

Ocular Drug Delivery System-A Review Based on Ocuserts

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ABSTRACT

The field of Ocular drug delivery is one of the interesting and challenging endeavors facing the pharmaceutical scientist. The most frequently used dosage forms i.e. ophthalmic solutions and suspensions are compromised in their effectiveness by several limitations, leading to poor ocular bioavailability. In ocular inserts the films are directly applied in the cul-de-sac, improving ocular bioavailability by increasing the duration of contact with corneal tissue, thereby reducing the frequency of administration. Ocular inserts are defined as preparations with a solid or semisolid consistency, whose size and shape are especially designed for ophthalmic application (i.e., rods or shields). Ocular diseases require localized administration of drugs to the tissues around the ocular cavity. In the recent years, there has been explosion of interest in the polymer based delivery devices. Utilization of the principles of controlled release as embodied by ocular inserts offers an attractive approach to the problem of prolonging pre-corneal drug residence times. In the present update, the authors discuss the basic concept of ocular inserts as drug delivery system and examine the few inserts, which are available in the market or are being developed by pharmaceutical companies for drug delivery. The article discusses about the various structures of the eye, its anatomy with the various diagrams of it. This article further states the classification and the various mechanisms of drug diffusion into an eye with special attention to biological/clinical performances, and potential for future applications and developments.

Keywords: Anatomy of eye, function and parts of eye, classification of various ocuserts, basic study on various ocuserts, mechanisms of drug diffusion.

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INTRODUCTION

The eye is a unique organ from anatomical and physiological point of view, in that it contains several highly different structures with specific physiologic function. For instance, the cornea and the crystalline lens are the only tissues in the body in addition to cartilage which have no blood supply, whereas choroid and ciliary processes are highly vascularized and exhibit very high blood flows. The retina with the optic nerve, an extension of the diencephalon of the central nervous system, has a very specific function in the visual perception and transduction phenomena. The eye has special attributes that allow local drug delivery into an eye and non-invasive clinical assessment of disease, but it is also a highly complex and unique organ, which makes understanding disease pathogenesis

and ocular drug delivery challenging. The specific aim of designing a therapeutic system is to deliver and achieves the optimal concentration of a drug entity at the active site for the appropriate duration. Ocular disposition and elimination of a therapeutic agent is dependent upon its physicochemical properties as well as the relevant ocular anatomy and physiology. The conventional ophthalmic solutions, suspension, and ointment dosage forms are no longer sufficient to combat these diseases.

In ocular inserts the films are directly applied in the cul-de-sac, improving ocular bioavailability by increasing the duration of contact within the corneal tissue, thereby reducing the frequency of administration.

Eye Structures

Anatomy of Eye [1-4]

The eye is essentially a globe suspended in the ocular orbit, specialized for sight through an arrangement of multiple tissues that function to focus, transmit and detect incoming light.

