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Advancements in Ocular in Situ Gelling System to Overcome Ocular Barriers

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ABSTRACT

Topical Application of Drugs is the method of choice under most circumstance because of its convenience and safety for ophthalmic chemotherapy. A significant challenge to the formulator is to circumvent (bypass) the protective barriers of the eye without causing permanent tissue damage. Development of newer, more sensitive diagnostic technique & novel therapeutic agents continue to provide ocular delivery system with high therapeutic efficacy . Thus, a conventional ocular dosage form has various disadvantages of its use in ocular disease. Hence, an ideal ocular delivery system has always been aimed, where the bioavailability of drug is maintained for a longer period of time. The present review aims to focus on the drawbacks of the conventional ocular therapy & the advantages of designing novel delivery system, with their certain specific advantages in ocular pharmacokinetics & the enhancement of bioavailability. A lot of research going on in this area proves the fact that in situ gelling system can be beneficial in the ocular drug delivery system.The compiled data presented in this review will act as a good information resources and reference point for further reseachers in the field of ocular drug delivery aiming non-invasive sustained release of drugs in the anterior and posterior segment of the eye.

Key words: Ocular drug delivery, intraocular barriers, Ocular bioavailability.

INTRODUCTION

Eye is most interesting organ due to its drug disposition characteristics. Generally, topical application of drugs is the method of choice under most circumstances because of its convenience and safety for ophthalmic chemotherapy.[1,2] A significant challenge to the formulator is to circumvent (bypass) the protective barriers of the eye without causing permanent tissue damage.2 Development of newer, more sensitive diagnostic techniques and novel therapeutic agents continue to provide ocular delivery systems with high therapeutic efficacy. Conventional ophthalmic formulations like solution, suspension, and ointment have many disadvantages which result into poor bioavailability of drug in the ocular cavity. The specific aim of designing a therapeutic system is to achieve an optimal concentration of a drug 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. A successful design of a drug delivery system, therefore, requires an integrated knowledge of the drug molecule and the constraints offered by the ocular route of administration.[3]

The various approaches that have been attempted to increase the bioavailability and the duration of the therapeutic action of ocular drugs can be divided into two categories. The first one is based on the use of sustained drug delivery systems, which provide the controlled and continuous delivery of ophthalmic drugs. The second involves maximizing corneal drug absorption and minimizing precorneal drug loss.[4, 5,6]

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 imperative to optimize ophthalmic drug delivery; and by addition of polymers of various grades, development of in situ gel or colloidal suspension or using erodible or non erodible insert to prolong the precorneal drug retention.

THE ANATOMY OF THE EYE [7]

The human eye, elegant in its detail and design, represents a gateway to the process we call vision. The eyeball is spherical in shape and about

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1 inch across. It houses many structures that work gether to facilitate sight. The human

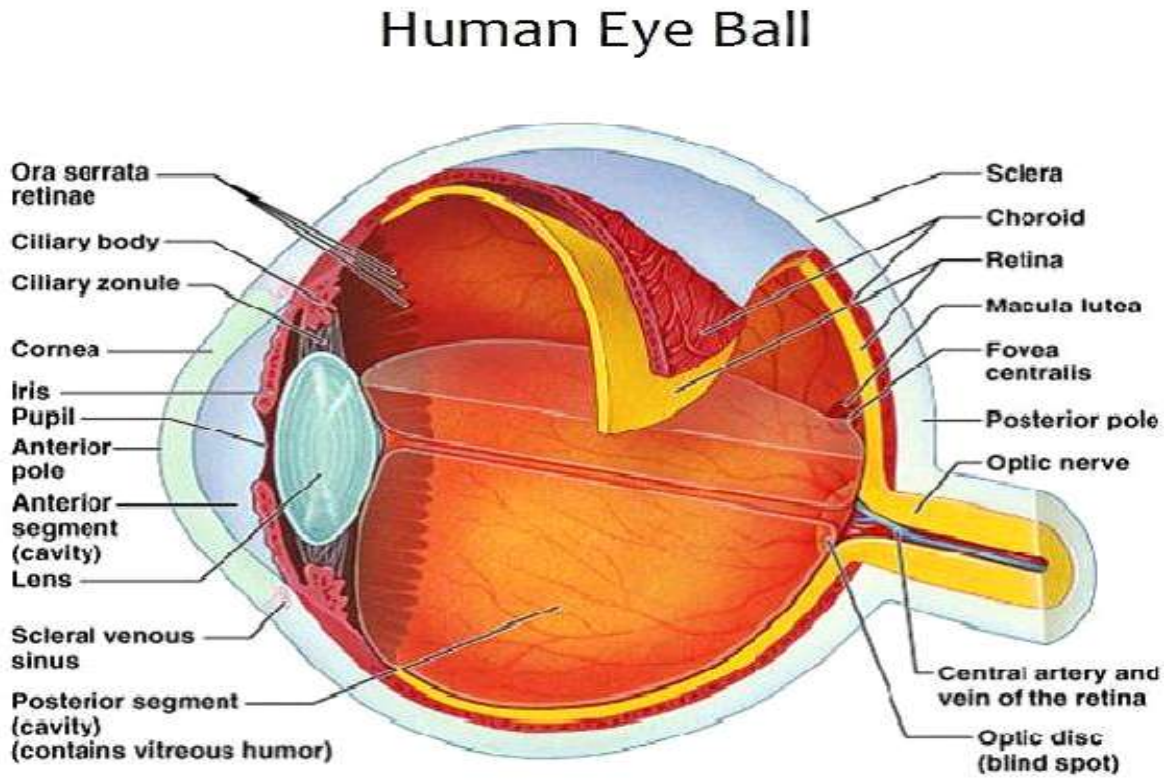

Figure 1: Structure of Eye-Ball

A. Sclera

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

B. Conjunctiva

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

C. Cornea

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

D.Aqueous humor

The aqueous humor is a jelly-like substance located in the outer/front chamber of the eye. It is a watery fluid that fills the "anterior chamber of the eye" which is located immediately behind the cornea and in front of the lens. The aqueous humor is very slightly alkaline salt solution that includes tiny quantities of sodium and chloride ions. It is continuously produced, mainly by the ciliary processes, flows from the posterior

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chamber through the pupil into the anterior chamber, and exits via the trabecular route at the angle and the uveoscleral route. Schlemm's canal (canal of Schlemm or the scleral venous sinus), is a circular channel that collects aqueous humour from the anterior chamber and delivers it into the bloodstream via the anterior ciliary veins. It is located at the junction of the cornea and the sclera.[8]

In human, the rate of aqueous humor turnover is approximately 1% - 1.5% of the anterior chamber volume per minute. The rate of aqueous formation is approximately 2.5 µl/min. Aqueous humor consists of pressure dependent and pressure independent pathways. The pressure dependent outflow refers to the trabecular meshwork-schlemm's canal-venous system, while pressure independent outflow refers to any non trabecular outflow and is called as uveoscleral outflow.

