flap in the cornea with a precise cutting device or a laser, following which, an excimer laser reshapes the cornea, improving nearsightedness, excessive farsightedness, and astigmatism.

→ *Radial keratotomy (RK):* A series of small incisions are made in the cornea to correct nearsightedness. Radial keratotomy is rarely used today.

→ *Photorefractive keratectomy (PRK):* A doctor rubs off the surface cells from the cornea, then uses a laser to improve nearsightedness. The corneal cells grow back and the eye heals very much like a corneal abrasion.

→ *LASEK (laser epithelial keratomileusis):* Similar to PRK, in which a flap is cut into the corneal substance. Instead of a surgical flap, though, the topmost layer of cornea cells is retracted or removed after which a laser is used to reshape the cornea.

→ *Artificial tears:* Eye drops with similar composition to natural tears, used to treat dry or irritated eyes.

→ *Cyclosporine eye drops (Restasis):* Dry eye is often associated with microscopic inflammation, and anti-inflammatory eye drops (like cyclosporine) can often help.

→ *Laser photocoagulation:* A doctor uses a laser to treat parts of the retina with poor circulation or to treat abnormal blood vessels directly. Laser photocoagulation is most often done for diabetic retinopathy but can also be used for sealing retinal tears.

→ *Cataract surgery:* The cloudy cataract is removed from the lens and replaced by a manmade lens.

- **Barriers for Ocular Delivery**[9,10]

Drug loss from the ocular surface

After instillation, the flow of lacrimal fluid removes instilled compounds from the surface of eye. Even though the lacrimal turnover rate is only about 1 µl/min the excess volume of the instilled fluid is flown to the nasolacrimal duct rapidly in a couple of minutes. Another source of non-productive drug removal is its systemic absorption instead of ocular absorption.

Systemic absorption may take place either directly from the conjunctival sac via local blood capillaries or after the solution flow to the nasal cavity.

Lacrimal fluid-eye barriers

Corneal epithelium limits drug absorption from the lacrimal fluid into the eye. The corneal epithelial cells form tight junctions that limit the paracellular drug permeation. Therefore, lipophilic drugs have typically at least an order of magnitude higher permeability in the cornea than the hydrophilic drugs. In general, the conjunctiva is leakier epithelium than the cornea and its surface area is also nearly 20 times greater than that of the cornea.

Blood-ocular barriers

The eye is protected from the xenobiotics in the blood stream by blood-ocular barriers. These barriers have two parts: blood-aqueous barrier and blood-retina barrier. The anterior blood-eye barrier is composed of the endothelial cells in the uveam (The middle layer of the eye beneath the the sclera. It consists of the iris, ciliary body, and choroid). This barrier prevents the access of plasma albumin into the aqueous humor, and also limits the access of hydrophilic drugs from plasma into the aqueous humor. The posterior barrier between blood stream and eye is comprised of retinal pigment epithelium (RPE) and the tight walls of retinal capillaries. Unlike retinal capillaries the vasculature of the choroid has extensive blood flow and leaky walls. Drugs easily gain access to the choroidal extravascular space, but there after distribution into the retina is limited by the RPE and retinal endothelia.

- **Mechanism of Ocular Drug Absorption[11]**

Drugs administered by instillation must penetrate the eye and do so primarily through the cornea followed by the non-corneal routes. These non-corneal routes involve drug diffusion across the conjunctiva and sclera and appear to be particularly important for drugs that are poorly absorbed across the cornea.

Corneal permeation

The permeation of drugs across the corneal membrane occurs from the precorneal space.

