

Review Article

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Ocular Drug Delivery System & Role of Ocular Inserts In Eye Disorder Treatment: A Review

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ABSTRACT

Eye is the organ of human body having main function of vision. Ocular drug delivery is the alternative route for the systemic treatment of disease and also a route for the treatment of eye diseases such as conjunctivitis, keratitis etc. Ocular inserts are the one of the most useful and innovative technique for the treatment of eye diseases by increase contact time and providing control release of drug. This review is generated to provide an overview of ocular drug delivery including role of ocular inserts in treatment of eye disorders.

Key-words: Ocular drug delivery, ocular insert, conjunctivitis.

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INTRODUCTION

The human eye can be classified into two segments: anterior and posterior segments. The cornea, conjunctiva, iris, ciliary body, aqueous humor and lens are included in the anterior segment and sclera, choroid, retina, vitreous humor are included in the posterior segment. The outermost transparent membrane of the eye is cornea such as the corneal epithelium, Bowman's membrane, stroma, Descemet's membrane, and endothelium. The anterior segment is a fluid of the eye which contains the source of nutrition to the crystalline lens and cornea. The iris sphincter and dilator muscles help to adjust the pupil size which regulates the amount of light entering to the eye.^[1, 2]

A ring-shaped muscle attached to the iris called ciliary muscles. It is important because contraction and relaxation of the ciliary muscle controls the shape of the lens. The choroid layer is located behind the retina and absorbs unused radiation.^[3]

The retina is a multi-layered sensory, light sensitive tissue contains millions of photoreceptors or photosensitive elements that capture light rays and convert them into electrical impulses. These impulses travel along the optic nerve to the brain, where they are converted into an image. A jelly-like substance known as vitreous humor, distributed between retina and lens.^[1, 2]

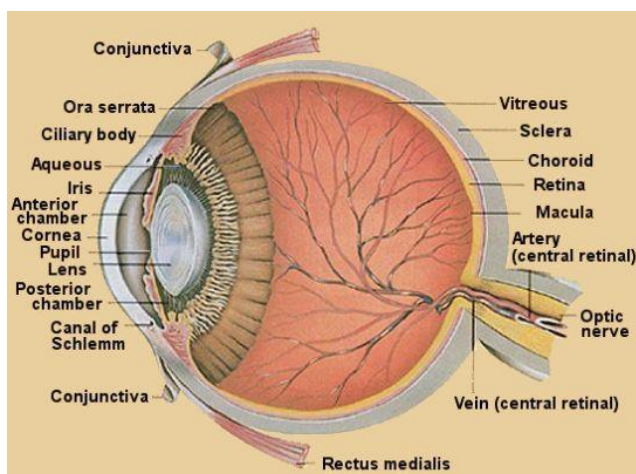


Fig. 1: Anatomy of Eye

MANAGEMENT OF EYE DISEASES

Conjunctivitis

Bacterial conjunctivitis is an inflammation of the conjunctiva caused by bacteria.^[4, 5]

Fluoroquinolones

Ciprofloxacin or Ofloxacin, Levofloxacin, Moxifloxacin, Gatifloxacin or Besifloxacin

Aminoglycosides

Tobramycin or Gentamicin

Macrolides

Erythromycin ^[6, 7]

Keratitis

Bacterial keratitis is an infection and inflammation of the cornea that cause pain, reduced vision, light sensitivity and tearing or discharge from the eye that can, in severe cases cause loss of vision. Treatment will include third-generation quinolone drops (ciprofloxacin and ofloxacin) or fourth generation drops (gatifloxacin or moxifloxacin).^[8]

OCULAR DRUG DELIVERY

Ocular drug delivery system is a system to deliver active pharmaceutical ingredient to ophthalmic route for local or systemic effect.

TYPES OF OCULAR DRUG DELIVERY

A multitude of ocular dosage forms are available for delivery of drugs to the eye. These can be classified as follows:

1. Liquids: Solutions, Suspensions, Sol to gel systems, Sprays
2. Solids: Ocular inserts, Contact lenses, Artificial tear inserts, Filter paper strips
3. Semi-solids: Ointments, Gels
4. Miscellaneous: Ocular iontophoresis, Mucoadhesive dosage forms.^[9]

Liquids

It is most popular and desirable state of dosage forms for the eye and drug absorption rate is fastest from this state then the other.

