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OCULAR DRUG DELIVERY SYSTEM: A REVIEW

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ABSTRACT

Ophthalmic drug delivery is one of the most interesting and challenging endeavors facing the pharmaceutical companies in the market. In ophthalmic formulation to the eye like solutions, suspensions, and ointments are available in the market shows drawbacks such as increased precorneal elimination, high variability in efficiency, and blurred vision. The major problem associated with the convent ional dosage forms is the bioavailability of drug. In the last three decades to improve the bioavailability by common to adding viscosity-enhancing agents or mucoadhesive polymers into dosage formulations. To overcome to conventional dosage formulations there were non-conventional technologies such as nanotechnology, microspheres, micro emulsion and ocular inserts could be developed in pharmaceutical market. This review focuses on recent development in conventional and non-conventional ophthalmic dosage formulation and products used to achieve prolonged contact time of drugs with the cornea and increases their bioavailability.

KEY WORDS: Eye, ophthalmic formulations, polymers, sustained release, nanotechnology**.**

1. INTRODUCTION

Ophthalmic drug delivery is one of the most interesting and challenging endeavors facing the pharmaceutical scientist. The anatomy, physiology, and biochemistry of the eye render this organ highly impervious to foreign substances. A significant challenge to the formulator is to circumvent the protective barriers of the eye without causing permanent tissue damage.[1] Development of newer, more sensitive diagnostic techniques and novel therapeutic agents continue to provide ocular delivery systems with high therapeutic efficacy. [2, 3]

1.1 EXTRA OCULAR STRUCTURE

The eye is protected by several structures.

1. Eyebrows
2. Eyelids and eyelashes
3. Lacrimal apparatus

Eyebrows protect the anterior aspect of eyeball from sweat, dust and foreign bodies. The eyelids have various layers of tissue including conjunctiva which protects the delicate cornea and front of the eye. When eye drops are administered, they are placed in lower conjunctival sac. The lacrimal glands secrete tears composed of water, mineral salts, antibodies and lysozyme, a bactericidal enzyme. Drainage of the eye drops through nasolacrimal system into gastrointestinal tract begins immediately on instillation. This takes place when either reflex tearing or the dosage form causes volume of fluid in peripheral tissue to exceed the normal lacrimal volume of 7-10 µl. The excess fluid volume enters the superior and inferior lacrimal puncta, moves down the canalicula into the lacrimal sac, and continues into the gastrointestinal tract. [4]

1.2 ANATOMY OF EYE

The human eyes are divided into anterior and posterior segment as shown in figure 1.

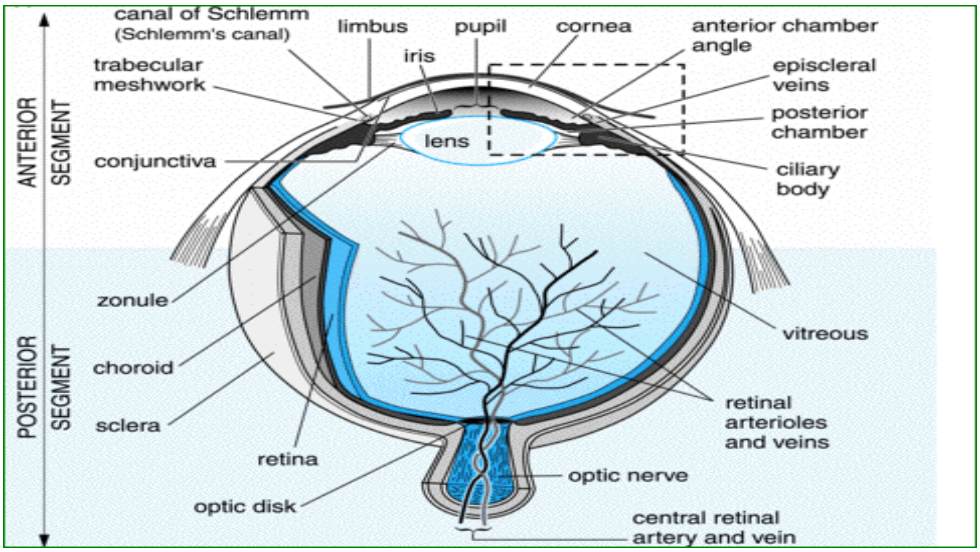

Figure 1: Anatomy Of Eye [4]

1.2.2 Anterior Segment

Anterior segment structure includes the cornea, limbus, anterior and posterior chambers, trabecular meshwork, schlemm's canal, iris, lens, zonule, and ciliary body. [5]

