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Ocular Inserts: A Novel Controlled Drug Delivery System

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ABSTRACT

The goal of pharmacotherapeutics is to achieve an effective drug concentration at the targeted site of action for the desired time. Ophthalmic drug delivery is one of the most interesting and challenging for the pharmaceutical scientist. The ocular inserts represent a significant advancement in the therapy of eye disease. The use of ocular inserts, which are the solid device to be placed on the cornea, represents one of the possibilities to reach increased residence time and to improve ocular drug bioavailability. Newer research in ophthalmic drug delivery systems is directed towards a combination of several drug delivery technologies, which includes developing a system which is not only prolonged the contact time of the vehicle at the ocular surface but which at the same time slow down the elimination of the drug. In this review, we have focused on the mechanism of action, classification, advantages, and disadvantages of ocular inserts. The present review is an attempt to present brief info about ocular inserts.

INTRODUCTION:

In developing a drug delivery strategy, issues of absorption, distribution, metabolism, elimination (ADME) must be considered. The eye presents unique opportunities and challenges when it comes to the delivery of pharmaceuticals. Ophthalmic drug delivery is one of the most interesting and challenging endeavors facing pharmaceutical scientists. The anatomy, physiology, and biochemistry of the eye render this organ exquisitely impervious to foreign substances. The challenge in front of formulations to circumvent the protective barriers of the eye without causing permanent tissue damage. The development of newer, more sensitive diagnostic techniques and therapeutic agents renders urgency to the development of maximum successful and advanced ocular drug delivery systems. The goal of pharmacotherapeutics is the attainment of an effective drug .concentration at the intended site of action for the desired period. Eye, as a portal for drug delivery, is generally used for the local therapy as against systemic therapy to avoid the risk of eye damage from high blood concentrations of drug which are not intended for the eye. The conventional ocular dosage forms are eye drops, eye ointments, eye gels, eye solutions, eye injections, eye irritation solutions, eye suspensions, sol to gel systems.

The most widely used are eye drops, eye ointments, and gels, which constitute 80% of the total ophthalmic preparations. The eye drop dosage form is easy to instill but suffers from the inherent drawback, however, these have limitations such as the requirement of frequent administration, unpredictable doses rapid precorneal elimination, loss of drug by drainage, sticking of eyelids, poor patient compliance, blurred vision, no true sustained effect, and even irritation.

It is generally agreed that the intraocular bioavailability of topically applied drugs is extremely poor ranging from 5-10% of the total administered. The primitive ophthalmic solution, suspension, etc are no longer sufficient to combat some present virulent diseases. Effective treatment of ocular diseases is a formidable challenge for scientists in the field, especially because of the nature of diseases and presence of the ocular barriers especially in posterior ocular segments.

Over the last several years, attempts have been made to improve ocular bioavailability through manipulation of product formulation such as viscosity and application of

mucoadhesive polymers. Thus far, these approaches to prolong corneal contact time have led to modest improvement in ocular bioavailability.

Consequently, it seems logical to consider non-conventional approaches such as nanotechnology, microspheres, liposomes, appropriate prodrug *in-situ* forming gel, and iontophoresis for effective delivery and to further enhance ocular absorption and reduce side effects. Because of poor ocular bioavailability, the frequent periodic instillation of eye drops becomes necessary to maintain a continuous sustained level of medication. This gives the eye massive and unpredictable dose of medication unfortunately higher drug concentrations cause both ocular and systemic side effects. To remove the constraints placed by these conventional ocular therapies. A newer approach for ocular drug delivery systems is being explored to develop extended duration and controlled release strategy. Current ophthalmic drug delivery: Drops (95%+ of $8-12 billion markets), ocular insert, gels, and ointments.

Ocular Inserts [2,3,4,5,6,7]

Ocular inserts are sterile, multi-layered, drug-impregnated devices placed into the cul-de-sac or conjunctival sac of the eye for the prolonged release of medication. The inserts are classified based on their physicochemical properties as insoluble, soluble, or bioerodible. Soluble inserts, also are erodible, for example, monocytic polymeric devices that undergo gradual dissolution while releasing the drug, and do not need removal. Insoluble inserts are further classified into Reservoir and matrix systems and they can usually deliver drugs in a controlled, predetermined rate, but need removal from the eye. Collagen shields, ocfit, minidisc ocular therapeutic systems are the ocular inserts later developed. In one study Hassan et al. formulated the brimonidine sodium alginate ocular inserts and observed the sustained drug release rate and Intraocular Pressure (IOP) reduction in the rabbit eyes. The release of the drug (*in vitro*) was for 6 h and the IOP reduction was 40%. The AUC values observed were ~4.5-folds higher than that of the instilled topical eye drops. Amar et al. investigated the release of Betaxolol hydrochloride from the ocular inserts and the drug release from *in vitro* studies was 98.76% at the end of 12 h. Alan et al. patented biodegradable controlled release ocular insert of chloramphenicol sodium monosuccinate impregnated with Polylactic Acid (PLA) as a treatment for infectious bovine kerato-conjunctivitis. The ophthalmic insert will be retained in the third eyelid of mammals and would be able to deliver drugs for seven consecutive days.

RECENT TRENDS IN OCULAR DRUG DELIVERY SYSTEM [8,9,10,11,12]

From the below newer approaches, the sensitive, successful extended duration and controlled release ocular delivery systems like ocular inserts, are being developed to attain better ocular bioavailability and sustained action of ocular drugs. Utilization of the principle of controlled release as embodied by ocular inserts, therefore, offer an attractive alternative approach to the difficult problem of prolonging precorneal drug residence time.

 Mucoadhesive dosage forms.

 Ocular inserts.

 Collagen shields or corneal shields.

 Artificial tear inserts.

 Drug-presoaked hydrogel type contact Lens.

 Ocular iontophoresis.

 Phase transition systems.

 Microspheres and nanoparticles.

COMMON EYE INFECTIONS [13,14,15]

Bacteria are the causative pathogens for a large number of eye infections. Also, viruses, fungus, and protozoans cause eye infections.

As such, eyes are prone to a number of diseases but more commonly found are mentioned here.

- Conjunctivitis.
- Blepharitis.
- Keratitis.
- Cataract.

- Iritis (anterior uveitis)
- Glaucoma.

Conjuvtivis:

Conjunctivitis, commonly known as pink eye as shown in Fig 1, is a clear membrane that covers the white part of the eye and lines the inner surface of the eyelids. The inflamed conjunctiva will usually make the eye appear red or pink because the tiny blood vessels that are normally within the conjunctiva get irritated and enlarged. It usually affects both eyes at the same time although it may start in one eye and spread to the other after a day or two days. It may be asymmetrical, affecting one eye more than the other. Pink eye can be infectious or noninfectious.

There are many causes of conjunctivitis, including.

 Bacterial conjunctivitis – staphylococci, streptococci.