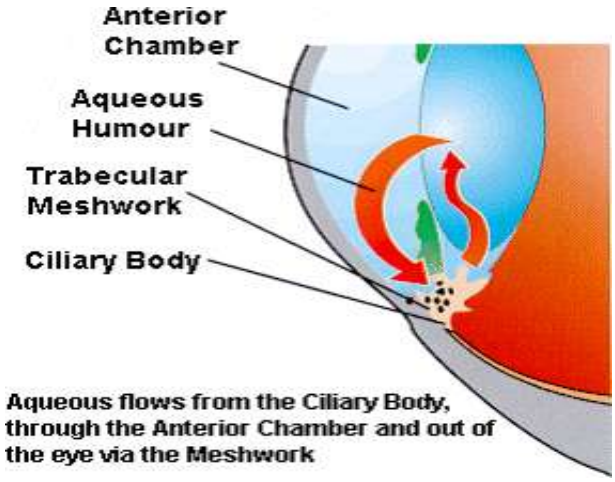

Figure2: Pathway of Aqueous Humor

E. Pupil

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

F. Iris

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

G. Ciliary Muscle

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

H. Lens

The lens is a transparent structure enclosed in a thin transparent capsule. It is located behind the pupil of the eye and encircled by the ciliary muscles. It helps to refract light travelling through the eye (which first refracted by the cornea). The lens focuses light into an image on the retina. It is able to do this because the shape of the lens is changed according to the distance from the eye of the object(s) the person is looking at. This adjustment of shape of the lens is called accommodation and is achieved by the contraction and relaxation of the ciliary muscles.

I. Vitreous Humour

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

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albuminous fluid enclosed in a delicate transparent membrane called the hyaloid membrane.

J. Retina

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

K. Macula

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

L. Choroid

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

M. Optic nerve

The optic nerve (a bundle of over 1 million nerve fibers) is responsible for transmitting nerve signals from the eye to the brain. These nerve signals contain information on an image for processing by the brain. The front surface of the optic nerve, which is visible on the retina, is called the optic disk.

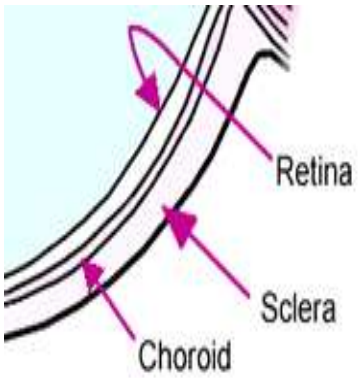

Figure 3: Posterior view of eye

ROUTES OF OCULAR DRUG DELIVERY[9]

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

1. 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.gels, gelifying formulations, ointments,and inserts).

2. Subconjunctival administration

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

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segment and to guide the healing process after surgery.

3. 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)

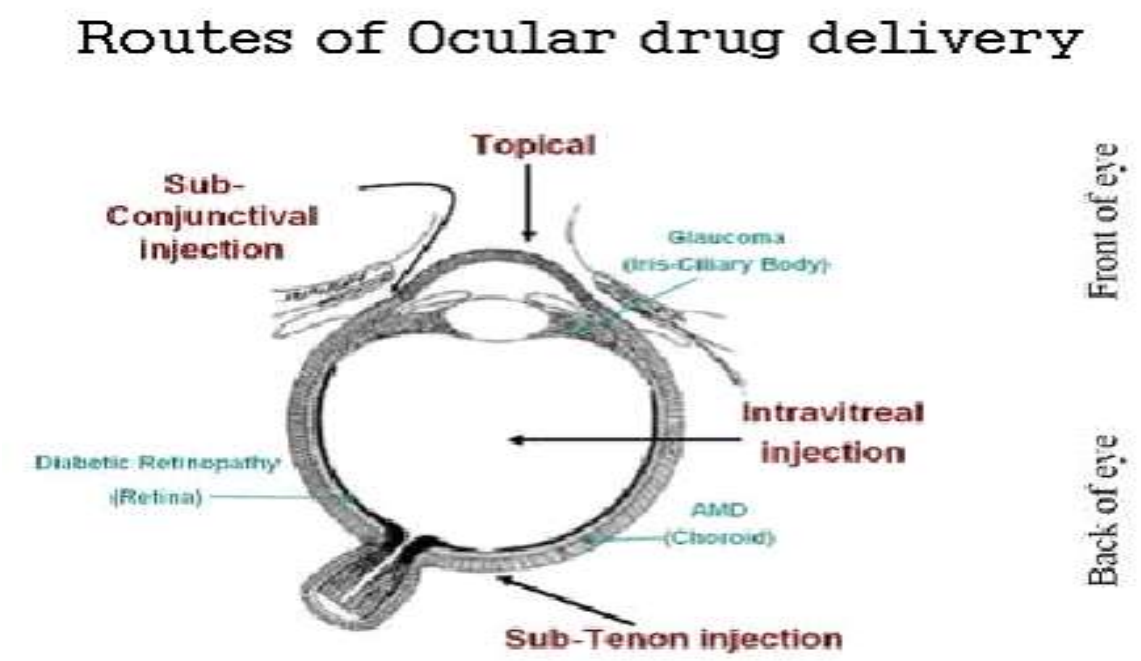

Figure 4: Different Routes for Ocular Drug Delivery

barrier. Small molecules are able to diffuse rapidly in the vitreous but the mobility of large molecules, particularly positively charged, is restricted.

BARRIERS FOR OCULAR DELIVERY

- **Drug loss from the ocular surface**

After instillation, the flow of lacrimal fluid removes instilled compounds from the surface of 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 blood stream by blood-ocular barriers. These barriers have two parts: blood-aqueous barrier and blood-retina barrier. The anterior blood-eye barrier is composed of the endothelial cells in the uvea (The middle layer of the eye beneath the the sclera. It consists of the iris, ciliary body, and choroid). This barrier prevents the access of plasma albumin into the aqueous humor, and also limits the access of hydrophilic drugs from plasma into the aqueous humor. The posterior barrier between blood stream and eye is comprised of retinal pigment epithelium (RPE) and the tight walls of retinal capillaries.

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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 endothelia.