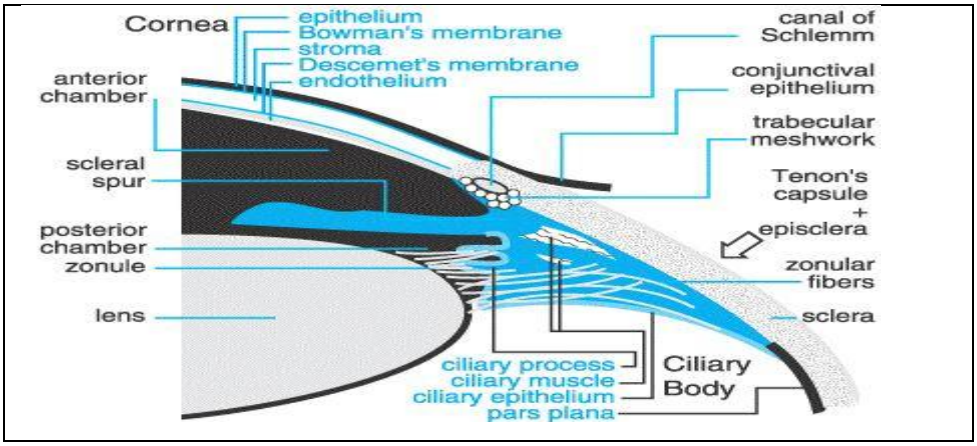

Figure 2: Anterior segment [4]

1.2.2.1 Cornea

The cornea is a strong clear bulge located at the front of the eye. Surface of the adult cornea has a radius of approximately 8mm. It has an important optical function as it refracts light entering the eye which then passes through the pupil and onto the lens (which then focuses the light onto the retina). The cornea, a non-vascular structure (does not contain any blood vessels) gets the necessary nutrients from the capillaries that terminate in loops at its circumference. It is supplied by many nerves derived from the ciliary nerves. These enter the laminated tissue of the cornea. It is therefore extremely sensitive. [6]

1.2.2.2 Iris

The iris is a thin circular contractile curtain located in front of the lens but behind the cornea. The iris is a diaphragm of variable size whose function is to adjust the size of the pupil to regulate the amount of light admitted into the eye. It is the coloured part of the eye (shades may vary individually like blue, green, brown, hazel, or grey).

1.2.2.3 Pupil

Pupil generally appears to be the dark "centre" of the eye, but can be more accurately described as the circular aperture in the centre of the iris through which light passes into the eye. The size of the pupil (and therefore the amount of light that is admitted into the eye) is regulated by the pupillary reflex (also known as the "light reflex").

1.2.2.4 Lens

The lens is a transparent structure enclosed in a thin transparent capsule. It is located behind the pupil of the eye and encircled by the ciliary muscles. It helps to refract light travelling through the eye (which first refracted by the cornea). The lens focuses light into an image on

the retina. It is able to do this because the shape of the lens is changed according to the distance from the eye of the object(s) the person is looking at. This adjustment of shape of the lens is called accommodation and is achieved by the contraction and relaxation of the ciliary muscles. [7]

1.2.2.5 Ciliary Muscle

The ciliary muscle is a ring of striated smooth muscles in the eye's middle layer that controls accommodation for viewing objects at varying distances and regulates the flow of aqueous humour into schlemm's canal. The muscle has parasympathetic and sympathetic innervation. Contraction and relaxation of the ciliary muscle alters the curvature of the lens. This process may be described simply as the balance existing at any time between two states: Ciliary Muscle relaxed (This enables the eye to focus on distant objects) and Ciliary Muscle contracted (This enables the eye to focus on near objects).

1.2.2.6 Conjunctiva

The conjunctiva is a thin transparent mucous epithelial barrier, lines the inside of the eyelids, and covers the anterior one-third of the eyeball. The respective portion of conjunctiva is referred to as the palpebral and bulbar conjunctiva. The conjunctiva is composed of two layers: an outer epithelium and its underlying stroma (substantia propria). The exposed surface of the eye includes conjunctiva and cornea and is covered with the tear film. The conjunctiva contributes to the formation of the tear film by way of secreting substantial electrolytes, fluid, and mucins.

1.2.2.7 Aqueous humor

The aqueous humor is a jelly-like substance located in the outer/front chamber of the eye. It is a watery fluid that fills the "anterior chamber of the eye" which is located immediately behind the cornea and in front of the lens. The aqueous humor is very slightly alkaline salt solution that includes tiny quantities of sodium and chloride ions. It is continuously produced, mainly by the ciliary processes, flows from the posterior chamber through the pupil into the anterior chamber, and exits via the trabecular route at the angle and the uveoscleral route. Schlemm's canal (canal of Schlemm or the scleral venous sinus), is a circular channel that collects aqueous humour from the anterior chamber and delivers it into the bloodstream via the anterior ciliary veins. It is located at the junction of the cornea and the sclera. In human, the rate of aqueous humor turnover is approximately 1% - 1.5% of the anterior chamber volume per minute. The rate of aqueous formation is approximately 2.5 µl/min. Aqueous

humor consists of pressure dependent and pressure independent pathways. The pressure dependent outflow refers to the trabecular meshwork-schlemm's canal-venous system, while pressure independent outflow refers to any non-trabecular outflow. [8]

1.2.3 The Posterior Segment

The posterior segment comprises the vitreous, retina, sclera, choroid, and optic nerves.

