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OPHTHALMIC DRUG DELIVERY SYSTEM WITH RECENT ADVANCES

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ABSTRACT

Eye is unique and very precious organ. There are many eye ailments which affect this organ and one can loss the eye sight also. Therefore many ophthalmic drug delivery systems are available. Promising management of eye ailments depends on effective concentration of drug at the eye for sufficient period of time. Dosage forms are administered directly to the eye for localized ophthalmic therapy. This article reviews the constraints for topical ophthalmic drug delivery system, with conventional topical delivery systems and explore various novel approaches including in-situ gels, colloidal particles, liposomes, nanoparticles, inserts, microparticles, implants, minidiscs, pharmacosomes, collagen shields etc to improve the ophthalmic bioavailability of drugs to the anterior chamber of eye.

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INTRODUCTION

Eye is unique and very precious organ. It is considered as window of the soul. We can enjoy and view the whole world only with this organ. There are many eye ailments which affect this organ and one can loss the eye sight also. Therefore many ophthalmic drug delivery systems are available. These are classified as conventional and newer drug delivery systems. Most commonly available ophthalmic preparations are eye drops and ointments. But these preparations when in-

stilled into the cul-de-sac are rapidly drained away from the ocular cavity due to tear flow and lacrimal nasal drainage. Only a small amount is available for its therapeutic effect resulting in frequent dosing.[1]Thus inefficient drug delivery into the eye occurs due to rapid tear turn over, lacrimal drainage and drug dilution by tear. Many parts of eye are relatively inaccessible by systemic administration, thus topical drug delivery remains the preferred route in treatment of various eye ailments.

Before reaching the anatomical barrier of the cornea, any drug molecule administered by the topical route has to cross the precorneal barriers. The medication, upon instillation, stimulates the protective physiological mechanisms, i.e., blinking and tears production, which exert defense against ophthalmic drug delivery. Thus the bioavailability of ocular delivery systems is affected by low residence volume i.e. only 7-10 µl, further it is affected by loss of administered amount due to rapid clearance by lachrymation, non- productive absorption through conjunctiva and through naso-lachrymal drainage.[2]

Ophthalmic preparations are defined in the USP as "sterile dosage forms, essentially free from foreign particles, suitably compounded and packed for instillation into the eye." Ophthalmic preparation can be in the form of aqueous or oily solution, suspension, ointment, gel, and certain solid dosage form.If we see historical background of ophthalmic drug delivery systems, the Egyptians used copper compound such as, malachite and chrysocalla, as green eye make-up with some beneficial effect against infection, owing to the antibacterial properties of copper. One of the earliest ointment or ointment bases for the treatment of eye disease or wound was prepared by Smith papyras (1700 B.C.) using grease, honey and lint. This review deals with description of anatomy and physiology of eye, ophthalmic drug delivery systems and challenges for the development of ophthalmic drug delivery systems. Furthermore this article include various drug delivery systems come under ophthalmic drug delivery system.

Anatomy of human eye:

The eye is one of the most vital organs in the body and provides one of human's most treasured senses: vision. After the skin eye is the most easily accessible site for topical administration of drug. The accessory structures of eye are eyelids, eye lashes, eyebrows, lachrymal apparatus, and extrinsic eye muscle.[3]

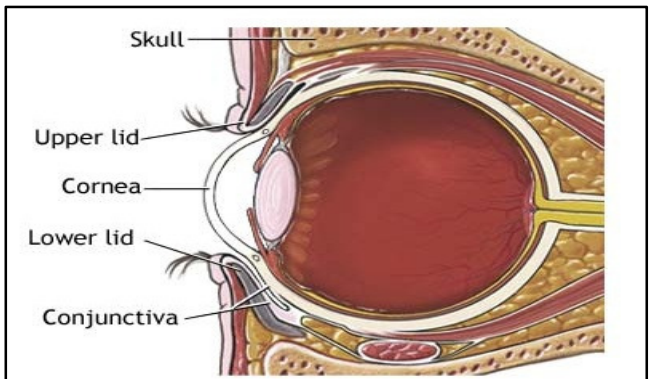


Figure 1: External eye

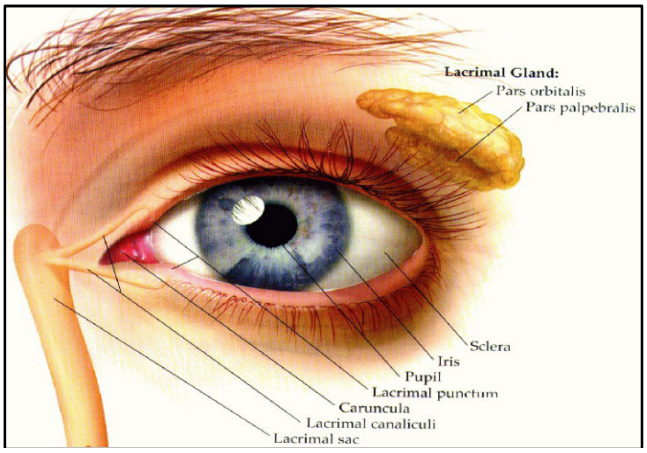


Figure 2: Surface anatomy of eye

Human eye is made up of following components (Figure 3):