 Viral conjunctivitis (often associated with the common cold) – adenovirus.

 Chlamydial conjunctivitis – Chlamydia trachomatis.

 Allergic conjunctivitis –allergic diseases such as hay fever, asthma, and eczema and by antigens like pollen, dust mites, or cosmetics.

 Reactive conjunctivitis or irritant conjunctivitis – chemicals, smoke, fumes, etc.

Signs and Symptoms of conjunctivitis are:-

 The blood vessels over the white of the eye are more visible and swollen.

 The lining of the eyelids also looks red or pinker due to inflammation.

 The eye is sticky, with a heavy discharge and tearing that may cause the lids to stick together, especially after sleeping.

 Inflammed and swollen eyelids.

 Blurred vision.

OCULAR ANATOMY AND PHYSIOLOGY [9,17,13,15]

The human eye is a complex anatomical device that remarkably demonstrates the architectural wonders of the human body. The human eye is a challenging organ for the topical administration of drugs. The basis of this can be found in the anatomical arrangement of the surface tissues and the permeability of the cornea. The protective function of the eyelids and the lachrymal system is such that there is the rapid removal of material instilled into the eye unless the material is suitably small in volume and chemically and physiologically compatible with surface tissues.

The eye is referred to as a globe and consists of two spheres, one set in the other, as shown in Fig 1. The front sphere is smaller and is bordered anteriorly by the sclera. The combined weight of both spheres has been given as 6.7-7.5gm, with a volume of approximately 6.5ml. The circumference of the eye is about 75mm. The eye is located in the bony orbital cavity of the head.

Eyeball

The wall of the human eyeball (globe) is composed of three concentric layers.

1. The outer fibrous layer.

The fibrous layer is made up of two parts.

a) Posterior (5/6th) is opaque and called the sclera.

b) Anterior (1/6th) is transparent and called the cornea.

2. A middle vascular layer – the uvea or uveal tract consisting of the choroid, the ciliary body and the iris.

3. A nervous layer-the retina.

Sclera

Contains the microcirculation, which nourishes the tissues of this anterior segment and is usually white.

Vascular Layer consists of three parts:-

The choroid – remains just behind the retina forming the posterior 5/6th of the middle coat, composed of numerous blood vessels and pigmented cells containing melanin.

The ciliary body – includes orbicularis ciliaris, ciliary processes and ciliary muscle.

The Iris nervous coat is called the retina, which contains photosensitive receptors.

The eyeball houses an optical apparatus which consists, of sequences of the precorneal film, the cornea, the aqueous humor, the pupil, the crystalline lens, the vitreous humor, and the retina. The aqueous and vitreous humor are layers of clear fluid or gel-like material interposed between the solid structures. The crystalline lens is a refractive element with variable power controlled and supported by a muscle incorporated in the ciliary body.

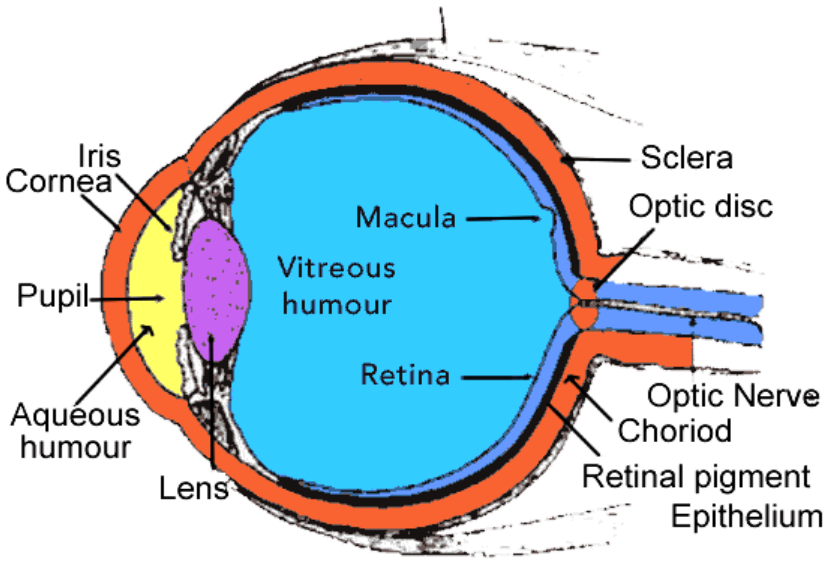

Figure No. 1: Anatomical structure of the human eyeball

Conjunctiva:

The conjunctival membrane covers the outer surface of the white portion of the eye and the inner aspects of the eyelids. It is attached loosely and thereby permits free movement of the eyeball. Except for the cornea, the conjunctiva is the most exposed portion of the eye.

Lachrymal System:

The conjunctival and corneal surfaces are covered and lubricated by a film of fluid secreted by the conjunctival and lachrymal glands. The secretion of the lachrymal glands, the tears are delivered through some fine ducts into the conjunctival fornix. The movement of the eye helps to spread the tears over the conjunctival surface. The excess fluid is directed into the lachrymal lake a small triangular area lying in the angle bound by the innermost portions of the lids. Tears are drained from the lachrymal lake, by two small tubes, the lachrymal canaliculi which leads into the upper part of the nasolacrimal duct. The act of blinking exerts a suction-force pump action in removing tears from the lachrymal lake and emptying them into the nasal cavity. Lacrimation is induced reflexly by stimulation of nerve ending of the cornea or conjunctiva, the turnover rate of nasolacrimal fluid is 16%. The eyeball is continually irrigated by a gentle stream of lacrimal fluid which prevents it from becoming dry and inflamed.

Composition of tear:

The secretion is a clear watery fluid containing numerous salts, glucose, other organic compounds, approximately 0.7% protein and the enzyme, lysozyme. Water: 98.2% Solids: 1.8%

Organic elements:- Protein-0.67%, Sugar-0.65%, Nacl-0.66%, NPN-0.05% Urea-0.03%.

Other mineral elements sodium, potassium, and ammonia-0.79%.

Precorneal Film:

Part of the tear fluid provides the moist surface to the cornea. The film, compatible with both aqueous and lipid ophthalmic preparations is composed of three layers, the thin outermost layer is a lipid and is secreted mainly by the meibomian glands. The lipid layer keeps the cornea moist by preventing evaporation of the underlying layers, a thicker middle aqueous layer, Secreted by the lacrimal gland, which helps in nourishing the cornea. It consists of water, salts, glucose, urea, proteins, lysozyme (an antibacterial enzyme) and immunoglobulin, and a thin inner mucous layer. It is secreted by the goblet cells of the tarsal conjunctiva. This layer is necessary for tear film stability. It smoothes the corneal epithelial surface, enhances tear spreading, lubricates the eye, and helps to trap debris. It is renewed during each blink and

when blinking is suppressed, it dries in patches. Although the tear film is typically only about 7µL in volume with fluid pH 7.4 and if blinking does not occur, the volume can go up to 30µL without spillage, the cul-de-sac is sterile due partly to the action of lysozyme in the tears.

