OCULAR DRUG DELIVERY

ROUTES OF OCULAR DRUG DELIVERY

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

Topical route

Typically topical ocular drug administration is accomplished by eye drops, but they have only a short contact time on the eye surface. The contact, and thereby duration of drug action, can be prolonged by formulation design (e.g.m gels, gelifying formulations, ointments, and inserts).

Subconjunctival administration

Traditionally subconjunctival injections have been used to deliver drugs at increased levels to the uvea. Currently this mode of drug delivery has gained new momentum for various reasons. The progress in materials sciences and pharmaceutical formulation have provided new exciting possibilities to develop controlled release formulations to deliver drugs to the posterior segment and to guide the healing process after surgery.

Intravitreal administration

Direct drug administration into the vitreous offers distinct advantage of more straightforward access to the vitreous and retina. It should be noted; however that delivery from the vitreous to the choroid is more complicated due to the hindrance by the RPE (Retinal Pigment Epithelium) barrier. Small molecules are able to diffuse rapidly in the vitreous but the mobility of large molecules, particularly positively charged, is restricted.

BARRIERS FOR OCULAR DELIVERY:

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 thereafterdistribution into the retina is limited by the RPE and retinal endothelia.

MECHANISM OF OCULAR DRUG ABSORPTION

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 [14].

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.

Various factors responsible for disposition of ocular drugs

Bioavailability of drugs administered to the eye is an important consideration. There are physiological factors, which can affect a drug's bioavailability including protein binding, drug metabolism and lachrymal drainage.

Protein bound drugs are incapable of penetrating the corneal epithelium due to the size of the protein drug complex. Because of the brief time in which an ophthalmic solution may remain present in the eye (due to lachrymal drainage), protein binding of a drug substance could quickly negate its therapeutic value by rendering it unavailable for absorption. One of the major problems encountered with conventional ophthalmic solutions is the rapid and extensive elimination of drugs from the precorneal lachrymal fluid. It must be noted that this high drainage rate is due to the tendency of the eye to maintain its residence volume at 7–10 µl permanently, whereas volumes topically instilled range from 20–50 µL. In fact it has been demonstrated in vivo that 90% of the dose was cleared within 2 min for an instilled volume of 50 µL and, within 4 min for an instilled volume of 10 µl. Consequently, the ocular residence time of conventional solutions is limited to a few minutes, and the overall absorption of a topically applied drug is limited to 1–10%. As in the case with other biological fluids, tears contain enzymes (such as lysozymes) capable of the metabolic degradation of the drug substance.

In addition to the physiological factors affecting ocular bioavailability, other factors as the physicochemical properties of the drug substance, and product formulation are important. Because the cornea is a membrane-barrier containing both hydrophilic and lipophilic layers, it is permeated most effectively by drug substances having both hydrophilic and lipophilic characteristics. It is advantageous for corneal penetration to adjust the pH of the solution to increase the proportion of unionized drug in the instilled dose. Drugs, which are highly water insoluble, do not readily permeate the cornea [14].

Nasolacrymal drainage system

The nasolachrymal drainage system consists of three parts: the secretory system, the distributive system and the excretory system. The secretory system consists of basic secretors that are stimulated by blinking and temperature change due to tear evaporation and reflex secretors that have an efferent parasympathetic nerve supply and secrete in response to physical or emotional stimulation.

The distributive system consists of the eyelids and the tear meniscus around the lid edges of the open eye, which spread tears over the ocular surface by blinking, thus preventing dry areas from developing. The excretory part of the nasolachrymal drainage system consists of: the lachrymal puncta, the superior, inferior and common canaliculi; the lachrymal sac and the nasolachrymal duct. In humans, the two puncta are the openings of the lachrymal canaliculi and are situated on an elevated area known as the lachrymal papilla. It is thought that tears are largely absorbed by the mucous membrane that lines the ducts and the lachrymal sac only a small amount reaches the nasal passage [15].

Interests of novel ophthalmic drug delivery:

Ophthalmic drug delivery is one of the most interesting and challengingendeavors facing the pharmaceutical scientist. The landscape of ophthalmic drug delivery is highly competitive and rapidly evolving. New classes of pharmaceuticals and biologics are fueling the demand for novel drug delivery.