It is a spherical structure with a wall consisting of three layers

- 1.Outer sclera
- 2.Middle choroids layer
- 3.The inner retina

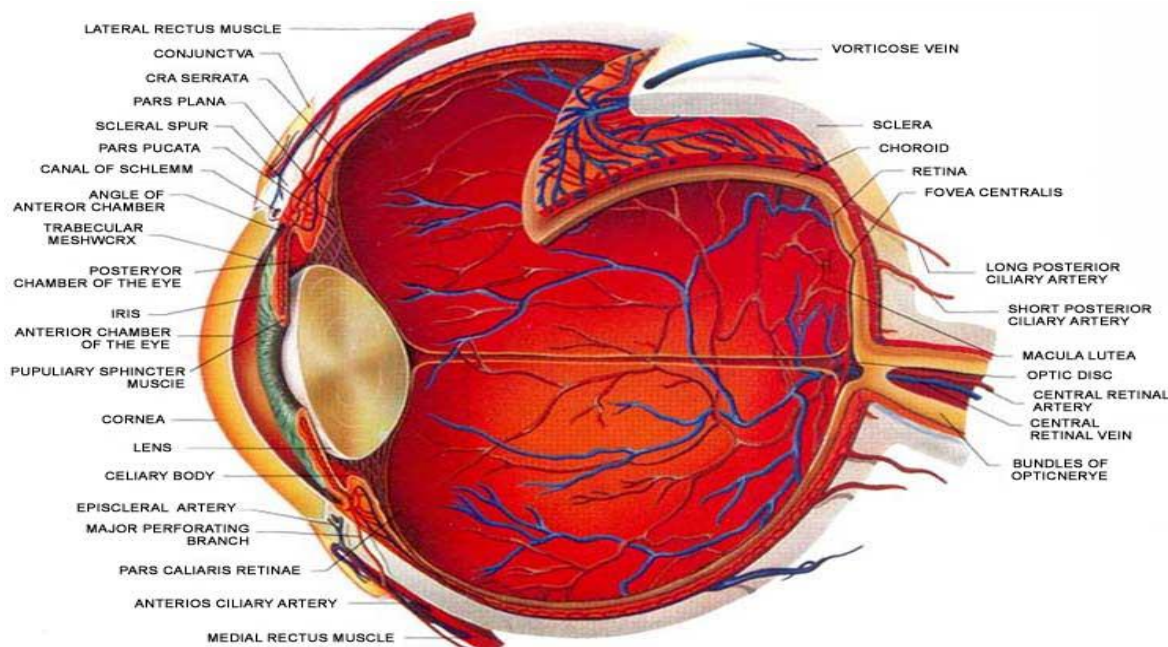


Figure 1: Structure of Eye Ball

1.Sclera: The sclera is commonly known as “the white of the eye.” It is the tough, opaque tissue that serves as the eye’s protective outer coat. Six tiny muscles connect to it around the eye and control the eye’s movements. The optic nerve is attached to the sclera at the very back of the eye.

In children, the sclera is thinner and more translucent, allowing the underlying tissue to show through and giving it a bluish cast. As we age, the sclera tends to become more yellow.

2.Choroid layer: The choroid lies between the retina and sclera. It is composed of layers of blood vessels that nourish the back of the eye. The choroid connects with the ciliary body toward the front of the eye and is attached to edges of the optic nerve at the back of the eye. It is situated inside the sclera, contains many blood vessels and is modified at the front of eye as the pigmented iris. The biconvex lens is situated just behind the pupil. The chamber behind the lens is filled with the vitreous humor, a gelatinous substance

occupying 80% of the eye ball. The anterior and posterior chambers are situated between the cornea and iris, and iris and lens, respectively and filled with aqueous humor. At the back of the eye is the light detecting retina.

3.The Cornea:

The cornea is the transparent, dome-shaped window covering the front of the eye. It is a powerful refracting surface, providing 2/3 of the eye’s focusing power. Like the crystal on a watch, it gives us a clear window to look through. Because there are no blood vessels in the cornea, it is normally clear and has a shiny surface. The adult cornea is only about 1/2 millimeter thick and is comprised of 5 layers: epithelium, Bowman’s membrane, stroma, Descemet’s membrane and the endothelium.

The cornea is an optically transparent tissue that conveys images to the back of the eye and covers about one-sixth of the total surface area of the eye ball. The cornea is considered to be the main pathway for the permeation of drugs into

the eye. It is 0.5 mm thick in the central region, increasing to approx. 0.7 mm at the periphery and composed of the five layers.

- i. The Epithelium
 - ii. The Bowman's Membrane
 - iii. The stroma or Substantia Propria
 - iv. The Descemet's Membrane
 - v. The Corneal Endothelium
- I. The Epithelium:-As the cornea's outermost region - comprising about 10 percent of the tissue's thickness - the epithelium functions primarily to: (1) block the passage of foreign material - such as dust or water - into the eye and other layers of the cornea (2) provide a smooth surface that absorbs oxygen and other needed cell nutrients that are contained in tears. This layer, which is about five cells deep, is filled with thousands of tiny nerve endings that make the cornea extremely sensitive to pain when rubbed or scratched.
 - II. The Bowman's Membrane: - This is an acellular homogenous sheet, about 8-14 μm thick. This is positioned between the