1.2.3.1 Sclera

The sclera (white portion of the eye) is the tough white sheath that forms the outer-layer of the ball. It is a firm fibrous membrane that maintains the shape of the eye as an approximately globe shape. It is much thicker towards the back/posterior aspect of the eye than towards the front/anterior of the eye.

1.2.3.2 Retina

The retina is located at the back of the human eye. The retina may be described as the "screen" on which an image is formed by light that has passed into the eye via the cornea, aqueous humour, pupil, lens, and finally the vitreous humour before reaching the retina. The function of the retina is not just to be the screen onto which an image may be formed but also to collect the information contained in that image and transmit it to the brain in a suitable form for use by the body. The retinal "screen" is therefore a light-sensitive structure lining the interior of the eye. It contains photosensitive cells (called rods and cones) and their associated nerve fibers that convert the light they detect into nerve impulses that are then sent onto the brain along the optic nerve.

1.2.3.3 Vitreous Humour

The vitreous humour (also known as the vitreous body) is located in the large area that occupies approximately 80% of each eye in the human body. The vitreous humour is a perfectly transparent thin-jelly-like substance that fills the chamber behind the lens of the eye. It is an albuminous fluid enclosed in a delicate transparent membrane called the hyaloid membrane.

1.2.3.4 Optic nerve

The optic nerve (a bundle of over 1 million nerve fibres) is responsible for transmitting nerve signals from the eye to the brain. These nerve signals contain information on an image for

processing by the brain. The front surface of the optic nerve, which is visible on the retina, is called the optic disk.

1.2.3.5 Macula

The center of the retina is called the macula. The macula contains a high concentration of photoreceptor cells which convert light into nerve signals. Because of the high concentration of photoreceptors, we are able to see fine details such as newsprint with the macula. At the very center of the macula is the fovea, the site of our sharpest vision.

1.2.3.6 Choroid

The choroid layer is located behind the retina and absorbs unused radiation and nourishes the outer portions of the retina. It is a thin, highly vascular (i.e. it contains blood vessels) membrane that is dark brown in colour and contains a pigment that absorbs excess light and so prevents blurred vision (due to too much light on the retina). The choroid has one of the highest blood flows in the body. The choroid is loosely attached to the inner surface of the sclera by the lamina fusa.[9]

1.3 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.

1.3.1 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.[10]

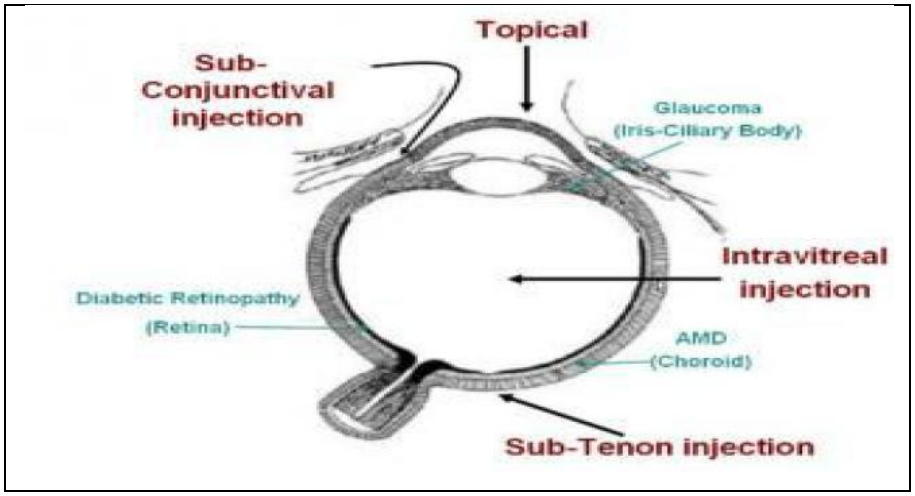

Figure 3:- Different routes for ocular drug delivery [5]

1.3.2 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.[11,12,13]

1.3.3 Intravitreal administration

Direct drug administration into the vitreous offers distinct advantage of more straightforward access to the vitreous and retina. 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 in the vitreous but the mobility of large molecules, particularly positively charged, is restricted.[14,15]

1.4 CONSTRAINS OF OCULAR DELIVERY

The different barriers for ocular drug delivery is depicted in table 1.

Table 1: Barriers for the Ocular Delivery

	Conjunctiva	Cornea	Sclera
Surface area (cm^2)	17.65 ±2.12	1.04±0.12	16-17
Thickness (mm)	-	0.57	0.4- 0.5
Structure composition	Mucus membrane Epithelium vasculature	5 layer	Collagen fiber Water Proteoglycans Elastic fibers Fibroblast

1.4.1 Drug loss from the ocular surface

After instillation, the flow of lacrimal fluid removes instilled compounds from the surface of the 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.[16, 17, 18]

1.4.2 Lacrimal fluid-eye barriers

Corneal epithelium limits drug absorption from the lacrimal fluid into the eye.[7] The corneal epithelial cells form tight junctions that limit the paracellular drug permeation.[8] Therefore,

lipophilic drugs have typically at least an order of magnitude higher permeability in the cornea than the hydrophilic drugs.[19] 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. [20, 21]

1.4.3 Blood-ocular barriers

The eye is protected from the xenobiotic 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 uvea (The middle layer of the eye beneath 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.[22, 23]

1.5 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, as depicted in figure 4.

