WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 5.990
Volume 4, Issue 11, 493-523. Review Article ISSN 2277– 7105

REVIEW ON OCULAR INSERTS

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Article Received on
05 Sep 2015,

Revised on 26 Sep 2015,
Accepted on 17 Oct 2015

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ABSTRACT

Ocular drug delivery is one of the most challenging and interesting task faced by pharmaceutical researchers .This review is based on the purpose to provide an update on the current knowledge about the field of ocular drug delivery. Major barriers in ocular medication included the ability to maintain the therapeutic level of drug at the site of action for prolonged period of time. That's why there are many ophthalmic drug delivery system are available which are sterile, buffered & isotonic solution. Eye drop solution is the most prescribed dosage form for the ocular therapy due to its easier and self administration. Ophthalmic preparations must be non irritating to the ocular tissues and homogeneous i.e.: particles must be dispersed uniformly, smooth and free from lumps or agglomerates. It must be relatively non greasy and should not cause blurred vision and also physically and chemically stable. New ocular drug delivery systems are now updated. For the prolongation of drug release the ophthalmic inserts are also used. Ocular inserts are comes under the new drug delivery system. Ocular inserts are described as the preparation which is having solid or semisolid consistency and are especially designed as the size and shape for ophthalmic application (i.e. rods or shields). This system generally includes delayed, controlled and or sustained release.

KEYWORDS – ocular drug delivery system, ocuserts, non erodible ocular insert, bio degradable ophthalmic insert.

INTRODUCTION

Eye is the most delicate and interesting organ because of its drug disposition characteristics. When we were developing the strategies for drug delivery then issues of absorption,

distribution, metabolism, elimination (ADME) must be included. The drug delivery system for eye gives many challenges, tasks and lots of opportunities to the researchers. Although ophthalmic drug delivery is one of the most challenging endeavours which is facing by the pharmaceutical researchers. For ocular drug delivery one of the major challenge is to maintain and obtain a therapeutic level at the site of action for desired period of time. The anatomy, physiology and biochemistry of the eye render this organ exquisitely impervious to foreign substance.

The eye as a portal for drug delivery is generally used for local therapy against systemic therapy to avoid the risk of eye damage due to high blood concentration of the drug, which is not intended.

The ocular organ impervious to foreign substance due to unique anatomy, biochemistry and physiology of the eye, thus presenting a constant challenge to the pharmaceutical formulator to circumvent the protective barriers of the eye without causing permanent tissue damage, therefore the target tissue absorbs a very less fraction of drug. Due to this reason, concentrated solution and frequent dosing are required for the instillation to achieve an adequate level of therapeutic effect. Polymeric film ocular drug delivery system / ocular inserts, which are gaining worldwide accolade, release drugs at a pre – programmed rate for prolonged period by increasing the pre corneal residence time.

Advantages of ocular drug delivery system

- Higher possibility of accurate dosing.
- Sustained and controlled drug delivery is provided.
- Ocular bioavailability of drug will increased by increasing the corneal contact time. This can be achieved by effective adherence to corneal surface.
- This system provides targeted delivery of drug within the ocular globe so as to prevent the loss to other ocular tissues.
- To circumvent the protective barriers like drainage, lacrimation and conjunctival absorption.
- Better patient compliance and comfort is provided and therapeutic performance of drug is also improved.
- To provide better housing of delivery system.

Common eye infections

For a large no. Of eye infections the major causative pathogens are bacteria but sometimes virus, fungus, and protozoan also cause eye infections. As such eyes are prone to no. Of disease but most commonly founded are here.

Conjunctives

Blepharitis

Keratitis

Cataract

Iritis

Glaucoma

Conjunctivitis: Conjunctivitis, commonly known as pink eye is the clear membrane that covers the white part of the eye and lines and 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 days. 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.

 Viral conjunctivitis (often associated with the common cold) – adenovirus.

 Chlamydia 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 or irritant conjunctivitis – chemicals, smoke, fumes 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 red 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.

 Inflamed and swollen eyelids.

 Blurred vision.

Recent forms of ocular drug delivery system

Now a day's newer ocular drug delivery systems are being explored for developing the controlled release strategies. 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 available

a. Membrane bound ocular insert (biodegradable and non-biodegradable) e.g. ocuserts.
b. Mucoadhesive dosage forms (ocular films, ophtha coil, polymer rods. HEMA hydro gel, dispersion, polysulfone capillary fiber).
c. Collagen shields, cyclodextrine based systems, ophthalmic rods (artificial tear inserts) e.g. lacriserts.
d. Filter paper strips (drug impregnated filter paper strips for staining agent – sodium fluorescent , lissamine green and rose Bengal).
e. Soft contact lenses, implants, flexible coils, and cotton pled gets (drug pre-soaked hydro gel type, polymeric gels).
f. Phase transition system (in situ gel formation system – ion activated based, pH changed base, temperature change based).
g. Nanoparticles (microspheres, nanosuspension, amphiphilogels, niosomes, liposomes, dendrimers, quantum dots).
h. Ocular iontophoresis and pumps.
i. Chemical delivery systems, vesicular systems.

Ocular anatomy and physiology: The human eye is a complex anatomical device that remarkably demonstrates the architectural wonders of the human body. The human eye is a challenging organ for topical administration of drugs. The basis of this can be found in the anatomical arrangement of the surface tissues and in the permeability of the cornea. The protective function of the eyelids and lachrymal system is such that there is rapid removal of material instilled into the eye unless the material is suitably small in volume and chemically and physiologically compatible with surface tissues. The eye is referred as a globe and consists of two spheres, one set in the other, as shown in Fig 1. The front sphere is smaller and is bordered interiorly by the sclera. The combined weight of both spheres has been given as 6.7-7.5 gm, with a volume of approximately 6.5ml. The circumference of the eye is about 75 mm. The eye is located in the bony orbital cavity of the head.

Eyeball

The wall of the human eyeball (globe) is composed of three concentric layers.