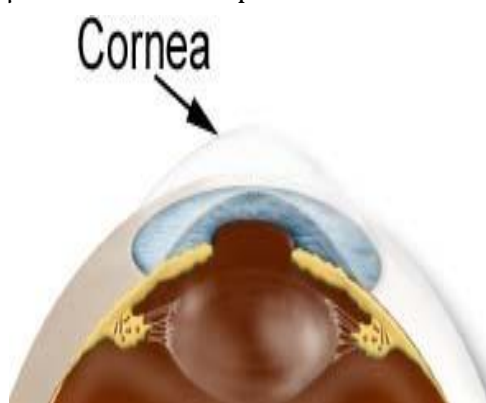


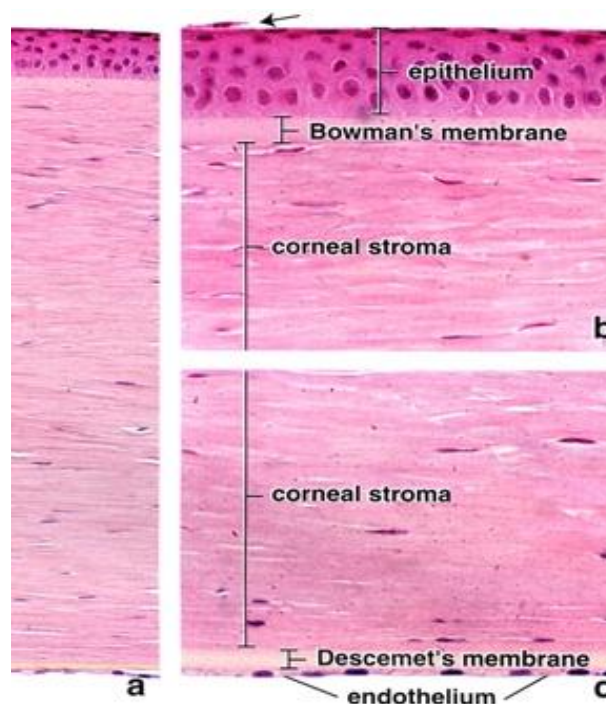
Figure 2: Cornea structures

4. The Conjunctiva:

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

basement membrane of the epithelium and the stroma.

- III. The stroma or Substantia Propria: - Located behind the epithelium, the stroma comprises about 90 percent of the cornea. It consists primarily of water (78 percent); layered protein fibers (16 percent) that give the cornea its strength, elasticity, and form; and cells that nourish it. The unique shape, arrangement, and spacing of the protein fibers are essential in producing the cornea's light-conducting transparency.
- IV. The Descemet's Membrane: This is secreted by the endothelium, lies between the stroma and the endothelium.
- V. The Corneal Endothelium: This single layer of cells is located between the stroma and the aqueous humor. Because the stroma tends to absorb water, the endothelium's primary task is to pump excess water out of the stroma. Without this pumping action, the stroma would swell with water, become hazy, and ultimately opaque.



outer regions of the cornea. The human conjunctiva is 2 to 30 times more permeable to the drugs than the cornea and it has been proposed that loss by this route is a major path for drug clearance.

