A Review Article on Ocular Drug Delivery System and Its Approach Towards Ocular Inserts

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Abstract*— Ocular drug delivery is an entrenched route of administration. The mechanism of the eye is such that it helps to remove various foreign substance i.e., invading microbes etc. that may obstruct the normal physiological function. A suitable drug delivery must release the drug in a controlled and sustained manner for a better therapeutic action. Conventional drug delivery system such as solutions, emulsions and eye drops deliver the appropriate amount of drug but due to barriers such as lacrimal drainage, tear flow etc. cause the drug to drain from the ocular surface. Due to this Novel methods of drug delivery to the eye were introduced. Approaches such as nanosuspensions, nanoparticles, liposomes, niosomes and ocuserts (also known as ocular inserts) came into practise to improve both bioavailability and release of drug in a controlled manner. One of the novel methods widely used are ocular inserts. These are the solid patches which when placed in conjunctival sac slows down the rate of release. They also overcome the problem of frequent dosing by maintaining concentration in an efficient manner. They are made of various techniques that make them soluble, erodible and insoluble. This article highlights the importance and mechanism of ocular inserts.

Indexed Terms-- Ocuserts, Anatomy, Physiology, Bioavailability, Conventional, Novel

I. INTRODUCTION

Topical application of drugs to the eye is the well-established route of administration for the treatment of various eye diseases like dryness, conjunctiva, eye flu etc.[1] For illness of the eye, topical administration is usually ideal over systemic administration, before reaching the anatomical barrier of the cornea, any drug molecule administered by the ocular route firstly crosses the precorneal barriers.[2]

The protective mechanisms of the eye such as Blinking, baseline and reflex lacrimation, and drainage decrease the bioavailability of drug and also help to remove rapidly foreign substances like the dust particles bacteria, including drugs from the surface of the eye. There are most commonly available ophthalmic preparations such as drops and ointments about 70% of the eye dosage formulations in market. But these preparations when instilled into eye they are rapidly drained away from the ocular surface due to blinking tear flow and lachrymal nasal drainage of the eye.

With conventional ophthalmic solution normal dropper is used which delivers about 50-75µl per drop and portion of these drops rapidly drain until the eye is back to normal i.e., with a resident volume of 7µl. Due to this drug loss in front of the eye, very small drug is available to enter the cornea and inner tissue of the eye. Actual corneal permeability of the drug is relatively low and very small corneal contact time (about 1-2 min) in humans for instilled solution usually less than 10%. Therefore, only small amount of drug actually penetrates the cornea and reaches intraocular tissue.

Anatomy of the Human Eye: The adult eyeball, often referred to as a spherical globe, with its largest diameter being 24 mm anteroposteriorly [4]. A schematic drawing of the human eye is shown below;

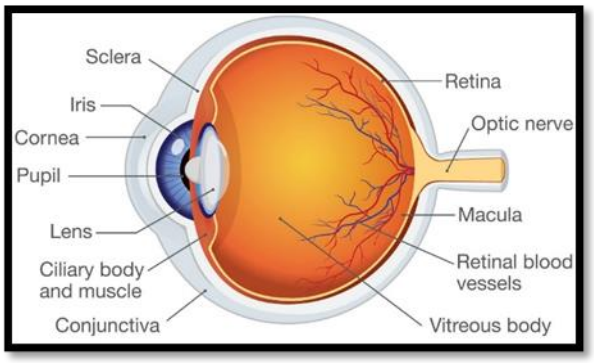

Fig 01 Anatomy of eye

The anterior portion of the eye consists of the cornea, iris, pupil, and crystalline lens. The pupil serves as an aperture which is adjusted by the surrounding iris, acting as a diaphragm that regulates the amount of light entering the eye. Both the iris and the pupil are covered by the convex transparent cornea, the major refractive component of the eye due to the huge difference in refractive index across the air-cornea interface [5]. Together with the crystalline lens, the cornea is responsible for the formation of the optical image on the retina. The crystalline lens is held in place by suspensory ligaments, or zonules, that are attached to the ciliary muscle. Ciliary muscle actions cause the zonular fibers to relax or tighten and thus provide accommodation, the active function of the crystalline lens. This ability to change its curvature, allowing objects at various distances to be brought into sharp focus on the retinal surface, decreases with age, with the eye becoming ‘‘presbyopia’’ i.e., gradual loss of the eyes ability to focus on nearby objects.