Solution and suspensions

Solutions are widely used to administer drugs that must be active on the eye surface or in the eye after passage through the cornea or the conjunctiva. The drug in the solution is in the solved state and may be immediately active. To increase the corneal contact time of a drug substance and provide a more sustained action we use ophthalmic suspensions.

Sol to gel system

It is a new concept of producing a gel in situ (eg. in the cul-de-sac of the eye) and widely accepted that in the precorneal region when viscosity of a drug formulation increased so the bioavailability will also increased, due to slower drainage from the cornea. These systems can be triggered by pH, temperature or by ion activation.

Spray

These sprays are used in the eye for dilating the pupil or for cycloplegic examination.

Solids

The concept of using solids for the eye is based on providing sustained release characteristics.^[9]

Ocular Inserts

Ophthalmic inserts are defined as sterile preparations, with a solid or a semi solid consistency, whose size and shape are especially designed for ophthalmic application. A number of ocular inserts were prepared utilizing different techniques to make soluble, erodible, non erodible, and hydrogel inserts.^[10]

Contact lenses

Contact lenses can absorb water soluble drugs when soaked in drug solutions.

Artificial tear inserts

This device is designed as a sustained release artificial tear for the treatment of dry eye disorders.

Filter paper strips

These strips are used to disclose corneal injuries and infections such as herpes simplex, and dry eye disorders. The example of filter paper strips are Sodium fluorescein and rose Bengal dyes.

Semisolids

To provide sustained effects Semi-solids dosage forms are used. Ophthalmic ointment is used to prolong drug contact time with the external ocular surface. Ophthalmic gels are composed of mucoadhesive polymers that provide localized delivery of an active ingredient to the eye.

Miscellaneous

Ocular iontophoresis

Iontophoresis is the process in which direct current drives ions into cells or tissues. When iontophoresis is used for drug delivery, the ions of importance are charged molecules of the drug. If the drug molecules carry a positive charge, they are driven into the tissues at the anode; if negatively charged, at the cathode.

Mucoadhesive dosage forms

Mucoadhesive polymers are usually macromolecular hydrocolloids with numerous hydrophilic functional groups such as carboxyl-, hydroxyl-, amide and sulphate, capable of establishing electrostatic interactions. The bioadhesive dosage form showed more bioavailability of the drug as compared to conventional dosage forms.^[9]

OCULAR INSERTS

Ophthalmic inserts are sterile preparations with a solid or a semisolid consistency, and whose size and shape are especially designed for topical or systemic treatment ophthalmic inserts.^[11]

Advantages over other ocular drug delivery system

- ❖ Increased ocular residence, hence a prolonged drug activity and a higher bioavailability with respect to standard vehicles
- ❖ Possibility of releasing drugs at a slow, constant rate
- ❖ Accurate dosing
- ❖ Reduction of systemic absorption
- ❖ Better patient compliance, resulting from a reduced frequency of administration and a lower incidence of visual and systemic side-effects
- ❖ Possibility of targeting internal ocular tissues through non-corneal routes
- ❖ Increased shelf life with respect to aqueous solutions
- ❖ Exclusion of preservatives, thus reducing the risk of sensitivity reactions
- ❖ Possibility of incorporating various novel chemical/technological approaches ^[12]

Characteristics required for drug

- ❖ The necessary characteristics for the material used to fabricate the ocular insert and obtain the desired drug metering effect are dependent on the particular drug used.
- ❖ Hydrophobic polymeric materials having a relatively high affinity for the drug should be used in forming the ocular insert. Otherwise, the drug will be rapidly released from the ocular insert and the objective of continuous and sustained release defeated.
- ❖ However, many hydrophobic polymers having the desired drug retention and release characteristics tend to be irritating to the eye and surrounding tissues.
- ❖ To provide compatibility with the eye and surrounding tissues. Since hydrophilic materials do not have the drug retention characteristics needed for many drugs, it has been necessary at times in

the past to select materials which compromise the desired comfort and tissue compatibility with the desired retention and release characteristics for the drug.