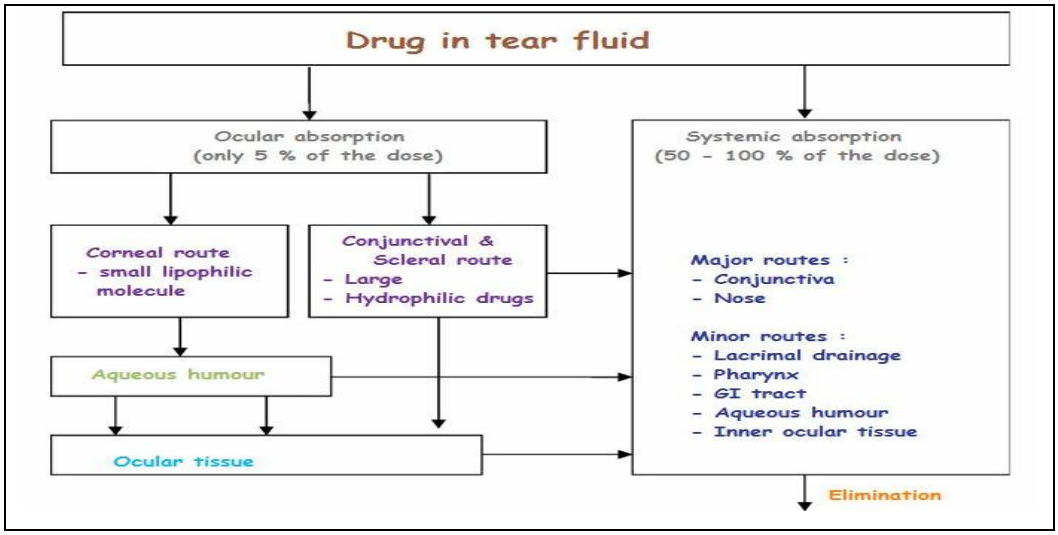

Figure 4: Ocular Drug Absorption [12]

1.5.1 Corneal permeation

The permeation of drugs across the corneal membrane occurs from the precorneal space. 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 occur. 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) as shown in figure 5.

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 is referred to as "differential solubility concept".

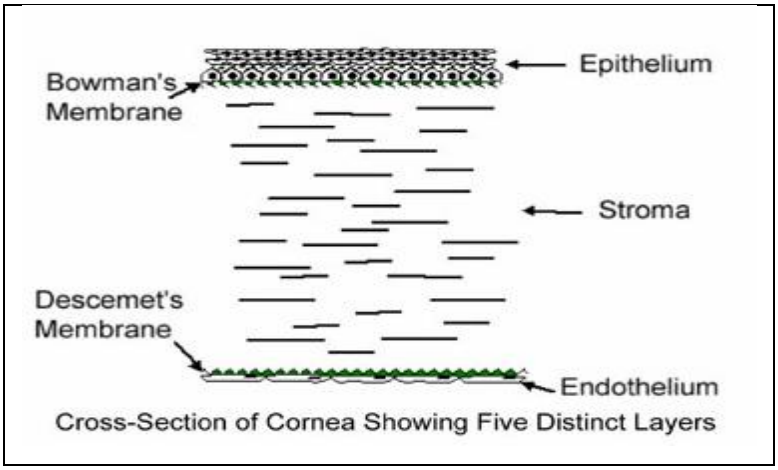

Figure 5: Corneal Membrane Depicting Various Barriers to Drug Absorption [12]

1.5.2 Non-corneal permeation

Primary mechanism of drug permeation is the sclera is likely to be diffusion across 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. [24, 25]

1.6 Disposition Of Ocular Drug

Bioavailability of drugs administered to the eye is 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 as shown in figure 6. One of the major problems encountered with conventional ophthalmic solutions is the rapid and extensive elimination of drugs from the precorneal lachrymal fluid, which may be 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%.