Besides the cornea and crystalline lens, both the vitreous and aqueous humour contribute to the dioptric apparatus of the eye, leading to an overall refractive power of about 60 dioptres [4]. The aqueous humour fills the anterior chamber between the cornea and iris, and also fills the posterior chamber that is situated between the iris and the zonular fibers and crystalline lens. Together with the vitreous humour, a loose gel filling the cavity between the crystalline lens and retina, the aqueous humour is responsible for maintaining the intraocular pressure and thereby helps the eyeball maintain its shape. Moreover, this clear watery fluid nourishes the cornea and crystalline lens. The film of this optical system is the retina, the multi layered sensory tissue of the posterior eyeball onto which the light entering the eye is focused, forming a reversed and inverted image. External to the retina is the choroid, the layer that lies between retina and sclera. The choroid is primarily composed of a dense capillary plexus, as well as small arteries and veins [5]. As it consists of numerous blood vessels and thus contains many blood cells, the choroid supplies most of the back of the eye with necessary oxygen and nutrients. The sclera is the external fibrous covering of the eye. The visible portion of the sclera is commonly known as the ‘‘white’’ of the eye.

Physiology of eye:

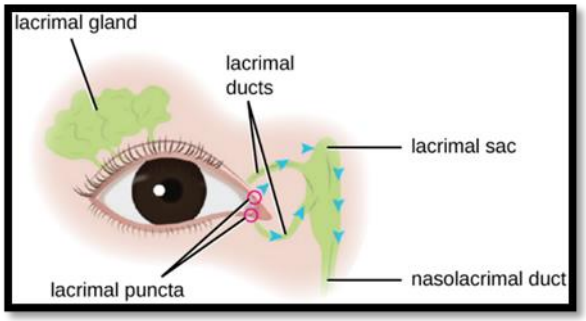

Fig 02: Physiology of eye

The eye consists of transparent cornea, lens, and vitreous body without blood vessels. The oxygen and nutrients are transported to this non-vascular tissue by aqueous humour which is having high oxygen and same osmotic pressure as blood. The aqueous humour in humans is having a volume of 300 µl that fills the anterior chamber of the eye which is in front of lens. The cornea is covered by a thin epithelial layer that continuous with the conjunctiva at the cornea-sclerotic junction. The main bulk of cornea is formed of criss-crossing layers of collagen and is bounded by elastic lamina on both front and back. Its posterior surface is covered by a layer of endothelium. The cornea is richly supplied with free nerve endings. The transparent cornea is continued posteriorly into the opaque white sclera which consists of tough fibrous tissue. Both cornea and sclera withstand the intra ocular tension constantly maintained in the eye. The eye is constantly cleansed and lubricated by the lacrimal apparatus which consists of four structures:

a. lacrimal glands

b. lacrimal canals
c. lacrimal sac
d. nasolacrimal duct.

The lacrimal fluid secreted by lacrimal glands is emptied on the surface of the conjunctiva of the upper eye lid at a turnover rate of 16% per min. It washes over the eye ball and is swept up by the blinking action of eye lids.

Muscles associated with the blinking reflux compress the lacrimal sac, when these muscles relax; the sac expands, pulling the lacrimal fluid from the edges of the eye lids along the lacrimal canals, into the lacrimal sacs. The lacrimal fluid volume in humans is 7 µl and is an isotonic aqueous solution of bicarbonate and sodium chloride of pH 7.4. It serves to dilute irritants or to wash the foreign bodies out of the conjunctival sac. It contains lysozyme, whose bactericidal activity reduces the bacterial count in the conjunctival sac.

The physiological barriers to diffusion and productive absorption of topically applied drug exist in the precorneal and corneal spaces. The precorneal constraints that are responsible for poor bioavailability of conventional ophthalmic dosage forms are solution drainage, lacrimation, tear dilution, tear turn over and conjunctival absorption.[3]

Disorders of human eye

Cataract

The term cataract refers to any cloudiness or opacity of the normally transparent crystalline lens of the eye. A cataract may or may not cause a loss of vision, depending on the size of the opacity, its density, and its location. Severe cataracts are a major cause of treatable blindness throughout the world.

Oxidative damage caused by free radicals is considered to be an important factor in aging and the development of chronic diseases, including cataract formation. For this reason, many of the dietary supplement recommendations focus on antioxidants which can neutralize the oxidative damage caused by free radicals.

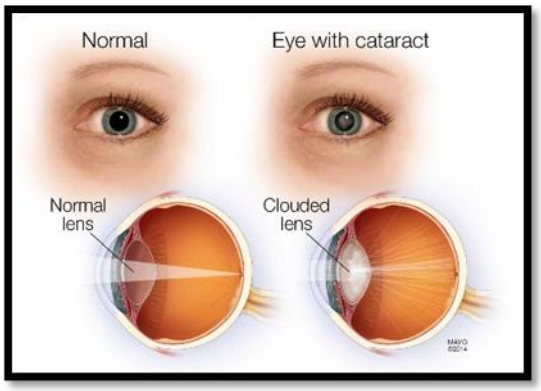

Fig 03: Cataract

Conjunctivitis

Conjunctivitis is an inflammation of the conjunctiva, the transparent mucous membrane lining the inside of the eyelids and the white of the eyeball. Normally the white, or sclera, is clearly visible through the conjunctiva, but when the conjunctiva is inflamed, its normally invisible blood vessels become engorged, making the eye appear red. Conjunctivitis may be caused by many types of infectious agents, such as viruses or bacteria, as well as by toxic, chemical, and allergenic irritants.

