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Opthalmic Drug Delevery System; a Promising Approach towards Eye-A Review

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ABSTRACT
Topical administration for ocular therapeutics is ideal because of smaller doses required compared to the systemic use, its rapid onset of action and freedom from systemic toxicity Topically applied ocular drugs have to reach the inner parts of the eye and transcorneal penetration is believed to be the major route for drug absorption. Corneal absorption is much slower process than elimination. 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. 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; one of the way to do so is 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 pre corneal drug retention. This review focused on controlled and sustained drug delivery has become the standard in modern pharmaceutical design and several possible routes of drug delivery into the ocular tissues.

Keywords: Ophthalmic drug delivery, Corneal drug delivery, Controlled and sustained drug delivery.

I. 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. 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 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. 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. 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; one of the way to do so is 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 pre corneal drug retention.

IN SITU FORMING GELS FOR OPTHALMIC DRUG DELIVERY

Recently, controlled and sustained drug delivery has become the standard in modern pharmaceutical design and an intensive research has been under taken in achieving much better drug product effective ness reliability and safety. In this regard many polymers are very useful which undergo reversible sol to gel phase transition in response to physiological stimuli. In situ gels are

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conveniently dropped as a solution into the conjunctival sac, where they underego a transition into a gel with its favourable residence time. The sol-gel transition occurs as a result of a chemical/ physical change induced by physiological environment. This type of gel combines the advantage of a solution being patient convenient with the favourable residence time of a gel for enhancing the ocular bioavailability. The sol-gel transition can be induced by a shift in the pH as for cellulose acetate phthalate, a shift in temperature as for the thermogellingPoloxamer 188 or by presence of cations as for deacetylatedgellan gum and alginates. Thus, the in situ gelling systems for ophthalmic use can be classified as pH sensitive, temperature sensitive and ion-activated systems. The rate of gel formation in situ, is important since when dropped in the eye, before a strong gel is formed, a solution or a weak gel is prone to elimination by the fluid mechanics of the eye. The ion activated in situ gelling system can be formulated using sodium alginate, the sodium salt of alginic acid, as a natural hydrophilic polysaccharide containing two types of monomers, β-D-mannuronic acid (M) and x-Lguluronic acid (G) which forms a gel in the cul-de-sac due to the presence of divalent calcium ions in the lacrimal fluid. Thus with the use of these in situ gelling systems, residence time of the drug in the eye is increased. Continuous delivery of drugs in a controlled manner to the anterior chamber of the eye will eliminate the requirement for frequent drug administration, causing better patient compliance and will result in extended duration of action, hence lower amount of total dose required, which in turn will minimize the local and/or systemic side effects.

THE ANATOMY OF THE EYE

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 1 inch across. It houses many structures that work together to facilitate sight. The human eye is comprised of layers and internal structures, each of which performs distinct functions. The detailed description of each eye part is given below.

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 chamber through the pupil into the anterior chamber, and exits via the trabecular route at the angle and the uveoscleral route. Schlemm's canal (canal of Schlemm or the scleral venous sinus), is a circular channel that collects aqueous humour from the anterior chamber and delivers it into the bloodstream via the anterior ciliary veins. It is located at the junction of the cornea and the sclera. In human, the rate of aqueous humor turnover is approximately 1% - 1.5% of the anterior chamber volume per minute. The rate of aqueous formation is approximately 2.5 µl/min. Aqueous humor consists of pressure dependent and pressure independent pathways. The pressure dependent outflow refers to the trabecular meshwork-schlemm's canal-venous system, while pressure

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independent outflow refers to any non trabecular outflow and is called as uveoscleral outflow.

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) and Ciliary 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 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 bedescribed 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 ofthe 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.