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. [26]

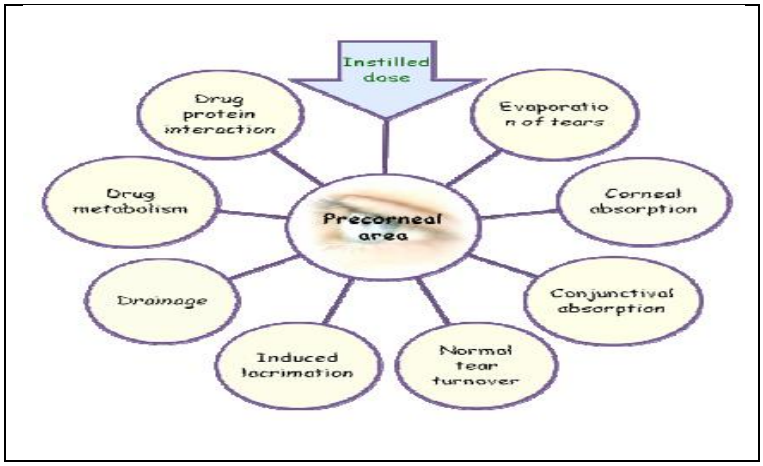

Figure 6: Reasons For Poor Ocular Bioavailability [26]

1. Nasolacrimal drainage system

The nasolacrimal 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 nasolacrimal drainage system consists of: the lachrymal puncta, the superior, inferior and common canaliculi; the lachrymal sac; and the nasolacrimal 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[14] as shown in figure 7. [27]

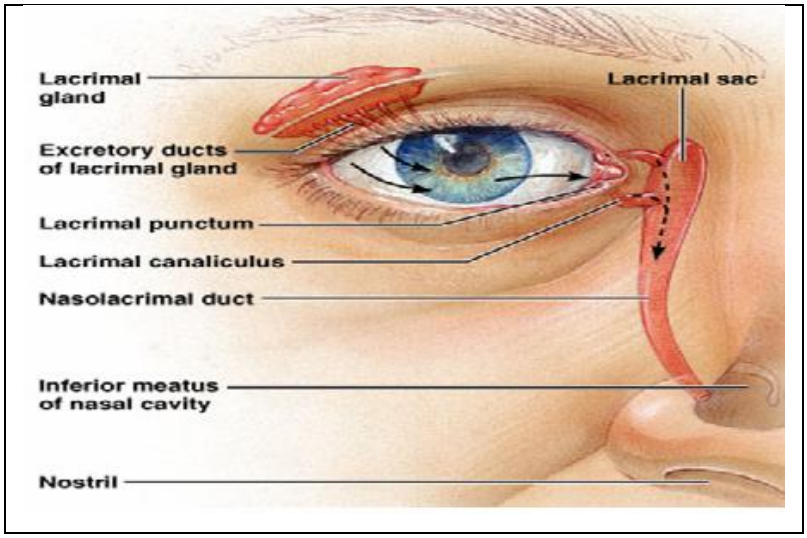

Figure 7: Nasolacrimal Drainage [27]

1.7 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 corneal ulcers, Endophthalmitis, Conjunctivitis.

1.7.1 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.

1.7.2 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.

1.7.3 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.

1.7.3.1 Viral conjunctivitis

Viral conjunctivitis is often associated with the common cold. This may be caused by a virus called 'adenovirus'. This type of conjunctivitis can spread rapidly between people and may cause an epidemic of conjunctivitis. The eyes are red and there may be a watery discharge. Often the eyelids are very swollen and even the conjunctiva on the white of the eye may be swollen, creating a glassy appearance. This type of conjunctivitis may also spread to affect the cornea (keratitis), and it may persist for several weeks and cause hazy vision.

1.7.3.2 Chlamydial conjunctivitis

This type of conjunctivitis is caused by an organism called Chlamydia trachomatis. This organism may also affect other parts of the body and can cause the sexually transmitted infection chlamydia. One or both eyes will be red with a sticky discharge and, sometimes, swollen eyelids. The cornea may also be involved in this condition.

1.7.3.3 Bacterial conjunctivitis

Bacterial conjunctivitis is one of the most commonly encountered eye problems in medicine. Most cases are acute, self-limited, and not a major cause of morbidity. However, because of

its high prevalance, it has a large societal impact in terms of missed days of school or work. Antibiotics can hasten the resolution of symptoms and microbial eradication and are therefore typically used to allow patients to return to their daily activities faster and to decrease the spread of disease. Chronic and hyperacute forms of bacterial conjunctivitis, typically due to Chlamydia trachomatis and Neisseria, respectively, are entirely different entities that are associated with high levels of ocular and systemic morbidity.

1.7.3.3.1 Disease

Bacterial conjunctivitis is an infection of the eye's mucous membrane, the conjunctiva, which extends from the back surface of the eyelids (palpebral and tarsal conjunctiva), into the fornices, and onto the globe (bulbar conjunctiva) until it fuses with the cornea at the limbus.

1.7.3.3.2 Etiology

Acute bacterial conjunctivitis is primary due to Staphylococcus aureus, Streptococcus pneumoniae and Haemophilus influenzae. Other pathogens responsible for acute disease are Pseudomonas aeruginosa, Moraxella lacunata, Streptococcus viridans, and Proteus mirabilis. These organisms may be spread from hand to eye contact or through adjacent mucosal tissues colonization such as nasal or sinus mucosa. Hyperacute conjunctivitis is primarily due to Neisseria gonorrhoeae, which is a sexually transmitted disease. Neisseria meningitidis is also in the differential and is important to consider as it can lead to potentially fatal meningeal or systemic infection.Chronic conjuctivitis is primarily due to Chlamydia trachomatis. However, chronically ill, debilitated, or hospital patients can become colonized with other virulent bacteria responsible for chronic conjunctivitis. Staphylococcus aureus and Moraxella lacunata may also cause chronic conjunctivitis in patients with associated blepharitis.