1. The outer fibrous layer.

The fibrous layer is made up of two parts.

a) Posterior (5/6th) is opaque and called the sclera.

b) Anterior (1/6th) is transparent and called the cornea.

2. A middle vascular layer – the uvea or uvula tract consisting of the choroid, the ciliary body and the iris.

3. A nervous layer-the retina.

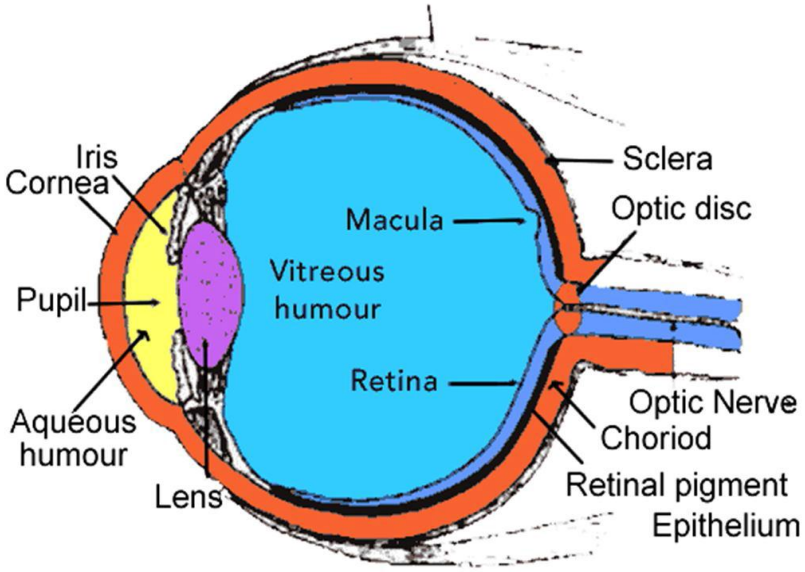


Fig 1:Anatomical structure of human eye ball.

Sclera

Contains the microcirculation, which nourishes the tissues of this anterior segment and is usually white.

Vascular Layer consists of three parts

The choroid – remains just behind the retina forming the posterior 5/6th of the middle coat, composed of numerous blood vessels and pigmented cells containing melanin.

The ciliary body – includes orbicularis ciliaris, ciliary processes, and ciliary muscle.

The Iris nervous coat is called retina, which contains photosensitive receptors. The eyeball houses an optical apparatus which consists, in sequences of the precorneal film, the cornea, the aqueous humor, the pupil, the crystalline lens, the vitreous humor and the retina. The aqueous and vitreous humors are layers of clear fluid or gel like material interposed between the solid structures. The crystalline lens is a refractive element with variable power controlled and supported by a muscle incorporated in the ciliary body.

Conjunctiva

The conjunctival membrane covers the outer surface of the white portion of the eye and the inner aspects of the eyelids. It is attached loosely and thereby permits free movement of the eyeball. Except for the cornea, the conjunctiva is the most exposed portion of the eye.

Lachrymal System

The conjunctival and corneal surfaces are covered and lubricated by a film of fluid secreted by the conjunctival and lachrymal glands. The secretion of the lachrymal glands, the tears are delivered through a number of fine ducts into the conjunctival fornix. The movement of the eye helps to spread the tears over the conjunctival surface. The excess fluid is directed into the lachrymal lake a small triangular area lying in the angle bound by the inner most portions of the lids. Tears are drained from the lachrymal lake, by two small tubes, the lachrymal canaliculi which lead into the upper part of the nasolacrimal duct. The act of blinking exerts a suction-force pump action in removing tears from the lachrymal lake and emptying them into the nasal cavity. Lacrimation is induced reflexly by stimulation of nerve ending of the cornea or conjunctiva, the turnover rate of nasolacrimal fluid is 16%. The eyeball is continually irrigated by a gentle stream of lachrymal fluid which prevents it from becoming dry and inflammed.

Composition of tear: The secretion is a clear watery fluid containing numerous salts, glucose, other organic Compounds, approximately 0.7% protein and the enzyme, lysozyme.

Water: 98.2%
Solids: 1.8%
Organic elements:- Protein-0.67%, Sugar-0.65%,
Nacl-0.66%, NPN-0.05%
Urea - 0.03%.
Other mineral elements sodium, potassium and Ammonia - 0.79%.

Pre corneal Film: Part of the tear fluid provides the moist surface to cornea. The film, compatible with both aqueous and lipid ophthalmic preparations is composed of three layers, the thin outermost layer is lipid and is secreted mainly by the meibomian glands. The lipid layer keeps the cornea moist by preventing evaporation of the underlying layers, a thicker middle aqueous layer, Secreted by the lachrymal gland, it helps in nourishing the cornea. It consists of water, salts, glucose, urea, proteins, lysozyme (an antibacterial enzyme) and immunoglobulin, and a thin inner mucous layer. It is secreted by the goblet cells of the tarsal conjunctiva. This layer is necessary for tear film stability. It smoothes the corneal epithelial surface, enhances tear spreading, lubricates the eye and helps to trap debris. It is renewed during each blink and when blinking is suppressed, it dries in patches. Although the tear film is typically only about 7µL in volume with fluid pH 7.4 and if blinking does not occur, the volume can go up to 30µL without spillage, the cul-de sac is sterile due partly to the action of lysozyme in the tears.

Cornea

The cornea 0.5-1 mm thick consists mainly of the following structures.

1) Corneal Epithelium.

2) Substantia Propria (stroma).

3) Corneal Endothelium.