Cornea:

The cornea 0.5-1 mm thick consists mainly of the following structures.

1) Corneal Epithelium.

2) Substantia Propria (stroma).

3) Corneal Endothelium.

The cornea is transparent to ordinary diffuse light because of a special laminar arrangement of the above structure, fibers, and because of the absence of blood vessels. The cornea derives its nutrition by diffusion and must have certain permeability characteristics. The corneal epithelium provides an efficient barrier against bacterial invasions.

Unless its continuity has been broken by an abrasion, pathogenic bacteria cannot gain a foothold. Any foreign body that either scratches the cornea or lodges and becomes embedded in the cornea is of serious concern because of the role it may play in permitting pathogenic bacteria to gain a foothold.

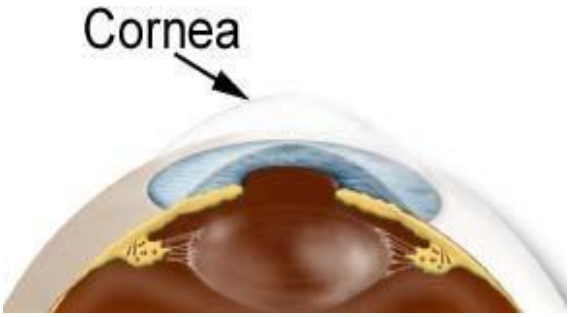

Figure No. 2: structure of the cornea

STRUCTURE AND FUNCTION OF EYE

The eye consists of several parts that resemble a camera (see diagram).

Sclera - the eye's white outer protective coat, normally seen as the "white of the eye".

Cornea - the transparent, curved structure at the front of the eye.

Iris - the colored part of the eye - blue, brown, green, grey, etc - that can be seen through the cornea.

Pupil - the black part of the eye in the middle of the iris. It constricts or dilates according to the amount of light passing through it.

Lens - the transparent disc (with both sides being convex) immediately behind the iris and pupil.

Aqueous humor - the transparent fluid (with a consistency similar to water) that circulates behind the cornea and in front of the lens.

Vitreous humor - the material (like transparent jelly) that fills the eyeball between the lens and the retina.

Retina - the light-sensitive layer of millions of nerve cells that line the back of the eyeball. The cells consist of two main groups, called rods and cones due to their appearance under the microscope.

Rods - more numerous, spread out over the entire retina with more toward the outer edge, respond to low levels of light.

Cones - far fewer, concentrated around the retina's center, respond to color and details. Macula - the small center of the retina, responsible for reading vision.

Retinal pigment epithelium - This is a dark-colored layer of cells at the back of the retina responsible for providing oxygen and other nutrients to the rods and cones.

Choroid - a large network of blood vessels (behind the retina) that transport oxygen and other nutrients to the retinal pigment cells.

Optic disc - a small yellow oval structure in the retina, to which nerve cell connections travel from all the rods and cones.

Optic nerve and beyond - the "cord" of nerve cell connections that pass from the eyeball to destinations throughout the brain.

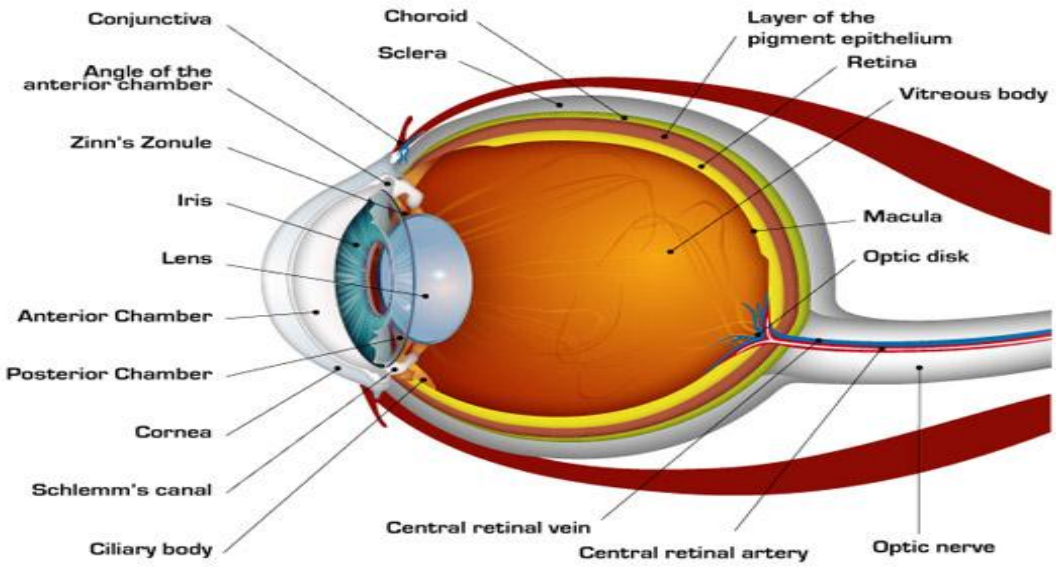

Figure No. 3: Structure of Eye

FUNCTION OF EYE

When you see an object, the light travels from that object to the cornea, then passes through the aqueous humor, pupil, lens, and vitreous humor to reach the retina. During this passage, the light becomes focused onto the macula. At the macula, the light causes chemical reactions in the cones, then passes through the aqueous humor, pupil, lens, and vitreous humor to reach the retina. During this passage, the light becomes focused onto the macula. At the macula, the light causes chemical reactions in the cones, which consequently sends electrical messages from the eye to the brain. The brain recognizes these messages and indicates to you that this particular object has been seen. The cones are therefore responsible for you being able to recognize colors and to read. The rods are essential for you to see in the dark, and to detect objects to the sides, above and below the object on which you are directly focused. This function prevents you from bumping into obstacles when moving around. All the retinal cells (rods and cones) are provided with oxygen and other nutrients from the retinal pigment cells (epithelium), which are kept supplied by the rich network of blood vessels in the choroid.

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 has 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.