1.7.3.3.3 Risk Factors

1. Since these bacteria are usually spread from other infected individuals, poor hygenic habits may increase the risk of infection
2. Poor contact lens hygiene
3. Contaminated cosmetics
4. Crowded living or social conditions such elementary schools, military barracks etc
5. Ocular diseases including dry eye, blepharitis, and anatomic abnormalities of the ocular surface and lids
6. Recent ocular surgery, exposed sutures or ocular foreign bodies
7. Chronic use of topical medications

8. Immune compromise
9. Neonates are at particularly high risk for conjunctivitis.

1.7.3.3.4 Primary prevention

1. Hand washing and good hygiene techniques

1.7.3.3.5 Diagnosis

History

Patients may complain of redness, discharge, crusting and sticking or gluing of the eyelids upon waking, blurry vision, light sensitivity and irritation.

1.7.3.3.6 Symptoms

1. Red eye: Either unilateral, bilateral, or sequentially bilateral
2. Discharge: Classically purulent, but may be thin or thick muco-purulent or watery
3. Irritation, burning, stinging, discomfort
4. Tearing
5. Light sensitivity
6. Intolerance to contact lens
7. Fluctuating or decreased vision

1.7.3.3.7 Signs

1. Bulbar conjunctival injection
2. Palpebral conjunctival papillary reaction
3. Muco-purulent or watery discharge
4. Chemosis
5. Lid erythema

1.7.3.3.8 Management Of Bacterial Conjunctivitis

General treatment

Bacterial conjunctivitis is a contagious condition, so patients are instructed in proper hygiene and hand washing. The exact period of time of contagion cannot be predicted and the amount of time suggested varies, with a recent survey of ophthalmologists recommending 1-3 days away from work or until the infection clears. Supportive therapy for conjunctivitis consists of cool compresses and artificial tears two-six times daily.

Medical therapy

Antibiotics may lead to quicker clinical and microbiological remission compared with placebo, at least in the first 2-5 days of therapy. This may result in decreased transmission of the disease and lower incidences within the population.Many antibiotics have been shown to be equivalent in the treatment of routine cases, and therefore the choice of antibiotics is often guided by cost, availability, and risk of side effects.The most common antibiotics used for acute bacterial conjunctivitis are as follows:

Fluoroquinolones

2nd Generation

Ciprofloxacin 0.3% drops or ointment or Ofloxacin 0.3% drops

3rd Generation

Levofloxacin 0.5% drops

4th Generation

Moxifloxacin 0.5% drops, Gatifloxacin 0.5% drops, or Besifloxacin 0.6% drops

Aminoglycosides

Tobramycin 0.3% drops

Gentamicin 0.3% drops

Macrolides

Erythromycin 0.5% ointment

Azithromycin 1% solution

Other

Bacitracin ointment

Bacitracin/Polymixin B ointment

Neomycin/Polymixin B/Bacitracin

Neomycin/Polymixin B/gramicidin

Polymixin B/Trimethoprim

Sulfacetamide

Chloramphenicol (In much of the world, outside the US, this cheap, broad spectrum drop is the most prescribed ocular antibiotic. However, because Chloramphenicol use, at least systemically, is associated with a potentially fatal side effect (aplastic anemia), this medicine is not available for topical use in the United States.) Fusidic Acid (Common treatment in the UK; not used in the US) [29, 30, 31]

1.8 OPHTHALMIC FORMULATIONS

1.8.1 Suspensions

Ophthalmic suspensions products is another part of the ocular drug delivery system and have many distinct advantages over others formulation. [32] Ophthalmic suspensions are more complex and challenging if compare with to ophthalmic (aqueous) solutions.

The formulation of an ophthalmic suspension many problems occurred such as nonhomogeneity of the dosage form, settling of particles, cake formation, aggregation of the suspended particles. [33, 34]

1.8.2 Eye Ointments

Ointments are the semi-solid preparations intended for external application. They are usually formulated using mixture of semisolid and solid hydrocarbons (paraffin) which have a melting or softening point close to the body temperature and are nonirritating to the eye. [35] Ointments are useful in improving the drug bioavailability and in sustaining drug release. The problems associated with ointments are poor patient compliance due to blurring of vision. So, they are often used as night time medication. [36]

1.8.3 Aqueous Gel

Aqueous gel (hydrogels) consists of high molecular weight, cross linked polymers that form a three dimensional network in water. Hydrogels are based on the addition of hydrocolloids to aqueous drug solutions. Gels permit longer residence time in the precorneal area then viscous solution.[37] The most important advantage of gel is increase in the contact time of the drug to the tissue. So, that drug can remain for longer period at the desired site. [38]