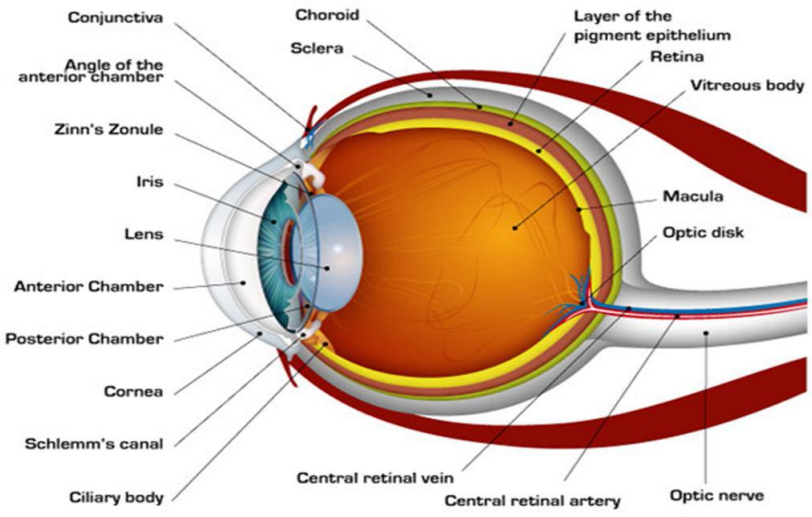


Figure 2. Structure of eye

The cornea is transparent to ordinary diffuse light because of a special laminar arrangement of the above structure, fibers and because of the absence of blood vessels. The cornea derives

its nutrition by diffusion and must have certain permeability characteristics. The corneal epithelium provides an efficient barrier against bacterial invasions. Unless its continuity has been broken by an abrasion, pathogenic bacteria cannot gain a foothold. Any foreign body that either scratches the cornea or lodges and becomes embedded in the cornea is of serious concern because of the role it may play in permitting pathogenic bacteria to gain a foot hold.

Structure of the Eye: The eye consists of several parts that resemble in diagram.

Sclera - the eye's white outer protective coat, normally seen as the "white of the eye".

Cornea - the transparent, curved structure at the front of the eye.

Iris - the coloured part of the eye - blue, brown, green, grey etc - that can be seen through the cornea.

Pupil - the black part of the eye in the middle of the iris. It constricts or dilates according to the amount of light passing through it.

Lens - the transparent disc (with both sides being convex) immediately behind the iris and pupil.

Aqueous humour - the transparent fluid (with consistency similar to water) that circulates behind the cornea and in front of the lens.

Vitreous humour - the material (like transparent jelly) that fills the eyeball between the lens and the retina.

Retina - the light-sensitive layer of millions of nerve cells that line the back of the eyeball. The cells consist of two main groups, called rods and cones due to their appearance under the microscope.

Rods - more numerous, spread out over the entire retina with more toward outer edge, respond to low levels of light.

Cones - far fewer, concentrated around the retina's centre, respond to colour and to details.

Macula - the small centre of the retina, responsible for reading vision. Retinal pigment epithelium - This is a dark coloured layer of cells at the back of the retina responsible for providing oxygen and other nutrients to the rods and cones.

Choroid - a large network of blood vessels (behind the retina) that transport oxygen and other nutrients to the retinal pigment cells.

Optic disc - a small yellow oval structure in the retina, to which nerve cell connections travel from all the rods and cones.

Function of the Eye

When you see an object, the light travels from that object to the cornea, then passes through the aqueous humour, pupil, lens and vitreous humour to reach the retina. During this passage, the light becomes focused onto the macula. At the macula, the light cause's chemical reactions in the cones, that consequently send electrical messages from the eye to the brain. The brain recognises these messages and indicates to you that this particular object has been seen. The cones are therefore responsible for you being able to recognise colours and to read .The rods are essential for you to see in the dark, and to detect objects to the sides, above and below the object on which you are directly focused. This function prevents you from bumping into obstacles when moving around .All the retinal cells (rods and cones) are provided with oxygen and other nutrients from the retinal pigment cells (epithelium), which are kept supplied by the rich network of blood vessels in the choroid.

Mechanism of ocular drug absorption

Topical delivery into the cul-de-sac is, by far, the most common route of ocular drug delivery. Absorption from this site may,

1. Corneal
2. Non-corneal

Classification of ocular drug delivery system

There are many ocular dosage forms are available for the delivery of drugs to the eye. They can be categorized according to their physical forms which is as follows –

Liquids – solution, suspension, sol to gel system, sprays.

Solids – ocular inserts, contact lenses, corneal shields, artificial tear inserts, filter paper strips.

Semi-solid – ointment, gels.

Miscellaneous – ocular iontophoresis, vesicular system, muco adhesive dosage form, particulates.

1. Liquids

Liquids are the most preferable, popular, and desirable state of dosage form used for the eye due to the better and faster absorption of drug from this state. The slow release of the drug from the suspended solid provides a sustained effect for a short duration of time.

- **Solution**

Solutions are the most widely preferred pharmaceutical forms for the administration of drugs that must be active on the eye surface or in the eye after passage through the cornea or the conjunctiva. In the solution the drug is present in dissolved state and may be immediately active. Solution form of the drug also having some drawbacks i.e. poor bioavailability (a major portion i.e. 75% of drug is lost via nasolachrymal drainage), solution stays for very short time at the eye surface, stability problems of the dissolved drug and the necessity of using preservatives. A considerable disadvantage of using eye drops is the rapid elimination of the solution and their poor bioavailability. This rapid elimination is due to the solution state of the preparation and may be influenced by the composition of the solution. The retention of a solution in the eye is influenced by viscosity, hydrogen ion concentration, the osmolality and the instilled volume.

- **Suspensions** are called as dispersion of finely divided relatively insoluble drug substance in an aqueous vehicle which contains suitable amount of suspending and dispersing agents. Because of a tendency for the particles to be retained in the cul-de-sac, the contact time and duration of action of a suspension exceed those of a solution. If the retention increases with an increase in particle size, it will cause the irritation to the eye. The particle size of the suspended drug decreases then the rate of dissolution is increases. So an optimum particle size must be selected for each type of drug and it is clearly recommended that the particles which are used for ophthalmic suspension should be not more than 10um in size.