Fig 04: Conjunctivitis

Macular Degeneration

Macular degeneration, also called “age-related macular degeneration” (AMD), is the most common cause of blindness and vision impairment among the elderly in the United States. AMD damages the macula, a small part of the eye's light-sensitive retina (the layer of tissue that sends signals for vision to the brain).

Because the macula is responsible for seeing sharp details directly in the centre of the field of vision, damage caused by AMD may interfere with a person's ability to see straight ahead (necessary for driving and

distance viewing, like TV watching) and for fine, detailed vision (newsprint reading, sewing, crafts and repairs).

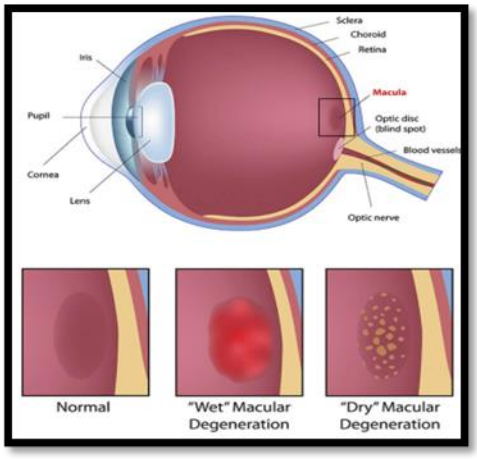

Fig 05: Macular degeneration

Night Blindness

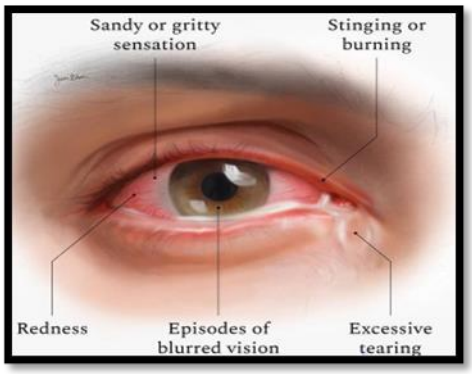

Fig 06: Night blindness

Impairment of the vision normally possible in dim light is called night blindness, or nyctalopia. It may be an early sign of vitamin A deficiency, because that vitamin plays a major role in the cells of the eye sensitive to dim light.

Night blindness is also a manifestation of various eye disorders such as glaucoma and optic nerve disease. It is often the earliest symptom of retinitis pigmentosa, a chronic and progressive inflammation of the retina. One form of the condition, called congenital stationary night blindness, is hereditary.

- Keratoconjunctivitis sicca (KCS)

Dry eye is a disorder of the tear film which occurs due to tear deficiency or excessive tear evaporation; it causes damage to the interpalpebral ocular surface and is associated with a variety of symptoms reflecting ocular discomfort.1 Dry eye syndrome, also known as keratoconjunctivitis sicca (KCS), is a common condition reported by patients who seek ophthalmologic care and is characterized by inflammation of the ocular surface and lacrimal glands.

Dry eye symptoms may be a manifestation of a systemic disease, therefore timely detection may lead to recognition of a life–threatening condition. Additionally, patients with dry eye are prone to potentially blinding infections, such as bacterial keratitis and also at an increased risk of complications following common procedures such as laser refractive surgery.

Conventional delivery systems

- Eye Drops
- Ointment and Gels
- Ocuserts and Lacrisert

Eye Drops: - Drugs which are active at eye or eye surface are widely administered in the form of Solutions, Emulsion and Suspension. Generally, eye drops are used only for anterior segment disorders as adequate drug concentrations are not reached in the posterior tissues using this drug delivery method. Various properties of eye drop like hydrogen ion concentration, osmolality, viscosity and instilled volume can influence retention of a solution in the eye. Less than 5 Percent of the dose is absorbed after topical administration into the eye. The dose is mostly absorbed to the systemic blood circulation via the conjunctival and nasal blood vessels. Ocular absorption is limited by the corneal epithelium, and it is only moderately increased by prolonged ocular contact. The reported maximal attainable ocular absorption is only about 10 Percent of the dose.