The main aim of pharmacotherapeutics is the attainment of effective drug concentration at the site of action for the sufficient period of time to elicit a response. The challenge is to provide a system with improved ocular drug bioavailability and prolonged duration of activity, but still with a minimum risk of ocular complications. A major problem of ophthalmic drug delivery is not the lack of efficient drugs but the attainment of their optimal concentration at the site of their optimal concentration at the site of action [14,15].

The emergence of new and innovative means for improving therapeutic efficacy suggests that a greater choice of dosage forms will be provided to physicians and patients in the next decade. Most of the formulation efforts aim at maximizing ocular drug absorption through prolongation of the drug residence time in the cornea and conjunctival sac, as well as to slow drug release from the delivery system and minimize precorneal drug loss. Various ophthalmic formulations and their residence time period in the ocular cavity are given below [16].

Ophthalmic drug formulations

Ophthalmic drugs are formulated to bring the active drugs in contact with the eye surface to allow for absorption. Extension of corneal contact time may result in increased drug penetration & higher intraocular drug delivery. In addition to the active drug, ophthalmic formulations should contain other ingredients to control various characteristics of the formulation, such as the buffering and pH, osmolality & tonicity, viscosity & antimicrobial preservatives. Although these ingredients are listed inactive, they can affect permeability of drug across the ocular surface barriers & alter the therapeutic effectiveness of the drug.

EYE INFECTIONS

Eyes can get infections from bacteria, fungi or viruses. Eye infections can occur in parts of the eye and can affect just one eye or both. Common eye infections are Conjunctivitis, Corneal ulcers & Endophthalmitis.

A) Conjunctivitis:

Conjunctivitis is swelling (inflammation) or infection of the membrane lining the eyelids (conjunctiva).It is characterized by cellular infiltration and exudation. Staphylococcus aureus is the most common cause of bacterial conjunctivitis and blepharo-conjunctivitis. Many other organisms like Haemophilus influenzae, Streptococcus pneumoniae also cause conjunctivitis. Conjunctivitis can be classified as

(1) Infective – Acute, Subacute & Chronic

(2) Allergic conjunctivitis.

B) Corneal ulcers/ Keratitis:

Inflammation of cornea (Keratitis) is characterized by corneal oedema, cellular infiltration & ciliary congestion. Being the most anterior part of eyeball, cornea is exposed to atmosphere & hence prone to get infected easily. Bacterial corneal ulcers are the most commonly caused by virulent organism. Common bacteria associated with corneal ulceration are Staphylococcus aureus, Pseudomonas pyocyanea, E.coli and Proteus etc.

C) Endophthalmitis:

It is severe form of intraocular inflammation (purulent uveitis) involving ocular cavities & inner coats of eyeball. Causative organisms include Streptococci, E.coli, Pseudomonas, etc.

Accordingly, the armamentarium of available antimicrobials used in the prevention and treatment of these infections includes antivirals, antifungals, and antibacterials. Common topical antibacterials used in the treatment of ocular infectious diseases include sulfonamides, aminoglycosides, polymyxin-based combinations, and fluoroquinolones.

The fluoroquinolones represent an expanding class of broad-spectrum antibacterials, which cover a host of Gram-negative and anaerobic species responsible for ocular infections. These antibacterials have gained popularity in them ophthalmology field since they have been shown to be equivalent to combination therapy in the treatment of many ocular infections. Fluoroquinolones are also effective against a variety of Gram-positive organisms, including *Streptococcal* and *Staphylococcal* species; however, resistance is emerging among some of these organisms. The classification and mechanism of action of fluoroquinolones are given below

MANAGEMENT OF OCULAR INFECTIONS

Ocular infections, both superficial and deep such as conjunctivitis, corneal ulcers and endophthalmitis are caused by diverse group of bacteria, viral and fungal pathogens. Accordingly the armamentarium of available antimicrobials used in the prevention and treatment of these infections includes antivirals, antifungals and antibacterials. Common topical antibacterials used in treatment of ocular infectious diseases include sulfonamides, aminoglycosides, polymyxin-based combinations and fluoroquinolones. These fluoroquinolones are indicated for severe bacterial keratitis, endophthalmitis, blepharo-conjunctivitis, corneal ulcers, chronic post-filtration hypotony etc. The fluoroquinolones represent an expanding class of broad spectrum antibacterials which cover a host of Gram negative and anaerobic species responsible for ocular infections. These antibacterials have gained popularity in the ophthalmology field since they have been shown to be equivalent to combination therapy in treatment of many ocular infections. Fluoroquinolones are also effective against a variety of Gram positive organisms including *Streptococcal* and *Staphylococcal species* [18].