- **Sol to gel system**

The new concept of producing a gel in situ (e.g. in the cul-de-sac of the eye) was suggested for the first time in the early 1980s. It is highly and clearly accepted that if the viscosity of drug formulation is increased in the pre corneal region then it will greatly enhance the bioavailability because of slower drainage from the cornea. For in situ gelling system there are several concepts have been investigated. This system can be triggered by change in pH, temperature, or by ion activation. An anionic polymeric dispersion shows a low viscosity up

to pH 5.0 and will coacervate in contact with tear fluid due to presence of a carbonic buffer system which regulates the pH of tears. When the temperature of polymeric dispersion is raised from 25-37 degree Celsius, in situ gelling is produced. Ion activation of polymeric dispersion occurred due to the presence of cations in the tear fluid.

- **Sprays**

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

2. Solids

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

- **Ocular inserts**

ocular inserts are solid dosage forms and can overcome the disadvantages reported with traditional ophthalmic systems like aqueous solution, suspensions, and ointments. The objectives of ophthalmic inserts are to retain for a prolonged duration in front of the eye. These solid devices are intended to be placed in the conjunctival sac and to deliver the drug at a comparatively slow rate. The eye drops provided pulse entry pattern of drug administration in the eye which is characterised by transient overdose, relatively short period of acceptable dosing, followed by prolonged periods of under dosing. The ocular inserts maintain an effective drug concentration in the target tissue and yet minimize the no. Of applications consonant with the function of controlled release system. Ophthalmic inserts are defined as sterile preparation with a thin, multilayered, drug impregnated, solid or semisolid consistency devices placed in to cul-de-sac or conjunctival sac and whose size and shape are especially designed for ophthalmic application. They are composed of polymeric support containing or not drug(s), the latter being incorporated as dispersion or a solution in the polymeric support. The inserts can be used for topical or therapy.

The advantages of these systems are as follows

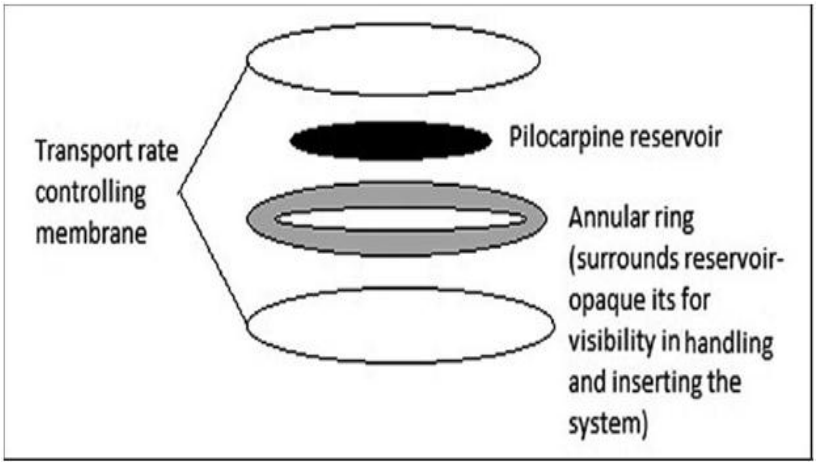
1. Ocular contact time is increased.
2. Accurate dosing is possible. Constant and predictable rate of drug release can be achieved.
3. Systemic absorption can be reduced and side effects can be reduced.
4. Increased shelf life.

5. Better patient compliance.
6. Targeting to internal ocular tissues can be done.

Classification of ocular inserts

➢ **Non erodible ocular insert –** it includes ocusert and contact lenses.

- **Ocusert** – The most widely used ocular insert is ocusert. The technology used in this is an insoluble delicate sandwich technology. In ocusert the drug reservoir is a thin disc of pilocarpine alginate complex sandwiched between two transparent discs of micro porous membrane fabricated from ethylene vinyl acetate copolymer. The micro porous membrane permits the tear fluid to penetrate into the drug reservoir compartment to dissolve drug from the complex.



- **Contact lenses:** When contact lenses are soaked in drug solution it can absorb water soluble drugs. Then these contact lenses loaded with drug are placed in the eye for releasing of drug for prolonged period. The hydrophilic contact lenses can be used to prolong the ocular residence time of the drugs. In humans, the bionite lens which was made from hydrophilic polymer (2-HEMC) has been shown to produce a greater penetration of fluorescein.

- **Corneal shield**

A non cross linked homogenized, procaine scleral collagen slice is developed. Topically applied antibiotics have been used in conjunction with the shield to promote healing of corneal ulcers. Collagen shields are fabricated with foetal calf skin tissue and originally developed as a corneal bandage. These devices, once softened by tear fluid, form a thin peliable film that confirms exactly to the corneal surface and undergoes dissolution up to 10,

24, & 72 hrs. Collagen film proved as a promising carrier for ophthalmic drug delivery system because of its biological inertness, structural stability and good biocompatibility.

➢ **Erodible ophthalmic insert –** The erodible ophthalmic inserts included the marketed device such as lacriserts, SODI, and minidisc.

• **Lacrisert** – Lacrisert is a sterile rod shaped device which is made up of hydroxyl propyl cellulose without using any preservatives and used for the treatment of dry eye syndromes. It is 12.7mm in diameter with a length of 3.5mm and weight is 5mg. Lacrisert is useful in the treatment of keratitis whose symptoms are difficult to treat with artificial tear alone. It is inserted into the inferior fornix where it imbibes water from the conjunctiva and cornea, forms a hydrophilic film which stabilise the tear film and hydrates and lubricates the cornea, it dissolves in 24 hrs.

• **SODI** –Soluble Ocular Drug Insert is a small oval wafer developed for cosmonauts who could not use eye drops in weightless conditions. It is an oval shaped sterile thin film made up of acryl amide, N-vinylpyrrolidone and ethylacrylate called as ABE. It weighs about 15-16 mg. It is used to treat glaucoma and trachoma. It is inserted into the inferior cul-de-sac and gets wet and softens in 10-15 seconds. After 10-15 min the film turns into a viscous polymer mass, after 30-60 minutes it turns into polymer solution and deliver the drug for about 24 hrs.

• **Minidisc** - The minidisc consists of a contoured disc with a convex front and concave back surface in the contact with the eyeball. It is like a miniature contact lens with a diameter of 4-5mm. The minidisc is made up of silicone based prepolymer-α-ψ-bis (4-methacryloxy) butyl polydimethyl siloxane. Minidisc can be hydrophilic or hydrophobic to permit extend release of both water soluble and insoluble drugs.