- ❖ Should be compatible with eye and surrounding tissues.
- ❖ In most cases hydrophobic polymers are used due to which sustain release of drug is achieved.
- ❖ Should not irritate ocular tissues.
- ❖ The surface of the ocular insert in contact with the eye and surrounding tissues should be soft and hydrophilic.
- ❖ Half life should not more.
- ❖ Protein binding should be low.
- ❖ Considerable bioavailability should be there.

Characteristics of ocular inserts

- ❖ Ocular inserts should not produce immunogenic & mutagenic reactions
- ❖ Ocular inserts are bio stable in nature & Biocompatible with tissue of eye
- ❖ They should have good mechanical strength
- ❖ Easily sterilizable
- ❖ They should not produce toxic & carcinogenic reactions
- ❖ Should be free from drug leakage
- ❖ They should be Retrievable & Release at a constant rate
- ❖ Non-interference with vision
- ❖ Successful oxygen permeability
- ❖ Ease of manufacture and low cost
- ❖ Sterility^[9,13, 14, 15]

CLASSIFICATION OF OPHTHALMIC INSERTS ^[14, 15, 16, 17]

Based upon their solubility behavior

1. Insoluble inserts; Diffusion, osmotic and contact lens etc.
2. Soluble; Natural polymers (eg. collagen), synthetic or semi synthetic polymers (eg. cellulose derivatives)
3. Bioerodible

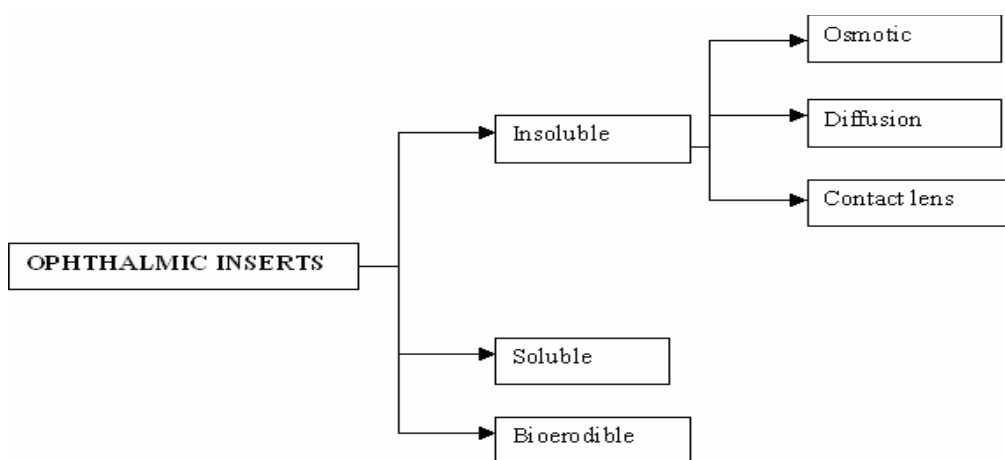


Fig.2. Classification of Ocular inserts

Insoluble ocular inserts

Diffusion

In diffusion inserts, the release of drug is based on diffusion mechanism. The diffusion systems are designed of a central reservoir of drug enclosed in a special semi permeable or micro porous membranes, which allow the drug to diffuse the reservoir at a precisely determined rate.

Osmotic

The osmotic inserts are generally divided into two types, in the first case the central part of the insert is surrounded by a peripheral part. The central part can be composed of a single reservoir, which is composed of the drug with or without an osmotic solute dispersed through a polymeric matrix, so that the drug is surrounded by the polymer as discrete small deposits.^[18] In the second case, the drug and the osmotic solutes are placed in two separate compartments, the drug reservoir is surrounded by an elastic impermeable membrane and the osmotic solute reservoir surrounded by a semi-permeable membrane. The peripheral part of these osmotic inserts is comprised of a film covering made of an insoluble semi-permeable polymer.^[19] The release of drug through the osmotic insert follows the zero-order drug release profile.^[20]

Contact lenses

When contact lenses soaked in drug solutions it absorbs water-soluble drugs. Contact lenses are used to provide extended release of drugs into the eye. In ophthalmic drug delivery systems, Contact lenses have certainly good prospects. The contact lenses are sub-divided into five groups; rigid, semi-rigid, elastomeric, soft hydrophilic and bio-polymeric.^[9, 14, 21]

Soluble ocular inserts

Soluble ocular inserts are divided into two types

Natural polymer

The first type of soluble inserts is based on natural polymer. Natural polymer used to produce soluble ophthalmic inserts is preferably collagen. 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.