Fluoroquinolones offer all the attributes of an ideal antimicrobial agent including broad antimicrobial spectrum, good tissue penetration and bioavailability, high rate of clearance, chemical and biological stability, low degree of toxicity, high binding affinity for melanin, better patient compliance, convenient dosage forms and dosing schedule and relatively low incidence of drug interactions.

MECHANISM OF ACTION

Fluoroquinolones act by inhibiting two enzymes involved in bacterial DNA synthesis, both of which are DNA topoisomerases that human cells lack and that are essential for bacterial DNA replication, thereby enabling these agents to be both specific and bactericidal. DNA topoisomerases are responsible for separating the strands of duplex bacterial DNA, inserting another strand of DNA through the break, and then resealing the originally separated strands.

DNA gyrase introduces negative superhelical twists in the bacterial DNA doublehelix ahead of the replication fork, thereby catalyzing the separation of daughter chromosomes. This activity is essential for initiation of DNA replication and allows for binding of initiation proteins. Topoisomerase IV is responsible for decatenation that is, removing the interlinking of daughter chromosomes thereby allowing segregation into two daughter cells at the end of a round of replication. Fluoroquinolones interact with the enzyme-bound DNA complex (i.e., DNA gyrase with bacterial DNA or topoisomerase IV with bacterial DNA) to create conformational changes that result in the inhibition of normal enzyme activity.

As a result, the new drug– enzyme–DNA complex blocks progression of the replication fork, thereby inhibiting normal bacterial DNA synthesis and ultimately resulting in rapid bacterial cell death. Older fluoroquinolones exhibit a relatively consistent pattern with respect to specificity of enzyme inhibition in different types of bacteria. The newer fourth generation fluoroquinolones like moxifloxacin, gatifloxacin have a dual-binding mechanism of action, inhibiting both DNA gyrase and topoisomerase IV, in Grampositive species [19,20].

Polymeric drug delivery

Hydrogels are one of the upcoming classes of polymer-based controlled release drug delivery systems. Polymeric drug delivery systems have been extensively studied in order to solve the potential problems associated with drugs or bioactive molecules including toxicity, site dependence, low effectiveness, poor solubility, short half life, rapid degeneration and rapid clearance from the body.

Considering various properties such as flexibility, structure, biocompatibility, and hydrophilicity, three dimensional matrices, hydrogels, are being extensively used as drug delivery carriers.

Advantages of polymeric drug delivery

- Reduce toxic effects on the healthy tissue and reach sites that are conventionally Inaccessible due to the presence of various barriers 9 by targeted drug delivery.
- Increase the half-life of drugs, preventing their rapid degradation, and reduce the rate of elimination, thus maintaining drug concentration within a therapeutically effective window.
- Reduce the amount of drug required to achieve therapeutic efficacy.
- Cut down the number of repeated invasive dosage required for certain conditions and thus helps to improve patient's compliance and offers better living [21,22].

Table 1. Barriers for the Ocular delivery

	Conjunctiva	Cornea	Sclera
Surface area	17.65 ± 2.12 cm^2	1.04 ± 0.12	16 – 17
Thickness	-	0.57 mm	0.4 -0.5 mm
Structural composition	Mucus membrane Epithelium Vasculature	5 layers Epithelium Bowman's membrane Stomata Descemet's membrane Endothelium	Collagen fibers Water Proteoglycans Monopolysaccharides Elastic fibers Fibroblast

Table 2. Commonly Used Fluoroquinolones in Ophthalmic Delivery

Anti biotic generation	Example	Activity
1 st GENEARTION	Nalidixic acid	Have limited activity against gram negative & gram positive organism
2 nd GENERATION	Oxolinic acid Cinoxacin Pipemic acid	Improvement in gram negative coverage including Antipseudomonal activity. Shows limited activity against Gram positive organism.
3 rd GENERATION	Norfloxacin Ciprofloxacin Leavofloxacin Ofloxacin	Having antipseudomonal activity against gram negative bacilli
4 th GENERATION	Ciprofloxacin Moxifloxacin Gatifloxacin	Having dual mechanism of action in gram positive bacteria in addition reducing efflux from the bacterial cell. Improved spectrum of Activity.