a) Orbital cavity
b) Eye ball
c) Eyelid
d) Conjunctiva
e) Lens

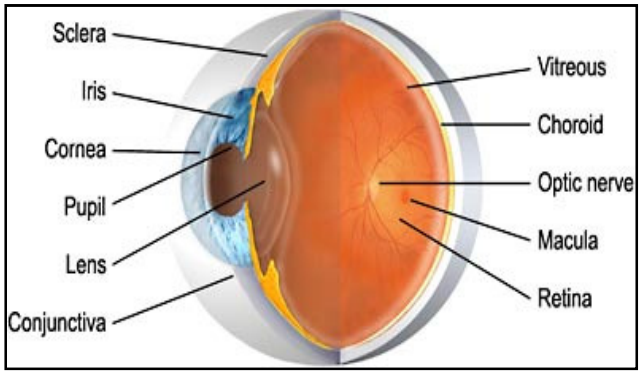


Figure 1: Anatomy of eye

Orbital cavity, a thick layer of areolar tissue, is interposed between the bone and eye. It is a cushion to protect the eye ball from external force.The adult eye ball measures about 24 mm in diameter. Of its total surface area, only anterior one-sixth is exposed. The remainder is recessed and protected by the orbit into which it fits.Anatomically, the wall of the eyeball can be divided into three layers; outer fibrous layer- Tunica fibrosa, middle vascular layer- Tunica vasculosa and inner nervous tissue layer- tunica nervosa

1) Tunica externa/ Tunica fibrosa: The fibrous tunic is the superficial coat of the eyeball which preserve shape of eye ball. It is avascular and consists of the anterior cornea and posterior sclera.

Cornea: It is a transparent coat that covers the coloured iris and has diameter of 12 mm horizontally and 11 mm vertically. Because it is curved, the cornea helps focus light on the retina. Cornea consists of outer non-keratinized stratified squamous epithelium, middle collagen fibres and fibroblasts, and the inner simple squamous epithelium.

Sclera: The white of the eye, is a coat of dense connective tissue made up mostly of collagen fibres and fibroblasts. Sclera gives shape to eye ball, makes it more rigid, and protects its inner part. At the junction of cornea and sclera is an opening known as the scleral venous sinus or canal of Schlemm.

2) Tunica media/ Tunica vasculosa: The vascular tunic or uvea is the middle layer of eyeball, which surrounds the eye ball completely except a small opening in front known as pupil. It has three portions; choroid, ciliary body, and iris.

Choroid: It lines the posterior five-sixth of the inner surface of the sclera and is composed of rich capillary plexus, small arteries and veins. It provides blood supply and absorbs scattered light.

Ciliary body: It is located anterior of the choroid. It consists of ciliary muscle (smooth muscle fibres) and secretory epithelial cells. It secrets aqueous humour and alters shape of lens for near and far vision (accommodation).

Iris: It is placed in front of lens. It is thin, coloured circular diaphragm made of two layers; constrictor papillae which is formed by circular muscle fibres and dilator papillae which is formed by radial muscle fibres

It regulates the amount of light entering the eye by altering the diameter of pupil.

3) Tunica interna/ Tunica nervosa: It lines the posterior three-quarters of the eyeball and is the beginning of the visual pathway. It includes light sensitive retina.

Retina: It is made up of ten layers and is receptor of vision. The retina consists of Pigment epithelium (nonvisual portion), a sheet of melanin containing epithelial cells and neural portion (visual portion), multilayered outgrowth of the brain.

a) Eyelid: Eyelids are 25 mm long and 11-12 mm wide. The margins of eyelids have sensitive hairs called cilia. Upper eye lids have 100-150 cilia and lower eyelids have 50-70 cilia. Meibomian glands and some sebaceous glands are situated in eyelids. These glands open into follicles of cilia. Eyelid protects the eyeball from foreign particles coming in contact with its surface and cut off light during sleep.

b) Conjunctiva: It is the outermost layer of eye. It is thin mucous membrane. The surface of conjunctiva is lubricated by thin tear film secreted by lachrymal glands. It protects exposed part of the eye.

c) Lens: It is suspended from the ciliary body by the suspensory ligaments. It is crystalline in nature. It is biconvex, transparent and possesses elastic property. It is formed of three components, capsule, a highly elastic membrane, anterior epithelium, made of single layer of cubical epithelial cells, and lens substance: It is formed by long lens fibers, derived from anterior epithelium. The lenses are prismatic in nature and are arranged in concentric layer.[3]

Physiology of human eye:

Sense of vision is a complex function of the two eyes and their central connections. The physiological activities involved in the normal functioning of the eyes are maintenance of clear ocular media, maintenance of normal intraocular pressure, the image forming mechanism, physiology of vision, physiology of binocular vision, physiology of pupil, and physiology of ocular motility.