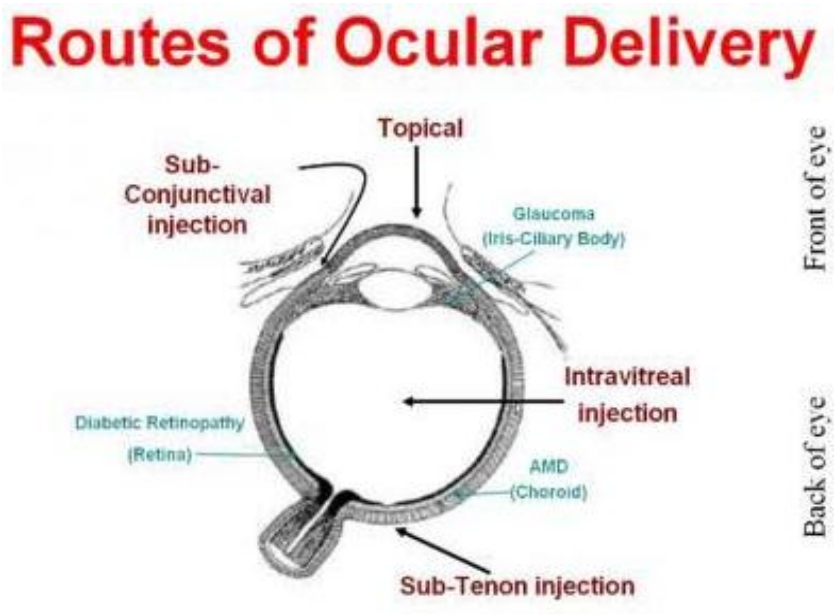

Figure No. 4: Routes of Occular Drug Delivery

BARRIERS FOR OCULAR DRUG DELIVERY:

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.

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 bloodstream by blood-ocular barriers. These barriers have two parts: the blood-aqueous barrier and the 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 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 bloodstream 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 thereafter distribution into the retina is limited by the RPE and retinal endothelial.

Blood-Retinal barriers

Blood-retinal barrier (BRB) restricts drug transport from the blood into the retina. BRB is composed of tight junctions of retinal capillary endothelial cells and RPE, called iBRB for

the inner and oBRB for the outer BRB, respectively (Figure 5). The function of iBRB is supported by Müller cells and astrocytes. The retinal capillary endothelial cells are not fenestrated and have a paucity of vesicles (Figure 5). The function of these endothelial vesicles has been described as endocytosis or transcytosis that may be receptor-mediated or fluid phase requiring adenosine triphosphate. A close spatial relationship exists between Müller cells and retinal capillary vessels to maintain the iBRB in the uptake of nutrients and the disposal of metabolites under normal conditions. Müller cells are known to support neuronal activity and maintain the proper functioning of the iBRB under normal conditions. They are involved in the control and homeostasis of K+ and other ions signaling molecules, and in the control of extracellular pH. Dysfunction of Müller cells may contribute to a breakdown of the iBRB in many pathological conditions, such as diabetes. Müller cells enhance the secretion of VEGF under hypoxic and inflammatory conditions. The *in-vitro* study has shown that VEGF-induced occluding phosphorylation and ubiquitination causes trafficking of tight junction and leads to increased retinal vascular permeability.

The astrocytes originate from the optic nerve and migrate to the nerve fiber layer during development. They are closely associated with the retinal capillary vessels and help to maintain capillary integrity. Astrocytes are known to increase the barrier properties of the retinal vascular endothelium by enhancing the expression of the tight junction protein ZO-1 and modifying endothelial morphology. Following systemic drug administration, drugs can easily enter into the choroid since choroid is highly vascularized tissue compared to retina. The choriocapillaris is fenestrated resulting in rapid equilibration of drug molecules present in the bloodstream with the extravascular space of the choroid. Therefore, oBRB (RPE) restricts further entry of drugs from the choroid into the retina. RPE is a monolayer of highly specialized hexagonal-shaped cells, located between the sensory retina and the choroid. The tight junctions of the RPE efficiently restrict intercellular permeation into the sensory retina.

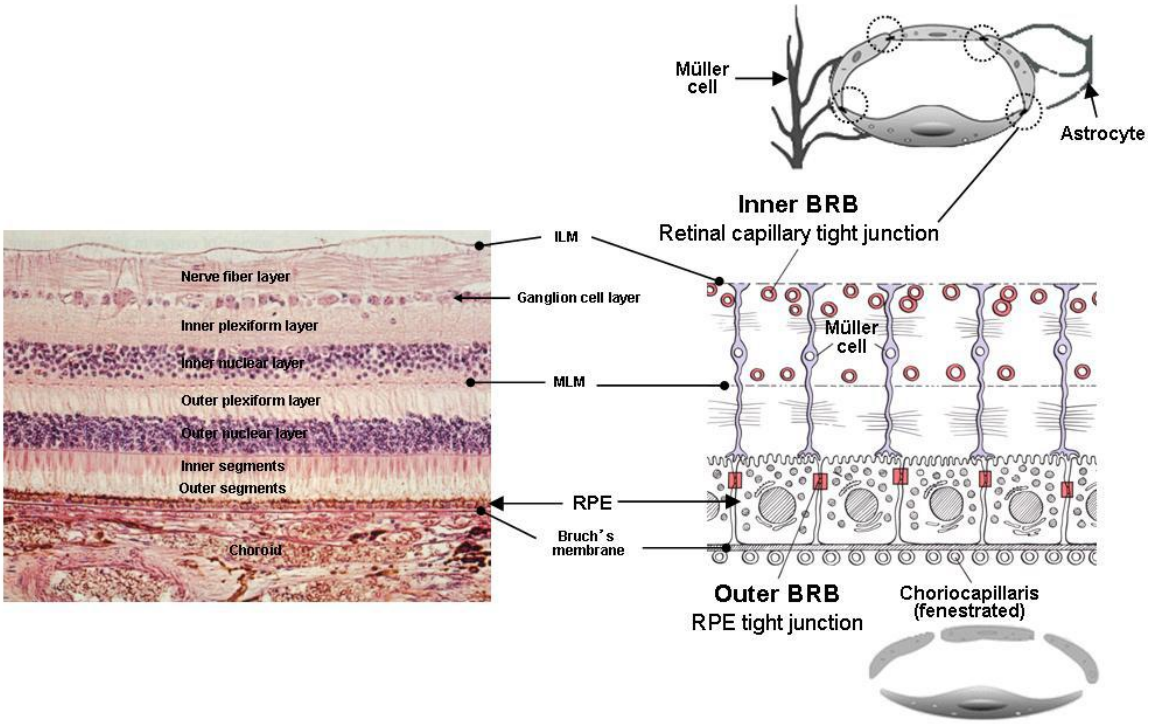

Figure No. 5: Schematic diagram of the blood-retinal barrier, and capillary wall in the retina and the choroid

Table No. 1: Barriers for the Ocular drug 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
Structural Composition	Mucous membrane Epithelium Vasculature	5 layers Epithelium Bowman's membrane Stomata Descemet's membrane Endothelium	Collagen fibers Water Proteoglycans Monopolysaccharides Elastic fibers Fibroblast

Table No. 2: Commonly Used Fluoroquinolones in Ophthalmic Delivery

Antibiotic generation	Example	Activity
1st GENERATION	Nalidixic acid	Have limited activity against gram-negative & gram-positive organism
2nd GENERATION	Oxolinic acid Cinoxacin Pipemic acid	Improvement in gram-negative coverage including Antipseudomonal activity. Shows limited activity against Gram-positive organisms.
3rd GENERATION	Norfloxacin Ciprofloxacin Levofloxacin Ofloxacin	Having antipseudomonal activity against gram-negative bacilli
4th GENERATION	Ciprofloxacin Moxifloxacin Gatifloxacin	Having a dual mechanism of action in gram-positive bacteria also reducing efflux from the bacterial cell. The improved spectrum of Activity