Various Barrieirs to drug Absorption

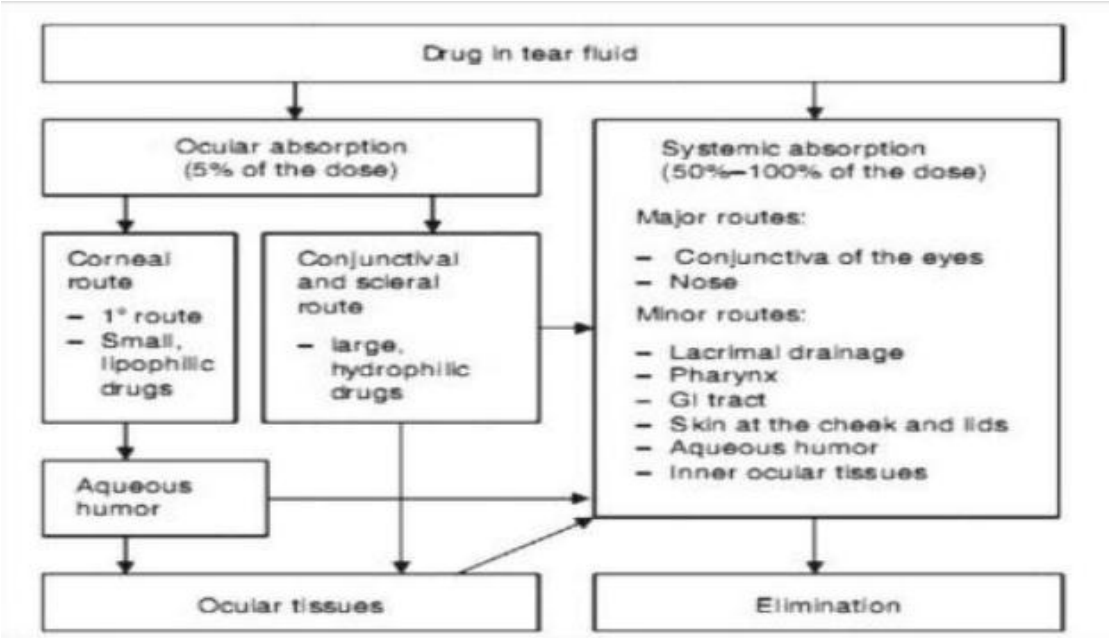
In tears have a direct bearing on efficiency of drug absorption into the inner eye. The productive absorption of most ophthalmic drugs results from diffusional process across corneal membrane. The efficiency of absorption process is a function of rate and extent at

which the transport processes of eye. The flux of any drug molecule across the biological membrane depends on the physicochemical properties of the permeating molecule and its interaction with the membrane. The extent to which the transport or absorption process occurs is also function of physiological mechanism of precorneal fluid drainage or turnover. In terms of transcorneal drug permeation, the cornea can be considered to consist of three primary layers (epithelium, stroma and endothelium). The epithelium and endothelium contain on the order of a 100 fold greater amount of lipid material than the stroma. Consequently, depending on the physicochemical properties of a diffusing drug, the resistance offered by the individual layers varies greatly. Epithelium, being lipodal, represents a diffusional barrier offering high resistance to ionic or other aqueous soluble or polar species. In contrast, compounds with relatively low polarity encounter a greater diffusional resistance in the hydrophilic stroma layer. This frequently cited concept of drug permeation across the corneal membrane ism referred to as "differential solubility concept".