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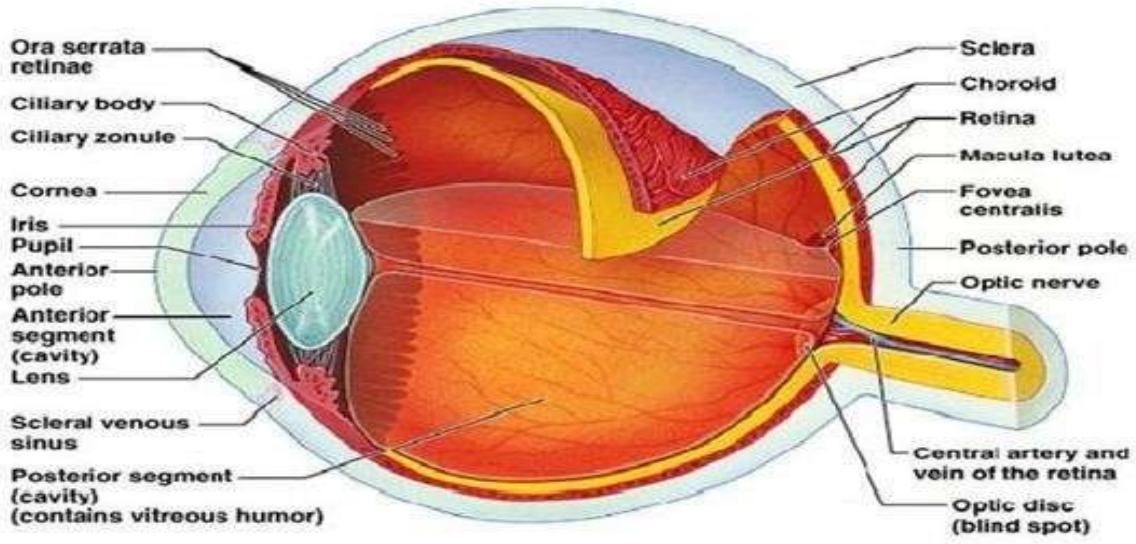

Fig 1. Anatomy of eye

ROUTES OF OCULAR DRUG DELIVERY

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

Topical route

Typically topical ocular drug administration is accomplished by eye drops, but they have only a short contact time on the eye surface. The contact, and thereby duration of drug action, can be prolonged by formulation design (e.g.m gels, gelifying formulations, ointments, and inserts).

Subconjunctival administration

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

Intravitreal administration

Direct drug administration into the vitreous offers distinct advantage of more straightforward access to the vitreous and retina. It should be noted; however that delivery from the vitreous to the choroid is more complicated due to the hindrance by the RPE (Retinal Pigment Epithelium) barrier. Small molecules are able to diffuse rapidly in the vitreous but the mobility of large molecules, particularly positively charged, is restricted.

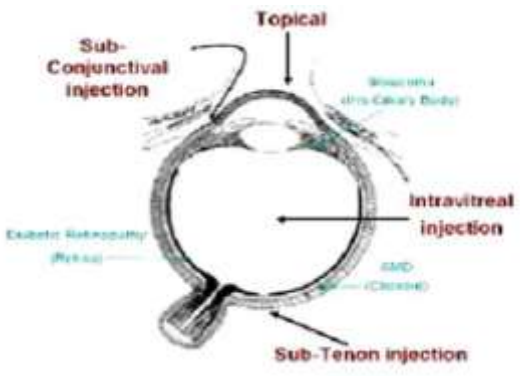

Fig 2. Different Routes for Ocular Drug Delivery

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BARRIERS FOR OCULAR DELIVERY:

Drug loss from the ocular surface

After instillation, the flow of lacrimal fluid removes instilled compounds from the surface of 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 uveam (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. 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 thereafterdistribution into the retina is limited by the RPE and retinal endothelia.

	Conjunctiva	Cornea	Sclera
Surface area	17.65 ± 2.12 cm^2	1.04 ± 0.12	16 – 17
Thickness	-	0.57 mm	0.4 -0.5 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

Table 1. Barriers for the Ocular delivery

MECHANISM OF OCULAR DRUG ABSORPTION

Drugs administered by instillation must penetrate the eye and do so primarily through the cornea followed by the non-corneal routes. These non-corneal routes involve drug diffusion across the conjunctiva and sclera and appear to be particularly important for drugs that are poorly absorbed across the cornea. Corneal permeation The permeation of drugs across the corneal membrane occurs from the precorneal space.

Various Barrieirs to drug Absorption:

In tears have a direct bearing on efficiency of drug absorption into the inner eye.The productive absorption of most ophthalmic drugs results from diffusional process across corneal membrane.The efficiency of absorption process is a function of rate and extent at which the transport processes of eye. 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 layersionic 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 ism referred to as "differential solubility concept".

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Non-corneal permeation

Primary mechanism of drug permeation is the sclera is likely to be diffusionacross 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.

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

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

A) Conjunctivitis:

Conjunctivitis is swelling (inflammation) or infection of the membrane lining the eyelids (conjunctiva).It is characterized by cellular infiltration and exudation. Staphylococcus aureus is the most common cause of bacterial conjunctivitis and blepharo-conjunctivitis. Many other organisms like Haemophilus influenzae, Streptococcus pneumoniae also cause conjunctivitis. Conjunctivitis can be classified as

(1) Infective – Acute, Subacute & Chronic

(2) Allergic conjunctivitis.