Related to the eye three types of liquids are consideredtear,aqueous humour and vitreous humour. Tears are complex mixture of water, lipids, salts, mucin, electrolytes and proteins. Tear layer is 6-9 µm thick and normal volume of tear is 7 µl. A human eye can accommodate up to 30 µl of solution in the absence of blinking. Tears are made in glands near the top of eye ball and spreads over the front of eyeball into the tear ducts and down to nose. The normal rate of tear secretion is 1.2 µl/min and the normal tear turnover rate is 16%/min. The tears are an isotonic solution (0.9-0.96% NaCl equivalent) with a pH ranging from 7.2 to 7.4. Tear in eye is important for its lubrication, nourishment, oxygen supply and protection from foreign matter. Tears are made up of three layers[4]

1) Oily layer: It is the outer layer which is secreted by small glands on edge of eye lids (Meibomian gland).It protects the aqueous layer beneath.
2) Aqueous layer: It is secreted by lachrymal glands. It cleans the eyes and forms the barrier between the oily and mucous layers.
3) Mucous layer: It is an inner most layer secreted by conjunctiva.

Aqueous humour is a thin fluid, which fills the space between the lens and cornea. Its volume is 0.13ml, pH is 7.5, viscosity is 1.029cps and refractive index is 1.34. Aqueous humour maintain proper intraocular pressure and provide substrate and remove metabolites from the avascular cornea and crystalline lens.Vitreous humour is a gelatinous substance present in vitreous body in the space between lens and retina. It is formed by a fine fibrillar network of peptidoglycan molecules. Various substances can enter vitreous body by means of diffusion.It maintains the shape of eyeball and keeps retina attached to choroid.

Physiology of vision

Physiology of vision is a complex phenomenon which is still poorly understood. The main mechanisms involved in physiology of vision are:

- Initiation of vision (photo-transduction), a function of photoreceptors (rods and cones)
- Processing and transmission of visual sensation, a function of image processing cells of retina and visual pathway, and
- Visual perception, a function of visual cortex and related areas of cerebral cortex.

Target sites for ophthalmic drug delivery

In eye drug is administered at various site such as corneal, conjunctival and scleral for better achievement of bioavailability and required effects related with the therapy (Table 1). The drugs for allergies, glaucoma, bacterial infections, conjunctivitis, keratitis, local anaesthetics and viral infection can be administered at the bellow mentioned target sites in the eye.[5]

Table 1: Target site in ocular drug delivery

Sr. No.	Target site	Salient features
1	Cornea	Bowman's capsule is lipophilic, allows diffusion of small lipophilic molecules. Stroma is hydrophilic, allows diffusion of hydrophilic and larger molecules.
2	Conjunctiva	Main barrier for drug absorption, allows absorption of hydrophilic and large molecules. Absorption of peptides is less due to enzymatic degradation.
3	Sclera	Some drugs (β-blockers) diffuse readily. Trans-scleral iontophoresis is used for intra-vitreal administration.
4	Aqueous humor	Drugs absorbed through cornea discharge through aqueous humor into systemic routes.
5	Vitreous	Drug absorbed through sclera and conjunctiva discharge through vitreous humor into systemic routes.

Routes of ophthalmic drug delivery:

There are various routes such as topical, sub-conjunctival, reterobulbar, peribulbar, intracameral and intraviteral, and respective dosage forms available for ophthalmic prophylaxis and treatment as mentioned in table 2.

Table 2: Routes for ophthalmic drug delivery

Sr. No.	Route	Dosage Forms	Advantages	Disadvantages
1	Topical	Solutions, Suspensions, Ointments, Gels etc.	Ease of administration	Poor bioavailability, suitable only for anterior segment, blurring vision.
2	Sub conjunctival	Injectables	Delivery of large molecular size drugs, sustained release of drug	Patient non-compliance, suitable for only water soluble drugs.
3	Retrobulbar	Injectables (used for anesthetization)	-	Perforation of globe, patient non- compliance.
4	Peribulbular	Injectables (used for anesthetization)	Avoidance of perforation of globe	Non-compliance in pediatrics patients and patient with mental disorders.
5	Intracameral	Injectables	Sustained delivery to aqueous humor	Patient non-compliance.
6	Intraviteral	Injectables	Sustained delivery of drug to posterior segment of the eye	Patient non-compliance.

