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## OCULAR INSERTS: AN OVERVIEW

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### ABSTRACT

Ocular route of drug delivery is one of the most interesting routes of drug delivery due to unique anatomy, physiology and biochemistry of eye. The main purpose of preparing ocular insert is to increase ocular bioavailability of drug. Ocular inserts maintain the drug concentration within a desired range. Fewer administrations are required so they increase patient compliance.

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Erodible, nonerodible ocular inserts, bioadhesive strength, swelling index, solvent casting method

## INTRODUCTION

Ophthalmic inserts are defined as sterile preparations, with a solid or a semi solid consistency, whose size & shape are especially designed for ophthalmic application. They are essentially composed of a polymeric support containing drug(s), the latter being incorporated as dispersion or a solution in the polymeric support. The inserts can be used for topical or systemic therapy [1]. Ocular inserts of various drugs for ex. acyclovir [2], chitosan [3], gatifloxacin [4], levofloxacin [5], natamycin [6], ofloxacin [7], phenylephrine [8], diclofenac sodium [9], idoxuridine [10], norfloxacin [11], pefloxacin [12], timolol maleate[13], brimodine [14] and pilocarpine [15].

The basic objective of controlled drug release is to achieve more effective therapies by eliminating the potential for both under and overdosing. Other advantages are the maintenance of drug concentration within a desired range, fewer administrations, optimal drug use and increased patient compliance [16].

The unique anatomy, physiology and biochemistry of the eye render this organ impervious to foreign substances, thus presenting a constant challenge to the formulator to circumvent the protective barriers of the eye without causing permanent tissue damage [17]. Topical ocular therapy is often impaired by natural physiologic defense mechanisms to drug application such as blinking and an increase in tear turnover. The intraocular bioavailability of topically applied drugs is extremely poor. This is mainly due to drainage of the excess fluid by the nasolacrimal duct as well as dilution and elimination of the solution by tear turnover. Ocular bioavailability of drugs is an important parameter influencing the efficacy of ophthalmic preparations. There remains, however, a need for a topical drug carrier that has the following capabilities:

- provides effective penetration of the inner ocular tissues;
- is target specific;
- offers controlled release of a drug in a manner that produces minimal systemic toxicities; and
- is biodegradable and eco-friendly[18]

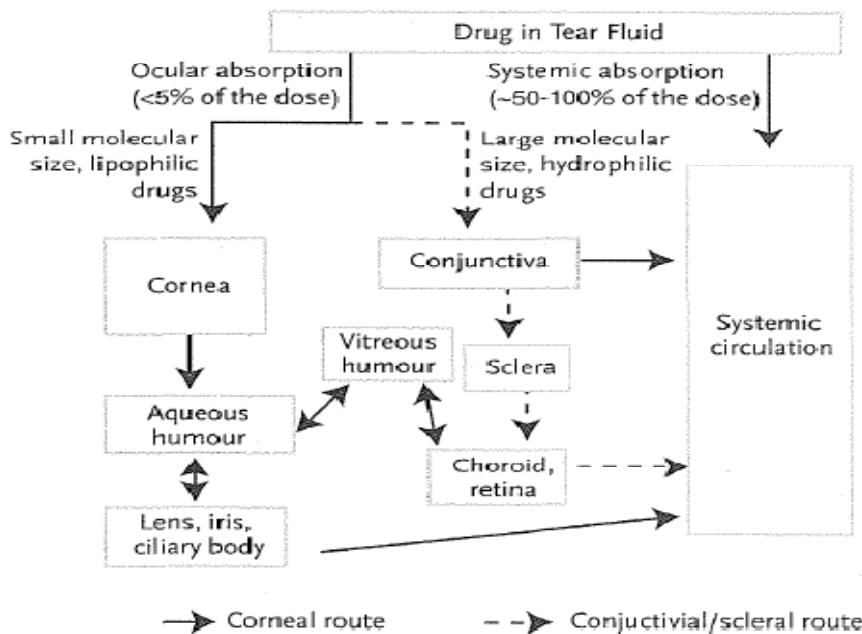
### Drawbacks of conventional drug delivery system:

The conventional ocular drug delivery systems like solutions, suspensions, and ointments show drawbacks such as

- increased precorneal elimination,
- high variability in efficiency,
- gel formation is a technique to enhance the viscosity of preparation. But, high viscosity may result in blurring of vision
- and matted eyelids which substantially reduce patient acceptability,
- Sterilization is another draw back for large scale production [19].
- Ocuserts do not optimize precorneal delivery of drug [20].

### Advantages of controlled ocular drug delivery systems

- Increased accurate dosing. To overcome the side effects of pulsed dosing produced by conventional delivery.
  - To provide sustained and controlled delivery.
  - To increase the ocular bioavailability of drug by increasing the corneal contact time.
  - To circumvent the protective barriers like drainage, lacrimation and conjunctival absorption.
- To provide better housing of delivery system [19].