B) Corneal ulcers/ Keratitis:

Inflammation of cornea (Keratitis) is characterized by corneal oedema, cellular infiltration & ciliary congestion. Being the most anterior part of eyeball, cornea is exposed to atmosphere & hence prone to get infected easily. Bacterial corneal ulcers are the most commonly caused by virulent organism. Common bacteria associated with corneal ulceration are Staphylococcus aureus, Pseudomonas pyocyanea, E.coli and Proteus etc.

C) 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 them 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 organisms.

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 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.

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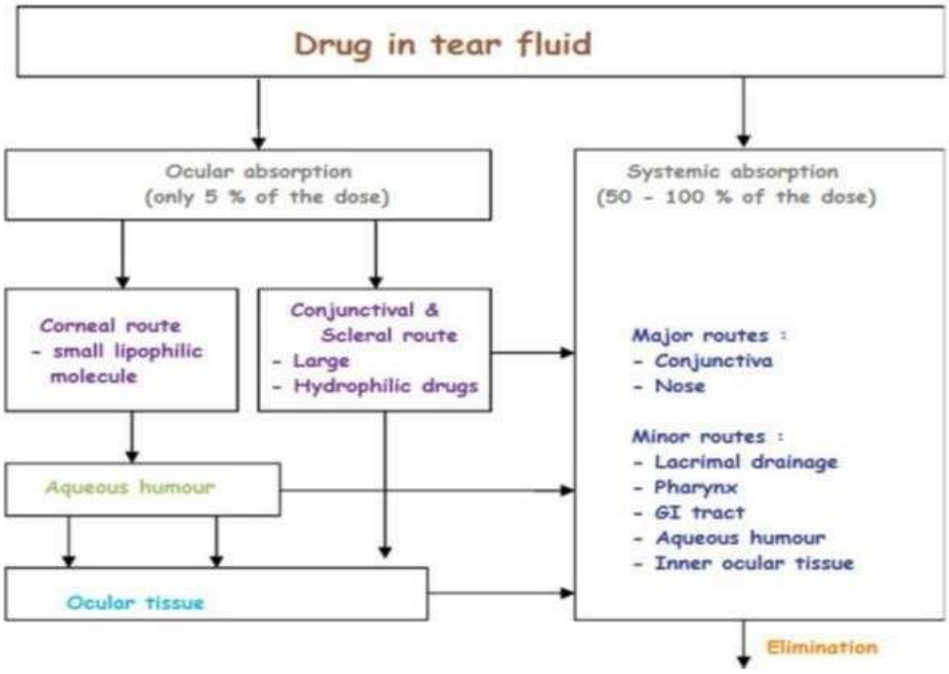

Contact Lenses;

After application, contact lens adheres to the film of tears over the cornea due to the surface tension. Drug loaded contact lens have been developed for ocular delivery of numerous drugs such as β-blockers, antihistamines and antimicrobials. It is postulated that in presence of contact lens, drug molecules have longer residence time in the post-lens tear film which ultimately led to higher drug flux through cornea with less drug inflow into the nasolacrimal duct. Usually, drug is loaded into contact lens by soaking them in drug solutions. These soaked contact lenses demonstrated higher efficiency in delivering drug compared to conventional eye drops observed much higher bioavailability of dexamethasone (DX) from poly (hydroxyethyl methacrylate) (PHEMA) contact lenses in comparison to eye drops. Indeed, efficient than topical drops, these soaked contact lenses suffers from disadvantages of inadequate drug loading and short term drug release. To overcome these obstacles, particle-laden contact lenses and molecularly imprinted contact lenses have been developed. In particle-laden contact lenses, drug is first entrapped in vesicles such as liposomes, nanoparticles or microemulsion and then these vesicles are dispersed in the contact lens material.

II. CONCLUSION

New ophthalmic delivery system includes ocular inserts, collagen shields, ocular films, disposable contact lens and other Novel drug delivery systems like hiosomes 20 and nanoparticles. Newer trend is a combination of drug delivery technologies for improving the therapeutic response of a non efficacious drug. This can give a superior dosage forms for topical ophthalmic application. Among these drug delivery systems, only few products have been, commercialized. An ideal system should have effective drug concentration at the target tissue for a tended period of time with minimum systemic effect. Patient acceptance is very important for the design of any comfortable ophthalmic drug delivery system. Major Improvements are required in each system like improvement in sustained drug release, large scale manufacturing and stability. Combination of drug delivery systems could open a new directive for improving the therapeutic response of a non-efficacious system. They can overcome the limitations and combine the advantages of different systems.

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