

REVIEW ARTICLE ON OPHTHALMIC INSERTS**Reshma Hegden P.*, Sreedevi T. T., Steffy P. Raju, Jiju V., Elesy Abraham**

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Pharmacy, Othara P.O,
Thiruvalla-689546.**ABSTRACT**

The ocular insert represents a significant advancement in the therapy of eye disease. Ocular drug delivery is one of the most challenging tasks faced by Pharmaceutical researchers. Major objective of ocular inserts is to maintain a therapeutic level of the drug at the site of action for a prolonged duration. The ophthalmic preparations are available as sterile, buffered, isotonic solution. Ocular inserts offer several advantages as increased ocular residence and sustained release of medication into the eye. Several types of dosage forms are applied as the delivery system for the ocular delivery of drugs. The most prescribed dosage form is the eye drop solution as drops are easier to

administer. Suspensions, gelled systems, ointment are also used for prolonged therapeutic action. Characteristics of ophthalmic preparations should be non-irritating to the ocular tissue, homogenous, relatively non-greasy, should not cause blurred vision and intolerable foreign body sensation. It should be sterile and adequately preserved, physically & chemically stable, efficacious. Prolonged drug release can be achieved using ophthalmic inserts, solid devices placed in the eye, but the inserts must then be removed when they are no longer needed. Ocular inserts are the new drug delivery systems which are designed in such a way that they release the drug at predetermined and predictable rates thus eliminating the frequent administration of the drug. The release of drug from the insert depends upon the diffusion, osmosis and bio erosion of the drug.

INTRODUCTION

Ocular inserts are defined as sterile, thin, multilayered drug impregnated, solid or semi solid consistency devices placed into the cul-de-sac, whose size and shape are designed for ophthalmic application. They are composed of a polymeric support that may or may not contain a drug.

In developing a drug delivery strategy, issues of absorption, distribution, metabolism, elimination (ADME) must be considered. The eye presents unique opportunities and challenges when it comes to delivery of pharmaceuticals. Ophthalmic drug delivery is one of the most interesting and challenging endeavors facing the pharmaceutical scientists. The anatomy, physiology and biochemistry of the eye render this organ exquisitely impervious to foreign substances. The challenge in front of formulator is to circumvent the protective barriers of the eye without causing permanent tissue damage. The development of newer, more sensitive diagnostic techniques and therapeutic agents render urgency to the development of maximum successful and advanced ocular drug delivery systems. The goal of pharmacotherapeutics is the attainment of an effective drug concentration at the intended site of action for a desired period of time. Eye, as a portal for drug delivery is generally used for the local therapy as against systemic therapy in order to avoid the risk of eye damage from high blood concentrations of drug which are not intended for eye. The conventional ocular dosage forms are eye drops, eye ointments, eye gels, eye solutions, eye injections, eye irritation solutions, eye suspensions, sol to gel systems. The eye drop dosage form is easy to administer, but has inherent drawback that most of the instilled volume is eliminated from the pre-corneal area resulting in poor bioavailability ranging from 1-10 % of the total administered dose. This occurs mainly due to conjunctival absorption, rapid solution drainage by gravity, induced lachrymation blinking reflex, low corneal permeability and normal tear turn over. To overcome this many ocular drugs are used in high concentration. This causes both ocular and systemic side effects.

OPHTHALMIC INSERTS

Ophthalmic inserts are sterile preparations with a solid or a semisolid consistency, and in size and shape are especially designed for ophthalmic application. 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 for topical or systemic treatment. The inserts are placed in the lower fornix and less frequently, in the upper fornix of the cornea.

Ocular inserts can overcome the disadvantages reported with traditional ophthalmic systems like eye drops, suspensions and ointments. The typical pulse entry type drug release behavior 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 releases embodied by ocular inserts offers an attractive approach to the problem of prolonging pre corneal drug residence times.

Ocular inserts also offer the potential advantage of improving patient compliance by reducing the dosing frequency. The typical pulse entry type drug release behavior 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.

The various formulations for CR ocular drug delivery are discussed below

A. Ophthalmic solution of Drug Resinates

The first successful CR ophthalmic product for topical application using ion exchange resin technology was betaxolol ionic suspension for treatment of glaucoma. The drug is bound to Amberlite resin a cationic exchange resin of sulphonic acid styrene vinyl copolymer. The solution also contains a carbomer to increase its viscosity and thus the residence time of product in the eye.