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. Ethyl cellulose, a hydrophobic polymer, can be used to decrease the deformation of the insert and thus to prevent blurred vision.^[17]

Bioerodible

The bioerodible inserts are composed of metrical homogeneous dispersion of a drug included or not into a hydrophobic coating which is substantially impermeable to the drug. 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. They are two in types; insoluble inserts and soluble inserts.^{[15,}

17]

METHOD OF PREPARATION

Solvent casting method

In this method using different ratio of drug and polymer and prepare no. of batches. Firstly, in distilled water the polymer is dissolved. In stirring condition a plasticizer is added to this solution. The weighed amount of drug was added to this solution and stirred to get a uniform dispersion. After mixing this solution poured in Petridish and covered with funnel to allow slow evaporation at room temperature for 48 h. The dried films thus obtained then cut into circular pieces of definite size containing drug. The ocular inserts were stored in a desiccators (air tight container) under ambient condition.^[22]

Gelfoam disc

A gelfoam disc which diameter is ≈ 4 mm and 0.5 mm thickness was punched from a slab of gelfoam sponge with a common hole punch and phenylephrine HCL 1.7 mg and tropicamide 0.6 mg were dissolved in a solution (25 μ l) of 50% (v/v) ethanol in water. The solution was placed on the Gelfoam disc. Under vacuum for at least 72 h, the wet matrices were dried. By this method placebo devices were also prepared but without drug. The dose of phenylephrine and tropicamide are equal to two drops each of Mydriacyl.^[23]

Mould preparation

Using appropriate amounts of polymer, drug and excipients we prepare, polymethylsiloxane rod- shaped silicone inserts. Into the aluminium moulds (diameter 0.9 mm, length 22.0 mm), the mixtures were injected, and were allowed to cure at 45°C for 24 h. The resulting rubbery cylinders (diameter 0.9 mm, length 22.0 mm) were appropriately cut to give a drug content of specific amount. The final lengths and weights were in the range 4-12 mm and 2.7-8.0 mg, depending on insert type. The rod shaped silicon inserts were used, as such and after poly- acrylic acid or polymethacrylic acid coating, for hydration tests and for in vitro/in vivo drug release studies.^[24]

EVALUATION PARAMETERS

Sterility study

The inserts were sterilized using gamma radiation before carrying out the eye irritancy and in vivo drug release study. No microbial or fungal growth was seen in any of the formulations, which indicate that the films were sterilized completely.^[25]

Surface pH determination

The pH of solutions, drops, suspensions, and in situ gels is most often determined using a potentiometric method. In this method, the pH value is determined by measuring potential difference between electrodes placed in examined and reference solutions of known pH or between measurement electrode and reference (calomel or silver chloride) electrode, both placed in examined preparation.^[26-28]

Clarity examination

Clarity examination involves the visual assessment of formulation in suitable lighting on white and black background. It is performed for liquid forms, with the exception of suspensions. This examination applies to eye drops and in situ gels before and after gelling.^[29, 30]

Another method of clarity examination involves transmittance measurement using a UV-Vis spectrophotometer. This method can be employed in research on contact lenses filled with active ingredients. The lenses are hydrated in physiological saline and placed on the surface of quartz cuvette. The transmittance is measured afterwards from 200 to 1000 nm wavelength.^[31]

Examination of size and morphology of particles

For examination of particles' size multiple methods are employed: optical microscopy (microscopic particle count test), light obscuration particle count test, dynamic imaging analysis, laser diffraction particle analyzers, electron microscopy, dynamic light scattering, coulter counter test and nanoparticle tracking analysis.^[32]

In-vivo characterization

Eye Irritancy Test (Draize Eye Test)

