1. INTRODUCTION TO OCULAR DRUG DELIVERY

Ophthalmic drug delivery is one of the most interesting and challenging endeavors facing the pharmaceutical scientists. The anatomy, physiology and biochemistry of the eye render this organ exquisitely impervious to foreign substances. The challenging to the formulator is to circumvent the protective barriers of the eye without causing techniques and therapeutics agents renders urgency to the development of successful and advanced ocular drug delivery systems.1,2

The goal of pharmacotherapeutics is the attainment of an effective drug concentration at the intended site of action for a desired length of time. Eye, as a portal for drug delivery is generally used for the local therapy as against systemic therapy in order to avoid the risk of eye damage from high blood concentrations of drug, which are not intended for eye.3,4

The conventional ocular dosage forms for the delivery of drugs are5,6

• Eye drops
• Eye ointments
• Suspensions

The eye drop dosage form is easy to instill but suffers from the inherent drawback that most of the instilled volume is eliminated from the precorneal area7,8 resulting in a bioavailability ranging from 1-10% of total administrated dose.9 The rapid precorneal elimination of drugs given in eye drops is mainly due to conjunctival absorption, solution drainage by gravity, induced lacrimation and normal tear turnover.9 Because of poor ocular bioavailability, many ocular drugs are applied in high concentrations.

This cause both ocular and systemic side effects10, which is often related to high peak drug concentrations in the eye and in systemic circulation. The frequent periodic instillation of eye drops becomes necessary to maintain a continuous sustained level of medication. This gives the eye a massive and unpredictable dose of medication. Suspension types of pharmaceutical dosage forms are formulated with relatively water insoluble drugs to avoid the intolerably high toxicity created by saturated solutions of after soluble drugs. However, the rate of drug release from the suspension is dependent upon the rate of dissolution of the drug particles in
the medium, which varies, constantly in its composition with the constant inflow and outflow of lacrimal fluid.

An ointment ensures superior drug bioavailability by increasing the contact time with the eye, minimizing the dilution by tears and resisting nasolacrimal drainage. Because these vehicles have the major disadvantages of providing blurred vision, they are now a days mainly used for either night time administration or for treatment on the outside and edges of the eyelids.

The therapeutic efficacy of an ophthalmic drug can be greatly improved by prolonging its contact with the corneal surface. For achieving this purpose, viscosityenhancing agents are added to eye drop preparations or the drug is formulated in a water insoluble ointment formulation to sustain the duration of intimate drug eye contact. Unfortunately, these dosage forms give only marginally maximum sustained drug-eye contact than eye drop solutions and do not yield a constant drug bioavailability. Repeated medications are still required throughout the day.

In order to remove the constrains placed by these conventional ocular therapy viz.

• Short residence time.
• Large drainage factor
• Frequent instillation
• Pulsed dosing of drug.

Newer delivery systems are being explored to develop extended duration and controlled release strategy. Some of the newer, sensitive and successful ocular delivery systems like inserts, biodegradable polymeric systems, and collagen shields are being developed in order to attain better ocular bioavailability and sustained action of ocular drugs.

The following recent trends are in vogue:

• Mucoadhesive dosage forms
• Ocular inserts
• Collagen shields
• Drug presoaked hydrogel type contact lens and pledgets
• Ocular iontophoresis
• Phase transition systems
• Microspheres and nanoparticles
• Chemical delivery systems vesicular systems.

Utilization of the principle of controlled release as embodied by ocular inserts therefore offers an attractive alternative approach to the difficult problem of prolonging precorneal drug residence time. Ocular disposition and elimination of a therapeutic agent is dependent upon its physicochemical properties as well as the relevant ocular anatomy and physiology.\textsuperscript{11} The successful design of a drug delivery system requires an integrated knowledge of the drug entity and the constraints to delivery offered by the ocular route of administration.

**COMMON EYE INFECTIONS**

Bacteria are the causative pathogens for a large number of eye infections. In addition virus, fungus and protozoans also cause eye infections.\textsuperscript{12} As such eyes are prone to number of diseases but more commonly found are mentioned here.

**Lid and ocular infections**

*Blepharitis*

Inflammation of the eye lid margin.

*Conjunctivitis*

An inflammation of the conjunctiva that may be caused by bacterial and viral infection, pollen and other allergens, smoke and pollutants.

*Keratitis*

An inflammation of the cornea caused by bacterial, viral or fungal infection.

*Glaucoma*

The build up of pressure in the anterior and posterior chamber of the choroids layer that occurs when the aqueous humour fails to drain properly.
**Iritis**

Commonly has an acute onset with the patient suffering pain and inflammation of the eye.

**CONJUNCTIVITIS**

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

- Bacterial conjunctivitis-staphylococci, streptococci or haemophilus.
- Viral conjunctivitis (often associated with the common cold)-adenovirus.
- Chlamydial conjunctivitis-Chlamydia trachomatis.
- Allergic conjunctivitis-allergic disease such as hay fever, asthma and eczema and by antigens like pollen, dust mites or cosmetics.
- Reactive conjunctivitis-chemical or irritant conjunctivitis- chemicals, smoke, fumes, chlorine etc.

