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AN INSIGHT INTO OCULAR INSERT

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ABSTRACT

Ocular inserts are sterile preparations, with a thin, multilayered, drug-impregnated, solid or semisolid consistency devices placed into cul-de-sac or conjunctiva sac. They are usually made up of polymeric vehicle containing drug. Ocular drug delivery is one of the most fascinating and challenging tasks being faced by the Pharmaceutical researchers. One of the major barriers of ocular medication is to obtain and maintain a therapeutic level at the site of action for prolonged period of time. The therapeutic efficacy of an ocular drug can be greatly improved by prolonging its contact with the corneal surface. Newer ocular drug delivery systems are being explored to develop extended duration and controlled release strategy. Some of the newer, sensitive and successful Ocular delivery systems like inserts, biodegradable polymeric systems, and collagen shields are being developed in order to attain better ocular bioavailability and sustained action of ocular drugs.

INTRODUCTION: Ocular drug delivery is one of the most fascinating and challenging tasks being faced by the Pharmaceutical researchers. One of the major barriers of ocular medication is to obtain and maintain a therapeutic level at the site of action for prolonged period of time. The challenges to the formulator are to circumvent the protective barriers of the eye without causing permanent tissue damage.

The development of newer, more sensitive diagnostic techniques and therapeutics agents renders urgency to the development of maximum successful and advanced ocular drug delivery systems. The therapeutic efficacy of an ocular drug can be greatly improved by prolonging its contact with the corneal surface. For achieving this purpose, viscosity enhancing agents are added to eye drop preparations or the drug is formulated in a water insoluble ointment formulation to sustain the duration of intimate drug-eye contact.

Unfortunately, these dosage forms give only marginally maximum sustained drug-eye contact than eye drop solutions and do not yield a constant drug bioavailability [1]. Repeated medications are still required throughout the day. These practical issues have stimulated the search for alternative methods for ocular drug delivery. Much of the work recently devoted to ocular inserts, which serves as the platform for the release of one or more active substances.

To overcome the constraints placed by conventional ocular therapies like short residence time, pulsed dosing of drug, frequent instillation, large drainage factors. Newer ocular drug delivery systems are being explored to develop extended duration and controlled release strategy. Some of the newer, sensitive and successful Ocular delivery systems like inserts, biodegradable polymeric systems, and collagen shields are being developed in order to attain better ocular bioavailability and sustained action of ocular drugs [2].

Ocular insert is defined as a preparation wih solid or semisolid consistency, whose size and shapes are especially designed for ophthalmic application (i.e., rod or shield). **Figure 1** shows a typical schematic diagram of an ocular insert.

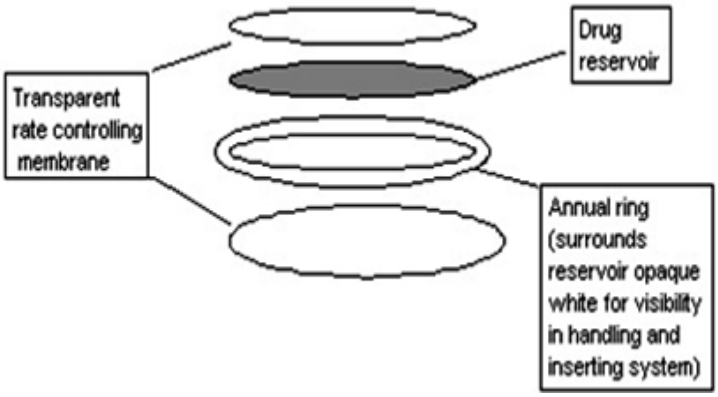

FIGURE 1: SCHEMATIC DIAGRAM OF OCULAR INSERTS

They are composed of a 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 therapy. 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 [3].

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 humor which is having high oxygen and same osmotic pressure as blood. The aqueous humor in human is having volume of 300µl that fills the anterior chamber of the eye which is in front of lens. It is shown in **figure 2**.