When eye drops are administered in the inferior fornix of the conjunctiva, very small amount of the dose reaches to the intraocular tissues and major fraction of the administered drug get washed away with the

lachrymal fluid or absorbed systemically in the nasolacrimal duct and pharyngeal sites.[8]

- Ointment and Gels:-

Prolongation of drug contact time with the external ocular surface can be achieved using ophthalmic ointment vehicle but, the major drawback of this dosage form like, blurring of vision and matting of eyelids can limits its use. Pilopine HS gel containing pilocarpine was used to provide sustain action over a period of 24 hours. A number of workers reported that ointments and gels vehicles can prolong the corneal contact time of many drugs administered by topical ocular route, thus prolonging duration of action and enhancing ocular bioavailability of drugs.[9]

An emulsion is a biphasic system composed of two immiscible phases. Ophthalmic emulsions can offer advantages improvement in drug solubility and bioavailability of previously water insoluble drugs. Pharmaceutical emulsions can be widely categorized as water in oil (w/o) and oil in water (o/w). Ophthalmic formulations widely utilize the o/w system, which consists of a hydrophobic drug mixed in oil and dispersed in an aqueous medium. An o/w emulsion is preferred over a w/o emulsion for the reasons of better ocular tolerability and lower ocular irritation due to the external aqueous phase. Some examples of marketed ophthalmic eye drops are Restasis®, AzaSite®. Restasis® is a 0.05% emulsion of Cyclosporine-A indicated for treatment of dry eye disease. AzaSite® is a 1% azithromycin ophthalmic emulsion used to treat bacterial conjunctivitis and various other ocular infections.

- Challenges in ophthalmic drug delivery systems

Challenges in ocular drug delivery systems are to design a therapeutic system which can provide an optimal concentration of a drug at the target region and with high therapeutic efficacy. Rapid absorption of drugs occurs due to the corneal anatomy, physiology and barrier functions, so quick instillations of eye drops are mandatory to balance the therapeutic level in tear film or at targeted sites. Side effects of using frequent dosing of drug solution are that it can induce toxicity at the ocular surface and cause cellular damage as well. Most of ocular dosage forms are poor in bioavailability, due to the precorneal loss, including solution drainage, lacrimation, tears dynamics, tear dilution, conjunctival absorption, non-productive absorption, the transient residence time in the cul-de-sac and tear turnover.

Other challenges include relative impermeability of corneal epithelial membrane, causing problems in delivering drugs at the anterior segment following topical administration. Approximately 1% or even less of the instilled dose of the drug reaches the intraocular tissues due to various anatomical and physiological hurdles, which reduces the absorption of a drug. For better clinical results, topical dosage form needs to maintain a balance between the lipophilicity and hydrophilicity along with higher contact time [12].

The challenges in ocular drug delivery systems are categorized as follows:

- Anterior segment delivery challenges

Topical formulations are mostly preferred over systemic formulations in the ocular delivery system because if any drug formulation is administered to eye, before reaching the anatomical barrier of the cornea, the drug molecule has to face the precorneal barriers, the tear film and conjunctiva, which come first in the pathway and slow the penetration of the active moiety in the eye.

Moreover, frequent instillations of eye drops are necessary to maintain a therapeutic drug level in the tear film or at the site of action, but the frequent use of highly concentrated drug solutions may induce toxic side effects and cellular damage at the ocular surface.

- Posterior segment delivery challenges

BRB inhibits the entry of topically applied ocular drugs at the posterior segment of eye. Delivery of drugs is inhibited by some factors at the posterior segment of ocular tissue and this effect is also responsible for poor ocular bioavailability. The BRB is responsible for limiting the effect of the intravenous route at the posterior site for drug delivery [13] and it also limits the entry of the systemically administered drug in the retina [14]. For curing diseases in the posterior segment of the

eye, there is a need for high concentration of vitreal drugs. BRB is permeable to more lipophilic molecules and so allows the entry of such drugs in the posterior segment of the eye. Frequent administration and high concentration of drug cause side effects systematically [18]. A major challenge to deliver drugs to the posterior segment of the eye is to maintain the therapeutic concentration of the drugs, for a longer period of time and minimizing the number of injections as well. Elimination of drug through the anterior route follows to the aqueous humour and, finally, outflows to the humour in the anterior chamber.

- Approaches in ophthalmic drug delivery systems

A number of approaches have been used in the early stages for better results. These approaches, categorized into two types, are:

- Bioavailability improvement and
- Controlled release drug delivery

The first type aims to maximize corneal drug absorption and minimize precorneal drug loss using viscosity and penetration enhancers, prodrugs, gels and liposomes. The second one is for the delivery of active ophthalmic moiety in the form of a sustained delivery system by providing controlled and continuous delivery like implants, inserts, nanoparticles, micro particulates, and colloids. There are a number of traditional approaches, such as viscosity enhancers, gel, penetration enhancer, prodrug and liposomes which enhance the bioavailability, while the newer developments, i.e., ocuserts, nanosuspension, nanoparticles, liposomes, niosomes and implants improve both bioavailability and release of drugs in a controlled manner in the anterior segment of the eye. In the posterior segment of the eye, drug reaches through intravitreal injections, iontophoresis, subconjunctival injection and periocular routes [15],[16].