Classification of patented ocular inserts (based on their solubility behaviour)

- **Insoluble inserts**
- **Soluble inserts**
- **Bio erodible inserts**
- **Insoluble ophthalmic inserts –** they are classified in to 3 categories

➢ **Diffusion system**
➢ **Osmotic systems**
➢ **Hydrophilic contact lenses**

The first two classes include a reservoir in contact with the inner surface of the rate controlling membrane and supplying drug to it. The reservoir contains a liquid, a gel, a colloid, a semisolid, a solid matrix or a carrier-containing drug homogeneously or heterogeneously dispersed or dissolved in it. Carriers can be made of hydrophobic, hydrophilic, organic, inorganic, naturally occurring or synthetic material. The third class includes the contact lenses. The main disadvantages of these devices are that they are insoluble, so they have to be removed after use.

Diffusion inserts

The diffusion systems consist of a central reservoir in which the drug is enclosed in especially designed semi permeable or micro porous membrane, which allow the diffusion of drug from reservoir at a predetermined rate.

Table 1: Components of diffusional inserts

Central reservoir	Glycerin, ethylene glycol, propylene glycol, water, methyl cellulose mixed with water, sodium alginate, poly (vinylpyrrolidone), poly ox ethylene stearate.
Micropores membrane	Polycarbonates, polyvinyl chloride, polysulfones, cellulose esters, crosslinked poly (ethyl oxide), cross-linked polyvinylpyrrolidone, and cross-linked polyvinyl alcohol.

Osmotic inserts - The osmotic inserts are generally composed of a central part surrounded by a peripheral part. The first central part can be composed of a single reservoir or of two distinct compartments. In single reservoir system, it is composed of a drug with or without an osmotic solute was added and dispersed through a polymeric matrix, so that the drug is surrounded by the polymer as discrete small deposits. In the two distinct compartment systems, the drug and the osmotic solutes are placed in two separate compartments; the drug reservoir was surrounded by an elastic impermeable membrane and the osmotic solute reservoir by a semi permeable membrane. The second peripheral part of these osmotic inserts preferred in all cases which is a covering film made of an insoluble semi permeable polymeric membrane. The tear fluid diffuse into peripheral deposits through the semi permeable polymeric membrane, it wets the membrane and induces their dissolution. The solubilised deposits generate a hydrostatic pressure against the polymer matrix which causes the rupturing of matrix in the form of apertures. Then the drug is released through these apertures from the deposits near the surface of device which is against the eye, by the help of

hydrostatic pressures. This corresponds to the osmotic part characterized by zero order drug release profile.

Table 2: Components of osmotic inserts.

Water permeable matrix	Ethylene - vinyl esters copolymers, Divers-plasticized polyvinyl chloride (PVC),polyethylene, cross-linked polyvinylpyrrolidone(PVP)
Semi permeable membrane	Cellulose acetate derivatives, Divers – Ethyl vinyl acetate (EVA), polyesters of acrylic and methacrylic acids (Eudragit ®).
Osmotic agents	Inorganic – magnesium sulfate, sodium chloride, potassium phosphate dibasic sodium carbonate and sodium sulfate. Organic- calcium lactate, magnesium succinate and tartaric acid. Carbohydrates – Sorbitol, mannitol, glucose and sucrose.

Soft contact lenses – They are made up of a covalently cross linked hydrophilic or hydrophobic polymer that can forms three dimensional network or matrix which is having the capability of retaining water, aqueous solution and or solid compartments.

When hydrophilic contact lenses are soaked in a drug solution, it absorbs the drug but does not deliver as precise as that provided by other non soluble ophthalmic systems. From such the system generally the drug is rapidly released at the beginning and declines exponentially with time. The release rate can be decreased by incorporating the drug homogeneously during the manufacture or by adding a hydrophobic component. Contact lenses have certainly good prospects as ophthalmic drug delivery systems.

Soluble Ophthalmic inserts - Soluble inserts correspond to the oldest class of ophthalmic inserts. They offer the great advantage of being entirely soluble so that they do not need to be removed from their site of application thus, limiting the interventions to insertion only.

Types

- Based on natural polymers e.g. collagen.
- Based on synthetic or semi synthetic polymers.

The soluble ophthalmic inserts containing synthetic/semi synthetic polymers

a) Based on products well adopted for ophthalmic use.

b) Easily processed by conventional methods – slow evaporating extrusion, compression or injection moulding.

The release of the drug from such system is by penetration of tears into the insert which induces release of the drug by diffusion and forms a gel layer around the core of the insert; this external gelification induces the further release, but still controlled by diffusion.

The release rate, J, is derived from Fick's law yields the following expression.

$$J = \frac{AdkCS}{L}$$

A- Surface area of the membrane

K – Diffusion coefficient of the drug

L – Membrane thickness

CS – Drug solubility in water

D- Diffusion coefficient of the ocuserts membrane.

Since all the terms on the right hand side of the above equation are constant, so is the release rate of the device. The other factors affecting drug release from these Ocuserts include

• Penetration of the inclusion.

• Swelling of the matrix.

• Dissolution of the drug and the polymers.

The soluble insert made of cellulose derivatives can be sterilized by exposure to gamma radiation without the cellulose components being altered. A decreased release rate is obtained by using a component of the matrix a polymer normally used for enteric coatings or by introducing a suitable amount of hydrophobic polymer capable of diminishing the tear fluid penetration and thus of decreasing the release of the drug without modifying the solubility of the insert when added in proper proportion.

Table 3: Components Of Soluble Inserts Containing Synthetic Polymers.

Soluble synthetic polymers	Cellulose derivatives –Hydroxypropyl cellulose methylcellulose, hydroxyethyl cellulose and hydroxypropyl cellulose. Divers – Polyvinyl alcohol, ethylene vinyl acetate copolymer.
Additives	Plastisizer – Polyethylene glycol, glycerin, propylene glycol Enteric coated polymer –Cellulose acetate phthalate, hydroxypropyl methylcellulose phthalate. Complexing agent – Polyvinyl pyrrolidone. Bioadhesives – Polyacrylic acids.