Pharmacology and therapeutics of ophthalmic medication

Drugs used in ocular drug delivery falls into one of the several categories including miotics, mydriatics (with or without cycloplegic activity), cycloplegics, anti-inflammatories, anti-infectives (including antibacterial, antiviral and antifungal), anti-glaucoma drugs, surgical adjuncts, diagnostics and a category of drugs for miscellaneous uses. The intended use of drug will define more precisely what drug or combination of drug is to be use, the appropriate dosage form and the route of administration. For example, depending on the location of ocular inflammation, a specific corticosteroid in a specific dosage form may be chosen. For instance, a corticosteroid of high potency may be used for the deep seated inflammation and a low potency corticosteroid may be used for superficial inflammation. It is now also possible to treat inflammation with non-steroidal anti-inflammatory agents such as diclofenac or ketorolac, drugs not expected to raise intra occular pressure.

Drugs for treatment of ocular infection are generally chosen based on the presumptive diagnosis of the causative agent by ophthalmologist. Laboratory confirmation by microbial culture and identification is routinely conducted concurrently with the initiative of the therapy. This is generally necessary because of the severity and sight-threatening nature of some infections.

For fungal and viral infection there are very few agents that the ophthalmologist can prescribe. These organism's resistance and similarity to mammalian tissue make it difficult to find effective and safe therapies. Drugs used as surgical adjuncts are primarily irrigating solutions, solutions of proteolytic enzymes, visco-elastics and miotics to preserve retinal integrity. Diagnostic agents such as sodium fluorescein are administered topically to aid in the diagnosis of conditions such as, corneal abrasions or ulcerations and various retinopathies.

Ocular bioavailability

Bioavailability of drugs administered to the eye is an important consideration. There are physiologic factors, which can affect a drug's ocular bioavailability including protein binding, drug metabolism and lacrimal 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 for which an ophthalmic solution may remain in the eye (due to lacrimal drainage), protein binding of a drug substance could quickly negate its therapeutic value by rendering it unavailable for absorption.

As in the case with other biological fluids, tears contain enzymes (such as lysozyme) capable of the metabolic degradation of drug substance. In addition to physiologic factors affecting ocular bioavailability, other factors as the physicochemical characteristics 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 solution to increase the proportion of unionized drug in the instilled dose. Drugs, which are highly water-soluble, do not readily permeate the cornea. Suspensions of drugs and ophthalmic ointments mix with lacrimal fluids less readily than do solutions, and thus, remain in the cul-de-sac for longer period of time, enhancing the bioavailability of the drug substance. Ophthalmic solutions of increased viscosity also remain in cul-de-sac longer than solutions with lower viscosity.
Topical delivery of eye drops into the lower cul-de-sac is the most common method for the administration of therapeutic agents in the treatment of ocular diseases and in diagnostics. However, one of the major problems encountered

with solutions is the rapid and extensive elimination of drugs from the pre-corneal lachrymal fluid by solution drainage, lachrymation, and non-productive absorption by the conjunctiva, which may cause undesirable side effects. The high drainage rate is due to the tendency of the eye to maintain its residence volume at 7-10 µl permanently, whereas volumes topically instilled range from 20-50 µl. It has been demonstrated in vivo that 90% of the dose was cleared within two minute for an instilled volume of 50 µl and, within 4 minutes 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%.

Thus the bioavailability of ocular delivery systems is affected by low residence volume (7-10 µl) and losses of administered amount due to rapid clearance by lachrymation, non- productive absorption through conjunctiva and drainage through naso-lachrymal drainage.Thenaso-lachrymal drainage system (Figure 4) consists of three parts; secretory system,distributive system, and excretory system.

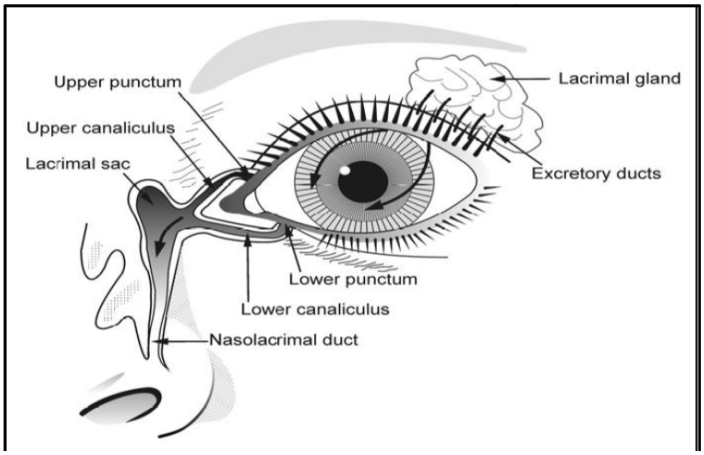


Figure 4: Nasolacrimal drainage system

The secretory system consists of basic secretors that are stimulated by blinking and temperature change due to tear evaporation and reflex secretors that have efferent parasympathetic nerves 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 naso-lachrymal drainage system consists of the lachrymal puncta, the superior, inferior and common canaliculi; the lachrymal sac; and the naso-lachrymal duct. In human, the two puncta are the openings of the lachrymal canaliculi and are situated on an elevated area known as the lachrymal papilla.