Table no 1: Barriers for the Ocular delivery

	Conjunctiva	Cornea	Sclera
Surface area	17.65 ± 2.12 cm2	1.04 ± 0.12	16 – 17
Thickness	-	0.57 mm	0.4 -0.5 mm
Structural composition	Mucus membrane □ □ Epithelium □ □ Vasculature	5 layers □ □ Epithelium □ □ Bowman's membrane □ □ Stomata □ □ Descemet's membrane □ □ Endothelium	□ □ Collagen fibers □ □ Water □□ Proteoglycans □ □ Monopolysaccharides □ □ Elastic fibers □ □ Fibroblast

MECHANISM OF OCULAR DRUG ABSORPTION [10]

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.

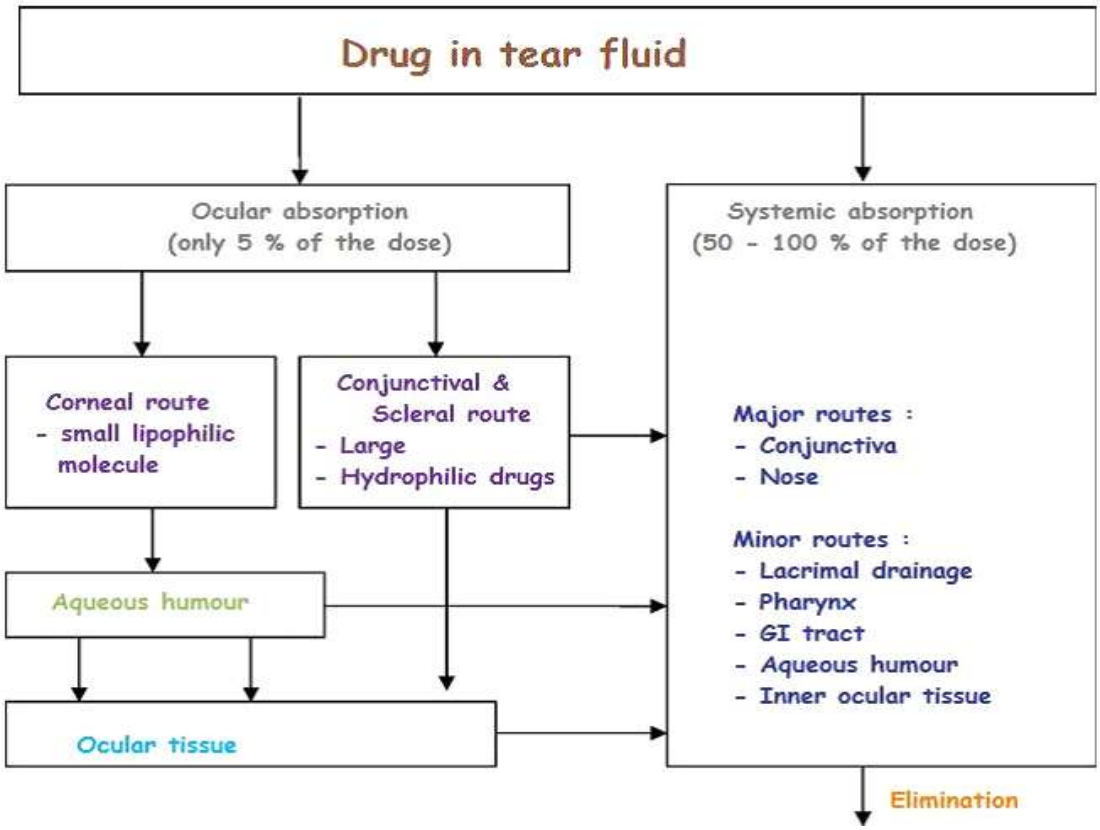

Figure 5: Ocular Drug Absorption

Corneal permeation

The permeation of drugs across the corneal membrane occurs from the precorneal space. Thus, the mixing and the kinetic behavior of drug disposition in tears have a direct bearing on efficiency of drug absorption into the inner eye.

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The productive absorption of most ophthalmic drugs results from diffusional process across corneal membrane. The efficiency of absorption process is a function of rate and extent at which the transport processes occur. The flux of any drug molecule across the biological membrane depends on the physicochemical properties of the permeating molecule and its interaction with the membrane. The extent to which the transport or absorption process occurs is also function of physiological mechanism of precorneal fluid drainage or turnover. In terms of transcorneal drug permeation, the cornea can be considered to consist of three primary layers (epithelium, stroma and endothelium). The epithelium and endothelium contain on the order of a 100 fold greater amount of lipid material than the stroma. Consequently, depending on the physicochemical properties of a diffusing drug, the resistance offered by the individual layers varies greatly. Epithelium, being lipodal, represents a diffusional barrier offering high resistance to ionic or other aqueous soluble or polar species. In contrast, compounds with relatively low polarity encounter a greater diffusional resistance in the hydrophilic stroma layer. This frequently cited concept of drug permeation across the corneal membrane is referred to as "differential solubility concept".

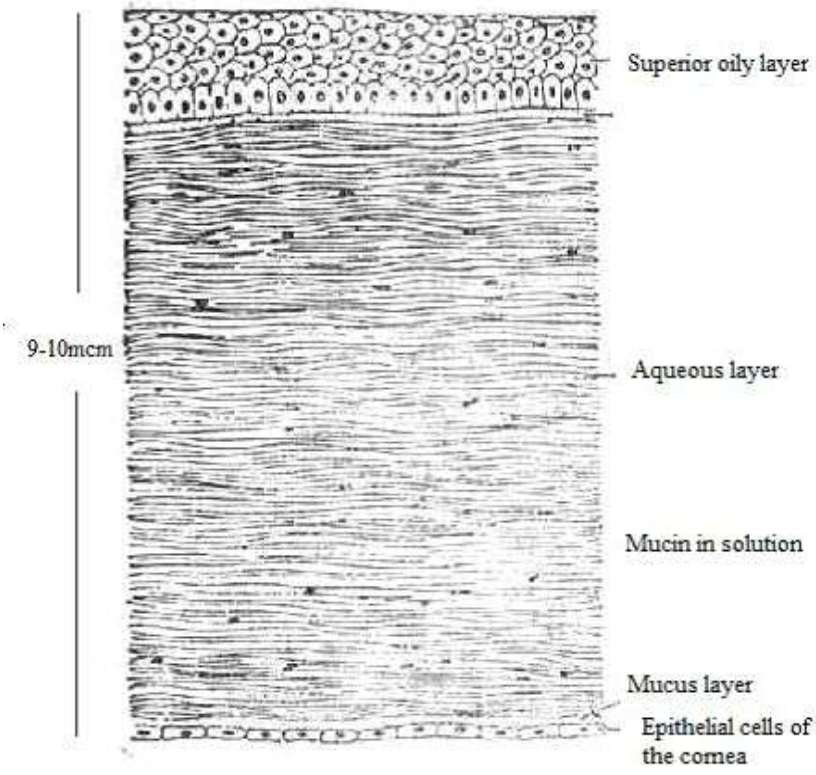

Figure 6: Structure of the tear film in the human eye

Non-corneal permeation

Primary mechanism of drug permeation is the sclera is likely to be diffusion across the intercellular aqueous media in the case of structurally similar corneal stroma. Therefore the possibility of partitioning mechanism cannot be eliminated.