B. Viscous solutions, Hydrogels and Mucoadhesive Formulations

Viscous solutions and hydrogels are based on the addition of hydrocolloids to aqueous drug solution. The most common polymers used in such formulations are cellulose derivatives, carbomers, polysaccharides, polyvinyl alcohol, PVP and recently, hyaluronic acid. Gels permit longer residence time in the precorneal area than viscous solutions. Hence, drug solutions that gel in the conjunctival cul-de-sac appear to be more acceptable. Such formulations are called as in-situ gel forming systems.

Three main mechanisms have been explored to induce the sol/gel transition in the conjunctival pouch-

1. Change in pH.
2. Change in temperature.
3. Change in ionic environment. Timolol formulation, based on gellan gum undergoes sol/gel transition due to the ionic content of the tears.

Besides the viscosity increase of the vehicle, bioadhesion of polymers also reduces the drainage loss of drug after instillation of ophthalmic formulations, hence improving drug absorption or prolonged local action. In liquid dosage forms such as viscous eye drops where polymer solutions are fully hydrated before instillation, the mucoadhesive performance is limited. Mucoadhesive is based on entanglement of non-covalent bonds between polymers and mucous. Many high molecular weight polymers with different functional groups (such as carboxyl, hydroxyl, amino and sulphate) capable of forming hydrogen bonds and not crossing biological membranes, have been screened as possible mucoadhesive excipients in ocular delivery systems.

C. Dispersed Systems

Dispersed systems based on liposomes, nanoparticles or nanocapsules have been extensively studied for potential ophthalmic use. The development of nanoproducts has been very challenging and a definitive technology has not yet been established. The major issues for this type of delivery system include-

1. Percentage of drug dispersed.
2. Stability and shelf-life.
3. Tolerance to surfactants presents preparations.
4. Large-scale manufacture of sterile preparations.

Particular system can be coated with flexible, mucoadhesive polymers to further enhance their controlled local action,

D. Dosage Solid Forms – inserts

Ophthalmic inserts are aimed at remaining for long period of time in front of the eye. These solid devices are intended to be placed in the conjunctival sac and to deliver the drug at a comparatively slow rate. These devices present advantages such as –

1. Increased ocular contact a compared to standard vehicles hence prolonged drug activity and a higher drug bioavailability.
2. Accurate dosing.
3. Ability to provide constant and predictable rate of drug release.
4. Possible reducing of system absorption which occur freely with standard eye-drop via the nasal mucosa and thus a reduction in side effect.
5. Better patient compliance, resulting from reduced frequency of medication and a lower incidences of visual and side-effects.

6. Possibility of targeting internal ocular tissues through non-corneal conjunctival-scleral penetration router.
7. Increased shelf life with respect to eye drop to the absence of water.

Some of the ophthalmic inserts are discussed below

1. Non-erodible ocular insert

One of the earliest ocular inserts in use was Ocusert, an insoluble delicate sandwich technology. In Ocusert, the drug reservoir is a thin disc of pilocarpine-alginate complex sandwich between two transparent discs of micro porous membrane fabricated from acetate copolymer. The micro porous membranes permit the tear fluid to penetrate into the drug reservoir compartment to dissolve pilocarpine from the complex. Pilocarpine molecular is then released at a constant rate of 20 to 40ug/h for a 4 to 7 days management of glaucoma.

However, these non erodible ocular insert suffered from following disadvantage

- Complexity and difficulty of usage, particularly in self – administration.
- Poor tolerability in the eye, mainly due to these rigidity or shape and size.
- Foreign body sensation and the necessity for their removal at the end of the dosing period,

2. Erodible ophthalmic inserts

These are composed of either soluble or degradable matrices and overcome certain drawbacks of non erodible system especially with regards to greater degree of comfort in the eyes. A product belonging to this category is **Lacrisert**, a soluble non medication mini-rod of hydroxyl propyl cellulose that dissolved with in 24 hours to treat dry – eye syndromes. Such system also suffer from the disadvantage of drug release rate and bioavailability of medicated system.

3. NODDS (New Ophthalmic Drug Delivery System)

These were developed with two primary objective –

- Provide a sterile preservative, water soluble, drug –loaded film to the eye.
- Serve as a unit-dose formulation for the delivery of a precise amount of drug to the ocular surface. Any sustained drug release achieved as a result of the expected minimization of reflux tearing and drainage was considered to be an added benefit.