Marketed product of Ocular drug delivery

Table 01: Marketed products of odds

Brand name	Dosage form	Uses
acuvail	4.5 mg/ml ketorolac tromethamine solution (045%) In a single use vial.	Cataract surgery
Alocril	2% is a clear, yellow, sterile solution	Allergic conjunctivitis
Elestat	0.05% epinastine hcl ophthalmic	Allergic conjunctivitis
Ozurdex	0.75mg dexamethasone intravitreal ocular implant	Retinal vein occlusion
Pred forte	1% prednisolone acetate ophthalmic suspension	Bulbar conjunctiva
Trivaris	80mg/ml triamicinolone acetonide injectable suspension	Sympathetic ophthalmia
Zymar	0.3% gatifloxacin ophthalmic solution	Bacterial conjunctivitis

OCULAR INSERTS

Ophthalmic inserts are sterile preparations with a solid or a semisolid consistency, and whose size and shape are especially designed for ophthalmic application. The inserts are placed in the lower fornix and less frequently, in the upper fornixor on the cornea. Ocular inserts can overcome the disadvantages reported with traditional.

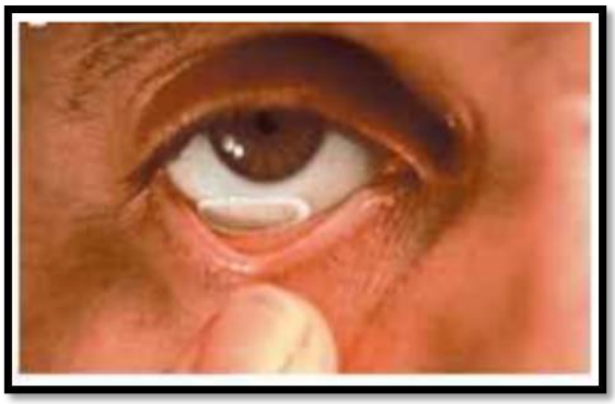

Fig 07 : ophthalmic inserts

Ophthalmic systems like eye drops, suspensions and ointments. The typical pulse entry type drug release behaviour observed with eye drops, suspensions and ointments is replaced by more controlled, sustained and continuous drug delivery using a controlled release ocular drug delivery system. In the recent years, there has been explosion of interest in the polymer-based delivery devices, adding further dimension to topical drug delivery thereby promoting the use of polymers such as collagen and fibrin fabricated into erodible inserts for placement in cul-de-sac. Utilization of the principles of controlled release as embodied by ocular inserts offers an attractive approach to the problem of prolonging precorneal drug residence times. Ocular inserts also offer the potential advantage of improving patient compliance by reducing the dosing frequency. The main objective of the ophthalmic inserts is to increase the contact time between the preparation and the conjunctival tissue to ensure a sustained release suited to topical or systemic treatment. They are composed of polymeric support with or without drugs, the latter being incorporated as dispersion or a solution in the polymeric support.(17,18,19)

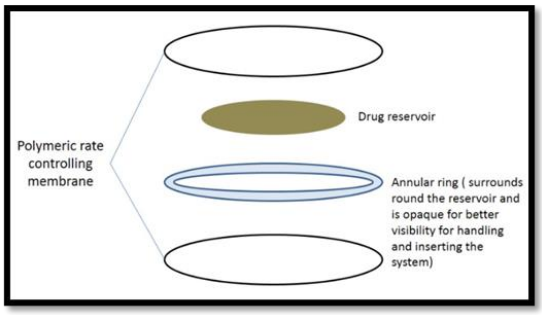

Fig 08: Structural organization of inserts

- Advantages of ocular inserts:

i. Increased ocular residence, hence a prolonged drug activity and a higher bioavailability with respect to standard vehicles;
ii. Possibility of releasing drugs at a slow, constant rate;
iii. 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);
iv. Reduction of systemic absorption (which occurs freely with eye drops via the nasolacrimal duct and nasal mucosa);
v. Better patient compliance, resulting from a reduced frequency of administration and a lower incidence of visual and systemic side-effects;
vi. Possibility of targeting internal ocular tissues through non-corneal (conjunctival scleral) routes;
vii. Increased shelf life with respect to aqueous solutions;
viii. Exclusion of preservatives, thus reducing the risk of sensitivity reactions;
ix. Possibility of incorporating various novel chemical technological approaches.

Such as pro-drugs, muco-adhesives, permeation enhancers, micro-particulates, salts acting as buffers, etc.

The potential advantages offered by inserts clearly explain why an active interest has been dedicated to these dosage forms in recent years, and why efforts to introduce them on the pharmaceutical market continue. Of course, not all of the benefits listed above can be present in a single, ideal device. Each type of insert represents a compromise between the desirable properties inherent to solid dosage forms and negative constraints imposed by the structure and components of the insert itself, by fabrication costs, as well as by the physical/physiological constraints of the application site.