There are many modifications of eye toxicity/irritancy test (Draize eye test) performed for dosage forms, that is, solutions, emulsions, ointments, solids, for example, inserts, and so forth. The most often used animal subspecies are albino (eg. New Zealand) rabbits, which are examined and weighed before the test and then placed in specifically adapted cages, designed so as to avoid accidental injuries. The examined preparations are introduced to conjunctival sac or applied directly on the cornea. At first, about 0.1mL of analyzed drug was being applied on the eyeball, but many later examinations pointed to reducing the amount, for example, to 0.01 mL, which more reflects real situations. In the test, one eyeball, usually the left one, is used as a control. After introducing a drug form on the eyeball, the eyelids are usually kept closed for a few seconds, although it is not required. Sometimes sterile solutions are additionally used for rinsing the eyeball surface. An assessment of eyeball condition before and after introducing the formulation is done by observation of the eyeball in suitable light, often using magnifying glass or a slit lamp, which ensures more precise evaluation. Auxiliary procedures which simplify visualization of changes include dyeing with fluorescein and taking photos of eyeball. Moreover, the discomfort level after application may be indicated by the number of blinkings or rubbings of the eye. The evaluation takes place usually after 1 h, 24 h, 48 h, and 72 h from introducing a drug form on the eyeball and, if essential, also after 7 or 21 days. Duration of examination, as well as its scheme, is individually adapted to the analyzed formulation.^[34-36]

Transcorneal Permeation Study

For transcorneal permeation study, as in the Draize eye test, healthy albino rabbits are chosen in the number which is suitable for obtaining reliable results. The amount of active substance in aqueous humor after introducing the formulation to conjunctival sac is marked in specified time intervals. Using a syringe with needle, after intramuscular or intravenous anaesthetic injection which may contain, depending on application, ketamine hydrochloride, xylazine hydrochloride, or pentobarbital sodium, a sample of aqueous humor is taken in the amount of about 150–200 μL and stored at negative temperature, for example, -20°C , before HPLC analysis.^[37-41] At times, additional inhalation anaesthesia is used, for example, in the form of mixture of 4% isoflurane-oxygen, shortly before or during paracentesis.^[38] Regional anaesthesia, for example, in the form of xylocaine solution, may also be applied.^[40] Noomwong with associates, during performed tests, added suitable amount of 2% $\text{ZnSO}_4 \cdot 7\text{H}_2\text{O}$ solution to the taken samples in order to salt out proteins contained in aqueous humor and then centrifuged the sample at the speed of 10000 rpm for 1 h at the temperature of -10°C . They used HPLC method to examine the amount of active ingredient in the obtained supernatant ^[38]. On the other hand, El-Laithy et al. and associates examined obtained samples using a spectrofluorometric method, which could have been employed due to natural fluorescence of used drug from fluoroquinolone group, moxifloxacin.^[39]

Brand name	Drug	Dosage form	Use
Dichol	Carbahol	Sterile solution/injection	In ophthalmic surgery
Dexcin	Dexamethasone	Eye drop	In eye infection
Ocupol	Polymixin-B	Eye drop/Ointment	Corneal ulcer
Acivir eye	Acyclovir	Ointment	Eye infection
Chloromycetin	Chloramphenicol palmitate	Ointment	Conjunctivitis
Pred forte	Prednisolone acetate	Suspension	Anti allergic
Ciplox	Ciprofloxacin	Eye drop	Conjunctivitis
Restasis	Cyclosporine	Emulsion	Dry eye
Refresh classic	Artificial tear fluid	Single use vials	Dry eye
Betnisol N	Betamethasone	Eye drop	Eye infection
Refresh tears	Hydroxypropyl methylcellulose	Eye drops	Eye lubricant
Geltear	Carbomer	Bioadhesive gel	Lubricant
Timolol xe	Timolol maleate	In-situ gel	Keratoconjunctivitis

Table: Marketed ophthalmic products[42]

CONCLUSION

Ocular delivery based formulations have great applications for local treatment of eye disease with relatively lesser side effects as compared to other route of drug delivery. Progress in the field of ocular drug delivery has been established recently with controlled loading and sustained release. Ocular formulations could be more acceptable and excellent drug delivery systems if prepared by using the biodegradable and water soluble polymers. Ocular inserts might be an alternate for the traditional system with many of benefits and best system for the treatment of eye disease as well as systemic disease.

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