Although like cornea, the conjunctiva is composed of an epithelial layer covering an underlying stroma, the conjunctival epithelium offers substantially less resistance than does the corneal epithelium.

Various factors responsible for disposition of ocular drugs [11]

Bioavailability of drugs administered to the eye is an important consideration. There are physiological factors, which can affect a drug's bioavailability including protein binding, drug metabolism and lachrymal drainage. Protein bound drugs are incapable of penetrating the corneal epithelium due to the size of the protein drug complex. Because of the brief time in which an ophthalmic solution may remain present in the eye

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(due to lachrymal drainage), protein binding of a drug substance could quickly negate its therapeutic value by rendering it unavailable for absorption.

One of the major problems encountered with conventional ophthalmic solutions is the rapid and extensive elimination of drugs from the precorneal lachrymal fluid. It must be noted that this high drainage rate is due to the tendency of the eye to maintain its residence volume at 7–10 µl permanently, whereas volumes topically instilled range from 20–50 µL. In fact it has been demonstrated in vivo that 90% of the dose was cleared within 2 min for an instilled volume of 50 µL and, within 4 min for an instilled volume of 10 µl. Consequently, the ocular residence time of conventional solutions is limited to a few minutes, and the overall absorption of a topically applied drug is limited to 1–10%. As in the case with other biological fluids, tears contain enzymes (such as lysozymes) capable of the metabolic degradation of the drug substance. In addition to the physiological factors affecting ocular bioavailability, other factors as the physicochemical properties of the drug substance, and product formulation are important. Because the cornea is a membrane-barrier containing both hydrophilic and lipophilic layers, it is permeated most effectively by drug substances having both hydrophilic and lipophilic characteristics.

It is advantageous for corneal penetration to adjust the pH of the solution to increase the proportion of unionized drug in the instilled dose. Drugs, which are highly water insoluble, do not readily permeate the cornea.

Figure 7: Reasons for poor ocular bioavailability

Nasolacrymal drainage system

The nasolachrymal drainage system consists of three parts: the secretory system, the distributive system and the excretory system. The secretory system consists of basic secretors that are stimuli to tear evaporation and reflex secretors that have an efferent parasympathetic nerve supply and secrete in response to physical or emotional stimulation. The distributive system consists of the eyelids and the tear meniscus around the lid edges of the open eye, which spread tears over the ocular surface by blinking, thus preventing dry areas

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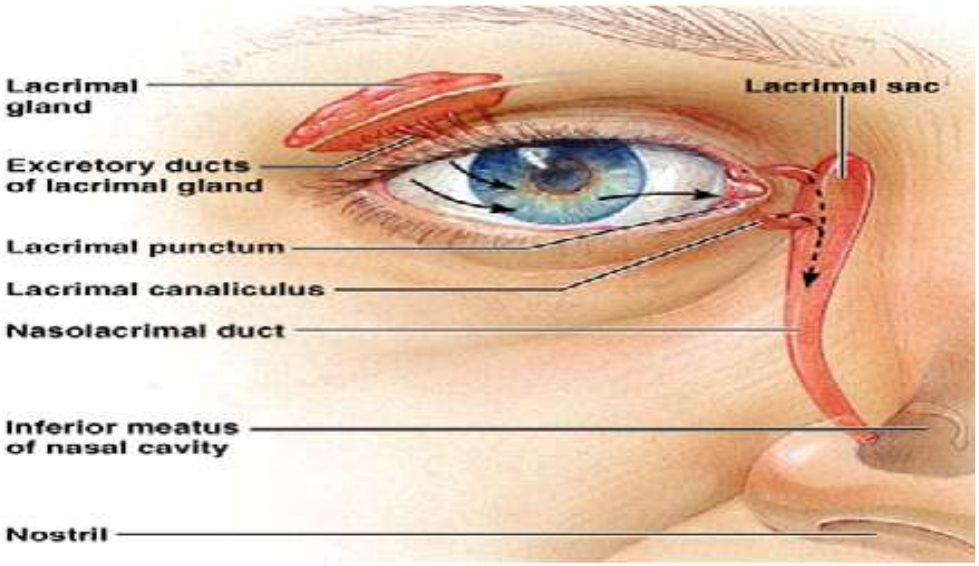

Figure 8: Nasolachrymal Drainage Apparatus

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

Interests of novel ophthalmic drug delivery

Ophthalmic drug delivery is one of the most interesting and challenging endeavors facing the pharmaceutical scientist. [12] The landscape of ophthalmic drug delivery is highly competitive and rapidly evolving. New classes of pharmaceuticals and biologics are fueling the demand for novel drug delivery. The main aim of pharmacotherapeutics is the attainment of effective drug concentration at the site of action for the sufficient period of time to elicit a response. The challenge is to provide a system with improved ocular drug bioavailability and prolonged duration of activity, but still with a minimum risk of ocular complications. A major problem of ophthalmic drug delivery is not the lack of efficient drugs but the attainment of their optimal concentration at the site of their optimal concentration at the site of action.

Most of the formulation efforts aim at maximizing ocular drug absorption through prolongation of the drug residence time in the cornea conjunctival sac, as well as to slow drug release from the delivery system and minimize precorneal drug loss. Various ophthalmic formulations and their residence time period in the ocular cavity are given below.