Pharmacokinetics of ophthalmic drug delivery:

For diseases and conditions affecting eye, topical or local administration is preferred over systemic administration. 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.

The penetration of drugs across the corneal membrane occurs from the pre-corneal space. Thus, the mixing and kinetic behaviour of drugs disposition in tears have a direct bearing on efficiency of drug absorption into the inner eye. The productive absorption of most ophthalmic drugs results from diffusion process across the 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 a 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 a function of physiological mechanism of pre-corneal fluid drainage or turnover.

In terms of trans-corneal drug penetration, the cornea can be considered to consist of three primary layers (epithelium, stroma and endothelium). The epithelium and endothelium contain on the order of a 100 fold greater amount of lipid material than the stroma. Consequently, depending on the physicochemical properties of a

diffusing drug, the resistance offered by the individual layers varies greatly. Epithelium, being lipoidal, represents a diffusion barrier offering high resistance to ionic or other aqueous soluble or polar species. In contrast, compounds with relatively low polarity encounter a greater diffusion resistance in the hydrophilic stromal layer. This frequently cited concept of drug permeation across the cornea membrane is referred to as differential solubility concept.[6]

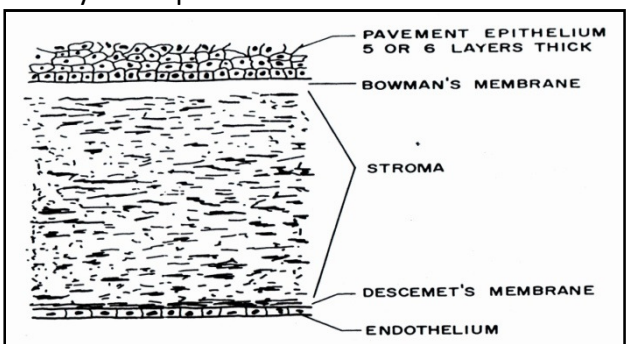


Figure 5: Cross section view of corneal membrane depicting various barriers to drug absorption

Primary mechanism of drug permeation in the sclera is likely to be diffusion across the intercellular aqueous media as 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.

Ophthalmic drug delivery systems:

Ideal ophthalmic drug delivery must be able to sustain the drug release and to remain in the vicinity of front of the eye for prolong period of time. Consequently it is important to optimize ophthalmic drug delivery, one of the way to do so is by addition of polymers of various grades, development of viscous gel, development of colloidal suspension or using erodible or non-erodible insert to prolong the precorneal drug retention. Characteristics which are required to optimize ocular drug delivery system are good corneal penetration, prolong contact time with corneal tissue, simplicity of instillation for the patient, non irritative and comfortable form (viscous solution should not provoke lachrymal secretion and reflex blinking), and appropriate rheological properties and concentrations of the viscous system.

Although lot of alternative dosage forms have been tested to avoid the drawbacks of conventional ophthalmic dosage form in last few years, each has been found to be deficient in one or more ways.A considerable amount of effort has been made in ophthalmic drug delivery since 1970's. The two main approaches attempted are improvement in bioavailability and controlled release drug delivery. Topical bioavailability can be improved by maximizing precorneal drug absorption and minimizing precorneal drug loss.Controlled drug-delivery are the preferred system of ophthalmic delivery as they would provide improved bioavailability and site-specific delivery with continuous drug release.[7]

1. Viscosity modifier

First attempt made to prolong the contact time of applied drug with cornea was to increase the viscosity of the preparation. The viscosity enhancers used were hydrophilic polymers such as cellulose, polyalcohol and polyacrylic acid. Polysaccarides such as xanthun gum was found to increase the viscosity and delay the clearance of the instilled solution by tear flow. Carbomer were used in liquid and semisolid formulations as suspending or viscosity increasing agents. Formulations including creams, gels and ointments were used as ophthalmic products. . These polymers have high molecular weight which cannot cross the biological membrane. Increase in corneal penetration of ophthalmic drug would be maximum at viscosity of about 15 to 150 cp.[8], but increase in viscosity is associated with blurring of vision and resistance to eyelid movements.

Formulation of polymers that display non newtonian properties offer significantly less resistance to the eyelid movements. Viscosity vehicles increases the contact time with no marked sustaining effect.

2. Penetration enhancers

Penetration enhancers act by increasing corneal uptake by modifying the integrity of comeal epithelium. Chelating agents, preservatives, surfactants and bile salts were studied as possible penetration enhances. But the effort was diminished due to the local toxicity associated with the penetration enhancers. Penetration enhancers have also been reported to reduce the drop size of conventional ophthalmic solutions.