MECHANISM OF CONTROLLED DRUG RELEASE INTO THE EYE

The mechanism of controlled drug release into the eye is as follows:

A. Diffusion, B. Osmosis, C. Bio-erosion.

A. Diffusion

In the Diffusion mechanism, the drug is released continuously at a controlled rate through the membrane into the tear fluid. If the insert is formed of a solid non-erodible body with pores and dispersed drug. The release of the drug can take place via diffusion through the pores. The controlled release can be further regulated by the gradual dissolution of a solid dispersed drug within this matrix as a result of inward diffusion of aqueous solutions. In a soluble device, true dissolution occurs mainly through polymer swelling. In swelling-controlled devices, the active agent is homogeneously dispersed in a glassy polymer. Since glassy polymers are essentially drug impermeable, no diffusion through the dry matrix occurs. When

the insert is placed in the eye, water from the tear fluid begins to penetrate the matrix, then swelling and consequently, polymer chain relaxation and drug diffusion takes place. The dissolution of the matrix, which follows the swelling process, depends on polymer structure: linear amorphous polymers dissolve much faster than cross-linked or partially crystalline polymers. Release from these devices follows in general Fickian 'square root of time' kinetics; in some instances, however, known as case II transport, zero-order kinetics has been observed.

B. Osmosis

In the Osmosis mechanism, the insert comprises a transverse impermeable elastic membrane dividing the interior of the insert into a first compartment and a second compartment; the first the compartment is bounded by a semi-permeable membrane and the impermeable elastic membrane, and the second compartment is bounded by an impermeable material and the elastic membrane. There is a drug release aperture in the impermeable wall of the insert.

The first compartment contains a solute that cannot pass through the semi-permeable membrane and the second compartment provides a reservoir for the drug which again is in liquid or gel form. When the insert is placed in the aqueous environment of the eye, water diffuses into the first compartment and stretches the elastic membrane to expand the first compartment and contract the second compartment so that the drug is forced through the drug release aperture.

C. Bioerosion

In the Bioerosion mechanism, the configuration of the body of the insert is constituted from a matrix of bioerodible material in which the drug is dispersed. Contact of the insert with tear fluid results in controlled sustained release of the drug by bioerosion of the matrix. The drug may be dispersed uniformly throughout the matrix but it is believed a more controlled release is obtained if the drug is superficially concentrated in the matrix. In truly erodible or E-type devices, the rate of drug release is controlled by a chemical or enzymatic hydrolytic reaction that leads to polymer solubilization, or degradation to smaller, water-soluble molecules. These polymers, as specified by Heller, may undergo bulk or surface hydrolysis. Erodible inserts undergoing surface hydrolysis can display zero-order release kinetics; provided that the devices maintain a constant surface geometry and that the drug is poorly water-soluble.

ABSORPTION OF DRUGS IN THE EYE

Topical delivery into the cul-de-sac is, by far, the most common route of ocular drug delivery, absorption from this site.

1. Corneal

2. Non-corneal routes.

Maximum absorption takes place through the cornea, which leads the drug into the aqueous humor. The non-corneal route involves absorption across the sclera and conjunctiva, this route is not productive as it restrains the entry of the drug into the intraocular tissues.

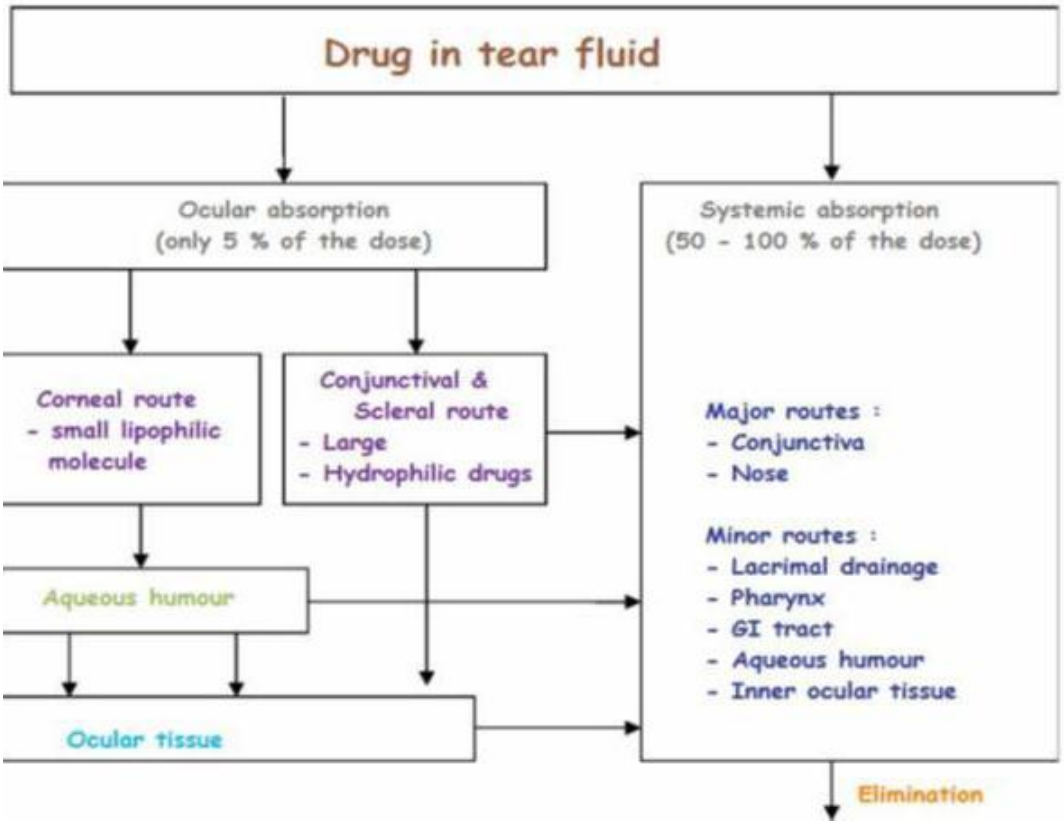

Figure No. 6: Ocular Drug Absorption

Physicochemical properties of the drug

Transcellular or the Paracellular pathway is the main route for drugs to penetrate across the corneal epithelium. The paracellular pathway involves passive diffusion through the intercellular spaces. (Hydrophilic drugs). The transcellular pathway involves the partitioning

of the drugs to cells (lipophilic drugs). For both pathways, the passive diffusion along their concentration gradient is the main permeation mechanism.