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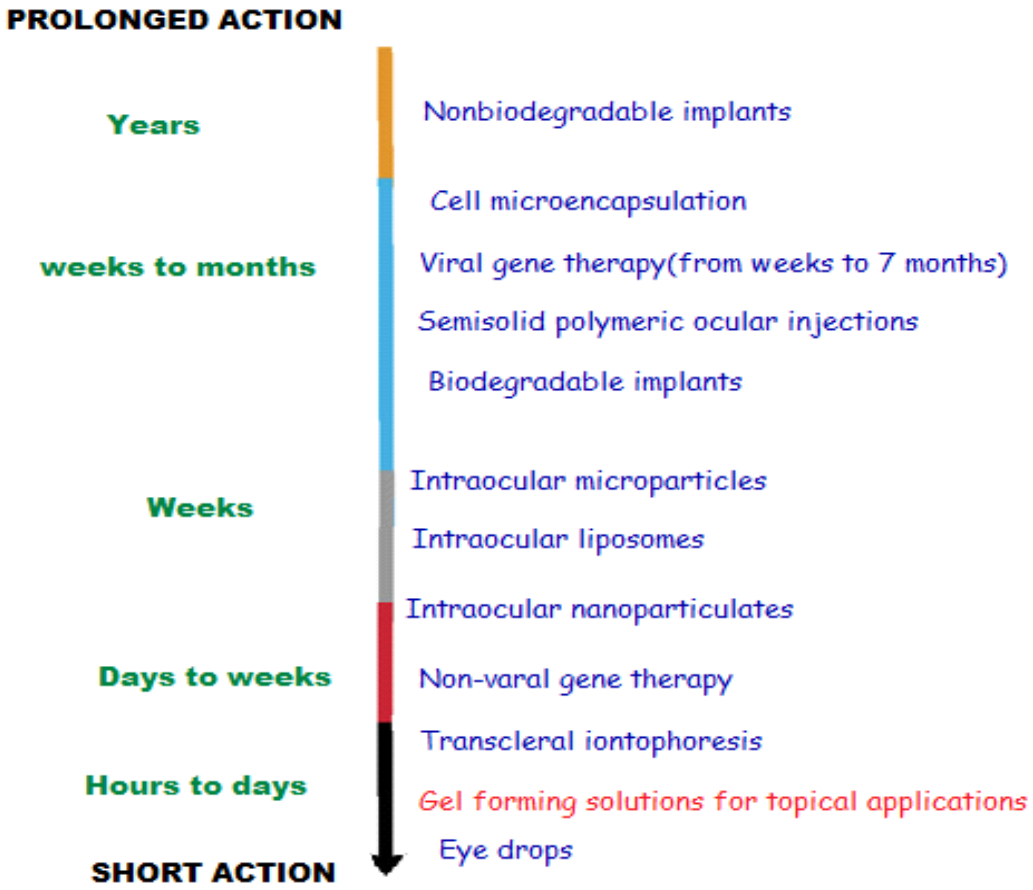

Figure 9: Duration of action of ocular drug delivery systems

Ophthalmic drug formulations

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

Eye Infections: [13]

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

Conjunctivitis:

Conjunctivitis is swelling (inflammation) or infection of the membrane lining the eyelids (conjunctiva).It is characterized by cellular infiltration and exudation. Staphylococcus aureus is the most common cause of bacterial conjunctivitis and blepharo-conjunctivitis. Many other organisms like Haemophilusinfluenzae, Streptococcus pneumoniae also cause conjunctivitis. Conjunctivitis can be classified as (1) Infective – Acute, Subacute & Chronic (2) Allergic conjunctivitis.

Corneal ulcers/ Keratitis:

Inflammation of cornea (Keratitis) is characterized by corneal oedema, cellular infiltration & ciliary congestion. Being the most anterior part of eyeball, cornea is exposed to atmosphere & hence prone to get infected easily. Bacterial corneal ulcers are the most ccus aureus, Pseudomonas pyocyanea, E.coli. Proteus etc.

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Endophthalmitis:

It is severe form of intraocular inflammation (purulent uveitis) involving ocular cavities & inner coats of eyeball. Causative organisms include Streptococci, E.coli, Pseudomonas, etc. Accordingly, the armamentarium of available antimicrobials used in the prevention and treatment of these infections includes antivirals, antifungals, and antibacterials. Common topical antibacterials used in the treatment of ocular infectious diseases include sulfonamides, aminoglycosides, polymyxin-based combinations, and **fluoroquinolones**.

The fluoroquinolones represent an expanding class of broad-spectrum antibacterials which cover a host of Gram-negative and anaerobic species responsible for ocular infections. These antibacterials have gained popularity in the ophthalmology field since they have been shown to be equivalent to combination therapy in the treatment of many ocular infections. Fluoroquinolones are also effective against a variety of Gram-positive organisms, including Streptococcal and Staphylococcal species; however, resistance is emerging among some of these Streptococcal and Staphylococcal species; however, resistance is emerging among some of these organisms. [7]

The classification and mechanism of action of fluoroquinolones are given below.

Antibiotic Generation	**Example**	**Activity**
1 ST GENEARTION	□ □ □ Nalidixic acid	• Have limited activity against gram negative & gram positive organism
2 ND GENERATION	□ □ Oxolinic acid □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ Cinoxa □ □ Pipemic acid	• Improvement in gram negative coverage including antipseudomonal Activity • Shows limited activity against gram positive organism
3 RD GENERATION	□ □ □ □ □ □ □ □ □ □ □ □ □ □ □ Norflox □ □ Ciprofloxacin □ □ □ Leavofloxacin □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ Ofloxac	• Having antipseudomonal activity against gram negative bacilli
4 TH GENERATION	□ □ □ □ □ □ □ □ □ □ □ □ □ □ □ Ciprofl □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ Moxiflo	• Having dual mechanism of action in gram positive bacteria in addition reducing efflux from the bacterial cell • Improved spectrum of Activity

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MECHANISM OF ACTION

Levofloxacin hemi hydrate is broad spectrum anti bacterial drug, which acts by inhibiting bacterial DNA gyrase enzyme which is required for DNA replication,gelrite is an anionic deacetylated exocellular polysaccharide secreted by Pseudomonas elodea, with a tetra saccharide repeating unit of one -L-rhamnose,one-D-glucuronic acid and two -D- glucose residues. It has the property of cation-induced and temperature dependent gelation.

TABLE NO: 1 CRITERIA FOR SELECTION OF OCULAR DOSAGE FORMS

GELS	INJECTIONS	INSERTS	OINTMENTS	ORALS	SOLUTIONS	SUSPENSIONS
Drug; Long duration required	Drug; Target site Accessibility Onset of response	Drug; Long Duration required	Drug; Long Duration required	Drug; Impermeable Topically Few systemic side effects	Drug; Soluble Less potent	Drug; Insoluble Drug potent
Low bioavailability	--	Low bioavailability	Low bioavailability	--	Required high concentration	--
Intermediate cost	Requires physician	High cost per dose	Low cost	Low to moderate cost	Low cost	Low cost
Some blurring	--	No blurring	Severe blurring	--	Little blurring	Little blurring
Selection; Simple administrational reduced frequent administration	Selection; Last alternative surgical application	Selection; Good control of rate of drug administration younger patient	Selection; Slight threatening	Selection; Drug designed not optimized	Selection; Convenient accepted	Selection; Convenient Accepted some extend duration
Safety	Safety	Safety; Unnoticed expulsion	Safety	Safety	Safety; Solution clear	Safety; Solutions cloudy

Polymeric drug delivery devices [14]

Hydrogels are one of the upcoming classes of polymer-based controlled release drug delivery systems.21 Polymeric drug delivery systems have been extensively studied in order to solve the potential problems associated with drugs or bioactive molecules including toxicity, site dependence, low effectiveness, poor solubility, short half life, rapid degeneration and rapid clearance from the body. Considering various properties such as flexibility, structure, biocompatibility, and hydrophilicity, three dimensional matrices, hydrogels, are being extensively used as drug delivery carriers.