- **Biodegradable ophthalmic inserts** – The biodegradable inserts are composed of material in which homogeneous dispersion of a drug included or not in to a hydrophobic coating which is substantially impermeable to the drug. They are made up of so called biodegradable polymers. For the ophthalmic use some successful biodegradable materials are poly (orthoesters) and poly (orthocarbonates). The drug is released from such a system is the consequence of the contact of the device of the tear fluid which induced a superficial diversion of the matrix.

3. Semi solids – There are a large no. Varieties of semisolid vehicles are used for topical ocular delivery. Generally they are classified into two categories.
Simple bases
Compound bases

Simple base refers to a single continuous phase. These includes white petrolatum, lanolin, and viscous gels prepared from polymers such as PVA, carbopol etc.

In case of compound base, they are usually biphasic type system which forms either water in oil or oil in water emulsions.

A drug which is either in simple or compound bases provides an increase in duration of action because of reduced dilution by tears, reduction in drainage by way of a sustained release effect and prolonged corneal contact time. The most commonly used semi solid preparation is ointment consisting of dispersion of a solid drug in an appropriate vehicle base. Semi solid preparations are applied once or twice daily and provide sustained effect. The objective of the ophthalmic ointment vehicle is to prolong drug contact time with the external ocular surface, but also having the disadvantage of causing blurring vision and matting of eyelids.

Ophthalmic gels are similar as ointments in viscosity and clinical usage. Semisolid vehicles were found to prolong the ocular contact time of many drugs, which ultimately leads to an enhanced bioavailability.

4. Miscellaneous

Vesicular systems – They have been developed to produce the enhancement in ocular contact time, providing sustained effect and reducing the side effect of entrapped drug.

Liposomes – They are phospholipids lipid vesicles in which the drug is targeted to the specific site in the body because of their structural versatility. They can incorporate any kind of drug substance regardless of its solubility. They improve the bioavailability by providing the controlled and selective drug delivery. Lipophilic compounds having great potential for ocular drug delivery as compared to hydrophilic compounds. Liposomes give the advantage of being completely biodegradable and relatively non toxic but are less stable than particulate polymeric drug delivery systems. Liposomes were found to be potential delivery system for administration of a no. of drugs to the eye.

Niosomes – In the case of liposomes it is concluded that there are several disadvantages like chemical instability, oxidative degradation of phospholipids, cost and purity of natural phospholipids but in case of niosomes they are chemically stable as compared to liposomes and can entrap both hydrophilic and hydrophobic drugs. They are non toxic and do not require special handling techniques.

Pharmcosomes – This is the term used for pure drug vesicles formed by the amphiphilic drugs. Any drug possessing a free carboxyl group or an active hydrogen atom (-OH, NH2) can be esterifies (with or without a spacer group) to the hydroxyl group of a lipid molecule, thus generating an amphiphillic pro drug. The amphiphillic pro drug is converted to pharmacosomes on dilution with water. The pharmacosomes show greater shelf stability, facilitated transport across the cornea, and a controlled release profile.

Muco-adhesive dosage form - This approach is applicable to the vehicles containing polymers which will attach, via non- covalent bonds, to conjunctival mucin (a glycoprotein) thus remaining in contact with the pre corneal tissues until mucin turnover cause elimination of the polymer. Muco-adhesive polymers are usually macromolecular hydrocolloids with numerous hydrophilic functional groups, such as carboxyl -, hydroxyl-, amide and sulphate which are capable of establishing electrostatic interactions. The bio adhesive dosage form showed more bioavailability of the drug as compared to conventional dosage forms.

Particulates (Nanoparticles / Micro particles) - Particulate polymeric drug delivery systems include micro- and nanoparticles. Particles in the micrometer size range >1mm are called Micro particles or microspheres, whereas those in the nanometre size range < 1mm (1000 nm) are called nanoparticles. Micro particles with a capsule wall enclosing a liquid or solid core are called microcapsules. The upper size limit for Micro particles for ophthalmic

administration is about 5-10 mm. above this size, a scratching feeling in the eye can result after ocular application. Microspheres and Nanoparticles represent promising drug carriers for ophthalmic application. The binding of the drug depends on the physicochemical properties of the drugs as well as of the nano or micro particle polymer. Particulates such as nanoparticles, nanocapsules, submicron emulsions, nanosuspensions improved the bioavailability of ocularly applied drugs.

Mechanism of controlled drug release into the eye – is as follows.

Diffusion – In diffusion mechanism the drug is released continuously at a controlled rate through the membrane into the tear fluid. If the insert is formed of a solid non-erodible body with pores and dispersed drug. The release of drug can take place via diffusion through the pores. Controlled release can be further regulated by gradual dissolution of solid dispersed drug within this matrix as a result of inward diffusion of aqueous solutions. 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.

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

the first compartment and contract the second compartment so that the drug is forced through the drug release aperture.

Bio erosion - In the Bio erosion mechanism, the configuration of the body of the insert is constituted from a matrix of bio erodible material in which the drug is dispersed. Contact of the insert with tear fluid results in controlled sustained release of the drug by bio erosion of the matrix. The drug may be dispersed uniformly throughout the matrix but it is believed a more controlled release is obtained if the drug is superficially concentrated in the matrix. In truly erodible or E-type devices, the rate of drug release is controlled by a chemical or enzymatic hydrolytic reaction that leads to polymer solubilisation, or degradation to smaller, Water-soluble molecules. These polymers, as specified by Heller, may undergo bulk or Surface hydrolysis. Erodible inserts undergoing surface hydrolysis can display zero order release kinetics; provided that the devices maintain a constant surface geometry and that the drug is poorly water-soluble.