OPTHALMIC INSERTS[9,17,18]

Ophthalmic inserts are sterile preparations with a solid or a semisolid consistency, and whose size and shape are specially designed for ophthalmic application. The inserts are placed in the lower fornix and less frequently, in the upper fornix oron the cornea. Ocular inserts can overcome the disadvantages reported with traditional. Ophthalmic systems like eye drops, suspensions, and ointments. The typical pulse entry type drug release behavior observed with eye drops, suspensions, and ointments are replaced by more controlled, sustained, and continuous drug delivery using a controlled release ocular drug delivery system.

In recent years, there has been an explosion of interest in the polymer-based delivery devices, adding a further dimension to topical drug delivery thereby promoting the use of polymers such as collagen and fibrin fabricated into erodible inserts for placement in the cul-de-sac.

Utilization of the principles of controlled release as embodied by ocular inserts offers an attractive approach to the problem of prolonging precorneal drug residence times. Ocular inserts also offer the potential advantage of improving patient compliance by reducing the dosing frequency. The main objective of the ophthalmic inserts is to increase the contact time between the preparation and the conjunctival tissue to ensure a sustained release suited to topical or systemic treatment. They are composed of polymeric support with or without drugs, the latter being incorporated as dispersion or a solution in the polymeric support.

Table No. 3: Types of Occular Inserts

Types	Description
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 but water-insoluble. 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.

Classification of ophthalmic inserts:- Based upon their solubility behavior.

(1) Insoluble:- a) Diffusion b) Osmotic and c) Contact lens

(2) Soluble:- a) Based on natural polymers e.g. collagen

b) Based on synthetic or semi-synthetic polymers e.g. cellulose derivatives like HPMC, HPC, MC etc.

Bioerodible

a. Insoluble ocuserts

Only the insoluble types can usually deliver drugs by a variety of methods sat controlled, predetermined rate, but need removal from the eye when empty.

b. Soluble ocuserts

Soluble(S) inserts generally defined as erodible (E), monolithic polymeric devices that undergo gradual dissolution while releasing the drug and do not need removal. True dissolution occurs mainly through polymer swelling, while erosion corresponds to a chemical

or enzymatic hydrolytic process. In swelling-controlled devices the active agent is homogeneously dispersed in a glassy polymer, glassy polymers are essentially drug impermeable so no diffusion takes place through the dry matrix. When the insert is placed in the eye water from the tear fluid begins to penetrate the matrix, then swelling and consequently polymer chain relaxation and drug diffusion take place releasing their drug content.

I. Insoluble ocular inserts

Inserts made up of insoluble polymer can be classified into two categories:

A. Reservoir systems B. Matrix systems

A. Reservoir systems

Each class of inserts shows different drug release profiles. The reservoir systems can release drugs either by diffusion or by an osmotic process. It contains, respectively, a liquid, a gel, a colloid, a semisolid, a solid matrix, or a carrier containing the drug. Carriers are made of hydrophobic, hydrophilic, organic, natural, or synthetic polymers.

They have been sub-classified into:

1. Diffusional inserts, e.g., 'Ocuserts'; 2. Osmotic inserts.

1. Diffusional insert or Ocuserts

Ocusert system is a novel ocular drug delivery system based on a porous membrane. The release of drug from diffusional inserts/Ocusert is based on a diffusional release mechanism. It consists of a central reservoir of drug enclosed in a specially designed micro porous membranes allowing the drug to diffuse from the reservoir at a precisely determined rate.

As pointed out by Urquhart, the Ocusert pilocarpine ocular therapeutic system, developed by Alza Corporation, is notable for several reasons. This product was the first rate-controlled, the rate specified pharmaceutical for which the strength is indicated on the label by the rate(s) of drug delivery *in-vivo*, rather than by the amount of contained drug. It provides predictable, time-independent concentrations of drug in the target tissues, a feat impossible to achieve with conventional, quantity-specified, pulse entry ophthalmic medications. The near-constant

drug concentration in ocular tissues markedly improves the selectivity of the action of pilocarpine.

A major advantage is that two disturbing side effects of the drug, miosis, and myopia, are significantly reduced, while the reduction of intraocular pressure (IOP) in glaucoma patients is fully maintained. Two types of Ocusert are available: the Pilo-20 and Pilo-40. The former delivers the drug at a rate of 20 µg/h for 7 days, and the latter at a rate of 40 µg/h for 7 days. This device, which is certainly well familiar to the readers of this review, has been exhaustively described and discussed in a series of specialized papers. Briefly, it consists of a reservoir containing pilocarpine alginate enclosed above and below by thin EVA (ethylene-vinyl acetate) membranes. The insert is encircled by a retaining ring of the same material, impregnated with titanium dioxide. The dimensions of the elliptical device are (for the 20 µg/h system): major axis- 13.4 mm, minor axis-5.7 mm, thickness-0.3 mm. The membranes are the same in both systems, but to obtain a higher release rate, the reservoir of the 40 µg/h system contains about 90 mg of di (2- Ethylhexyl) phthalate as a flux enhancer.

Osmotic inserts

The osmotic inserts are generally composed of a central part surrounded by a peripheral part and are of two types:

Type 1: The central part is composed of a single reservoir of a drug with or without an additional osmotic solute dispersed throughout a polymeric matrix so that the drug is surrounded by the polymer as discrete small deposits. The second peripheral part of these inserts comprises a covering film made of an insoluble semipermeable polymer. The osmotic pressure against the polymer matrix causes its rupture in the form of apertures. The drug is then released through these apertures from the deposits near the surface of the device.

Type 2: The central part is composed of two distinct compartments. The drug and the osmotic solutes are placed in two separate compartments, the drug reservoir is surrounded by an elastic impermeable membrane and the osmotic solute reservoir by a semi-permeable membrane. The second peripheral part is similar to that of type 1. The tear diffuses into the osmotic compartment inducing an osmotic pressure that stretches the elastic membrane and contracts the compartment including the drug so that the active component is forced through the single drug release aperture.

B. Matrix systems

The second category, matrix system, is a particular group of insoluble ophthalmic devices mainly represented by contact lenses. It comprises of covalently cross-linked hydrophilic or hydrophobic polymer that forms a three-dimensional network or matrix capable of retaining water, aqueous drug solution, or solid components. The hydrophilic or hydrophobic polymer swells by absorbing water. The swelling caused by the osmotic pressure of the polymer segments is opposed by the elastic retroactive forces arising along the chains or crosslinks are stretched until a final swelling (equilibrium) is reached.