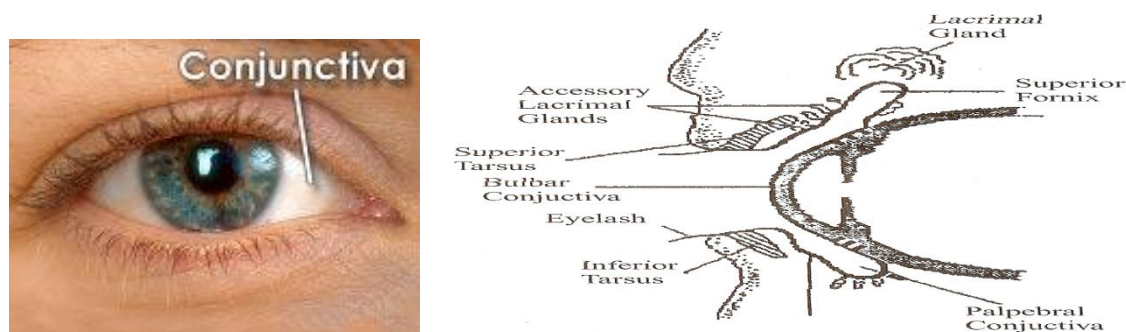


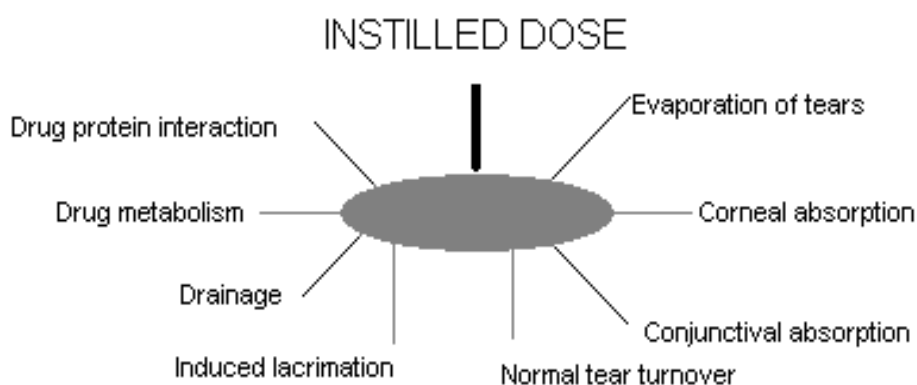
Figure 3: Conjunctiva structures.

1.2 Constraints to ocular drug delivery [5].

Precorneal constraints to ocular drug delivery which generally include solution drainage, lacrimation and tear dilution, tear turnover, and conjunctival absorption. Drug solution drainage from the precorneal area has been shown to be the most significant factor in reducing the ocular contact time and bioavailability of solution dosage forms. The instilled dose leaves within 5 minutes of instillation in humans. The natural tendency of the cul-de-sac is to reduce its volume to 7-10 microlitres. The typical ophthalmic dropper delivers 30 microlitres, most of which is rapidly lost through nasolacrimal drainage. The drainage may then allow the drug to be systemically absorbed across the nasal mucosa or the gastrointestinal tract. The drug, the pH, and the tonicity of the dosage forms can induce lacrimation. Normal human tear turnover is 16 % per minute and it also contributes to remove drug solution from the conjunctival cul-de-sac [5].

The physiological barriers to topical corneal absorption are very significant. As a result, the clinician is forced to recommend frequent doses of drugs at extremely high concentration. This pulsed type of dosing not only results in extreme fluctuations in ocular drug concentrations but may also cause many untoward side effects. Drugs are mainly eliminated from the precorneal lachrymal fluid by solution drainage, lacrimation, nonproductive absorption to the conjunctiva of the eye. These factors and the corneal barrier limit the penetration of the topically administered drug into the eye. Only a few percentages of applied doses are delivered into intraocular tissue, while the major parts (50-100%) of the doses are absorbed systemically. Precorneal constraints to ocular drug delivery include-

1. Spillage of drug by over flow
2. Dilution of drug by tears turn over
3. The Nasolachrymal Drainage/Systemic drug absorption
4. Conjunctival absorption
5. Enzymatic metabolism



Elimination of Instilled via Different Routes

a) Spillage of drug by over flow: - The normal volume of tears is 7ml and if blinking doesn't occur human eye can accommodate 30ml without spillage from the palpebral fissure. With an estimated drop volume of 50ml, 70% of administered dose is expelled from the eye by over flow and if blinking occurs only the residual volume approximately 10ml is left indicating that 90% of the dose is expelled.

b) Dilution of drug by tears turn over: - Tears turn out to have a major share in removing the drug solution from conjunctival cul-de-sac in an eye. Normal human tear turnover is

approximately 16% per minute, which is stimulated by many factors like drug entity, pH, and tonicity of dosage form and formulation adjuvant. These factors render topical application of ophthalmic solutions into cul-de-sac extremely inefficient.

Nasolachrymal Drainage or Systemic drug absorption: Most of the administered drug is lost through nasolachrymal drainage immediately after dosing. The drainage allows drug to be systemically absorbed across the nasal mucosa and the gastrointestinal tract leading to multifarious effects.

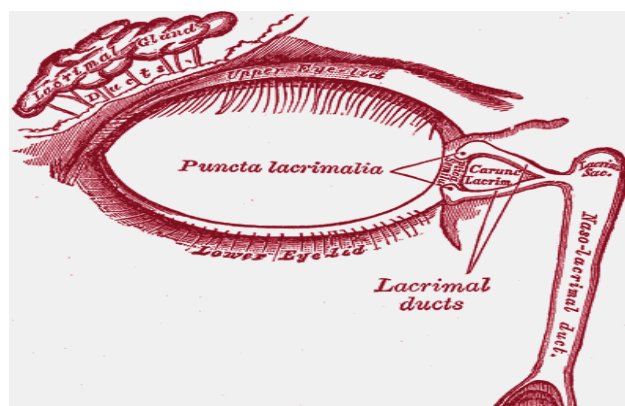


Figure 4: The nasolachrymal drainage system consists of three parts.