3. Prodrug

Prodrugs enhance corneal drug permeability by modifyinghydrophilicity or lipophilicity of the drug. The method includes modification of chemical structure of the drug molecule, thus making it selective, site specific and a safe ocular drug delivery system. Drugs with increased penetrability through prodrug formulations are-epinehrine, phenylephrine, timolol, pilocarpine and albuterol.

4. Mucoadhesive polymers

The mucoadhesive polymers adhere to the mucin coat covering the conjunctiva and the comeal surfaces of the eye, thus prolonging the residence time of a drug in the conjunctival sac. Large number of mucoadhesive polymers are available that can be natural, semisynthetic or synthetic. Polyanions are better in bioadhesiveness and toxicity as compare to polycations. Mucoadhesive polymers which have been used in ophthalmic drug delivery system are carbopol, polycarbophill, carboxymethyi cellulose, hyaluronic acid, chitosan, xanthan, etc.[9-12]

5. Cyclodextrin

Cyclodextrins act as carriers by keeping the hydrophobic drug molecules in solution and delivering them to the surface of the biological membrane, where the relatively lipophilic membrane has a much lower affinity for the hydrophilic eyclodextrin molecules, therefore they remain in the aqueous vehicle system.

6. Insitu gels

In early eighty's concept of in situ gelling come existsnace.In situ-forming gels are liquid upon instillation and undergo phase transition in the ocular cul-de-sac to form viscoelastic gel and this is a response to environmental changes, such as temperature change, pH change or contact with monovalent or divalent ions present in the ophthalmic secretions.[13]

a. Thermally triggered system- Are the in situ systems, which are liquid at room temperature (20-25^{o}C) and form semisolid at physiological temperature (35-37^{o}C). Examples of temperature sensitive polymers are xyloglucan, methyl cellulose, poly oxy ethylene-polypropylene copolymer (poloxamers), n-isopropyl acryl amide (NIPAM), etc.[14-15]

b. pH triggered system- Are in situ systems, which are liquid under non-physiological conditions and forms semisolid gel when exposed to the physiological (pH 7.5) conditions. pH sensitive polymers are cellulose acetate phthalate (CAP), carbomer (carbopol).[16]

c. Ion activation- These in situ systems are liquid under non-physiological conditions and form semisolid gel after contact with the monovalent and divalent ions present in tears. Polymers used for such systems are gellan gum, sodium alginate, etc.[17]

7. Colloidal particles

The potential use of polymeric colloidal particles as ophthalmic drug delivery systems started in late 1970's. Main object in optimization of ocular drug delivery is to increase the contact time of drug with

conjunctiva. Colloidal carriers like liposomes and nanoparticles found to be useful to prolong the corneal contact time and hence more and more tested in ocular drug delivery.[18]

a. **Liposomes**- The use of liposomes as a topically administered ocular drug delivery system began in the early stage of research into ophthalmic drug delivery. Drug's physicochemical properties have significant influence on the effect of liposomes. Favorable result with liposomes found essentially with lipophilic drugs as hydrophilic drug escape rapidly out of the liposomes than lipophilic drugs. Charge on liposomes also influence drug concentration in ocular tissues.[19]Corneal epithelium is covered by negatively charged mucin thus positively charged liposomes increase drug concentration in ocular tissues. Coating with bioadhesive polymers to liposomes, prolong the precomea retention of liposomes. Carbopol coated pilocarpine containing liposomes were shown to produce a longer duration of action.[20]

b. **Nanoparticles-**Nanoparticles are polymeric colloidal particles ranging in size from 10-100nm. Various polymers like polyacrylamide, polymethylmethaacrylate, albumin gelatin, polyalkylcynoacrylate, polylactic-co-glycolic acid, ε-caprolactone used in the preparation of nanoparticles.[21-22]Nanoparticles provide sustained release-and prolonged therapeutic activity when retained in the cul-de-sac after topical administration and the entrapped drug must be released from the particles at an appropriate rate. To enhance particle retention the particles are fabricated with bioadhesive materials. Biodegradation is also a highly desirable property for the fabrication of nanoparticles. Nanoparticles as an ophthalmic drug delivery have been demonstrated for both hydrophilic and hydrophobic drugs.[23]

8. Microspheres

These are the drug containing, micron sized polymeric particles suspended in a liquid medium. Drugs can be physically dispersed in the polymer backbone. The drug is released in cul-de-sac through diffusion, chemical reaction, and polymer degradation. Acyclovir loaded chitosan microspheres and Pilocarpine-loaded albumin or gelatin microspheres are available.

9. Implants

The poly lactic acid and its copolymers with glycolic acid have been used extensively as implants. An ocular implant for delivering ganciclovir for the treatment of cytomegalovirus has also been developed, which delivered drug directly to the retina for over 5 months. These systems are less popular as they require minor surgery.