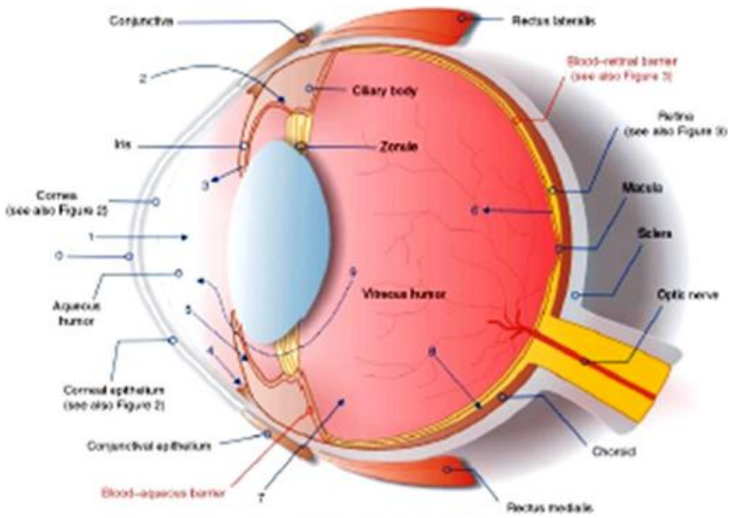

FIGURE 2: PHYSIOLOGY OF EYE

The cornea is covered by a thin epithelial layer 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 [4].

The eye is constantly cleansed and lubricated by the lacrimal apparartus which consists of four structures. lacrimal glands, lacrimal canals, lacrimal sac, 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 7µl 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 conjuctival sac. It contains lysozyme, whose bactericidal activity reduces the bacterial count in the conjuctival sac [5]. 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 conjuctival absorption

Diseases of Eye: The eye is a sensory and sensitive organ which is located on the surface of the body, is easily injured and infected .

According to the location of diseases, ocular disorders are grouped as:-

1. Periocular diseases,
2. Intraocular diseases.

The periocular diseases are explained as follows:

- **Conjunctivitis:** It is a condition where redness of the eye and the presence of a foreign body sensation are evident. There are many causes of conjunctivitis, but the great majority is the result of acute infection or allergy. Bacterial conjunctivitis is the most common ocular infection.

- **Keratitis:** The condition in which patients have a decreased vision, ocular pain, red eye, and often a cloudy/opaque cornea. Keratitis is mainly caused by bacteria, viruses, fungi, protozoa and parasites.

- **Trachoma**: The conjunctival inflammation is called "active trachoma" and usually is seen in children, especially pre-school children. It is characterized by white lumps in the undersurface of the upper eyelid and by non-specific inflammation and thickening often associated with papillae. This is caused by the organism Chlamydia trachomatis. Active trachoma will often be irritating and have a watery discharge.

- **Dry Eye:** If the composition of tears is changed, or an inadequate volume of tears is produced, the symptom of dry eye will result. Dry eye conditions are not just a cause for ocular discomfort where it also results in corneal damage. Periocular diseases such as these are relatively easily treated using topical formulations.

The intraocular diseases are explained as follows: One of the intraocular diseases is intra-ocular infection which includes infection in the inner eye, including the aqueous humor, iris, vitreous humor and retina. They are more difficult to manage and occur commonly after ocular surgery, trauma or may be due to endogenous causes. Such infections carry a high risk for damage to the eye and also afford the possibility of spreading the infection from the eye to the brain. Other common intraocular disease is glaucoma, considered to be one of the major ophthalmic clinical problems in the world. More than 2% of the population over the age of 40 has this disease, in which an increased intraocular pressure (IOP) greater than 22 mm Hg ultimately compromises blood flow to the retina and thus causes death of the peripheral optic nerves. This process results in visual field loss and ultimately blindness [6]. Apart from these common problems of eye cataract and macular degeneration [7] are sometimes diseases which may be of a systemic origin such as diabetes or hypertension effect the eye.

Advantages of Ocular Inserts: In comparison with the traditional ophthalmic preparation i.e., eye drops, the solid ophthalmic devices presents some advantages: [8, 9, 10]

1. Increasing contact time and thus improving bioavailability.

2. Possibility of providing a prolong drug release and thus a better efficacy.

3. Reduction of systemic side effects and thus reduced adverse effects.

4. Reduction of the number of administrations and thus better patient compliance.

5. Reduction in systemic absorption.

6. Possibility of targeting inner ocular tissues through non-corneal (conjunctival sclera) routes.

7. Possibility of incorporation of various novel chemicals and technological approaches such as pro-drug, mucoadhesives, permeation enhancers, microparticulate, salts acting as buffers.

Of course not all benefits listed above can present in single, ideal device. Each type of inserts represents compromise between desirable properties inherent by solid dosage forms and negative constraints imposed by structure and components of insert itself, by fabrication cost, as well as by the physical/physiological constrains of application site.