Contact lenses

Contact lenses are shaped structures and initially used for vision correction. Their use has been extended as potential drug delivery devices by presoaking them in drug solutions. The main advantage of this system is the possibility of correcting vision and releasing drugs simultaneously. Refojo has proposed a subdivision of contact lenses into 5 groups.

a) Rigid

b) Semi-rigid

c) Elastomeric

d) Soft hydrophilic

e) Bio-polymeric

Rigid contact lenses have the disadvantage of being composed of polymers (e.g., polymethyl methacrylic acid) hardly permeable to moisture and oxygen, a problem that has been overcome by using gas permeable polymers such as cellulose acetate butyrate. However, these systems are not suitable for prolonged delivery of drugs to the eye and their rigidity makes them very uncomfortable to wear. For this reason, soft hydrophilic contact lenses were developed for prolonged release of drugs such as pilocarpine, chloramphenicol, and tetracycline prednisolone sodium phosphate. The most commonly used polymer in the composition of these types of lenses is hydroxyethyl methyl methacrylic acid copolymerized with poly (vinyl pyrrolidone) or ethylene glycol dimethacrylic acid (EGDM). Poly (vinyl pyrrolidone) is used for increasing water of hydration, while EGDM is used to decrease the

water of hydration. The soft hydrophilic contact lenses are very popular because they are easy to fit and are tolerated better. The drug incorporation into contact lenses depends on whether their structure is hydrophilic or hydrophobic. When contact lens (including 35 to 80% water) is soaked in the solution, it absorbs the drug. Drug release depends markedly on the amount of drug, the soaking time of the contact lens, and the drug concentration in the soaking solution.

II. Soluble ocular inserts

These soluble inserts offer the advantage of being entirely soluble so that they do not need to be removed from their site of application, thus limiting the intervention to insertion only. They can be broadly divided into two types, the first one being based on natural polymers and the other on synthetic or semi-synthetic polymers.

A. Natural polymers

The first type of soluble inserts is based on natural polymer used to produce soluble ophthalmic inserts are preferably collagen. The therapeutic agent is preferably absorbed by soaking the insert in a solution containing the drug, drying, and re-hydrating it before use on the eye. The amount of drug loaded will depend on the amount of binding agent present, the concentration of the drug solution into which the composite is soaked as well as the duration of the soaking. As the collagen dissolves, the drug is gradually released from the interstics between the collagen molecules.

B. Synthetic and semi-synthetic polymer [25]

The second type of soluble insert is usually based on semi-synthetic polymers (e.g., cellulose derivatives) or synthetic polymers such as polyvinyl alcohol. A decrease of release rate can be obtained by using Eudragit, a polymer normally used for enteric coating, as a coating agent of the insert. Saettone *et al*. have observed in rabbits that Eudragit coated inserts containing pilocarpine-induced a miotic effect of a longer duration, compared to the corresponding uncoated ones. However, the inherent problems encountered with these soluble inserts are the rapid penetration of the lachrymal fluid into the device, the blurred vision caused by the solubilization of insert components, and the risk of expulsion due to the initial dry and glassy consistency of the device. Ethylcellulose, a hydrophobic polymer, can be used to decrease the deformation of the insert and thus to prevent blurred vision. As for the

risk of expulsion, several authors have incorporated carbomer, a strong but well-tolerated bio-adhesive polymer.

The soluble inserts offer the additional advantage of being of a generally simple design, of being based on products well adapted for ophthalmic use and easily processed by conventional methods. The main advantage is the decreased release rate but still controlled by diffusion.

III. Bio-erodible ocular inserts

These inserts are formed by bio-erodible polymers (e.g., cross-linked gelatin derivatives, polyester derivatives) that undergo hydrolysis of chemical bonds and hence dissolution. The great advantage of these bio-erodible polymers is the possibility of modulating their erosion rate by modifying their final structure during synthesis and by addition of anionic or cationic surfactants.

A cross-linked gelatin insert was used by Attia *et al*. to increase the bioavailability of dexamethasone in the rabbit eye. The dexamethasone levels in the aqueous humor were found to be four-fold greater compared to a dexamethasone suspension. However, erodible systems can have significantly variable erosion rates based on individual patient physiology and lachrymation patterns, while degradation products and residual solvents used during the polymer preparation can cause an inflammatory reaction. In the following paragraphs, some important ocular inserts are discussed which are available commercially (SODI) or in advanced stages of development (collagen shields, Ocufit, NODS, and Minidisc).

Soluble ophthalmic drug insert

Soluble ophthalmic drug insert (SODI) is a small oval wafer, which was developed by soviet scientists for cosmonauts who could not use eye drops in weightless conditions. SODI is together with the collagen shields, the first modern revival of the gelatin 'lamellae', which disappeared from pharmacopeias in the late forties. The SODIs is the result of a vast collaborative effort between eminent Russian chemists and ophthalmologists, and led eventually (in 1976) to the development of a new soluble copolymer of acrylamide, *N* - vinylpyrrolidone and ethyl acrylate (ratio 0.25: 0.25: 0.5), designated ABE. A comparison of medicated eye films prepared with different polymers showed that ABE produced the highest concentration of drugs in rabbit ocular tissues. After large-scale preclinical and clinical

testing, the ABE copolymer was used for the industrial manufacture of the SODI in the form of sterile thin films of an oval shape (9 x 4.5 mm, thickness 0.35 mm), weighing 15-16 mg, and color-coded for different drugs (over 20 common ophthalmic drugs, or drug combinations). After the introduction into the upper conjunctival sac, a SODI softens in l0-15 s, conforming to the shape of the eyeball. In the next l0-15 min the film turns into a polymer clot, which gradually dissolves within 1 h while releasing the drug. The sensation of an 'extraneous body' in the eye disappears in 5- 15 min.

Collagen shields

Collagen is the structural protein of bones, tendons, ligaments, and skin and comprises more than 25% of the total body protein in mammals. This protein, which is derived from intestinal collagen, has several biomedical applications, the main of which is probably catgut suture. Bloomfield *et al*. are credited for first suggesting, in 1977 and 1978, the use of collagen inserts as tear substitutes and as delivery systems for gentamicin. They compared the levels of gentamicin in tears, cornea, and sclera of the rabbit eye after application of a collagen insert, drops, an ointment, or following subconjunctival administration. After 3 h, they found that the collagen insert gave the highest concentration of gentamicin in the tear film and the tissue. Other treatments using collagen shields impregnated with gentamicin and dexamethasone have been described. In rabbits, aqueous humor levels of dexamethasone and gentamicin achieved with collagen shields were compared to subconjunctival injections. The authors concluded that the use of collagen shields impregnated with gentamicin-dexamethasone was comparable to the subconjunctival delivery of these drugs over a 10-h period. Some drawbacks of these devices, however, need mentioning. To apply the collagen shield, the cornea is anesthetized while the physician uses a blunt forceps to insert the hydrated or unhydrated shield. Contrary to medicated contact lenses, collagen shields often produce some discomfort and interfere with vision. In rabbits, collagen shields have been found to exacerbate ulcerations of alkali-burned corneas. [A new preparation referred to as collasomes consists of small pieces (1 mm x 2 mm x 0.1 mm) of collagen suspended in a 1% methylcellulose vehicle. Kaufman and co-workers recently reported that collasomes provide the same therapeutic advantages of the shields (high and sustained levels of drugs and/or lubricants to the cornea), while not presenting their disadvantages.