**Signs and symptoms of conjunctivitis are**

- The blood vessels over the white of the eye are more visible and swollen.
- The lining of the eyelids also looks redder or pinker due to inflammation.
- Eye is sticky, with a heavy discharge and tearing that may cause the lids to stick together, especially after sleeping.
- Red bumps on the underside of the eyelids.
- Sandy or scratchy feeling in the eye.
- Inflamed and swollen eyelids.
- Blurred vision.
OCULAR INSERTS AS CONTROLLED DRUG DELIVERY SYSTEMS

Ocular inserts are defined as preparations with a solid or semisolid consistency, whose size and shape are especially designed for ophthalmic application (i.e., rods or shields). These inserts are placed in the lower fornix and, less frequently, in the upper fornix or on the cornea. They are usually composed of a polymeric vehicle containing the drug and are mainly used for topical therapy.\textsuperscript{1}

Adantages of ocular inserts

Ocular inserts offer several advantages, \textsuperscript{1,13} which can be summarized as follows:

- Increased ocular residence, hence a prolonged drug activity and a higher bioavailability with respect to standard vehicles.
- Possibility of releasing drugs at a slow and constant rate.
- Accurate dosing contrary to eye drops that can be improperly instilled by the patient and are partially lost after administration, each insert can be made to contain a precise dose which is fully retained at the administration site.
- Reduction of systemic absorption (which occurs freely with eye drops via the nasolacrimal duct and nasal mucosa).
- Better patient compliance due to reduction in frequency of administration.
- Increased shelf life with respect to aqueous solutions.
- Exclusion of preservatives, thus reducing the risk of sensitivity reactions.
- Possibility of incorporating various novel chemical/technological approaches.

Disadvantages of ocular inserts

The disadvantages \textsuperscript{1,14} of ocular inserts are as follows:

- A capital disadvantage of ocular inserts resides in their solid consistency, which means that they are perceived by patient as a foreign body in the eye. This may constitute a formidable physical and psychological barrier to user acceptance and compliance.
- Their movement around the eye, in rare instances, the simple removal is made more difficult by unwanted migration of the insert to the upper fornix.
- The occasional inadvertent loss during sleep or while rubbing the eyes.
• Their interference with vision.
• Difficult placement of the ocular inserts and removal for insoluble types.

MECHANISM OF DRUG RELEASE

The mechanism of controlled drug release into the eye is as follows:
A. Diffusion
B. Osmosis
C. Bioerosion.

A. Diffusion

In the diffusion mechanism,\textsuperscript{15,16} the drug is released continuously at a controlled rate through the membrane into the tear fluid, if the insert is formed of a solid nonerodible body with pores and dispersed drug. The release of drug can take place via diffusion through the pores. Controlled release can be further regulated by gradual dissolution of solid dispersed drug within this matrix as a result of inward diffusion of aqueous solutions. In a soluble device, true dissolution occurs mainly through polymer swelling. In swelling controlled devices, the active agent is homogeneously dispersed in a glassy polymer. Since glassy polymers are essentially drug impermeable, no diffusion through the dry matrix occurs. When the insert is placed in the eye, water from the tear fluid begins to penetrate the matrix, then swelling and consequently polymer chain relaxation and drug diffusion take place. The dissolution of the matrix, which follows the swelling process, depends on polymer structure; linear amorphous polymers dissolve much faster than cross-linked or partially crystalline polymers. Release from these devices follows in general fickian ‘square root of time’ kinetics; in some instances, however, known as case II transport, zero order kinetics has been observed.

B. Osmosis

In the osmosis mechanism, the insert comprises a transverse impermeable elastic membrane dividing the interior of the insert into a first compartment and a second compartment; the first compartment is bounded by a semipermeable membrane and the impermeable elastic membrane and the second compartment is bounded by an impermeable material and the elastic membrane. There is a drug release aperture in the impermeable wall of the insert. The first compartment contains a solute which cannot pass through the semi-permeable membrane
and the second compartment provides a reservoir for the drug which again is in liquid or gel form. When the insert is placed in the aqueous environment of the eye, water diffuses into the first compartment and stretches the elastic membrane to expand the first compartment and contract the second compartment, so that the drug is forced through the drug release aperture.\textsuperscript{16}

C. Bioerosion

In the Bioerosion mechanism, the configuration of the body of the insert is constituted from a matrix of bioerodible material in which the drug is dispersed. Contact of the insert with tear fluid results in controlled sustained release of the drug by bioerosion of the matrix. The drug may be dispersed uniformly throughout the matrix but it is believed a more controlled release is obtained if the drug is superficially concentrated in the matrix. In truly erodible devices, the rate of drug release is controlled by a chemical or enzymatic hydrolytic reaction that leads to polymer solubilization, or degradation to smaller, water-soluble molecules. These polymers may undergo bulk or surface hydrolysis. Erodible inserts undergoing surface hydrolysis can display zero order release kinetics, provided that the devices maintain a constant surface geometry and that the drug is poorly water soluble.\textsuperscript{17}