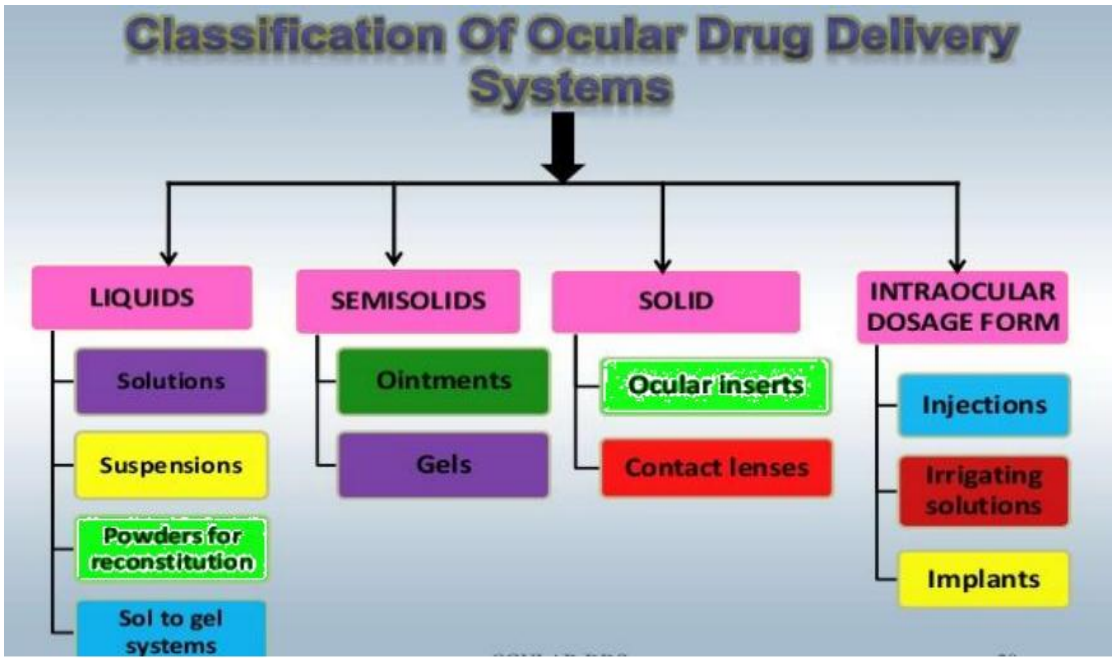
Non-corneal permeation

Primary mechanism of drug permeation is the sclera is likely to be diffusionacross the intercellular aqueous media in the case of structurally similar corneal stroma. Therefore the possibility of partitioning mechanism cannot be eliminated. Although like cornea, the conjunctiva is composed of an epithelial layer covering an underlying stroma, the conjunctival epithelium offers substantially less resistance than does the corneal epithelium.

- **Ocular Absorption Pathway**[10]



- **Ocular Drug Delivery System:- Classification**[12-17]



1) Eye drops

Drugs which are active at eye or eye surface are widely administered in the form of Solutions, Emulsion and Suspension. Various properties of eye drops like hydrogen ion concentration, osmolality, viscosity and instilled volume can influence retention of a solution in the eye. Less than 5% of the dose is absorbed after topical administration into the eye. Eye drops are saline-containing drops used as an ocular route to administer.

Recent work done in eye drops

New Eye Drops Can Dissolve Cataracts with No Need for Surgery Zhang and his research team went on to develop eye drops that contained lanosterol as a drug treatment for cataracts.

2) Ointment

Eye ointments can deliver medicine directly to your eyes, keep your eyes moist and help with redness, itching and watering and prolongation of drug contact time with the external ocular surface. Ointment base is sterilized by heat and filtered while molten to remove foreign particulate matter. The entire ointment may be passed through a previously sterilized colloid mill. It is important to be sure the dropper or tube is clean. Do not let it touch the eye, eyelid, lashes or any surface. This will keep it free from bacteria.

Advantages

✓ Longer contact time and greater storage stability.

- ✓ Flexibility in drug choice.
- ✓ Improved drug stability.

Disadvantages

- ✓ Sticking of eyes lids.
- ✓ Blurred vision.
- ✓ Poor patient compliance
- ✓ Interfere with the attachment of new corneal epithelial cells to their normal base.
- ✓ Matting of eyelids

3) Gels

Gels are defined as a substantially dilute cross-linked system, which exhibits no flow when in the steady-state. By weight, gels are mostly liquid, yet they behave like solids due to a three-dimensional cross-linked network within the liquid. Ophthalmic gels are composed of mucoadhesive polymers that provide localized delivery of an active ingredient to the eye. These polymers extend the contact time of the drug with the biological tissues and improve ocular bioavailability. Most commonly used polymers in ocular gels are gellan gum, alginic acid, xyloglucan, pectin, chitosan, poloxamer, gellan gum, sodium alginate.

Advantages

- ✓ Longer contact time
- ✓ Greater storage stability

Disadvantages

- ✓ Blurred vision.
- ✓ Poor patient compliance

Recent work done

A new eye gel containing sodium hyaluronate and xanthan gum for the management of posttraumatic corneal abrasions.

Vesicular system

4) Liposomes

Liposomes are biocompatible and biodegradable lipid vesicles made up of natural lipids and about 25 –10 000 nm in diameter. They are having an intimate contact with the corneal and conjunctival surfaces which is desirable for drugs that are poorly absorbed, low partition

coefficient, poor solubility or high molecular weights and thus increases the ocular drug absorption.