ROUTES OF OCULAR DRUG DELIVERY

There are several possible routes of drug delivery into the ocular tissues (Fig 4). The selection of the route of administration depends primarily on the target tissue. Traditionally topical ocular and subconjunctival administrations are used for anterior targets and intravitreal administration for posterior targets. Design of the dosage form can have big influence on the resulting drug concentrations and on the duration of drug action.

Topical ocular: 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).

During the short contact of drug on the corneal surface it partitions to the epithelium and in the case of lipophilic compounds it remains in the epithelium and is slowly released to the corneal stroma and further to the anterior chamber .After eye drop administration the peak Concentration in the anterior chamber is reached after 20–30 min, but this concentration is typically two orders of magnitude lower than the instilled concentration even for lipophilic compounds. From the aqueous humour the drug has an easy access to the iris and ciliary body, where the drug may bind to melanin. Melanin bound drug may form a reservoir that is released gradually to the surrounding cells, thereby prolonging the drug activity.

Sub-conjunctival administration: Traditionally sub conjunctival 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 (e.g. glaucoma surgery) Secondly, the development of new therapies for macular degeneration (antibodies, oligonucleotides) must be delivered to the retina and choroid . After subconjunctival injection drug must penetrate across sclera which is more permeable than the cornea. Interestingly the scleral permeability is not dependent on drug lipophilicity. In this respectit clearly differs from the cornea and conjunctiva. Even more interesting is the surprisingly high permeability of sclera to the large molecules of even protein size. Thus, it would seem feasible to deliver drugs across sclera to the choroid. However, delivery to the retina is more complicated, because in this case the drug must pass across the choroid and RPE. The role of blood flow is well characterise kinetically but the based on the existing information, there are good reasons to believe that drugs may be cleared significantly to the blood stream in the choroid.

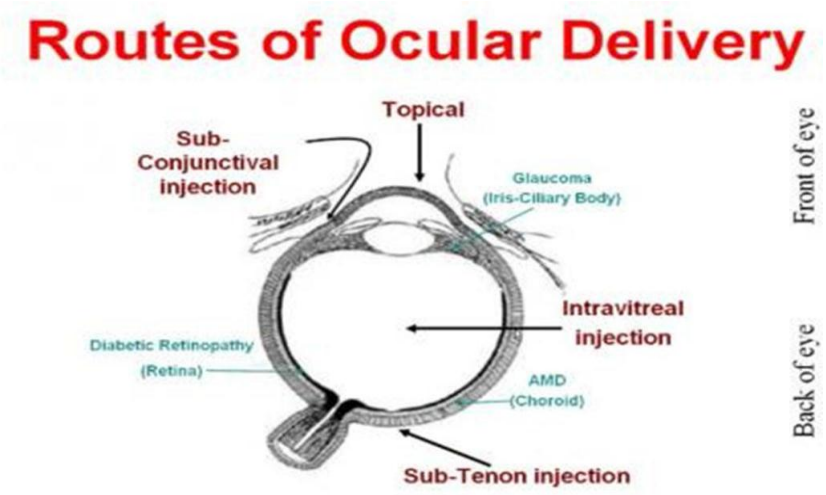


Figure 4.

BARRIERS TO OCULAR DRUG DELIVERY

Drug loss from the ocular surface: After instillation, the flow of lachrymal fluid removes instilled compounds from the surface of the eye. Even though the lachrymal turnover rate is only about 1 µl/min the excess volume of the instilled fluid is flown to the naso lachrymal 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.

Lachrymal fluid-eye barriers: Corneal epithelium limits drug absorption from the lachrymal fluid into the eye. The corneal barrier is formed upon maturation of the epithelial cells. They migrate from the limbal region towards the centre of the cornea and to the apical surface. The most apical 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. Despite the tightness of the corneal epithelial layer, transcorneal permeation is the main route of drug entrance from the lachrymal fluid to the aqueous humour. In general, the conjunctiva is more leaky epithelium than the cornea and its surface area is also nearly 20 times greater than that of the cornea. Drug absorption across the bulbar conjunctiva has gained increasing attention recently, since conjunctiva is also fairly permeable to the hydrophilic and large molecules. Therefore, it may serve as a route of absorption for larger bio-organic compounds such as proteins and peptides. Clinically used drugs are generally small and fairly lipophilic. Thus, the corneal route is currently dominating. In both membranes, cornea and conjunctiva, principles of passive diffusion have been extensively investigated, but the role of active transporters is only sparsely studied.

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.

This barrier prevents the access of plasma albumin into the aqueous humor, and limits also the access of hydrophilic drugs from plasma into the aqueous humor. Inflammation may disrupt the integrity of this barrier causing the unlimited drug distribution to the anterior chamber. In fact, the permeability of this barrier is poorly characterised. 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 thereafter distribution into the retina is limited by the RPE and retinal endothelia. Despite its high blood flow the choroidal blood flow constitutes only a minor fraction of the entire blood flow in the body. Therefore, without specific targeting systems only a minute fraction of the intravenous or oral drug dose gains access to the retina and choroid. Unlike

blood brain barrier, the blood-eye barriers have not been characterised in terms of drug transporter and metabolic enzyme expression.

FORMULATION METHODS OF OCUSERT

Solvent Casting Method: In this method using different ratios of drug and polymer a no. of batches are prepared. The polymer is dissolved in distilled water. A plasticizer is added to this solution under stirring conditions. The weighed amount of drug was added to above solution and stirred to get a uniform dispersion. After proper mixing the casting solution was poured in clean glass Petri dish and covered with an inverted funnel to allow slow and uniform evaporation at room temperature for 48 h. The dried films thus obtained were cut by cork borer into circular pieces of definite size containing drug. The ocular inserts were then stored in an airtight container (desiccator) under ambient condition.