1.8.4 Microspheres and Nanoparticles

These are the promising drug carriers for ophthalmic applications; the drug absorption is enhanced significantly in the eye in comparison to eye drop solution owing to the much slower ocular elimination rate of particles. Smaller particles are better tolerated by the patients than longer particles therefore nanoparticles may represent very comfortable

ophthalmic prolonged action delivery systems. However, albumin microspheres reportedly cause adverse reaction in the eye. [39, 40]

1.8.5 Ophthalmic solution

Today most of the topical ophthalmic preparations are in the form of aqueous solutions. A sterile homogeneous solution dosage form have many advantages over the other dosage such as formulation, including the easily commercially capability produce on large scale manufacture. There are various factors that must be consider during the formulating aqueous solution includes selection of appropriate salt of the drug, solubility in solvents, therapeutic systemic effect, ocular toxicology, pKa of formulation, and the effect of pH of the formulation. Others stability parameters includes such as solubility, the solubility and stability, and corneal permeability of the drugs are depends on pH of the formulation. Others stability parameters includes such as solubility, tonicity, viscosity, buffering capacity, compatibility with formulation ingredients and effect of packaging components, choice of appropriate preservative, ocular comfort and dosing administration. [41, 42]

A factor pH of the formulation is a best possible compromise between stability and bioavailability of the drug. Ophthalmic solutions should be formulated in between pH range 4.0 to 8.0. If the pH range of the formulation is outside the physiological pH range of eye, can cause discomfort, irritation and also decrease the bioavailability of the drug, due to the secretion of fluid and to aid in the restoration of normal physiological conditions. The excessive tearing from the nasolacrimal gland also results into rapidly flushing of the drug. So it necessary, proper choices of buffering agents and buffer capacity are essential to optimize drug bioavailability as well as ocular efficacy of drug. [43]

1.9 General Safety Consideration

1.9.1 Sterility

Every ophthalmic product must be manufactured under condition validated to render it sterile in its final container for the self-life of the product. Sterility testing is considered on each lot of ophthalmic product by suitable procedures, as set forth in the appropriate pharmacopeia and validated in each manufacturer's laboratory. While the majority of ophthalmic preparations contain preservative for multiple-dose use, sterile preparation in special containers for individual use on a single patient must made available.

1.9.2 Ocular Toxicity and Irritation

Assessment of the potential for ocular irritation and toxicity of ophthalmic solution represents an extremely important step in the development of both over the counter (OTC) and prescriptive pharmaceuticals. The USP presents guidelines for a 72hrs ocular irritation test in rabbits using saline and cottonseed oil extracts of plastic containers are cleaned and sterilized as in the final packaging product to determine acceptability of the packaging system. Current guidelines for toxicity evaluation of ophthalmic formulation involve both single and multiple applications, dependent on the proposed clinical use. The multiple applications may extend over a9-month period and incorporate evaluations of ocular irritation, systemic toxicity, and determination of systemic exposure (toxicokinetics). [44]

1.9.3 Preservatives

Preservatives are included as a major component of all multiple-dose eye solution for the primary purpose of maintaining that sterility in the opened products over its lifetime of use.[45]

Table2:- Classification of Preservatives

Class	Example
Quaternary ammoniums	Benzalkonium chloride (BAK) Polyquaternium-1,benzodidecinium bromide, benzethonium chloride, cetylpyridinium chloride, Cetrimide
Mercurials	Phenyl mercuric nitrate, Phenyl mercuric acetate/ borate, Thiomersal
Alcohols	Chlorbutanol, Benzyl alcohol, phenoxyethanol, phenylethyl alcohol
Carboxylic acid	Sorbic acid
Phenols	Methyl/propyl paraben
Amidines	Chlorhexidine
Other	Disodium EDTA, Oxy-Chloro Complex

1.10 PHARMACEUTICAL REQUIREMENT

The therapeutically inactive ingredients in ophthalmic solution and suspension dosage forms necessary to perform one or more of the following functions: adjust the concentration and tonicity, buffer and pH, and stabilize the active ingredients against decomposition, increase solubility, impart viscosity, and act as solvent. The use of unnecessary ingredients is to be avoided, and the use of ingredients solely to impart a color, odor, or flavor is prohibited. The choice of a particular excipient and its concentration is based not only on physical and

chemical compatibility, but also on biocompatibility with the sensitive and delicate ocular tissues.

1.10.1 Tonicity and Tonicity Adjusting Agents

Lacrimal fluid is isotonic with blood, having an isotonicity value corresponding to that of a 0.9% sodium chloride solution. Ideally, an ophthalmic solution should have this isotonicity value; but the eye can tolerate isotonicity values as low as that of a 0.6% sodium chloride solution and as high as that of a 2.0% sodium chloride solution without marked discomfort. Some ophthalmic solutions are necessarily hypertonic in order to enhance absorption and provide a concentration of the active ingredient(s) strong enough to exert a prompt and effective action. Where the amount of such solutions used is small, dilution with lacrimal fluid takes place rapidly so that discomfort from the hyper tonicity is only temporary. However, any adjustment toward isotonicity by dilution with tears is negligible where large volumes of hypertonic solutions are used as collyria to wash the eyes. It is, therefore important that solutions used for this purpose be approximately isotonic. A common tonicity-adjusting ingredient includes NaCl, KCl, buffer salts, dextrose, glycerin, propylene glycol, and mannitol.