Fig 1. Anatomy of eye

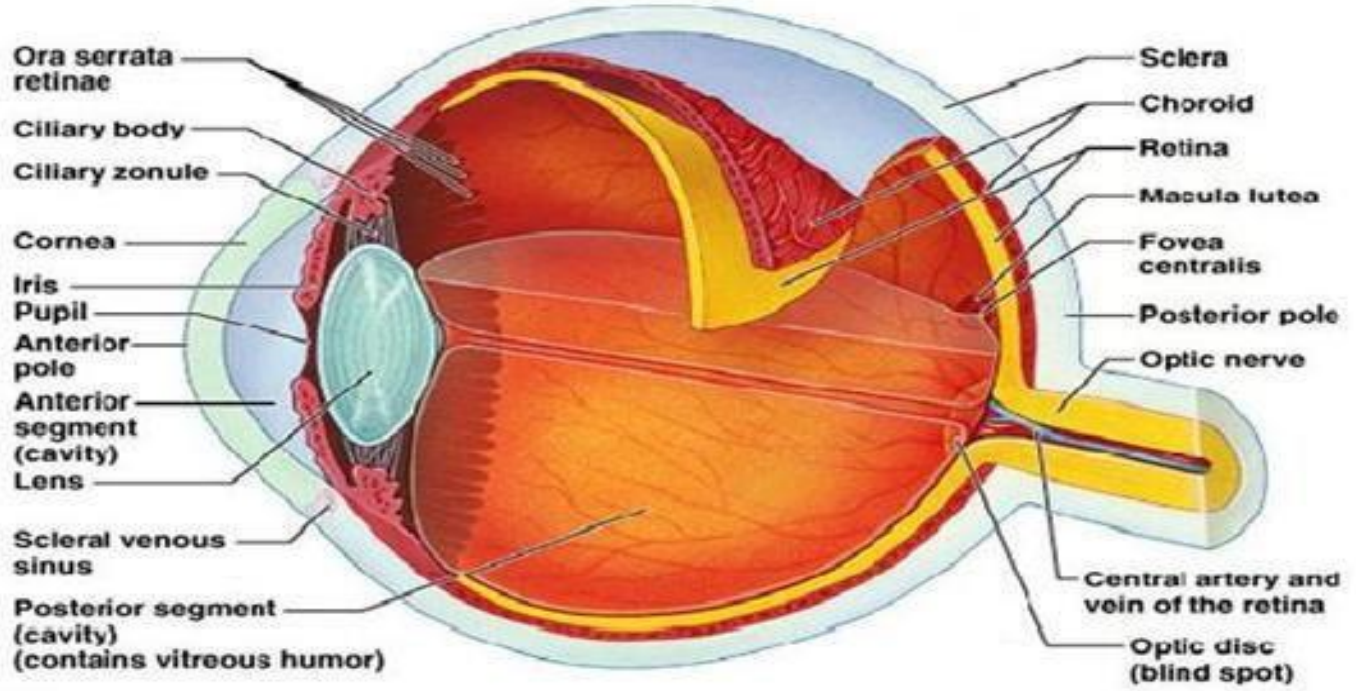


Fig 2. Pathway of Aqueous Humor

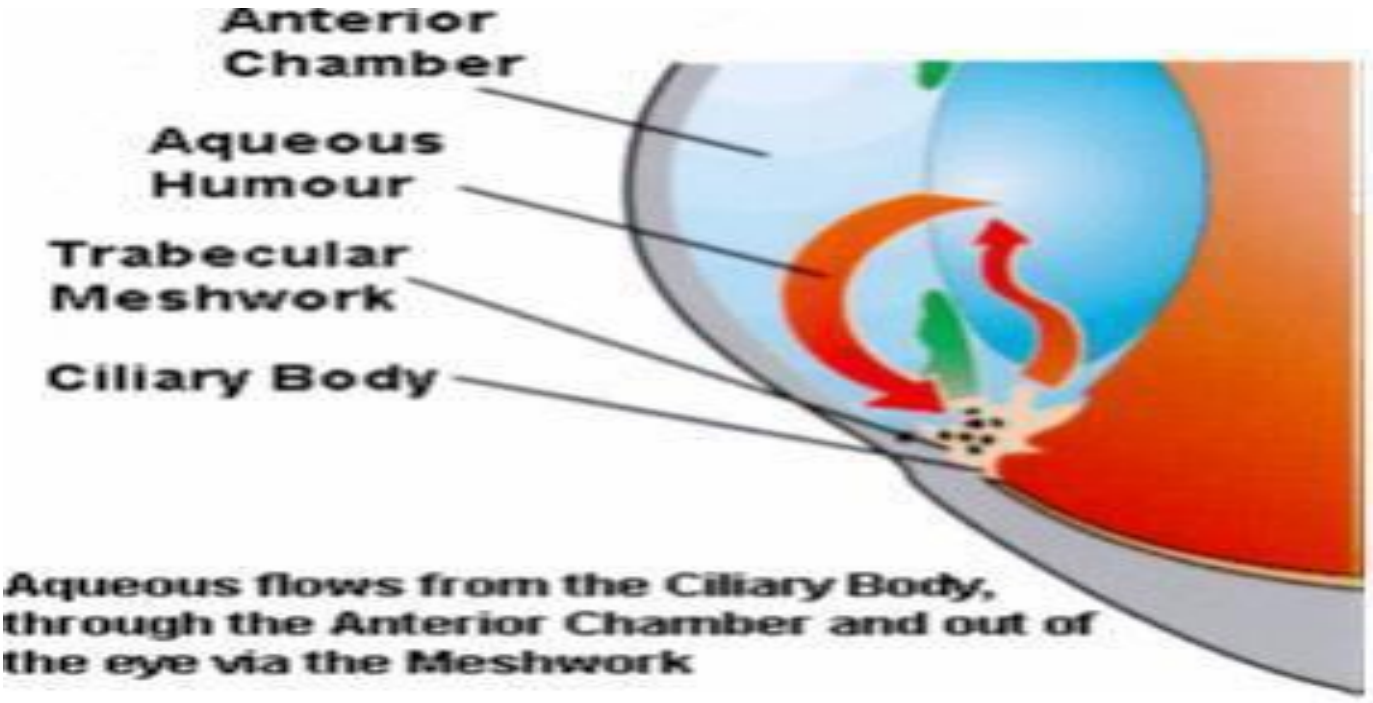


Fig 3. Posterior view of eye

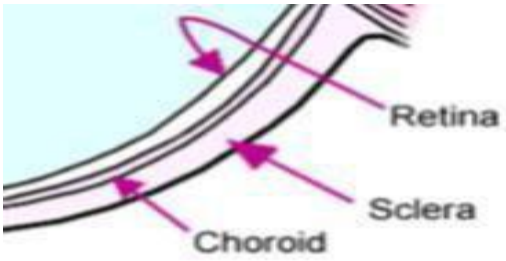


Fig 4. Different Routes for Ocular Drug Delivery

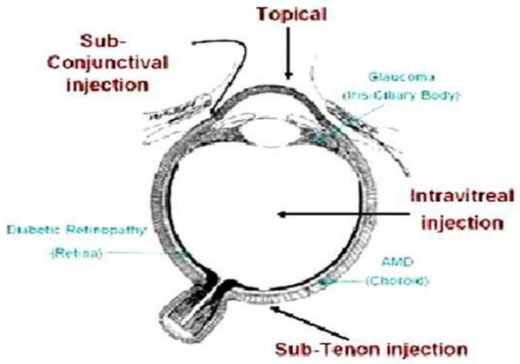


Fig .5 Ocular Drug Absorption