ADVANTAGES OF POLYMERIC DRUG DELIVERY

□ □ □ Reduce toxic effects on the healthy tissue and reach sites that are conventionally inaccessible due to the presence of various barriers 9 by targeted drug delivery.

□ □ □ Increase the half life of drugs, preventing their rapid degradation, and reduce the rate of elimination, thus maintaining drug concentration within a therapeutically effective window.

□ □ □ Reduce the amount of drug required to achieve therapeutic efficacy.

□ □ □ Cut down the number of repeated invasive dosage required for certain conditions and thus helps to improve patient's compliance and offers better living.

REQUISITES OF CONTROLLED OCULAR DRUG DELIVERY SYSTEM

- It provides the better housing to the delivery system.
- To circumvent the protective barriers like drainage, lacrimation and diversion of exogenous chemicals into the systemic circulation by the conjunctiva.
- To increase the ocular bioavailability of drug by increasing corneal contact time. This can be achieved by effective coating or adherence to

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corneal surface so that the released drug actively reaches the anterior chamber.
- To overcome the side effects of pulsed dosing produced by conventional dosage forms.
- To provide comfort and compliance to the patient and yet improve the therapeutic performance of the drug over conventional dosage forms.
- To provide controlled and sustained drug delivery.
- To provide targeting with in the ocular globe, so as to prevent their loss to other ocular diseases.

IN SITU HYDROGELS [15]

In-situ: at the place. Improved local bioavailability, reduced dose concentration, less total drug, improved patient acceptability, reduced dosing frequency.

In-situ forming hydrogels are liquid upon instillation and undergo phase transition in the ocular cul-de-sac to form visco-elastic gel and this provides a response to environmental changes.

Hydrogels are polymeric networks that absorb large quantities of water while remaining insoluble in aqueous solutions due to chemical or physical crosslinking of individual polymer chains. They resemble natural living tissue more than any other class of synthetic biomaterials due to their high water content; furthermore, the high water content of the materials contributes to their biocompatibility.23 Hydrogels show minimal tendency to adsorb proteins from body fluids because of their low interfacial tension. Further, the ability of molecules of different sizes to diffuse into (drug loading) and out of (drug release) hydrogels allows the possible use of dry or swollen polymeric networks as drug delivery systems for oral, nasal, buccal, rectal, vaginal,ocular and parenteral routes of administration.

These are polymers endowed with an ability to swell in water or aqueous solvents and induce a liquid–gel transition. [61] Currently, two groups of hydrogels are distinguished, namely preformed and in situ forming gels. Preformed hydrogels can be defined as simple viscous solutions which do not undergo any modifications after administration. The use of preformed hydrogels still has drawbacks that can limit their interest for ophthalmic drug delivery or as tear substitutes. They do not allow accurate and reproducible administration of quantities of drugs and, after administration; they often produce blurred vision, crusting of eyelids, and lachrymation. Thus in situ hydrogels can be instilled as eye drops and undergo an immediate gelation when in contact with the eye. In situ-forming hydrogels are liquid upon instillation and undergo phase transition in the ocular cul-de-sac to form viscoelastic gel and this provides a response to environmental changes. Three methods have been employed to cause phase transition on the surface: change in temperature, pH, and electrolyte composition.

Increase in solution viscosity by using polymers improves retention of product on the corneal surface. More recently, the approach to improve precorneal retention is based on the use of mucoadhesive polymers. The principle for use of bioadhesive vehicles relies on their ability to interact with the mucin-coating layer present at the eye surface. The polymers chosen to prepare ophthalmic hydrogels should meet some specific rheological characteristics. It is generally well accepted that the instillation of a formulation should influence tear behavior as little as possible. Because tears gave a pseudo plastic behavior, pseudo plastic vehicles would be more suitable as compare to Newtonian formulations, which have a constant viscosity independent of the shear rate, whereas pseudo plastic solution exhibit decreased viscosity with increasing shear rate, thereby offering lowered viscosity during blinking and stability of the tear film during fixation. [16, 4]

Drug release from hydrogels:

Hydrogels have a unique combination of characteristics that make them useful in drug delivery applications. Due to their hydrophilicity, hydrogels can imbibe large amounts of water (N90 wt. %). Therefore, the molecule release mechanisms from hydrogels are very different from hydrophobic polymers. Both simple and sophisticated models have been previously developed to predict the release of an active agent from a hydrogel device as a function of time.

These models are based on the rate limiting step for controlled release and are therefore categorized as diffusion, swelling & chemically controlled mechanism.

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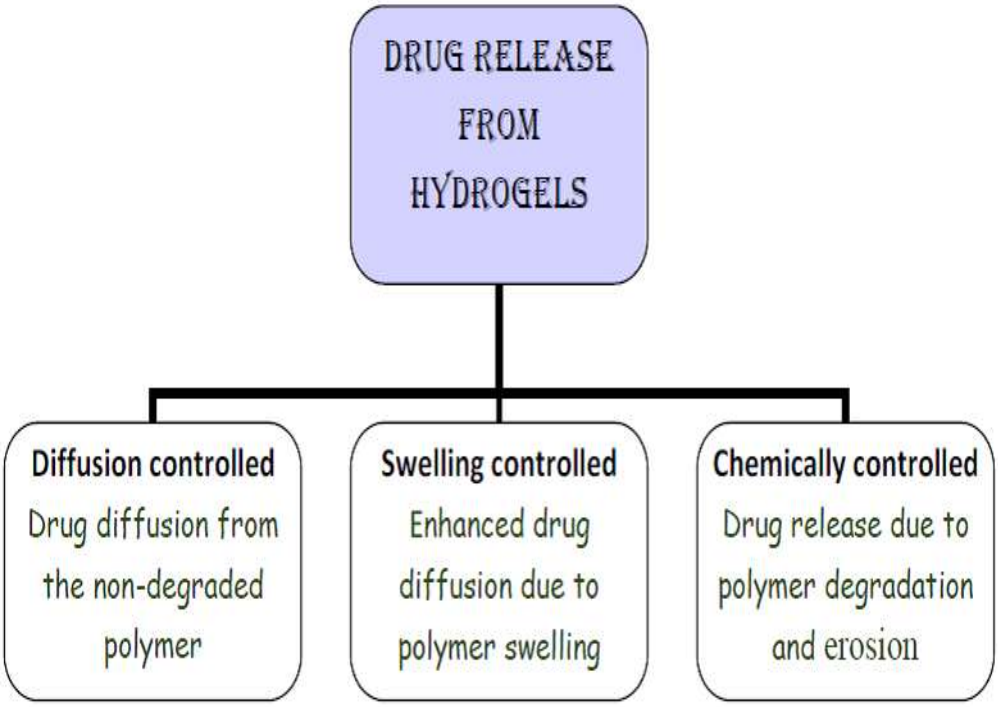