**Figure 1: Various pathway of drug absorption**

A polymeric support is must for the ocular inserts which may or may not contain the drug. The drug is later entrapped or dispersed or the drug can be incorporated as a solution in the polymeric supports which have advantages as they increase the residence of the drug in the eye so a sustained release dosage form would be formulated [21].

#### Criteria for Successful Ocular Inserts:

- Comfort and noninterference with vision
- Successful oxygen permeability
- Biocompatibility and stability
- Reproducibility of release kinetics
- Applicability to a variety of drugs
- Ease of sterility and nontoxicity
- Ease of handling ( insertion and removal)
- Ease of manufacture and low cost

#### Types of Ocular Inserts:

- Erodible and
- Nonerodible ocular inserts

#### Advantages of Nonerodible Ocular Inserts in Comparison to Erodible Ocular Inserts are:

- Better release kinetics of drug

- Ease of detection when they are expelled
- Greater reliability

#### Disadvantage of Nonerodible Ocular Insert in Comparison to Erodible Ocular Inserts are:

- They have to be removed after the intended drug delivery period.

#### Marketed Nonerodible Ocular Inserts are:

- Contact lenses and the ocusert

#### Marketed Erodible Ocular Inserts are:

- Lacrisert
- SODI( soluble ocular drug insert)
- Collagen shield [22]

#### Various Methods of Preparation:

1. 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 petridish 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 [4].

2. 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- $\beta$  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 center of leveled 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, nonirritating, water insoluble gum. They were wrapped in aluminium foil separately and stored in a desiccator [3].
3. 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 charged to the barrel of Melt Flow Rate apparatus and extruded. The extrudate was cut into appropriate size and packed in polyethylene lined aluminium foil, heat sealed and sterilized by gamma radiation (2.5 Mrad for 4 h) [23].

### **Different Methods of Evaluation:**

1. Thickness of Insert
2. Weight variation test
3. Surface pH determination
4. Drug content uniformity
5. Mechanical strength
6. Ex vivo bioadhesive strength
7. Swelling index of prepared ocular inserts
8. In vitro drug release study
9. Ocular tolerance

#### 1.Thickness of Insert:

Thickness of the inserts is measured using dead weight thickness gauge. After initial settings, the foot is lifted with the help of the lifting lever fixed on the side of the dial gauge. Insert is placed on the anvil such that the area where the thickness is to be measured lies below the foot. Readings of the dial gauge are recorded after gentle lowering of foot.

#### 2.Weight variation test:

Inserts from each batch are randomly selected and weighed individually on electronic balance. Mean weight of inserts of each formulation is recorded.

#### 3.Surface pH determination:

Inserts are left to swell for 5 h on agar plate prepared by dissolving 2% (w/v) agar in warm simulated tear fluid (STF; sodium chloride: 0.670 g, sodium bicarbonate: 0.200 g, calcium chloride. 2H<sub>2</sub>O: 0.008 g, and purified water q. s. 100 g) of pH 7.4 under stirring and then pouring the solution into Petri dish till gelling at room temperature. After the time of soaking, the pH of the wet surface is measured by placing the electrode in contact with the surface of the insert [24-25].

#### 4. Drug content uniformity:

Uniformity of the drug content is determined by assaying the individual inserts. Each insert is grounded in a glass pestle mortar and STF is added to make a suspension. The suspension so obtained is filtered and the filtrate is assayed spectrophotometrically.

#### 5. Mechanical strength:

Ocular insert with good tensile strength and percent elongation would resist tearing due to stress generated by the blinking action of eye. The insert is cut into strips. Tensile strength and elongation at break is determined. The apparatus consisted of a base plate with a pulley aligned on it. One aluminum clip is fixed on one end of the base plate, to which the insert is clipped. The other end of the insert is clipped to movable aluminum clip. A thread is tied to movable clip and passed over the pulley, to which a small pan is attached to hold weights. A small pointer is attached to the thread that travels over the scale affixed on the base plate. The weights are gradually added to the pan till the insert (that is affixed between two clips) is broken. The weight necessary to break the insert is noted as break force and the simultaneous distance traveled by the pointer on the scale indicated the elongation at break. The following parameters are calculated as per equations:

Tensile strength ( $\text{g/mm}^2$ ) = break force (g)/cross-sectional area of the sample ( $\text{mm}^2$ )

Elongation at break (E/B) (%) = increase in length at break point (mm) ( $L_s - L_o$ )/original length ( $L_o$ ) (mm) X 100