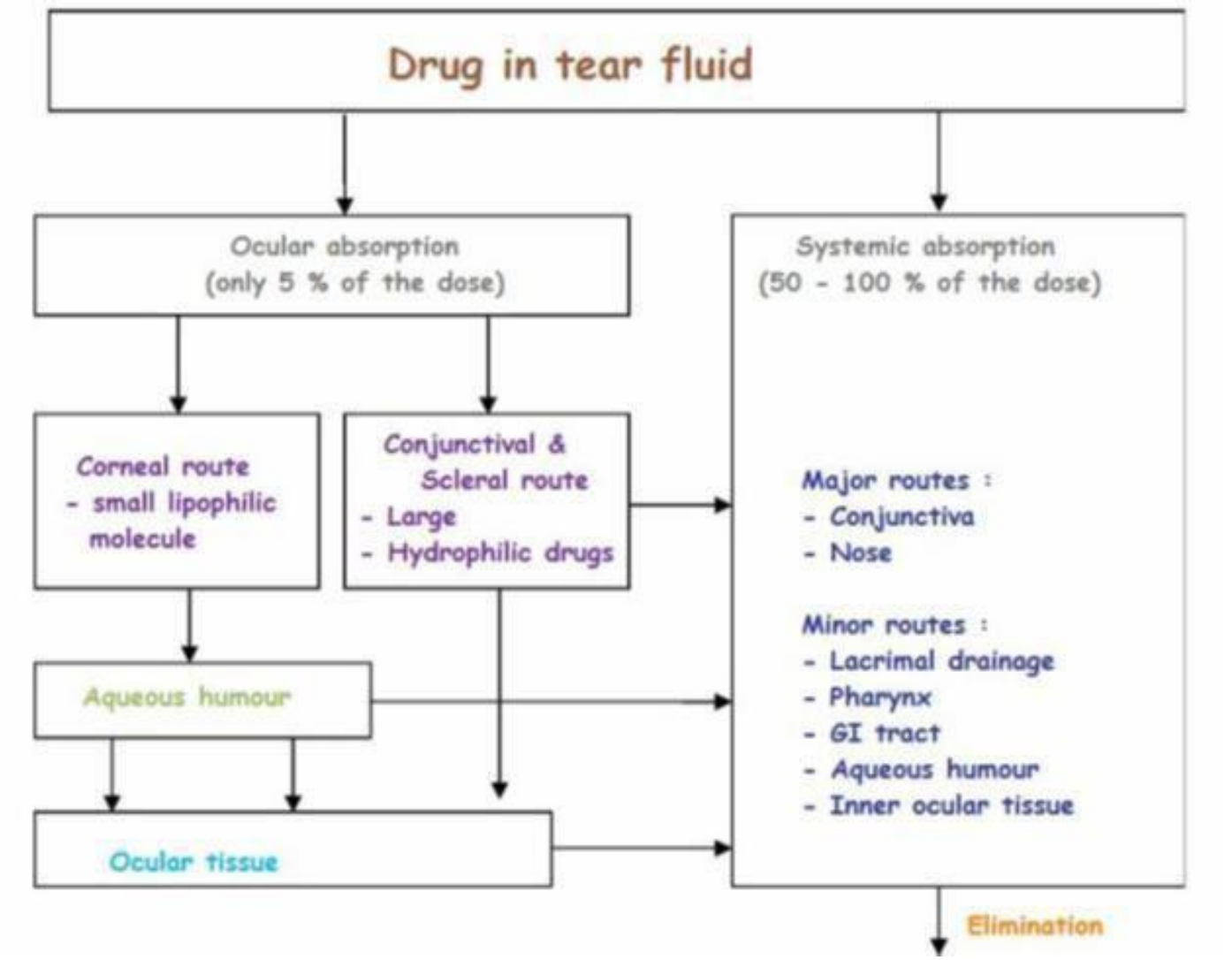


Fig 6. Corneal Membrane Depicting

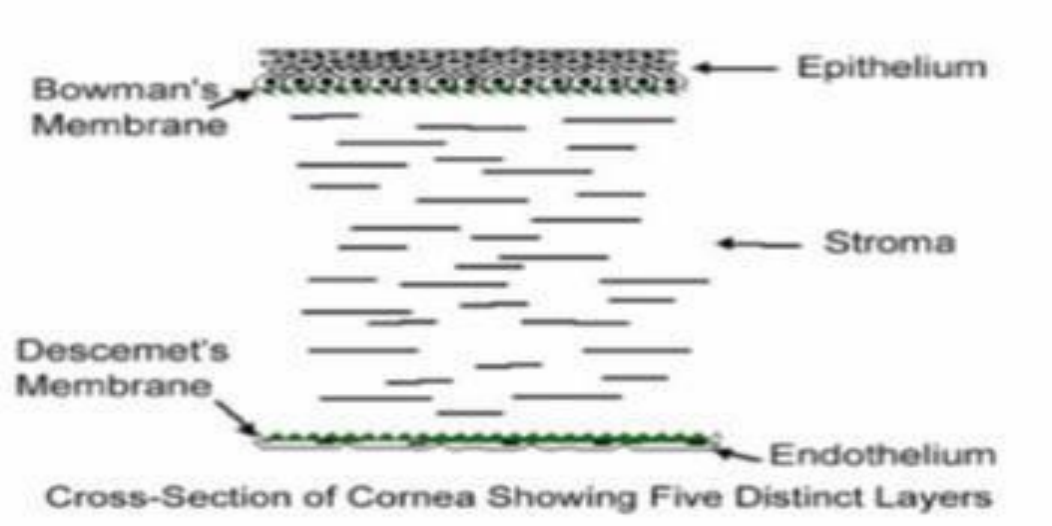


Fig 7. Nasaolachrymal Drainage Apparatus

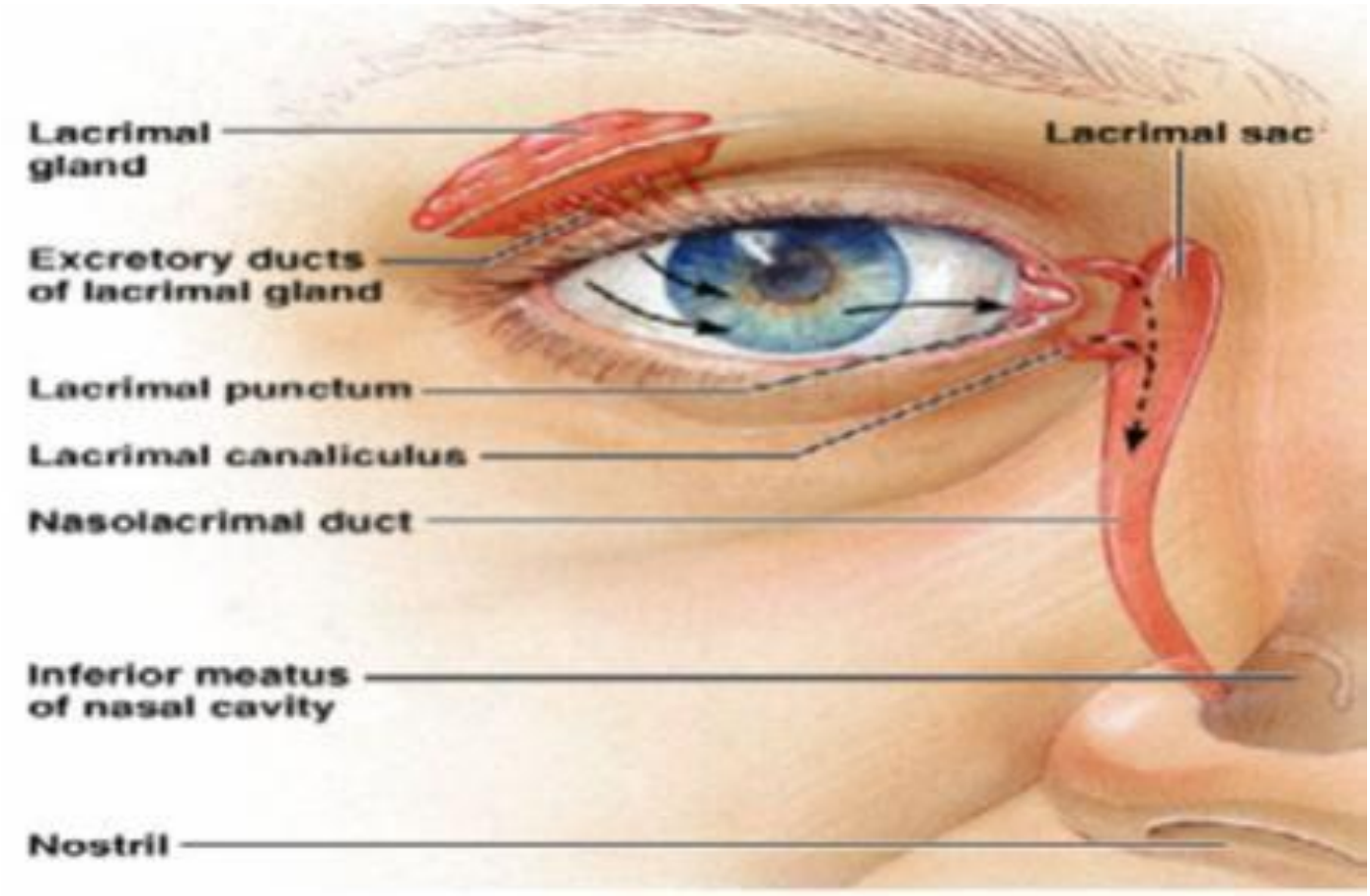
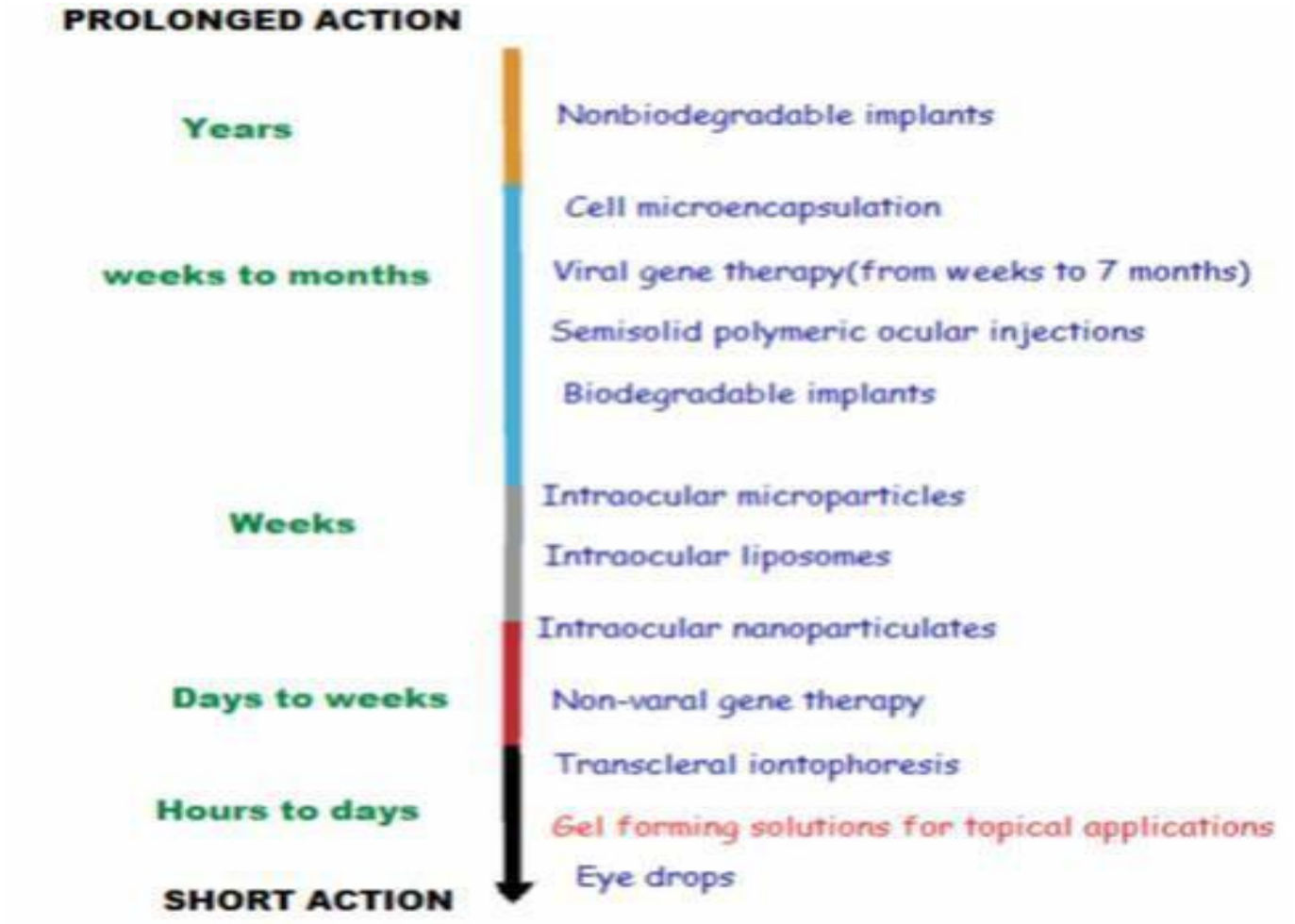


Fig 8. Duration of action of ocular drug delivery systems



CONCLUSION

New ophthalmic delivery system includes ocular inserts, collagen shields, ocular films, disposable contact lens and other Novel drug delivery systems like hiosomes 20 and nanoparticles. Newer trend is a combination of drug delivery technologies for improving the therapeutic response of a non efficacious drug. This can give a superior dosage forms for topical ophthalmic application. Among these drug delivery systems, only few products have been, commercialized. An ideal system should have effective drug concentration at the target tissue for a tended period of time with minimum systemic effect. Patient acceptance is very important for the design of any comfortable ophthalmic drug delivery system. Major Improvements are required in each system like improvement in sustained drug release, large scale manufacturing and stability. Combination of drug delivery systems could open a new directive for improving the therapeutic response of a non-efficacious system. They can overcome the limitations and combine the advantages of different systems.

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