I. The secretory system: - It 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.

II. The distributive system: - It 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.

III. The excretory system: - The excretory part of the nasolachrymal drainage system consists of - lachrymal puncta, the superior, inferior and common canaliculi; the lachrymal sac; and the nasolachrymal duct. In humans, the two puncta are the openings of the lachrymal canaliculi and are situated on an elevated area known as the lachrymal papilla. It is thought that the tears are largely absorbed by the mucous membrane that lines the ducts and the

lachrymal sac; only small amount reaches the nasal passages.

The cul-de-sac of the eye normally holds around 7-9 μ l. If care is taken not to blink, the normal tear flow rate is 1 μ l /min and pH is maintained at 6.5-7.6.

C) Conjunctival absorption: Another mechanism that competes for the drug absorption into the eye is the superficial absorption of drug into pulpebral and bulbar conjunctiva with concomitant removal from the ocular tissues by peripheral blood stream.

d) Enzymatic metabolism: Enzymatic metabolism may operate in the precorneal space or in the cornea which, results in the further loss of those drugs entities possessing labile bonds. Clearly, the physiological barriers restraining the entry of the drug into the eye are formidable, restricting the bioavailability to 1-3% of the instilled dose [6].

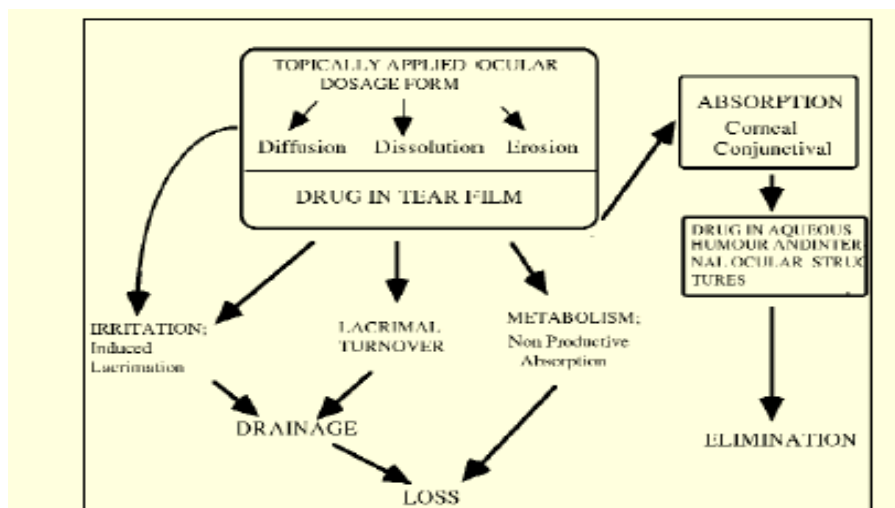


Figure 5: Schematic Illustration of the Ocular Disposition of Topically Applied Formulations

CLASSIFICATION OF OCULAR DRUG DELIVERY SYSTEMS [7-10]

A multitude of ocular dosage forms are available for delivery of drugs to the eye. These can be classified on the basis of their physical forms as follows:

1. Liquids: - Solutions, Suspensions, Sol to gel systems, Sprays
2. Solids: - Ocular inserts, Contact lenses, Corneal shield, Artificial tear inserts, Filter paper strips
3. Semi-solids: Ointments, Gels
4. Miscellaneous: Ocular iontophoresis, Vesicular systems, Muco-adhesive dosage forms, Particulates.

1. Liquids: - Liquids are the most popular and desirable state of dosage forms used for the eye. This is because the drug absorption is fastest from this state. The slow release of the drug from the suspended solids provides a sustained effect for a short duration of time.

- **Solutions and Suspensions**

Solutions are the pharmaceutical forms most widely used to administer drugs that must be active on the eye surface or in the eye after passage through the cornea or the conjunctiva. The drug in the solution is in the dissolved state and may be immediately active. This form also have disadvantages; the very short time the solution stays at the eye surface, its poor bioavailability (a major portion i.e. 75% is lost via nasolacrimal drainage), the instability of the dissolved drug, and the necessity of using preservatives. A considerable disadvantage of using eye

drops is the rapid elimination of the solution and their poor bioavailability. This rapid elimination is due to solution state of the preparation and may be influenced by the composition of the solution. The retention of a solution in the eye is influenced by viscosity, hydrogen ion concentration, the osmolality and the instilled volume.