Disadvantages of Ocular Inserts:

1. A capital disadvantage of ocular inserts reside in their 'solidity', i.e., in the fact that they are felt by the (often oversensitive) patients as an extraneous body in the eye [8, 9, 10].

2. Their movement around the eye, in rare instances, the simple removal is made more difficult by unwanted migration of the inserts to upper fornix.
3. The occasional inadvertent loss during sleep or while rubbing the eyes.
4. Their interference with vision.
5. Difficult placement of the ocular inserts (and removal, for insoluble types).

Classification of occusert: They are classified on the basis of their solubility [11];

a) Insoluble ophthalmic inserts.

b) Soluble ophthalmic inserts.

c) Bioerodible ophthalmic inserts.

a) **Insoluble ophthalmic inserts:** Sub classified into:-

- Diffusional Inserts.
- Osmotic Inserts.
- Contact Lenses.

- **Diffusional Inserts:** The diffusional inserts are composed of a central reservoir of drug enclosed in specially designed semi permeable, which allow the drug to diffuse from the reservoir at precisely determined rate. The lacrimal fluid permeating through the membrane until the sufficient internal pressure is reached to drive the drug out of reservoir controls the drug release from such a system. The principle for its operation can be operated by the Fick's diffusion equation. J=-DAdc/dx J=solute flux D=Difference co-efficient for the drug within the polymer membrane A= Area of membrane dc/dx= Drug concentration gradient within the membrane along the direction of drug flow.

- **Osmotic Inserts:** The osmotic inserts are composed of two distinct compartments. One compartment contains drug and other contains osmotic solute, which is sandwiched between the rate controlling membrane. The tears diffuse into osmotic compartment inducing an osmotic pressure due to which drug diffuses.

- **Contact Lenses:** Contact lenses are covalently cross-linked hydrophilic or hydrophobic polymer that forms a three-dimensional network capable of retaining water aqueous drug solution or solid components.

b) **Soluble ophthalmic inserts:** These types of inserts are entirely soluble so that they do not need to be removed from their site of application. The release of drug from this type of inserts due to penetration of tear fluid into the inserts that induces high release rate of drug by diffusion and forms a gel layer around the core of the insert.

c) **Bioerodible Ophthalmic Inserts:** The biodegradable inserts are composed of material homogeneous dispersion of a drug included or not into a hydrophobic coating which is substantially impermeable. The release of the drug from such a system is the consequence of the contact of the device with the tear fluid inducing a superficial diversion of the matrix.

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.

1. **Thickness of Film:** Film thickness is measured by using dial caliper at different points and the mean value is calculated. Readings are taken over the area of circular films. The standard deviation in thickness is computed from the mean value [14].

2. **Drug Content Uniformity:** To check the uniformity of the drug in the ocular insert film, the 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 diluted. The solution is analyzed by spectrophotometer using pH 7.4 phosphate buffer as blank. The drug content is calculated using the following formula:

Mg of drug = As X Cr in one patch Ar

Where; As = Absorbance of sample solution, Ar = Absorbance of standard solution, Cr = Concentration of drug in Standard solution, Same procedure is adopted for all the batches of cast films in triplicates and mean drug content and standard deviation of variance are calculated.

3. **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 determined by using the digital balance. The mean value is calculated. The standard deviation of weight variation is computed from the mean value [15].

4. **Percentage moisture absorption:** The percentage moisture absorption test is carried out to check physical stability or integrity of ocular inserts. Ocular inserts are weighed and placed in a desiccators containing 100 ml of saturated solution of aluminum chloride and 79.5% humidity is maintained. After three days the ocular inserts are taken out and reweighed. The percentage moisture absorption is then calculated using the formula:

Percentage moisture absorption = Final weight –Initial weight x 100 Initial weight [12]

5. **Percentage Moisture Loss:** The percentage moisture loss is carried out to check integrity of the film at dry conditions. Ocular inserts are weighed and kept 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:

Percentage moisture loss = Initial weight – Final weight x 100 Initial weight.

6. ***In-vitro* drug Release:** To simulate the actual physiological conditions prevailing in the eye, an *in-vitro* dissolution procedure is used. *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 tied at one end of the open cylinder, which acts as the donor compartment. The ocular insert is placed inside the donor compartment.