- Disadvantages of ocular inserts:

a) A capital disadvantage of ocular inserts resides in their ‘solidity’, i.e., in the fact that they are felt by the (often oversensitive) patients as an extraneous body in the eye. This may constitute a formidable

physical and psychological barrier to user acceptance and compliance.

b) 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,

c) The occasional inadvertent loss during sleep or while. (20,21,22)

MECHANISM OF CONTROL DRUG RELEASE INTO THE EYE

The mechanism of controlled drug release into the eye is as follows: -

- Diffusion
- Osmosis
- Bio-erosion

- Diffusion

In this mechanism, the drug is released continuously at a controlled rate through the membrane. If the insert is formed of a solid non-erodible body having pores and drug is in a dispersed form, the drug release takes place via diffusion through the pores. Controlled release of the drug can be maintained by a gradual dissolution of the solid dispersed drug in the matrix, as a result of the 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. As glassy polymers are essentially drug-impermeable, no diffusion occurs through the dry matrix. When the insert is placed in the eye, water from the tear fluid begins to penetrate the matrix, swelling occurs, and consequently polymer chain relaxation occurs and drug diffusion takes place. The dissolution of the matrix, followed by the swelling process depends on the polymer structure. A linear amorphous polymer dissolves at a faster rate than a cross-linked or partially crystalline polymer. (23,24)

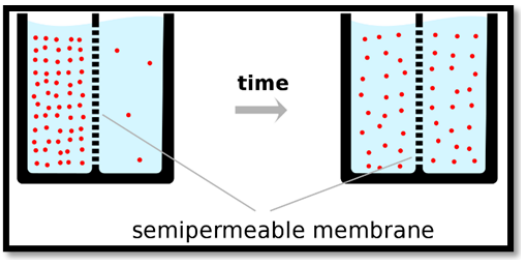

Fig 09: Diffusion

- Osmosis

In the Osmosis mechanism, the insert is made of a transverse impermeable elastic membrane, which divides the interior of the insert into two compartments, first and second; the first compartment is surrounded by a semi-permeable membrane and the impermeable elastic membrane, and the second compartment is surrounded by an impermeable material and the elastic membrane. There is a drug release orifice in the impermeable membrane of the insert. The first compartment contains a solute that cannot pass through the semi-permeable membrane and the second compartment provides a reservoir for the drug, which is in liquid or gel form. When the insert is placed in the aqueous environment of the eye, water diffuses in the first compartment, which stretches the elastic membrane to expand the first compartment and contract the second compartment so that the drug is forced to come out through the drug release orifice.(24)

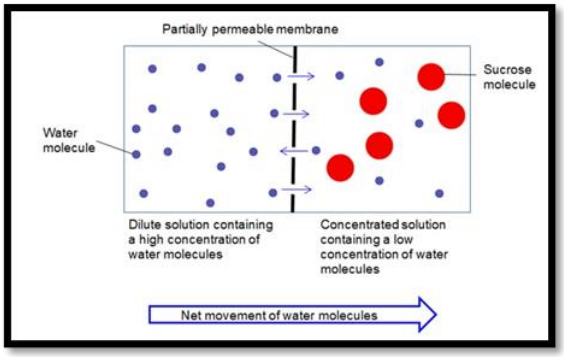

Fig 10: Osmosis

- Bioerosion

In the bioerosion mechanism, the insert is comprised of a matrix of bio-erodible material in which the drug is dispersed. Contact of the insert with the tear fluid results in controlled sustained release of the drug by bioerosion of the matrix. The drug is dispersed uniformly throughout the matrix, but it is believed that a more controlled release is obtained if the drug is superficially concentrated in the matrix. In truly erodible or E-type devices, the drug release is controlled by a chemical or enzymatic hydrolytic reaction that leads to polymer solubilization, or degrades to smaller, water-soluble molecules. These polymers may undergo bulk or surface hydrolysis,

which displays zero order release kinetics; provided the devices maintain a constant surface geometry and the drug is poorly water soluble.

- Classification Of Ocular Inserts:

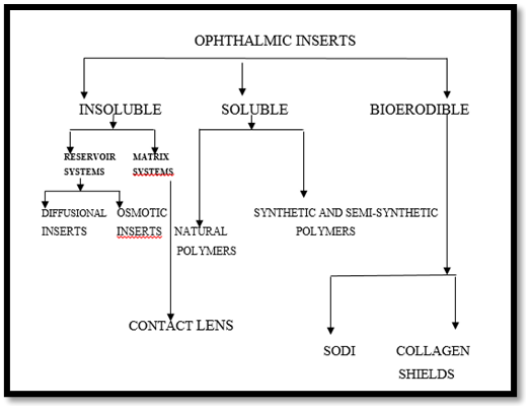

Fig 11: Classification of Ocular Inserts

I. Insoluble ophthalmic inserts

The insoluble inserts have been classified into three groups:-

i. Diffusion inserts
ii. Osmotic inserts
iii. Hydrophilic contact lenses.