Figure 11: Drug release from hydrogels

SMART HYDROGELS

"Smart" hydrogels, or stimuli-sensitive hydrogels, are very different from inert hydrogels in that they can "sense" changes in environmental properties such as pH and temperature and respond by increasing or decreasing their degree of swelling. The volume-changing behavior of 'smart' hydrogels is particularly useful in drug delivery applications as drug release can be triggered upon environmental changes. These "intelligent" or "smart" polymers play important role in drug delivery since they may dictate not only where a drug is delivered, but also when and with which interval it is released. The stimuli that induce various responses of the hydrogel systems include physical (temperature) or chemical (pH, ions) ones.

Temperature-sensitive hydrogels are probably the most commonly studied class of environment-sensitive polymer systems in drug delivery research. These hydrogels are able to swell or deswell as a result of changing in the temperature of the surrounding fluid. In case of pH sensitive hydrogels, the pH-sensitive polymers contain pendant acidic or basic groups that either accept or release protons in response to changes in environmental pH. The polymers with a large number of ionizable groups are known as polyelectrolytes. Swelling of hydrogel increases as the external pH increases in the case of weakly acidic (anionic) groups, but decreases if polymer contains weakly basic (cationic) groups. Another mechanism of in situ hydrogel is ion induced gelation. In this, polymers may undergo phase transition in presence of various ions. Gellan gum commercially available as Gelrite® is an anionic polysaccharide that undergoes in situ gelling in the presence of mono- and divalent cations, including Ca2+, Mg2+, K+ and Na+. Gelation of the low-methoxypectins can be caused by divalent cations, especially Ca2+.

Advantages of In-situ forming gel:

- Generally more comfortable than insoluble or soluble insertion Less blurred vision as compared to ointment Increased bioavailability due to –Increased precorneal residence time.
- Decreased nasolacrimal drainage of the drug.
- Chances of undesirable side effects arising due to systemic absorption of the drug through naso-lacrimal duct is reduced.
- Drug effect is prolonged hence frequent instillation of drug is not required

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METHODS OF IN –SITU GELLING SYSTEM[16]

Change in temperature :

Sustained drug delivery can be achieved by use of a polymer that changes from sol to gel at the temperature of the eye. Temperature dependent systems include pluronics and tetronics. The poloxamers F127 are polyols with thermal gelling properties whose solution viscosity increases when the temperature is raised to the eye temperature (32-34 C) from a critical temperature (16^{o}c).

Change in pH :

Change in pH triggered systems show sol to gel transformation when the pH is raised by the tear fluid to pH 7.4. pH triggered systems include- cellulose acetate hydrogen phthalate latex, (pH 5.0 to 7.2-7.4 forms a gel with LF). Carbopol (polyacrylic acid 0.5%, polycarbophil) pH 4.0 to 7.4 sol to gel transformation Cellulose acetophthlate (CAP) is a polymer with potentially useful properties for sustained drug delivery to the eye, since latex is a free flowing solution at a pH of 4.4 which undergoes coagulation when the pH is raised by the tear fluid of pH 7.4. pH triggered In-situ gelling system are low viscosity polymeric dispersion in water which undergoes spontaneous coagulation and gelation after instillation in conjuctival cul-de-sac.

Change in electrolyte composition :

Change in electrolyte composition Ion activated system show sol to gel transformation in the presence of the mono or divalent cations (Na+, Ca2+ etc.) typically found in the tear fluids. Ion activated system include Gelrite® (Gommegellan) and alginates. These system shows sol to gel transformation in the presence of ions. Gellan gum is an anionic extracellular polysaccharide secreted by Pseudomonas elodea. Gellan gum formulated in aqueous solution, forms clear gels in the presence of the mono or divalent cations.

Table no 2: External stimuli Mechanism Examples

External stimuli	Mechanism	Examples
Temperature	• Formulation is liquid at room temperature(20-25°c) which undergoes gelation in contact with body fluid(35-37°c) • Temperature increases degradation of polymer chains which leads to formation of hydrophobic domains & transition of an aqueous liquid to hydrogel network	• Poloxamer/ Pluoronics • Copolymers of Polyethylene oxide PEO • Copolymers of Polypropylene oxide PPO • Polyesters • Xyloglucan • Cellulose derivative
Ionic interactions	• Formulation undergoes liquid- gel transition under influence of an increase in ionic strength • Gel formation takes place because of complexation with polyvalent cations (like Ca^{2+}) in lacrimal fluid	• Chitosan • Gallen gum • Alginate
pH change	• Sol to gel transition when pH raised from 4.2 to 7.4(eye pH) • At higher pH polymer forms hydrogen bonds with mucin which leads to formation of hydrogel network	• Pseudolatexes • Acrylates (carbopol) • Cellulose acetate phthalate (CAP) • Polyox