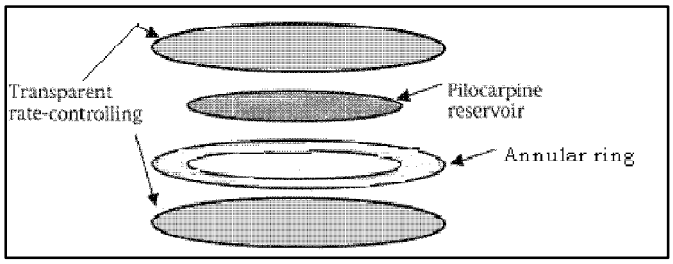
10. Minidisc

Minidisc is a controlled release matrix type device consisting of a disc with a convex front and a concave back surface. The principle component is A (1) bis (4-methacryloxybutyl)-polydimethylsiloxane. They can be made hydrophilic and hydrophobic for extended release of both water soluble and water insoluble drugs.[24]

11. Ocular inserts

Ocular or ophthalmic inserts are sterile polymeric systems meant for introduction in upper conjunctival sac. They offer several advantages as increase ocular residence, possibillty of releasing drug at a slow constant rate, accurate dosing and increased shelf life with respect to aqueous solutions. Ocusert®, pilocarpine ocular therapeutic system is the first product marketed by Alza incorporation USA from this category. Inserts can be soluble or insoluble. Insoluble inserts are polymeric systems into which the drug is incorporated as a solution or dispersion, polymers used can be alginate salts, PVP, modified collagen and HPC with silicon matrix. The release of drug can be extended from 2 to 22 weeks. Whereas soluble inserts consists of all monolytic polymeric devices that at the end of their release dissolve or

erode. Soluble ophthalmic drug inserts is a soluble copolymer of acrylamide, N-vinyl pyrrolidone and ethyl acrylate. The system soften in 10-15 sec after introduction and gradually dissolves within 1 h, while releasing the drug.[25]



Figur 6: Ocusert

Due to difficulty with self-insertion, foreign body sensation, only few insert products are listed and pharmaceutical manufacturers are not actively developing inserts for commercialization.

12. Soft contact lens

Soft contact lenses are widely prepared using poly-2-hydrosyethylmethacrylate. Its copolymers with PVP can be used to correct eyesight and hold and deliver drugs. Controlled release can be obtained by binding the active ingredient via biodegradable covalent linkages.[26]

13. Pharmacosomes

They are the vesicles formed by the amphiphilic drugs. Any drug possessing a free carboxyl group or an active hydrogen atom (-OH, -NH2) can be esterifies to the hydroxyl group of a lipid molecule, thus generating an amphiphilicprodrug. These are converted to pharmacosomes on dilution with water. They show greater stability, facilitated transport across the cornea and a controlled release profile.

14. Ocular iontophoresis

Ocular iontophorosis offers drug delivery system that is fast pain less safe and result in delivery of high conc of drug to specific site. Iontophoresis application of antibiotics may enhance bactericidal activity of the antibiotics and reduce the severity of the disease.[27]

15. Collagen shields

Collagen shields are manufactured from porcine scleral tissue, which bears a collagen composition similar to that of human cornea. Drug is loaded by simply soaking shield in drug solution. They are hydrated before being placed on the eye, also they provide a layer of collagen solution that lubricates the eye. Collagen shields presoaked in tobramycin were used to treat Pseudomonas aeruginosa infected cornea excoriation. But shield are not fully transparent and thus reduce visual activity, but they are appropriate delivery systems for both hydrophilic and hydrophobic drugs with poor penetration properties.[28]

CONCLUSION

An ideal ophthalmic system should have effective drug concentration at the target tissue for a required period of time with minimum systemic effect. Patient acceptance is also very important for the design of ophthalmic drug delivery system. All the above approaches improve ocular drug bioavailability by increasing ocular drug residence time, diminish side effect due to systemic absorption and diminishing the necessary therapeutic amount of drug for therapeutic response in anterior chamber. However, all systems have some disadvantages associated with them. Major Improvements are required in each system like improvement in sustained drug release, large scale manufacturing and stability. Among these drug delivery systems, only few products have been, commercialized. Surprisingly after so many years of research in ophthalmic drug delivery and development of novel ophthalmic systems, the eye drops are still choice of the drug delivery system in ophthalmic market.