The first two classes include a reservoir in contact with the inner surface of the rate controller and supplying drug thereto. 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 therein (25). Carriers can be made of hydrophobic, hydrophilic, organic, inorganic, naturally occurring or synthetic material. (26)

The third class including the contact lenses. The insoluble of these devices is their main disadvantages, since they have to be removed after use.

- Diffusion inserts

The diffusion systems are compared of a central reservoir of drug enclosed in specially designed semi permeable or micro porous membranes, which allow the drug to diffuse the reservoir at a precisely determined rate. The drug release from such a system is controlled by the lachrymal fluid permeating through the membrane until a sufficient internal pressure is reached to drive the drug out of the reservoir. The drug delivery rate is controlled by diffusion through the membrane, which one can be controlled. (27)

Components of diffusional inserts*:*

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

- Osmotic inserts:

The osmotic inserts are generally compared of a central part surrounded by a peripheral part (28). The first central part can be composed of a single reservoir or of two distinct compartments.

In first case, it is composed of a drug with or without an additional osmotic solute dispersed through a polymeric matrix, so that the drug is surrounded by the polymer as discrete small deposits(29). In the second case, the drug and the osmotic solutes are placed in two separate compartments, the drug reservoir being surrounded by an elastic impermeable membrane and the osmotic solute reservoir by a semi permeable membrane. The second peripheral part of these osmotic inserts comprises in all cases a covering film made of an insoluble semi permeable polymer(30).

The tear fluid diffuse into peripheral deposits through the semi permeable polymeric membrane wets them and induces their dissolution. The solubilized deposits generate a hydrostatic pressure against the polymer matrix causing its rupture under the form of apertures. Drug is then released through these apertures from the deposits near the surface of the device which is against the eye, by the sole hydrostatic pressure.(30) This corresponds to the osmotic part characterized by zero order drug release profile.

Components of osmotic inserts

Water permeable matrix	Ethylene- vinyl esters copolymers Divers- plasticized polyvinyl chloride (PVC) Polyethylene, cross-linked Polyvinylpyrrolidine(PVP)
Semi permeable membrane	Cellulose acetate derivation, 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

These are shaped structure made up of a covalently crosslinked hydrophilic or hydrophobic polymer that forms a three-dimensional network or matrix capable of retaining water, aqueous solution or solid components. (31)

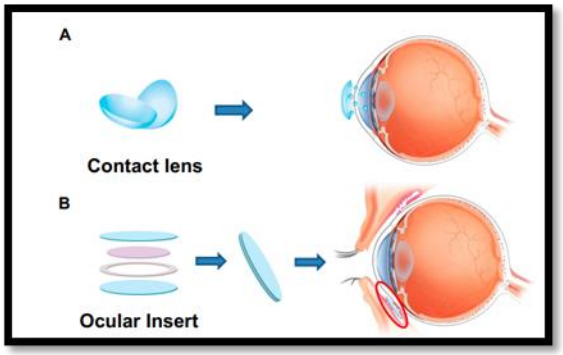

Fig 12: Contact lens

When a hydrophilic contact lens is soaked in a drug solution, it absorbs the drug, but does not give a delivery as precise as that provided by other non-soluble ophthalmic systems. The drug release from such a system is generally very rapid at the beginning and then declines exponentially with time. The release rate can be decreased by incorporating the drug homogeneously during the manufacture (32) or by adding a hydrophobic component. Contact lenses have certainly good prospects as ophthalmic drug delivery systems. (33) 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. (34)

- Types:

a) Based on natural polymers e.g., collagen.
b) Based on synthetic or semi synthetic polymers.
The therapeutic agents are preferably absorbed by soaking the insert in a solution containing the drug, drying and rehydrating in before use on the eye. The amount of drug loaded will depend upon the amount of binding agent, upon the concentration of the drug solution into which the composite is soaked, as well as the duration of the soaking. (35)

II. Soluble ocular inserts

These soluble inserts offer the advantage of being entirely soluble so that they do not need to be removed from their site of application, thus limiting the intervention to insertion only.

They can be broadly divided into two types, the first one being based on natural polymers and the other on synthetic or semi-synthetic polymers.

A. Natural polymers

The first type of soluble inserts is based on natural polymer Natural polymer used to produce soluble ophthalmic inserts is preferably collagen. The therapeutic agent is preferably absorbed by soaking the insert in a solution containing the drug, drying, and re-hydrating it before use on the eye. The amount of drug loaded will depend on the amount of binding agent present, the concentration of the drug solution into which the composite is soaked as well as the duration of the soaking. As the collagen dissolves, the drug is gradually released from the interstices between the collagen molecules.