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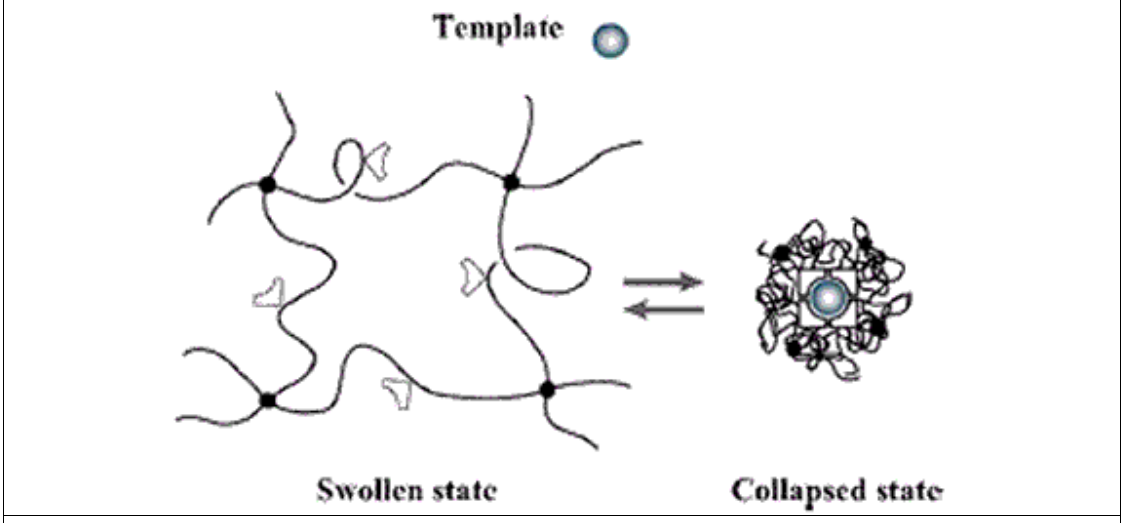

Figure 6. The volume phase transition of the hydrogel -induced by an external stimuli (e.g., a change in pH, temperature or electrical field) modifies the relative distance of the functional groups inside the imprinted cavities. This alters their affinity for the template.

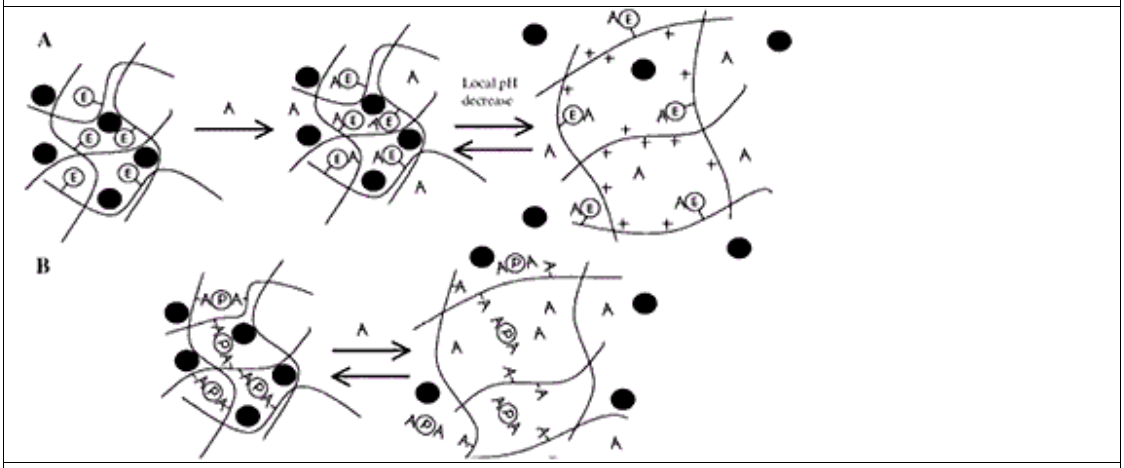

Figure 7. (A) Induced Swelling - As analyte (A) binds, the enzymatic reaction (E denotes covalently attached enzyme) produces a local pH decrease. For the cationic hydrogel, which is weakly basic, the result is ionization, swelling, and release of drug, peptide, or protein (filled circle). When A decreases in the bulk concentration, the gel shrinks. (B) Loss of Effective Cross-links - Analyte competes for binding positions with the protein (P). As free analyte binds to the protein, effective cross-links are reversibly lost and release occurs.

REFERENCE

[1]. **Sangitakute D, SomnathSakoreC ,BaswatCakraborty S.** Formulation approaches in ocular drug delivery system. Int J Pharm Tech .2010;Vol 2,(2) : 118-145.

[2]. **Rathore K S, Nema R K, Sisodia S S.** An overview and advancement in ocular drug delivery systems. Int J Pharm Sci Res. 2010: Vol 1,(10): 11-23.

[3]. **Rathore K S, Nema R K.** An insight into ophthalmic drug delivery system. Int J Pharm Sci Drug Res. 2009; 1(1): 1-5.

[4]. **Rathore K S.** In-situ gelling ophthalmic drug delivery system:An overview. Int J Pharm Pharm Sci. 2010; Vol 2, (4): 30-34.

[5]. **Arul Kumaran K S G, Karthika K, Padmapreetha J.** Comparative review on conventional and advanced ocular drug delivery formulations. Int J Pharm Pharm Sci. 2010; Vol 2, (4): 1-5.
[6]. **Saettone.** Progress and problems in ophthalmic drug delivery. Pharm Tech. 2002; 1-6.
[7]. **Ashim Mitra K.** Ocular drug delivery system. 2nd ed. Revised and Expanded, Marcel Dekker, INC, 2005,1.
[8]. **Nirmal H B, Bakliwal S R, Pawar S P.** In-situ gel: New trends in controlled and sustained drug delivery system. Int J Pharm Tech Res. 2010; Vol 2, No.2: 1398-1408.
[9]. **Geeta Patel M, Madhabhaipatel M.** Recent advances and challenges in ocular drug delivery system article. Pharma Times. 2007; Vol 39, No.1: 21-25.
[10]. **Patel PB ,Shastri DH, Shelat PK, Shukla AK.** Ophthalmicdrug delivery system: Challenges and approaches. Systematic Reviews In Pharmacy . 2010; Vol 1, Issue 2: 113 – 120
[11]. **Akansha Tiwari, Raj Kumar Shukla.** Novel ocular drug deliveysystems:An overview. J Chem Pharm Res. 2010; 2(3): 348-355.
[12]. **Paudel K R, Rauniar G P, Bhattacharya S K, Das B P.** Recent advancement in drug delivery system. Kathmandu Univ Med J. 2008; Vol 6, 2, Issue 22 :262-267.
[13]. **British National Formulary**, Anti infective eye preparations: 11.3.1.
[14]. **Patel PB ,Shastri DH, Shelat PK, Shukla AK.** Ophthalmicdrug delivery system: Challenges and approaches. Systematic Reviews In Pharmacy . 2010; Vol 1, Issue 2: 113 – 120
[15]. **Sarim Imam, Abhishek Bansalb, Bushetti S S, Arpita Singh, HimansuChopra.** Novel ocular dosage form in the treatment of glaucoma. Pharma Res year. 2009; vol 01: 72-81.
[16]. **Mahesh mali N, Ashok Hajare A.**In situ gel-forming systems for sustained ocular drug delivery. Euro Ind Pharm. 2010; (5): 17-20.