Extensive work has been done to prolong ocular retention of drugs in the solution state by enhancing the viscosity or altering the pH of the solution (7-8).

Suspensions are called as dispersion of finely divided relatively insoluble drug substances in an aqueous vehicle which contains suitable amount of suspending and dispersing agents. Because of a tendency for the particle to be retained in the cul-de-sac, the contact time and duration of action of a suspension exceed those of a solution. While the retention increases with an increase in the particle size, so does the irritation of the eye. The rate of the dissolution of the suspended drugs increases with decreasing particle size. Thus an optimum particle size has to be selected for each type of drug, and it is recommended that the particles in an ophthalmic suspension should be not more than 10 μm in size.

- **Sol-Gel Systems**

The new concept of producing a gel in situ (e.g. in the cul-de-sac of the eye) was suggested for the first time in the early 1980s. It is widely accepted that increasing the viscosity of a drug formulation in the

precorneal region will lead to an increased bioavailability, due to slower drainage from the cornea. Several concepts for the in situ gelling systems have been investigated. These systems can be triggered by change in pH, temperature or by ion activation. An anionic polymeric dispersion shows a low viscosity up to pH 5.0, and will coacervate in contact with tear fluid due to presence of a carbonic buffer system which regulates the pH of tears. In situ gelling by a temperature change is produced when the temperature of polymeric dispersion is raised from 25 to 37°C. Ion activation of polymeric dispersion occurred due to the presence of cations in the tear fluid.

A solution containing 1.5% methyl cellulose and 0.3% carbopol at pH 4.0 and 25°C was found to be an easily flowing liquid capable of administration as a drop and showed an increase in viscosity and conversion to a gel on changing pH to 7.4 by addition of 0.5 M NaOH [9].

- Sprays [10,11]

Although not commonly used, some practitioners use mydriatics or cycloplegics alone or in combination in the form of eye spray. These sprays are used in the eye for dilating the pupil or for cycloplegics examination.

2. Solids: - The concept of using solids for the eye is based on providing sustained release characteristics.

- Ocular inserts

Ocular inserts are solid dosage form and can overcome the disadvantage reported with traditional ophthalmic systems like aqueous solutions, suspensions and ointments. The typical pulse entry type drug release behavior observed with ocular aqueous solutions (eye drops), suspensions and ointments is replaced by more controlled, sustained and continuous drug delivery using a controlled release ocular drug delivery system. The eye drops provided pulse entry pattern of drug administration in the eye which is characterized by transient overdose, relatively short period of acceptable dosing, followed by prolonged periods of under dosing. The ocular inserts maintain an effective drug concentration in the target tissues and yet minimize the number of applications consonant with the

function of controlled release systems. Limited popularity of ocular inserts has been attributed to psychological factors, such as reluctance of patients to abandon the traditional liquid and semisolid medications, and to occasional therapeutic failures (e.g. unnoticed expulsion from the eye, membrane ruptures etc.). A number of ocular inserts were prepared utilizing different techniques to make soluble, erodible, non-erodible, and hydrogel inserts [16-36].

- Insoluble insert

These are solid or semisolid sterile preparations. Of appropriate size and shape, designed to be inserted behind the eyelid or held on the eye and to deliver drugs for topical or systemic effects these are polymeric systems into which the drug is incorporated as a solution or dispersion.

- Ocular therapeutic system(OTS) or minidisc

These are controlled – release monolithic matrix-type devices consisting of a contoured disc with a convex front and a concave back surface, designed so as to fit the eyeball. The OTS can be made hydrophilic or hydrophobic to permit extended release of both water-soluble and water-insoluble drugs. They were reported to be very comfortable when placed behind the top or bottom of the eyelid.

- Contact lenses [37]

Contact lenses can absorb water soluble drugs when soaked in drug solutions. These drug saturated contact lenses are placed in the eye for releasing the drug for long period of time. The hydrophilic contact lenses can be used to prolong the ocular residence time of the drugs. In humans, the Bionite lens which was made from hydrophilic polymer (2-hydroxy ethyl methacrylate) has been shown to produce a greater penetration of fluorescein.