1.10.2 pH Adjustment and Buffers

The pH and buffering of an ophthalmic solution is probably of equal important to proper preservation, since the stability of most commonly used ophthalmic drugs is largely controlled by the pH of their environment. In addition to stability effects, pH adjustment can influence comfort, safety, and activity of the product. Eye irritation is normally accompanied by an increase tear fluid secretion (a defense mechanism) to aid in the restoration of normal physiological conditions. Ideally, every product would be buffered to a pH of 7.4, considered the normal physiological pH of tear fluid. The tears have some buffer capacity of their own, and it is believed that they can neutralize the pH of an instilled solution if the quantity of solutions is not excessive and if the solution does not have a strong resistant to neutralization. The pH values of ophthalmic solution are adjusted within a range to provide an acceptable shelf life. Since the buffer capacity is determined by buffer concentration, the effect of buffers on tonicity must also be taken into account- another reason that ophthalmic products are usually only lightly buffered.

1.10.3 Stabilizers

Stabilizers are ingredients added to a formula to decrease the rate of decomposition of the active ingredients. Antioxidants are the principal stabilizers added to some ophthalmic solutions, primarily epinephrine and other oxidizable drugs. Ascorbic acid and acetylcysteine, sodium bisulfite, 8-hydroxyquinolone, and isoascorbic acid are other commonly used antioxidants.

1.10.4 Surfactant

The use of surfactants is greatly restricted in formulating ophthalmic solutions. The order of surfactant toxicity is anionic > cationic >> nonionic. Several nonionic surfactants are used in relatively low concentrations to aid in dispersing steroids in suspensions and to achieve or to improve solution clarity. Those principally used are the sorbitan ether esters of oleic acid (Polysorbate or tween 20 and 80), polymers of oxyethylated octyl phenol (Tyloxapole), and polyoxyl 40 stearate. The lowest concentration possible is used to perform the desired function.

1.10.5 Viscosity-Imparting Agent

Polyvinyl alcohol, methylcellulose, Hydroxypropyl methylcellulose, hydroxyethylcellulose, and carbomers are commonly used to increase the viscosity of ophthalmic solution and suspensions. Although they reduce surface tension significantly, their primary benefit is to increase the ocular contact time, thereby decreasing the drainage rate and increase drug bioavailability. The acceptance percent limit of viscosity modifier are given in table 3.

Table 3:- Commonly used viscosity enhancer in ocular delivery

Viscosity Enhancer	Maximum Concentration (%)
Carmellose sodium	2 %
Hydroxyethylcellulose	0.8 %
Hydroxypropylmethylcellulose	1.0 %
Methylcellulose	2.0 %
Polyvinyl alcohol	1.4 %
Polyvinylpyrrolidone	1.7 %

1.10.6 Vehicle

Ophthalmic drops are, with few exceptions, aqueous fluids using purified water USP as the solvent. Purified water meeting USP standards may be obtained by distillation, deionization, or reverse osmosis. All ophthalmic drops must be rendered sterile. Oils have been used as

vehicles for several topical eyedrops products that are extremely sensitive to moisture. When oils are used as vehicle in ophthalmic fluids, they must be of the highest purity. Vegetable oils such as olive oil, castor oil, and sesame oil have been used extemporaneous compounding. These oils are subjected to rancidity and, therefore, must be used carefully. Some commercial oils, such as peanut oil, contain stabilizers that could be irritating. The purest grade of oil, such as that used for parenteral products, would be advisable for ophthalmic.[46]

1.11 Manufacturing Of Aqueous Ophthalmic Solution

The manufacturing process should meet requirement of GMP.

Production under clean conditions followed by sterilization by autoclaving

Typically ophthalmic solutions may be manufactured and packaged in the final container under clean conditions. Sterilization may then be performed using moist-heat sterilization (assuming the therapeutic agent is chemically stabile under these conditions).

Production under clean or aseptic conditions followed by aseptic sterilization by filtration

If the therapeutic agent is thermo labile then sterilization by heat should be avoided. The production of ocular solutions is then performed by initially manufacturing the dosage form under clean or aseptic conditions. Clarification of the solution is performed by filtration through an appropriate filter, followed by sterilization filtration (0.22-µm filter) and packaging (both under aseptic conditions).

Production under aseptic conditions

Ophthalmic suspensions may not be sterilized by filtration. Therefore, the manufacture of these systems usually involves the dispersion of the sterile therapeutic agent into the sterile vehicle (with added excipients) and subsequent packaging, both under aseptic conditions.[47]

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