OCUFIT

The Ocufit is a sustained release, the rod-shaped device made of silicone elastomer, patented in1992, and currently developed by Escalon Ophthalmics Inc. (Skillman, NJ). It was designed to fit the shape and size of the human conjunctival fornix. Accordingly, it does not exceed 1.9 mm in diameter and 25-30 mm in length, although smaller sizes for children and newborn babies are planned. The superiority of the cylindrical shape can be traced in an earlier paper by Katz and Blackman. They reported the effect of the size and shape of the inserts on tolerance and retention by human volunteers. These workers found that the expulsion of rod-shaped units was significantly ($P < 0.01$) less frequent than the expulsion of an oval, flat inserts. A typical example of a rod-shaped insert is the Lacrisert (Merck and Co., Inc.), a cellulosic device used to treat dry-eye patients. The insoluble Ocufit reportedly combines two important features, long retention and sustained drug release. When placed in the upper fornix of volunteers, placebo devices were retained for 2 weeks or more in 70% of the cases. Moreover, active disease (bacterial, allergic and adenoviral conjunctivitis, trachoma, episcleritis, anterior uveitis, cornea1 ulcers or scars) did not overtly affect the ability of the patients to retain the inserts. Tetracycline-loaded inserts released *in vitro* 45% of the drug over the 14 days with an initial burst on the first day followed by a constant rate over the remaining period.

THE MINIDISC OCULAR THERAPEUTIC SYSTEM

This monolithic polymeric device, originally described by Bawa *et al*. (Bausch and Lomb Rochester, New York) and referred to as Minidisc ocular therapeutic system (OTS), is shaped like a miniature (diameter 4-5 mm) contact lens, with a convex and a concave face, the latter conforming substantially to the sclera of the eye. The particular size and shape reportedly allow easy placement of the device under the upper or lower lid without compromising comfort, vision, or oxygen permeability. When compared with another standard insert, the Lacrisert, the Minidisc was reported to require less time and less manual dexterity for insertion. Different versions of the device have been evaluated, such as non-erodible hydrophilic, non-erodible hydrophobic, and erodible. *In vitro* tests showed that the hydrophilic OTS (based on polyhydroxymethyl methacrylate) released sulfisoxazole for 118 h, while the hydrophobic unit (based on a proprietary Bausch and Lomb pre-polymer) released gentamicin sulfate for more than 320 h. Clinical trials on placebo units demonstrated that the devices were well tolerated when placed either in the upper or lower conjunctival sac.

In the eyes of healthy volunteers, the hydrophilic OTS released sulfisoxazole continuously for 3 days. Further studies conducted on the hydrophobic Minidisc showed that gentamicin sulfate was efficiently released in rabbit eyes for 14 days.

Table No. 4: Ocular Insert Devices

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

ADVANTAGES OF OCULAR INSERTS [22,23,24]

Ocular inserts offer several advantages, which can be summarized as follows:

- Increased ocular residence, hence a prolonged drug activity and a higher bioavailability concerning standard vehicles;

- Possibility of releasing drugs at a slow, constant rate;

- Accurate dosing (contrary to eye drops that can be improperly instilled by the patient and are partially lost after administration, each insert can be made to contain a precise dose which is fully retained at the administration site);

- Reduction of systemic absorption (which occurs freely with eye drops via the nasolacrimal duct and nasal mucosa);

- Better patient compliance, resulting from a reduced frequency of administration and a lower incidence of visual and systemic side-effects;

- Possibility of targeting internal ocular tissues through non-corneal (conjunctival scleral) routes;

- Increased shelf life concerning aqueous solutions;

- Exclusion of preservatives, thus reducing the risk of sensitivity reactions;

- Possibility of incorporating various novel chemical/ technological approaches. Such as pro-drugs, mucoadhesives, permeation enhancers, microparticulate, salts acting as buffers, etc.

The potential advantages offered by inserts clearly explain why an active interest has been dedicated to these dosage forms in recent years, and why efforts to introduce them to the pharmaceutical market continue. Of course, not all of the benefits listed above can be present in a single, ideal device. Each type of insert represents a compromise between the desirable properties inherent to solid dosage forms and negative constraints imposed by the structure and components of the insert itself, by fabrication costs, as well as by the physical/physiological constraints of the application site.

DISADVANTAGES OF OCULAR INSERTS [22,23,24]

The disadvantages of ocular inserts are as follows:

- A capital disadvantage of ocular inserts resides in their ‘solidity’, i.e., in the fact that they are felt by the (often oversensitive) patients as an extraneous body in the eye. This may constitute a formidable physical and psychological barrier to user acceptance and compliance.

- Their movement around the eye, in rare instances, the simple removal is made more difficult by unwanted migration of the insert to the upper fornix,

- The occasional inadvertent loss during sleep or while rubbing the eyes,

- Their interference with vision, and
- Difficult placement of the ocular inserts (and removal, for insoluble types)

MARKETED PREPARATIONS:

MARKETED PRODUCTS(3)

Brand Name	Drug	Dosage Form	Use
DICHOL	Carbachol	Sterile solution and prefilled syringes	Used in ophthalmic surgery
REFRESH TEARS®	Hydroxypropyl-methylcelluose	Drops	Eye lubricants and dryness of eye
GELTEAR/ VISCOTEAR	Corbomer	Bioadhesive gel	Treatment of soreness, burning
Timolol® XE	Timolol maleate	In-situ gel	Keratoconjuctivitis
PRED FORTE®	prednisolone acetate	suspensions	Antiallergic and anti-inflammatory
ACIVIR EYE	Acyclovir	Ointment	Anti-infective
REFRESH® Classic	Artificial tear fluid	convenient single use vials	Moisturizes and relieves dry eyes
RESTASIS®	Cyclosporine	emulsion	Chronic dry eye diseases

CONCLUSION:

The ocular insert represents a significant advancement in the therapy of eye disease. Ocular inserts are defined as sterile, thin, multilayered, drug-impregnated, solid, or semisolid consistency devices placed into the cul -de- sac or conjunctiva sac, whose size and shape are specially designed for ophthalmic application. They are composed of polymeric support that may or may not contain a drug. Advantages with ocuserts such as Accurate dosing Capacity to provide a constant rate and prolong drug release thus a better efficacy. Increasing contact time and thus improving bioavailability. Possible reduction of systemic absorption and thus reduced systemic adverse effects. Reduced frequency of administrations and thus better patient compliance with a lower incidence of visual side effects. Administration of an accurate in the eye and thus a better therapy Possibility of targeting internal ocular tissues through non-corneal conjunctival – sclera penetration routes; and Increased shelf life concerning eye-drops due to the absence of water.

Advantages of inserts as dosage form Ease of handling and insertion Lack of expulsion during wear Reproducibility of release kinetics Applicability to a variety of drugs Non-interference with vision and oxygen permeability, Sterility, Stability, Ease of manufacture, etc.

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