- Corneal shield

A non cross-linked homogenized, porcine scleral collagen slice is developed by a company (Bio-cor (Bausch and Lomb pharmaceuticals). Topically applied antibiotics have been used in conjunction with the shield to promote healing of corneal ulcers. Collagen shields are fabricated with foetal calf skin tissue and

originally developed as a corneal bandage. These devices, once softened by the tear fluid, form a thin pliable film that conforms exactly to the corneal surface, and undergoes dissolution up to 10, 24 or 72 hours. Collagen film proved as a promising carrier for ophthalmic drug delivery system because of its biological inertness, structural stability and good biocompatibility. Gussler et al investigated the delivery of trifluoro thymidine (TFT) in collagen shields and in topical drops in the cornea of normal rabbits and corneas with experimental epithelial defects. It was found that highest drug concentrations were found in the eyes treated with shields as compared to eye drops [38].

- Artificial tear inserts [39].

A rod shaped pellet of hydroxypropyl cellulose without preservative is commercially available (Lacrisert). This device is designed as a sustained release artificial tear for the treatment of dry eye disorders. It was developed by Merck, Sharp and Dohme in 1981.

- Filter paper strips

Sodium fluorescein and rose Bengal dyes are commercially available as drug impregnated filter paper strips. These dyes are used diagnostically to disclose corneal injuries and infections such as herpes simplex, and dry eye disorders.

3. Semi solids

A wide variety of semisolids vehicles are used for topical ocular delivery which falls into two general categories: simple and compound bases. Simple bases refer to a single continuous phase. These include white petrolatum, lanolin and viscous gels prepared from polymers such as PVA, carbopol etc. Compound bases are usually of a biphasic type forming either water in oil or oil in water emulsions. A drug in either a simple or compound base provide an increase in the duration of action due to reduction in dilution by tears, reduction in drainage by way of a sustained release effect, and prolonged corneal contact time. The most commonly used semisolid preparation is ointments consisting of dispersion of a solid drug in an appropriate vehicle base.

Semi-solids dosage forms are applied once or twice daily and provide sustained

effects. The primary purpose of the ophthalmic ointment vehicle is to prolong drug contact time with the external ocular surface. But they present a disadvantage of causing blurring of vision and matting of eyelids. Ophthalmic gels are similar in viscosity and clinical usage to ophthalmic ointments. Semi-solids vehicles were found to prolong the ocular contact time of many drugs, which ultimately leads to an enhanced bioavailability [40-42].

4. Miscellaneous

- Vesicular systems

Vesicular systems have been developed to provide improvement in ocular contact time, providing sustained effect and reducing side effects of the drug(s) entrapped.

- Liposome's

Liposome's are phospholipids-lipid vesicles for targeting the drugs to the specific sites in the body. Because of their structural versatility they can incorporate any kind of drug substance regardless of its solubility. They provide the controlled and selective drug delivery and improved bioavailability and their potential in ocular drug delivery appears greater for lipophilic than hydrophilic compounds. Liposome's are vesicles composed of a lipid membrane enclosing an aqueous volume. Liposome's offer the advantage of being completely biodegradable and relatively nontoxic but are less stable than particulate polymeric drug delivery systems. Liposome's were found to be potential delivery system for administration of a number of drugs to the eye [43-46].

- Niosomes

In order to circumvent the limitations of liposome's as chemical instability, oxidative degradation of phospholipids, cost and purity of natural phospholipids, niosomes are developed as they are chemically stable as compared to liposome's and can entrap both hydrophilic and hydrophobic drugs. They are non toxic and do not require special handling techniques [47].

- Pharmacosomes [48]

This is the term used for pure drug vesicles formed by the amphiphilic drugs. Any drugs possessing a free carboxyl group or

an active hydrogen atom (-OH, NH₂) can be esterified (with or without a spacer group) to the hydroxyl group of a lipid molecule, thus generating an amphiphilic prodrug. The amphiphilic prodrug is converted to pharmacosomes on dilution with water. The pharmacosomes show greater shelf stability, facilitated transport across the cornea, and a controlled release profile.

- **Muco-adhesive dosage form**

This approach relies on vehicles containing polymers which will attach, via non-covalent bonds, to conjunctival mucin (a glycoprotein) thus remaining in contact with the precorneal tissues until mucin turnover cause elimination of the polymer. Muco-adhesive polymers are usually macromolecular hydrocolloids with numerous hydrophilic functional groups, such as carboxyl -, hydroxyl-, amide and sulphate capable of establishing electrostatic interactions.