#### 6. Ex vivo bioadhesive strength:

Freshly excised conjunctiva of an adult goat is used as a model membrane for the measurement of bioadhesive strength. Whole eye bulbus of an adult goat is obtained from a local slaughter house, the underlying skin is removed to obtain freshly excised conjunctiva. The preparation is placed in an aerated saline at  $4^\circ\text{C}$  and later washed with distilled water and isotonic phosphate buffer (pH 7.4,  $37^\circ\text{C} \pm 1^\circ\text{C}$ ) before use. Bioadhesive strength of insert is measured on a modified 2-arm physical balance. The pan at the left arm of the balance is detached and to the lever of left arm, is hanged a vertical thread, which has a rubber stopper tied to its end, hanging downward. Insert to be tested was adhered to the downward facing side of the rubber stopper. Goat conjunctival membrane is tied onto the open mouth of a glass vial filled with isotonic phosphate buffer. Vial is fitted in the center of a glass beaker filled with STF (pH 7.4,  $37^\circ\text{C} \pm 1^\circ\text{C}$ ). The apparatus is set such

that the vial (conjunctival membrane tied on it, facing upward) lies exactly below the rubber stopper (insert tied on it, facing downward). The rubber stopper is lowered so as to make the insert come in contact with the membrane. After facilitating the contact between the two, weight is put on right limb of balance, (gram force) required to detach the insert from the conjunctival surface gave the measure of detachment stress, calculated by:

$$\text{Detachment stress (dyne/cm}^2\text{)} = [m.g/A]$$

Where, m is the weight required for detachment of insert, g the acceleration due to gravity considered as  $980 \text{ cm/s}^2$  and A the area of tissue exposed ( $\text{cm}^2$ ).

#### 7. Swelling index of prepared ocular inserts:

Swelling of the polymer depends on the concentration of the polymer, ionic strength, and the presence of water. To determine the swelling index of prepared ocular inserts ( $n = 3$ ), initial weight of insert is taken, and then placed in agar gel plate (2% w/v agar in STF, pH 7.4) and incubated at  $37^\circ\text{C} \pm 1^\circ\text{C}$ . For 5 h, insert is removed from plate after every 1 h, surface water is removed with help of filter paper, and insert is reweighed. Percent hydration is calculated.

Hydration % or (Sw) % =  $[\text{wt} - \text{wo}/\text{wo}] \times 100$

(Sw) % = equilibrium percent swelling, wt = weight of swollen insert after time t,

wo= original weight of insert at zero time

#### 8. In vitro drug release study:

The bichambered donor-receiver compartment model, designed using commercial semi-permeable membrane of transparent and regenerated cellulose type (Sigma dialysis membrane), is used to carry out the in vitro drug release studies. Semi-permeable membrane is used to mimic in vivo conditions, such as corneal epithelial barrier. The insert is placed in the donor compartment, and STF with pH 7.4 is maintained at the same level throughout the study in the donor compartment to simulate tear volume. The entire surface of the membrane is in contact with the reservoir compartment

that contained STF with pH 7.4, which is stirred continuously using a magnetic stirrer to simulate blinking action. Drug release is determined by withdrawing a defined quantity of sample from the sampling port at periodic intervals, which is replaced with equal volume of phosphate buffer pH 7.4. The drug content is analyzed. The release data are kinetically analyzed using different kinetic models (zero-order, first-order, and Higuchi diffusion model). In order to determine the release model that best describes the pattern of drug release, the in vitro release data were fitted to zero-order, first-order, and diffusion controlled release mechanisms according to the simplified Higuchi model. The equations used are as follows:

Zero-order kinetic model:  $C = C_0 - K_0 t$

First-order kinetic model:  $\log C = \log C_0 - K_t / 2.303$

Higuchi diffusion model:  $Q = 2C_0 (D \sqrt{t})^{1/2}$

where,  $C_0$  is the initial drug concentration;  $C$  the drug concentration (released) at time  $t$ ;  $T$  the time of release;  $Q$  the amount of drug released/unit area;  $K_0$  the zero-order rate constant;  $K$  the first-order rate constant; and  $D$  the diffusion coefficient, and it is calculated according to the following equation:

$D = (\text{slope}/2C_0)2\pi$ [26-28].

### Ocular tolerance:

For ocular tolerance determination, modified hen's egg chorioallantoic membrane (HET-CAM) test is carried out. Briefly, fertilized hen's eggs are obtained from poultry farm. These eggs are incubated in humidified incubator at a temperature of  $37^\circ\text{C} \pm 0.5^\circ\text{C}$  for 3 days. The trays containing eggs are rotated manually in a gentle manner after every 12 h. On day 3, egg albumin is removed by using aseptic techniques from the pointed end of the egg. The hole is sealed by 70% alcohol-sterilized parafilm with the help of a heated spatula. The eggs are kept in the equatorial position for the development of

chorioallantoic membrane away from the shell. The eggs are candled on the fifth day of incubation and every day, thereafter, nonviable embryos are removed. On the tenth day, a window is made on the equator of the eggs through which formulations are instilled. A placebo film (0.6% carbopol and 1.4% HPMC) is used as a control as it is reported to be practically nonirritant [26]

### **CONCLUSION**

Ocular inserts do optimize precorneal delivery of drug. The drug is entrapped or dispersed or the drug can be incorporated as a solution in the polymeric supports which have advantages as they increase the residence of the drug in the eye. They circumvent the protective barriers like drainage, lacrimation and conjunctival absorption.

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