The basic design of NODDS consists of three- component strip –

- Water- solution. Drug loaded film attached via,

- Thin, water soluble membrane film to,
- Thicker, water soluble, handle film,

All the above three film are made using the same grade of polyvinyl alcohol (PVA) in aqueous medium, but at three different concentration for ease and robustness in handling, the handle film is sandwiched between paper strip before the whole unit is sealed in a moisture proof paper/aluminum foil pouch.

4. BODI (Bioadhesive Ophthalmic Drug Inserts)

These belong to the group of soluble –inserts made of synthetic and semi synthetic polymers. The major composition of BODI inserts consists of a ternary mixture of hydroxyl propyl cellulose, ethylcellulose and carbomer. The product has been developed to overcome the drawback of available inserts which are sometime displaced or heat stable by eyeball movements BODI are rod-shaped inserts obtained by the extrusion of a dried powder mixture composed of the polymeric vehicle and the active compound using a special designed ram extruder. However, the high extrusion temperature limit drug candidates to those that are heat stable.

Release of drug from the BODI system is characterized by two phase –

- The first one corresponds to the penetration of tears fluid into the insert inducing a high release rate of drug by diffusion and forming a gel layer around the core of the insert.
- The external gelification induces the second period which correspond to a slower release rate, but which is still controlled by a diffusion mechanism.

Utilization of the principles of controlled release as embodied by ocular inserts offers an attractive approach to the problem of prolonging pre corneal drug residence times. Ocular inserts also offer the potential advantage of improving patient compliance by reducing the dosing frequency.

Classification of ophthalmic inserts

Based upon their solubility behavior.

(1) Insoluble

a) Diffusion

b) Osmotic and

c) Contact lens

(2) Soluble: - a) Based on natural polymers e.g. collagen

b) Based on synthetic or semi synthetic polymers

E.g. cellulose derivatives like HPMC, HPC etc.

SCOPE OF OCULAR INSERTS

- ❖ Possibility of providing a prolonged drug release and thus a better efficacy.
- ❖ Administration of an accurate dose in the eye and thus a better therapy.
- ❖ Reduction of systemic side effects and thus reduced adverse effects.
- ❖ Reduction of the number of administrations and thus better patient.
- ❖ Compliance, Comfort.
- ❖ Lack of explosion.
- ❖ Ease of handling and insertion.
- ❖ Non-interference with vision and oxygen permeability.
- ❖ Reproducibility of release kinetics.
- ❖ Sterility.
- ❖ Stability.
- ❖ Exclusion of preservatives.
- ❖ Increased shelf life with comparison to aqueous solutions due to absence of water.

LIMITATIONS OF OCULAR INSERTS

- ❖ The insert may be lost immediately.
- ❖ Sometimes the insert twists to form 'a figure eight', which diminishes the delivery rate.
- ❖ A leakage may occur.
- ❖ Dislocation of the device in front of the pupil.
- ❖ Ocular inserts resides in their solidity state that is, they are felt by the patients as an extraneous body in the eye.
- ❖ The occasional unintentional loss during sleep or while rubbing the eyes.

CONCLUSION

The ocular insert represents a significant advancement in the therapy of eye disease. Ocular drug delivery system provide local as well as systemic delivery of the drugs. The limitation of existing medical therapies for ocular disorders include low drug bioavailability, no specificity, side effects and poor treatment adherence to therapy. These limitations may be overcome through the use of sustained release intraocular drug delivery systems. In the area of topical ocular administration, important efforts concern the design and the conception of new ophthalmic drug delivery systems able to prolong the residence time. These solid

ophthalmic devices present the advantage of avoiding a pulsed release due to multiple applications. Finally concluded that the present review work has been reveals that the ophthalmic disease and their treatment by using ocuserts.

REFERENCE

1. Davis JL, Gilger BC, Robinson MR. Novel approaches to ocular drug delivery. *Curr Opin Mol Ther.*2004; 6: 195–205.
2. Neefe CW. Contact lens for ocular drug delivery. *US Patent.* 1974; 3: 786–812.
3. Manvi FV, Nanjwade BK, Hiremath S P & Chalikwar S S. Formulation and Evaluation of Diclofenac Sodium Ophthalmic Inserts. *The Eastern Pharm,* 2004; 25: 55- 57.
4. D.M.Brahmankar et al,“ Biopharmaceutics and Pharmacokinetics a treatise, Vallabh Prakashan, 2010; 470-475.
5. Barbu E, Sarvaiya I, Green KL, Nevel TG & Tsibouk J. Vinylpyrrolidone-co- (meth) acrylic acid insert for ocular drug delivery: synthesis and evaluation. *J Biomed Mater Res A* 2005; 74: 343-9.