   The semi-permeable membrane is used to simulate ocular in vivo condition like corneal epithelial barrier. In order to simulate the tear volume, 0.7 m1 of distilled water is placed and maintained at the same level through out 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 replaced with equal volume of distilled water. The drug content is analyzed at the wavelength of the particular drug against reference standard using pH 7.4 phosphate buffer as blank on a UV/visible spectrophotometer [16, 17].

7. ***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 100mg of pure drug, which are spread to a thin layer. This Petri dish along with polyethylene bags and forceps are placed in UV sterilization chamber (hood). The inserts and other materials are exposed to UV radiation for one hour. After sterilization, inserts are transferred into polyethylene bag with the help of forceps inside the sterilization chamber itself.

   The pure drugs which are sterilized along with inserts are analyzed for potency by UV spectrophotometer after suitable dilution with pH 7.4 phosphate buffer. The male albino rabbits, weighing between 2.5-3.0kg are required for the experiment. The animals are housed in individual cages and customized to laboratory conditions for

1 day. Free access to food and water is enabled. The ocular inserts containing drug are taken for in-vivo study which are previously sterilized on the day of the experiment and are placed into the lower conjunctivas cul-de-sac. The inserts are inserted into each eye of seven rabbits at same time and each eye is serving as control. Ocular inserts are removed carefully at 2, 4, 6, 8, 10, 12 and 24 hours and analyzed for drug content as dilution mentioned in drug content uniformity.

The drug remaining is subtracted from the initial drug content of inserts which will give the amount of drug released in the rabbit eye. Observation for any fall out of the inserts is also recorded throughout the experiment. After one week of wash period the experiment is repeated for two times as before.

8. **Accelerated Stability Studies:** The accelerated stability studies are carried out to predict the breakdown that may occur over prolong period of storage at normal shelf condition. The films of the formulation are taken in a separate Petri dish and are kept at three different temperatures 40^0C, 50^0C and 60^0C and the period for break down or degradation of the ocular inserts is checked. When ocular inserts show degradation the time in days is noted and subjected to determine the drug content of each individual film using the drug content uniformity procedure [13].

Conventional Ocular Formulations for Ocular Drug Delivery: The conventional drug delivery systems like solutions, suspensions and ointments are no longer sufficient to fulfill the present day requirements of providing a constant rate delivery and prolonged time. The advantages and disadvantages of using conventional dosage form [20] of ophthalmic drug delivery system are shown in **Table 1**.

TABLE 1: COMPARISON FOR OPTHALMIC DOSAGE FORM

Dosage forms	Advantages	Disadvantages
Solutions	Convenience	Rapid pre-corneal elimination, Loss of drug by drainage, **No** sustained action.
Suspensions	Patient compliance, Best for drugs with slow dissolution	Drug properties decide performance, Loss of both solution and suspended solid.
Emulsions	Prolonged release of drug from vehicle Enhanced pulsed entry	Patient non compliance. Blurred vision Possible oil entrapment.
Gels	Comfortable Less blurred vision than ointment	No rate control on diffusion, Matted eyelids after use.
Ointment	Flexibility in drug choice, Improved drug stability, Increased tissue contact time, Inhibition of dilution by tears, Resistance to naso-lachrymal drainage	Sticking of eyelids Poor patient compliance, Blurred vision, No true sustained effect, Drug choice limited by partition co-efficient

Inclusions of Currently Explored Formulation Trends:

1. Polymeric solutions [19]
2. Phase transitions systems
3. Muco-adhesive/bio-adhesive systems
4. Pseudolattices
5. Collagen shields
6. Ocular penetration enhancers
7. Ocular drug delivery devices
8. Particulate systems for ocular drug delivery
9. Vesicular systems for ocular drug delivery

1. **Polymeric solutions:** The additions of polymers like methylcellulose, polyvinyl alcohol, hydroxypropyl methylcellulose and polyvinyl pyrrolidone to the eye drop solution increases the corneal penetrations of drug.

2. **Phase transition systems:** These are liquid dosage forms which shift to the gel or solid phase when instilled in the cul-de- sac. Polymers that are normally used are luterol c-127 and polxamer- 407 whose viscosity increases, when its temperature raised to 37°C .Cellouse acetate phthalate too coagulates, when its native pH of 4.5 is raised by tear fluid to pH 7.4.

3. **Muco-adhesive dosage forms:** Any polymer solution/suspension placed in the eye, first encounters mucin at the cornea and conjunctival

surface. If the polymer adheres to the mucin, the interaction is referred to as muco-adhesion, mucus on the corneal surface is provided by the goblet containing conjunctiva that is not tightly bound so that a corneal adhesive would attach to cornea itself and to be a true bio-adhesion.