These formulations are mainly composed of phosphatidylcholine and other constituents such as cholesterol and lipid-conjugated hydrophilic polymers. Phospholipids used- Phosphotidylcholine, Phosphotidic acid, Sphingomyline, Phosphotidyleserine, Cardiolipine. Liposomes are Biodegradable, Non-toxic and biocompatible in nature. Current approaches for topical delivery of liposomes are focused in improving the corneal adhesion and permeation by incorporating various bioadhesive and penetration enhancing polymers.

Types

1. MLV
2. ULV-SUV (upto 100 nm)
3. LUV (more than 100 nm)

Advantages

- ✓ Drugs delivered intact to various body tissues.
- ✓ Liposomes can be used for both hydrophilic and hydrophobic drug.
- ✓ Possibility of targeting and decrease drug toxicity.
- ✓ The size, charge and other characteristics can be altered according to drug and desired tissue.

Disadvantages

- ✓ Costly preparation.
- ✓ Stability problem and oxidative degradation.
- ✓ Requires special packaging and storing facility.

5) Niosomes

The major limitations of liposomes are chemical instability, oxidative degradation of phospholipids, cost and purity of natural phospholipids. To avoid limitations of liposomes niosomes are developed as they are chemically and can entrap both hydrophobic and hydrophilic drugs. Niosomes are nonionic surfactant vesicles that have potential applications in the delivery of hydrophobic or amphiphilic drugs. Niosomes are non-ionic surfactant based multilamellar (>0.05µm), small unilamellar (0.025-0.05µm) or large unilamellar vesicles (>0.1µm) in which an aqueous solution of solute(s) is entirely enclosed by a membrane

resulted from organization of surfactant macromolecules as bilayers. They are non toxic and do not require special handling techniques.

Advantages

- ✓ Niosomes can entrap both hydrophilic and lipophilic drug.
- ✓ Enhance skin penetration therapy improving bioavailability of drug.
- ✓ Niosomes are depository for releasing drug in sustained or prolonged manner.
- ✓ More stable than liposomes.
- ✓ Better patient compatibility better therapeutic effect than conventional.
- ✓ Bio degradable, bio compatible and non immunogenic to the body.

Disadvantages

- ✓ Physical instability.
- ✓ Aggregation.
- ✓ Leaking of entrapped drug.
- ✓ Controlled release.

6) Pharmacosomes

A novel approach based on lipid drug delivery system has evolved, pharmacosomes. Pharmacosomes are colloidal, nanometric size micelles, vesicles drug dispersions attached covalently to the phospholipid. This term is used for pure drug vesicles formed by the amphiphilic drugs. This type of vesicular system improves permeation of drugs across the biomembranes and thus results in an improvement in the bioavailability and can also improve the pharmacodynamic properties of various types of drug molecules.

Advantages

- ✓ Delayed elimination of rapidly metabolized drugs facilitate sustained release.
- ✓ This system reduces the adverse effects and provides better targeting to body tissues and specific sites.

7) Discomes

Soluble surface active agents when added in critical amount to vesicular dispersion leads to solubilization or breakdown of vesicles & translates them into mixed micellar systems e.g: Egg yolk phosphatidyl choline liposomes by the addition of non ionic surfactants of poly oxy ethylene cetyl ether till the lamellar and mixed lamellar coexist.

Advantages

- ✓ Minimal opacity imposes no hinderance to vision.
- ✓ Increased patient compliance
- ✓ Zero order release can be easily attained.

8) Ocular inserts

Types of ocular inserts

Erodible inserts:	The fabrication polymer is hydrophobic but biodegradable. Drug is released through the erosion of the surface of the insert.
Soluble inserts:	The fabrication polymer is hydrophilic and water soluble. Drug release characteristics: Diffusion control for soluble drugs. Dissolution control for less soluble drugs
Hydrophilic but water insoluble inserts:	The fabrication polymer is hydrophilic and water soluble. Drug release characteristics: Diffusion control for soluble drugs. Dissolution control for less soluble drugs
Inserts using osmotic system:	A polymeric matrix in which the drug is dispersed as discrete small domains. Upon placement in the cul-de-sac, tears are imbibed into the matrix because of an osmotic pressure gradient created by the drug, where upon the drug is dissolved and released.
Membrane controlled diffusional inserts:	The drug core is surrounded by a hydrophobic polymer membrane; this controls the diffusion of the drug from the core to the outside.