Glass substrate technique: Drug reservoir film: 1% w/w polymer for example chitosan was soaked in 1%v/v Acetic acid solution for 24hrs, to get a clear solution of chitosan in acetic acid solution. The solution was filtered through a muslin cloth to remove undissolved portion of the polymer (chitin). Required quantity of drug-β CD complex was added and vortexed for 15minutes to dissolve the complex in chitosan solution. 1%w/v propylene glycol (plasticizer) was added to it and mixed well with stirrer. The viscous solution was kept aside for 30 minutes for complete expulsion of air bubbles. The rate controlling films were prepared. The films were casted by pouring solution into the centre of levelled glass mould and allowing it to dry at room temperature for 24hrs. After drying, films were cut into ocuserts of desired size so that each contains equal quantity of the drug. Then, the matrix was sandwiched between the rate controlling membranes using non-toxic, non-irritating, water insoluble gum. They were wrapped in aluminium foil separately and stored in a desiccator

Melt extrusion technique: Drug for ex. acyclovir and the polymer were sieved through 60#, weighed and blended geometrically. The plasticizer was added and blended. The blend was then charge the blend was then charged to the barrel of Melt Flow Rate apparatus and extruded. Theextrudate was cut into appropriate size and packed in polyethylene lined Al foil, heat sealed and sterilized by gamma radiation.

Evaluation of Ocular Inserts

1. Film thickness
2. Content uniformity

3. Uniformity of Weight
4. Percentage moisture absorption
5. Percentage moisture loss
6. In-vitro drug release
7. In-vivo drug release
8. Accelerated stability studies.
9. Compatibility study.

Thickness of Film: Film thickness is measured by using dial caliper at different points and the mean value was calculated .Reading were taken over an circular film of area of 38.5 mm square. The standard deviation in thickness was computed from the mean value.

Drug Content Uniformity: To check the uniformity of the drug in the To check the uniformity of the drug in the cast film inserts are cut at different places in the cast films and each film is place in vials containing 5 ml of pH 7.4 phosphate buffer and shaken to extract the drug from patch. 1 ml from above resulting solution is taken and dilute. The solution is analyzed by spectrophotometer using pH 7.4 phosphate buffer as blank. The drug content was calculate using the following formula

$$\text{Mg of drug in one patch} = \frac{\text{As.Cr}}{\text{Ar}}$$

Where

As =Absorbance of sample solution.

Ar =Absorbance of standard solution.

Cr =Concentrat.ion of drug in Standard solution.

Same procedure is adopts for all the batches of cast films in triplicates and mean drug content and standard deviation of variance are calculate.

Uniformity of Weight: The weight variation test is carried out by weighing three patches cut from different places of same formulation and their individual weights are determine by using the digital balance. The mean value is calculated. The standard deviation of weight variation is compute from the mean value.

Percentage moisture absorption: The percentage moisture absorption test is carried out to check physical stability or integrity of ocular inserts. Ocular inserts are weigh and place in a desiccators containing 100 ml of saturated solution of aluminium chloride and 79.5%

humidity is maintain. After three days the ocular inserts are taken out and reweigh. The percentage moisture absorption is calculate using the formula.

$$\text{Percentage moisture absorption} = \frac{\text{final weight} - \text{initial weight}}{\text{inital weight}} \times 100$$

Percentage Moisture Loss: The percentage moisture loss is carries out to check integrity of the film at dry condition. Ocular inserts are weighing and keep in a desiccators containing anhydrous calcium chloride. After 3 days, the ocular inserts are taken out and reweigh, the percentage moisture loss is calculate using the formula

$$\text{Percentage moisture loss} = \frac{\text{initial weight} - \text{final weight}}{\text{inital weight}} \times 100$$

In-vitro drug Release: To simulate the actual physiological conditions prevailing in the eye an in-vitro dissolution is use in the present work.

In-vitro release studies are carried out using bi-chamber donor-receiver compartment model design using commercial semi-permeable membrane of transparent and regenerated cellulose type (sigma dialysis membrane). It is tie at one end of the open cylinder, which acts as the donor compartment. The ocular insert is place inside the donor compartment. The semi permeable membrane is use to simulate ocular in vivo condition like corneal epithelial barrier in order to simulate the tear volume, 0.7 m1 of distilled water is place and maintain at the same level throughout the study in the donor compartment. The entire surface of the membrane is in contact with reservoir compartment, which contains 25ml of pH 7.4 phosphate buffers and stirs continuously using a magnetic stirrer. Samples of 1ml are withdrawn from the receptor compartment at periodic intervals and replace with equal volume of distilled water. The drug content is analyze at 246 nm against reference standard using pH 7.4 phosphate buffer as blank on a UV/visible spectrophotometer.

In-vivo Drug Release Rate Study: The inserts are sterilized by using UV radiation before in-vivo study. Inserts are taken in a Petri dish along with 100 mg of pure drug, which are spread to a thin layer. This Petri dish along with polyethylene bags and forceps are place in UV sterilization chamber (hood). The inserts and other materials are exposing to UV radiation for one hour. After sterilization, inserts are transferee into polyethylene bag with the help of forceps inside the sterilization chamber itself. The pure drugs which are sterilized along with inserts are analyzing for potency by UV spectrophotometer after suitable dilution

with pH 7.4 phosphate buffer. The male albino rabbits, weigh between 2.5-3.0 kg are require for the experiment. The animals are house on individual cages and customized to laboratory conditions for 1 day. Receive free access to food and water. The ocular inserts containing drug are taken for in-vivo study which are previously sterilize on the day of the experiment and are place into the lower conjunctivas cul-de-sac. The inserts are inserting into 7 eyes at same time and each one eye of seven rabbits is serving as control.

Ocular inserts are removing carefully at 2, 4, 6, 8, 10, 12 and 24 hours and analyze for drug content as dilution mention in drug content uniformity. The drug remaining is subtracted from the initial drug content of inserts which will give the amount of drug release in the rabbit eye. Observation for any fall out of the inserts is also recording throughout the experiment. After one week of wash period the experiment is repeating for two times as before.

Accelerated Stability Studies: The accelerated stability studies are carries out to predict the breakdown that may occur over prolong periods of storage at normal shelf condition. The films of the formulation are taken in a separate Petri dish and are keep at three different temperatures 400C, 500C and 600C and the period for break down or degradation of the ocular inserts is check. When ocular inserts show degradation the time in days is note and subject to determine the drug content of each individual film using the drug content uniformity procedure.

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