4. **Collagen Shields:** Collagen shields promote wound healing and perhaps more important to delivery to deliver a variety of medications to the cornea and other ocular tissues. Collagen is structural protein of bones, tendons ligaments and skin. Collagen comprises more than 25% of the total body portion in mammals. It is main constituent of food grade gelatin.

5. **Pseudolattices**: Pseudolattices are a new class of polymeric colloidal dispersion and films forming agents used for typical application into the animals and human being used for sustaining the drug activity in-vivo. Organic solution of polymer is dispersed in an aqueous phase to form an o/w type emulsion.

6. **Ocular Penetration Enhancers:** Like acting filament inhibitors, surfactants, bile salts, chelators and organic compounds have been used to increase the bioavailability of topically applied peptides and protein which are otherwise poorly absorbed due to unfavorable molecular size, charge, hydrophilic as well as their susceptibility to degradation by peptidases in the eye.

7. **Ocular Drug Delivery Devices:** There are three types;

    1) Matrix type drug delivery systems

    2) Capsule type delivery systems

    3) Implantable drug delivery systems

1) **Matrix type drug delivery systems:** These are the devices that have the therapeutic agent, which is incorporated or impregnated with in the polymer, for controlled release of drug. E.g.; Hydrophilic soft contact lenses, soluble ocular insert.

    - **Hydrophilic soft contact lenses:** Several kinds of polymers have been used for the preparation of these lenses. They are made up of hydro gels that absorb certain amounts of aqueous solution, because of this property they have been found useful for drug delivery to anterior of the eye.

    - **Soluble ocular inserts:** Soluble ocular inserts, such as polyvinyl alcohol insert, the soluble ophthalmic drug inserts and polypeptides devices are matrix type polymeric devices used for drug delivery to eye.

2) **Capsular type drug delivery systems:** These are the devices that have a therapeutic agent encapsulated with in closed compartment surrounded by a polymer membrane. E.g.:-Occuserts. A truly continuous controlled release and zero order kinetic fashion was achieved using an ocular insert.

3) **Implantable drug delivery:** Implantable devices which have been developed and used include an osmotic mini-pump, a drug pellet coated with polyvinyl alcohol and ethylene acetate and poly sulfone capillary fiber.

Recent Trends: The following recent trends are in existence:

a) Membrane-bound ocular inserts (biodegradable and non-biodegradable)

b) Mucoadhesive dosage forms (ocular films or sheath, ophthaCoil, polymer rods, HEMA hydrogel, Dispersion, polysulfone capillary fiber)

c) Collagen shields, cyclodextrine based system, ophthalmic rods.

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 pledgets (Drug presoaked hydrogel type, polymeric gels)

f) Phase Transition systems (in-situ gel formation system: ion- activated based, pH changed based, temperature change based).

g) Nanoparticles (Microspheres, nanosuspension, Amphiphilogels, Niosomes, Liposomes, Dendrimers and Quantom dots)

h) Ocular Iontophoresis and pumps

i) Chemical delivery systems vesicular systems Utilization of the principal of controlled release as embodied by ocular inserts therefore offers an attractive alternative approach to the difficult problem of prolonging pre-corneal drug residence time [22].

CONCLUSION: In conclusion, an ideal ocular insert as a therapeutic system should be bio stable, biocompatible with minimal tissue-implant interaction, stable, nontoxic, non carcinogenic, retrievable and should release the drug at a constant programmed rate for a predetermined duration of medication. As ocular inserts release the drug for prolong period, so it reduces the no. of administrations and increases patient complaience. The concept of ocular inserts as a drug delivery system to the eye though conceived long back was commercialized only after the uses of bio-compatible polymers as described earlier were developed. Different categories of drugs like antiglaucoma, antibacterials, antivirals, anaesthetics, NSAIDs can be loaded through the ocular inserts for the treatment of eye disorders. The use of Pilocarpine for glaucoma treatment in the form of ocular inserts is the most widely used technique in ocular therapeutics. In spite of this investigation development of an ideal and bio-compatible polymer free from toxic and allergic manifestation is yet to be brought about. However, with the available polymer a reasonably good ocular insert device with minimal tissue interaction, nontoxic, non carcinogenic, have been developed commercially. The use of ocular inserts and other forms of ocular drug delivery have been reviewed in several excellent texts; in future also the research in this field will definitely take a momentum.

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