Non erodible

1. Ocusert

The Ocusert therapeutic system is a flat, flexible, elliptical device designed to be placed in the inferior cul-de-sac between the sclera and the eyelid and to release Pilocarpine continuously at a steady rate for 7 days.

The device consists of 3 layers….

a. Outer layer - ethylene vinyl acetate copolymer layer.

b. Inner Core - Pilocarpine gelled with alginate main polymer.

c. A retaining ring - of EVA impregnated with titanium di oxide

Advantages

- ✓ Increased contact time and thus improved bio-availability.
- ✓ Lack of explosion.

Disadvantages

- ✓ The inserts may be lost immediately.
- ✓ A leakage may occur.

- ✓ Dislocation of the device in front of the pupil.
- ✓ Expensive.

Erodible inserts

The solid inserts absorb the aqueous tear fluid and gradually erode or disintegrate. The drug is slowly leached from the hydrophilic matrix. They quickly lose their solid integrity and are squeezed out of the eye with eye movement and blinking. Do not have to be removed at the end of their use.

Three types

1) Lacriserts

2) Sodi

3) Minidisc

Lacriserts

Sterile rod shaped device made up of hydroxyl propyl cellulose without any preservative. For the treatment of dry eye syndromes. It weighs 5 mg and measures 1.27 mm in diameter with a length of 3.5 mm. It is inserted into the inferior fornix.

SODI

Soluble ocular drug inserts. Small oval wafer. Sterile thin film of oval shape. Weighs 15-16 mg.

Use – glaucoma.

Advantage – Single application.

MINIDISC

Countered disc with a convex front and a concave back surface. Diameter – 4 to 5 mm.

Advantages

- ✓ Effective.
- ✓ Flexibility in drug type & dissolution rate.
- ✓ Need only be introduced into eye and not removed.

Disadvantage

- ✓ Patient discomfort.
- ✓ Require patient insertion.

- **Contact Lens**

Contact lenses are among the fastest progressing topics in optometry and the last decade has seen a number of significant developments occurring in the field. Among these has been the increasing dominance of soft lens materials in the market, albeit with substantial differences between countries. Optical designs have improved, allowing the optimisation of distance vision through the use of aspherics, enhanced range of clear focus with multifocals and more predictable toric designs for astigmatic correction. Silicone hydrogel technology has increased oxygen permeability to the eye, with improved corneal and ocular surface physiology being the result. Due, however, to their mechanical properties, deposition profiles and care system interactions, clinical problems have not been entirely absent, especially with non-compliant wearers. Efforts to eliminate end of day discomfort, a major cause of drop-out, have included incorporating viscous solutions into lens materials, as well as manipulating both multipurpose care solutions and agents within the blister-packaging in which lenses are delivered.

New Contact Lenses for Dry Eyes

New contact lenses are launched regularly in an effort to improve comfort. They have come a long way since the original RGP hard contact lens which today is still considered by most opticians to be the healthiest option and the one which give the best clarity of vision. However, with the invention of silicon hydrogel materials came daily disposable contact lenses which were both more comfortable and more hygienic. There are now also extended wear lenses that can be worn consistantly for one month. However, an even better alternative for dry eye sufferers are overnight contact lenses because they are worn for fewer hours and leave the eyes free to lubricate and oxygenate for the whole day.

- **Control Delivery System**

Implants

Implants have been widely employed to extend the release of drugs in ocular fluids and tissues particularly in the posterior segment. Implants can be broadly classified into two categories based on their degradation properties: (1) Biodegradable (2) Non biodegradable With implants, the delivery rate could be modulated by varying polymer composition. Implants can be solids, semisolids or particulate-based delivery systems. For chronic ocular diseases like cytomegalo virus (CMV) retinitis, implants are effective drug delivery system. Earlier non biodegradable polymers were used but they needed surgical procedures for

insertion and removal. Presently biodegradable polymers such as Poly Lactic Acid (PLA) are safe and effective to deliver drugs in the vitreous cavity and show no toxic signs.