B. Synthetic and semi-synthetic polymer

The second type of soluble insert is usually based on semi-synthetic polymers (e.g., cellulose derivatives) or on synthetic polymers such as polyvinyl alcohol. A

decrease of release rate can be obtained by using Eudragit, a polymer normally used for enteric coating, as a coating agent of the insert . Saettone et al . have observed in rabbits that Eudragit coated inserts containing pilocarpine induced a miotic effect of a longer duration, compared to the corresponding uncoated ones. However, the inherent problems encountered with these soluble inserts are the rapid penetration of the lachrymal fluid into the device, the blurred vision caused by the solubilization of insert components and the risk of expulsion due to the initial dry and glassy consistency of the device. (36) Ethyl cellulose, a hydrophobic polymer, can be used to decrease the deformation of the insert and thus to prevent blurred vision. As for the risk of expulsion, several authors have incorporated carbomer, a strong but well tolerated bio-adhesive polymer. The soluble inserts offer the additional advantage of being of a generally simple design, of being based on products well adapted for ophthalmic use and easily processed by conventional methods. The main advantage is decreased release rate, but still controlled by diffusion.

III. Bio-erodible ocular inserts

These inserts are formed by bio-erodible polymers (e.g., cross-linked gelatin derivatives, polyester derivatives) which undergo hydrolysis of chemical bonds and hence dissolution. The great advantage of these bio-erodible polymers is the possibility of modulating their erosion rate by modifying their final structure during synthesis and by addition of anionic or cationic surfactants.

A cross-linked gelatine insert was used to increase bioavailability of dexamethasone in the rabbit eye. The dexamethasone levels in the aqueous humor were found to be four-fold greater compared to a dexamethasone suspension.

However, erodible systems can have significantly variable erosion rates based on individual patient physiology and lacrimation patterns, while degradation products and residual solvents used during the polymer preparation can cause inflammatory reaction. (37)

The solid inserts absorb aqueous tear fluid and gradually erode or disintegrate. Then the drug is slowly leached from hydrophilic matrix. After completion of drug delivery bio-erodible ocular inserts are not needed to be removed. The marketed devices of erodible drug inserts are Lacriserts, SODI, and Minidisc.

A. Soluble ophthalmic drug insert

Soluble Ocular Drug Insert (SODI) is a small oval wafer developed for space pilots who could not use eye drops in weightless conditions. It is sterile thin film of oval shape made from acryl amide, N-vinyl pyrrolidone and ethyl acrylate called as ABE. It weighs about 15-16 mg. It is used in treatment of glaucoma and trachoma. It is inserted into inferior cul-de-sac and gets wets and softens in 10-15 seconds. After 10-15 min film turns into a viscous polymer mass, after 30-60 minutes it turns into polymer solutions and delivers drug for about 24 hours. (38)

B. Collagen Shields

Collagen is the structural protein of bones, tendons, ligaments, and skin and comprises more than 25% of the total body protein in mammals. This protein, which is derived from intestinal collagen, has several biomedical applications, the main of which is probably catgut suture. developed as a corneal bandage to promote wound healing. Tear fluid makes these devices soft and form a thin pliable film which is having dissolution rate up to 10, 24 or 72 hours. Because of its structural stability, good biocompatibility and biological inertness, collagen film proved as a potential carrier for ophthalmic drug delivery system. Collagen ophthalmic inserts are available for delivery of drug to the eye. (39)

C. Ocufit/ Lacrisert

The Ocufit is a sustained release, rod shaped device made of silicone elastomer, patented in 1992 and currently developed by Escalon Ophthalmics Inc. It was designed to fit the shape and size of the human conjunctival fornix. Accordingly, it does not exceed 1.9 mm in diameter and 25-30 mm in length, although smaller sizes for children and new-born babies are planned. They lack preservative useful for dry eye syndrome. Lacrisert is useful in treatment of keratitis whose symptoms are difficult to treat with artificial tear alone. It is inserted into cul-de-sac cavity where it absorbs water from conjunctiva and cornea, forms a hydrophilic film which stabilizes tear film for

hydration and lubrication of cornea. It dissolves in 24 hours. (40)

CONCLUSION

Conventional dosage form needs frequent administration at every 4 hours and formation of crystalline deposits on cornea due to its pH-dependent solubility which is very low. Ocular inserts are developed to accommodate the increasing number of patients requiring treatment with minimized side effects. Ocuserts reduced number of dose administration thus improving better patient compliance. Ocular insets have been found advantageous as it eliminates side effect of pulsed dosing of conventional dosage form by providing controlled and sustained drug delivery with increase in bioavailability and corneal contact time, preventing the loss of drug with better patient compliance improving drug efficacy. Various classes of ocular insert have been developed till date like soluble, insoluble, and bio-degradable ocular insert which are further categorized in different types depending upon material used and its behavior in drug delivery like soluble ocular insert based natural, synthetic or semi-synthetic polymer, insoluble ocular inserts including diffusion insert, osmotic insert and soft contact lenses while bio-erodible involve lacrisert, SODI, Minidisc and collagen shield. It increases contact time and thus improve bioavailability. Systemic side effects can be decreased, hence reducing in adverse effect. Ocuserts are novel approaches in the era of ocular drug delivery compliance with ethical standards.

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