Hui and Robinson synthesized polymers of acrylic acid cross-linked with divinyl glycol and 2, 5 - dimethyl - 1, 5 - hexadiene and examined their utility in ocular drug delivery. The bioadhesive dosage form showed more bioavailability of the drug as compared to conventional dosage forms [50].

- **Particulates(Nanoparticles/Microparticles)**
Particulate polymeric drug delivery systems include micro- and nanoparticles. Particles in the micrometer size range >1mm are called Microparticles or microspheres, whereas those in the nanometer size range < 1mm (1000 nm) are called nanoparticles. Microparticles with a capsule wall enclosing a liquid or solid core are called microcapsules. The upper size limit for Microparticles for ophthalmic administration is about 5-10 mm. above this size, a scratching feeling in the eye can result after ocular application. Microspheres and Nanoparticles represent promising drug carriers for ophthalmic application [55]. The binding of the drug depends on the physicochemical properties of the drugs as well as of the nano or micro particle polymer. Particulates such as nanoparticles, nanocapsules, submicron emulsions, nanosuspensions improved the bioavailability of ocularly applied drugs [50-59].

Mechanism of diffusion [74]

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 drug can take place via diffusion through the pores. Controlled release can be further regulated by gradual dissolution of solid dispersed drug within this matrix as a result of inward diffusion of aqueous solutions [74].

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 take 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 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 which 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.

Table: 1 Basic Study on Various Ocuserts

Sr. No.	Drug	Summary of the study	Journal/year	References
ANTIBIOTICS				
1.	Pefloxacin mesylate	Eudragit RS100, Eudragit RL100 (PVP—K30, propylene glycol 10% dibutyl thallate)	Acta. Pharm./2005	Yasmin sultana et al. [60]
2.	Norfloxacin	HPMC, ethyl cellulose, PVPK30	Turk. Journal Med. Sci./2004	Venkateshwar Rao et al. [61]
3.	Ofloxacin	PEO	Int. Journal pharm./2001	Di colo et al. [62]
4.	Chloramphenicol	HPMC, EC, Eudragit RL100	The Eastern Pharmacist/2001	Vijaya et al. [63]
5.	Gentamicin	-----	Drug development and industrial Pharmacy./1999	Devarajan et al. [64]
6.	Gentamicin	HP	Journal ocul. Pharmacol./1998	Baeyens et al [65]
7.	Ciprofloxacin	HPMC, EC, Eudragit, MC	Indian Drugs/1997	Manvi et al. [66]
8.	Ciprofloxacin	HPMC, ME, PVP	Ind. Journal Pharm. Sci./1993	Udupa et al. [67]
ANTI-INFLAMATORY				
9.	Cromolyn sodium	PVA, sodium alginate	Journal Pharm. Sci./2004	Dandagi et al [68]
10.	Indomethacin	Gelrite, Gellan gum	Acta. Pharm./2003	Jayaprakash et al. [69]
11.	Indomethacin	PVA	Indian J. Pharm. Sci./2003	Pandit et al. [70]
12.	Ketorolac	HPMC, PVC, EC	Ind. J. Pharm. Sci. /200	Jayaprakash et al. [71]
13.	Dexamethasone	Gelatin, PVA, HPC, CAP, Eudragit	Int. J. Pharm./1988	Attia et al. [72]
14.	Diclofenac	MC, PVP	Eastern Pharmacist. /1998	Manikandar et al. [73]

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 bio erosion 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, which 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.

CONCLUSION

The solid drug-releasing devices, in spite of the advantages demonstrated by extensive investigations and clinical tests, have not gained a wide range of acceptance by ophthalmologists. At this moment, the

Ocusert systems are the only medicated inserts marketed in Western countries, and the acceptance of these devices has been, to the present date, far from enthusiastic. According to recent information the NODS project will not be further developed [75]. As said before, the commercial failure of inserts has been attributed to psychological factors, such as the reluctance of ophthalmologists and patients to abandon the traditional liquid and semi-solid medications, to price factors and to occasional therapeutic failures (e.g., unnoticed expulsion from the eye, membrane rupture, etc.).

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