Intophorosis

In Iontophoresis direct current drives ions into cells or tissues. For iontophoresis the ions of importance should be charged molecules of the drug. If the drug molecules carry a positive charge, they are driven into the tissues at the anode; if negatively charged, at the cathode. Requires a mild electric current which is applied to enhance ionized drug penetration into tissue. Ocular iontophoresis offers a drug delivery system that is fast, painless, safe, and results in the delivery of a high concentration of the drug to a specific site. Ocular iontophoresis has gained significant interest recently due to its non-invasive nature of delivery to both anterior and posterior segment. Iontophoretic application of antibiotics may enhance their bactericidal activity and reduce the severity of disease. Can overcome the potential side effects associated with intraocular injections and implants. Iontophoresis is useful for the treatment of bacterial keratitis.

Dendrimer

Dendrimers can successfully used for different routes of drug administration and have better water-solubility, bioavailability and biocompatibility.

Microemulsion

Microemulsion is dispersion of water and oil stabilized using surfactant and co- surfactant to reduce interfacial tension and usually characterized by small droplet size (100 nm), higher thermodynamic stability and clear appearance. Selection of aqueous phase, organic phase and surfactant/co-surfactant systems are critical parameters which can affect stability of the system.

Nano suspensions

Nano suspensions have emerged as a promising strategy for the efficient delivery of hydrophobic drugs because they enhanced not only the rate and extent of ophthalmic drug absorption but also the intensity of drug action with significant extended duration of drug effect. For commercial preparation of nano suspensions, techniques like media milling and high pressure homogenization have been used.

Marketed formulation for ocular drug delivery system

Sr. NO	DISEASE	PRODUCT	BRAND NAME	MFG BY	DOSAGE FORM
1	Inflammation	Ketorolac	ACUVAIL	Allergan	Eye-drops
		Diclofenac			
2	Inflammation	Chloramphenicol	VOLTARIN	Novartis	Eye- drops
		Pilocarpin Hcl			
3	Infection	Ganciclovir	CHLOPTIC	Allergan	Eye-drops
4	Miotics	Gatifloxacin			
		Dexamethasone	PILOPINI	Alcon	Gel
5	Viral	Laxobetolol Hcl	ZIRGAN	Alliance	Gel
		Flurometholone			
6	Infection	Azithromycin	ZYMER	Allergan	Eye-drops
		Bipostain			
7	Inflammation	Besifloxacin	TOBRADEX	Alcon	Eye Ointment
8	Glaucoma	Betaxolol	BETAXON	Alcon	Eye- drops
9	Inflammation	Ciprofloxacin	FML	Allergan	Susoension
10	Conjunctivitis	Ciprofloxacin	AZASITE	Catalent	Eye-drops
			BESIVANCE	Baush	Suspension

- **Patents on ocular formulations**

Sr no.	Formulation	Patent Application no	Title of patent
1	Eye drops	US 14/512,365	Antioxidant eye drops
2	Opthalmic ointment	US 06/505,984	Eye ointment formulation including the disodium salt of 1,3-bis(2-carboxychromon-5-yloxy)propan-2-ol
3	Opthalmic gel	US 08/092,574	Opthalmic gel composition and method of treating eye infections
4	Ocular liposomes	PCT/EP2011/052061	Liposome system for ocular administration
5	Ocular inserts	US 05/520,277	Ocular inserts

- **CONCLUSION**

The solid drug-releasing devices, in spite of the advantages demonstrated by extensive investigations and clinical tests, have not gained a wide range of acceptance by ophthalmologists. At this moment, the Ocusert systems are the only medicated inserts marketed in Western countries, and the acceptance of these devices has been, to the present date, far from enthusiastic. According to recent information the NODS project will not be

further developed. As said before, the commercial failure of inserts has been attributed to psychological factors, such as the reluctance of ophthalmologists and patients to abandon the traditional liquid and semi-solid medications, to price factors and to occasional therapeutic failures (e.g., unnoticed expulsion from the eye, membrane rupture, etc.).

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