REFERENCES

1. Agarwal ML, Agarwal S, Gupta LC, Ophthalmology, 1st ed, Jaypee Brothers, New Delhi, 1996, 42-58.
2. Nema HV, Nema N, Textbook of ophthalmology, 3rd ed, Jaypee Brothers, New Delhi, 1998, 38-43.
3. Tortora GS, Derridkson B, Principal of Anatomy and Physiology, 10thed, John Wiley and Sons, Hoboken, 2003, 579-587.
4. Guyton AC, Hall TE, Textbook of Medical Physiology, 11thed, Elsevier Saunders, Philadelphia, 2006, 613-617.
5. Hopkins G, Pearson R, Ophthalmic dosage forms, 4thed,Batterworth, Oxford, 1999, 62-73.
6. Maurice DM, The dynamics and drainage of tears, International ophthalmology, Clin, 13, 1973, 103-115.
7. Mathiowitz E, Encyclopedia of Controlled Drug delivery, Vol 2, John Wiley and Sons, New York, 1999, 605-622.
8. Patton TF, Robinson JR, Ocular evaluation of PVA vehicle in rabbits, Journal of Pharmaceutical Science, 64, 1975, 1312-1315.
9. Saettone MF, Chetrni P, ToraccaMT,Burgalas S, Evaluation of mucoadhesive properties and in vitro activity of opthalmicvehicles based on hyluronic acid, International Journal of Pharmaceuticals, 1989, 203-212.
10. Smart JD, Kellaway IW, Worthington EC, In vitro investigtion of mucoadhesive material for use in Controlled Drug Delivery, Pharma. Pharmacol., 36, 1984, 295-299.
11. Ditigen M, Oestereich S, Eckhardt D, Influence of bioadhesives on elimination of drug from the eye and on their penetration ability across the pig cornea, Pharmaceutical Science, 2, 1, 1992, 93-97.
12. Park H, Robinson JR, Mechanisms of mucoadhesion of polyacrylic acid and hydrogels, Pharmaceutical Research, 4, 1987, 457-464.
13. Nirmal HB, Bakliwal SR, Pawar SP, In-Situ gel: New trends in Controlled and Sustained Drug Delivery System, International Journal of PharmTech Research, 2, 2010, 1398-1408.
14. Ghandhi G et al, Poloxamer-407: A novel in situ temperature triggered gel forming ophthalmic drug delivery system. Indian Pharmaceutical Congress abstracts, 2006, 15.
15. Vadnere M, Amidon G, Linderbaam S,Haslum JL, Thermodynamic studies on the gel-sol transition of some pluronicpolyols, International journal of Pharmaceuticals, 22, 1984, 207-218.
16. Gurny R, Ibrahim H, Buri P, The development and use of in situ formed gels triggered by pH- in biopharmaceutics of ocular drug delivery, CRS press, 1993, 81-90.
17. Talat F, Sadhana RS, Azmat MS, Nityanand Z, Syed AA, Formulation development and evaluation of in situ ophthalmic gel of sodium cromoglycate,Der Pharmacia Sinica, 2013, 4, 2, 109-118.
18. Mezei M, Meisner D, Liposomes and nanoparticles as ocular drug delivery systems: in biopharmaceutics of ocular drug delivery, CRS press, 1993, 91-104.
19. Smolin G, Okumoto M, FeilerS, Condon D, Idoxuridine- liposomes therapy for herpes simplex keratitis, Journal ofOpthamology, 91, 1981, 220-225.
20. Singh K, Mezei M, Liposomal opthalmic drug delivery system: triamicinoloneacetonide, Int. J. Pharm., 16, 1983, 339-344.
21. Rolland A, Gibassier D, Sado P, Leverge R, Methodologie de preparation de vecteursnanoparticulaires a base de polymers acryligues", J. Pharm. Belg., 14, 2, 1986, 83-93.
22. Kramer PA, Albumin microsphere as vehicle for achieving specificty in drug delivery, J. Pharm. Sci., 63, 1974, 1646-1647.
23. Oppenheim JJ, Marty JJ,Slewart NF, The labelling of gelatin nanoparticles with technetium and in vitro distribution after intravenous injection, Austrl. J. Pharm. Sci., 7, 1978, 113-117.
24. Bawa R, Ocular inserts, In: Mitra A K(ed), Ophthalmic drug delivery sytems. Marcel Dekker Inc., New York, US,1993, 223-260.
25. Gurtler F,et al., Long acting soluble bioadhesive ophthalmic drug insert containing gentamicin for veternaryuse:optimization and

clinical investigation, Journal of controlled release. 33, 1995, 231-236.
26. O'Brien TP, et al. Use of collagen corneal shields versus soft contact lenses to enhance penetration of topical tobramycin, Journal of Cataract and refractive surgery, 14, 1988, 505-507.
27. Colasanti BK, Trotter RR, Enhanced ocular penetration of the methyl ester of (+/-) alpha-methyl-para-tyrosine after lontophoresis, Arch. Int. Pharmacodyn. Ther., 228, 1977,171.
28. Unterman SR, et al. Collagen shield drug delivery: therapeutic concentration of tobramycin in the rabbit cornea and aqueous humour, Journal of Cataract and refractive surgery, 15, 1988, 500-504.

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