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## Review Article

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### REVIEW ON: INTRAOCCULAR DRUG DELIVERY SYSTEM

Rewar S<sup>\*1</sup>, Bansal BK<sup>1</sup>, Singh CJ<sup>2</sup>

1. Department of pharmaceuticals, Arya College of pharmacy, Jaipur – 302028, Rajasthan
2. Department of pharmacology, Arya College of pharmacy, Jaipur – 302028, Rajasthan

\*Corresponding Author: Email [Ph.12sr@gmail.com](mailto:Ph.12sr@gmail.com)

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#### ABSTRACT

Ocular drug delivery is the most fascinating and challenging task faced by pharmaceutical researchers. Conventional dosage forms such as eye drops are the most used dosage form by ocular route, in spite of their low bioavailability and the pulsed release of the drug where it is expected that direct application of the drug to the eye will give maximum response; however after instillation of an eye drop, about 70% of the administered volume can be seen to be lost by different factors. For this reason new ocular drug delivery vehicles have been developed in order to minimize the amount of the drug lost from the eye and at the same time provide maximum response with reduced frequency of administration. Transport of drugs applied by traditional dosage forms is restricted to the eye, and therapeutic drug concentrations in the target tissues are not maintained for a long duration since the eyes are protected by a unique anatomy and physiology. Major problems encountered by conventional ocular dosage forms include rapid pre-corneal drug loss due to naso-lacrimal drainage; tear turnover and drug dilution resulting in poor bio-availability. Therefore, efforts to improve ocular drug bio-availability led to development of novel drug delivery dosage forms such as nano particles, liposomes, hydrogels, ocuserts and muco-adhesive formulations.

**Keywords:** Ocular delivery system, ocular barriers, Ophthalmic, intravitreal implant.

#### INTRODUCTION

Ocular drug delivery systems are developed to treat eye locally, where as past formulations are targeted to reach systemic circulation and these are designed to overcome all the disadvantages of conventional dosage forms such as ophthalmic solutions <sup>[1]</sup>.

The main problem with conventional dosage forms is eye irritation (due to drug particle size and shape) which induces lacrimation i.e. overflow onto lids, tear turnover, and due to pharmacokinetic responses like metabolism, nonspecific binding and different mechanisms like diffusion, dissolution and erosion the conventional dosage forms are less advantageous <sup>[2]</sup>.

The eye drop dosage form is easy to instill but suffers from the inherent drawback that the majority of the medication it contains is immediately diluted in the tear film as soon as the

eye drop solution is instilled into the cul-de-sac and is rapidly drained away from the pre corneal cavity by constant tear flow, a process that proceeds more intensively in inflamed than in the normal eyes, and lacrimal - nasal drainage. Therefore, only a very small fraction of the instilled dose is absorbed into the target tissues i.e. about 1.2% is available to the aqueous humor and relatively concentrated solution is required for instillation to achieve an adequate level of therapeutic effect<sup>[3]</sup>. The frequent periodic instillation of eye drops becomes necessary to maintain a continuous sustained level of medication. If there is high drug concentration in eye drop solution it may give, the eye massive and unpredictable dose of medication as well as it creates greater loss of lacrimal - nasal drainage system. Subsequently this may lead to systemic side effects. Most drugs for ophthalmic use like pilocarpine, epinephrine, local anesthetics, atropine, etc

are weak bases which are generally formulated at acidic pH to enhance stability. But due to their highly ionized form, ocular diffusion is poor. This, coupled with tear drainage, further reduces the rate and extent of absorption. Moreover, if the drug has short half-life, the problems become more complicated. Frequent dosing of large doses of such drugs becomes necessary to achieve the therapeutic objective which often results in corresponding increase in local and systemic side effects[4]. So research on Novel ophthalmic drug delivery systems is in progress to overcome all these disadvantages of conventional ophthalmic dosage forms.

#### ANATOMY 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 300  $\mu$ l that fills the anterior chamber of the eye which is in front of lens.

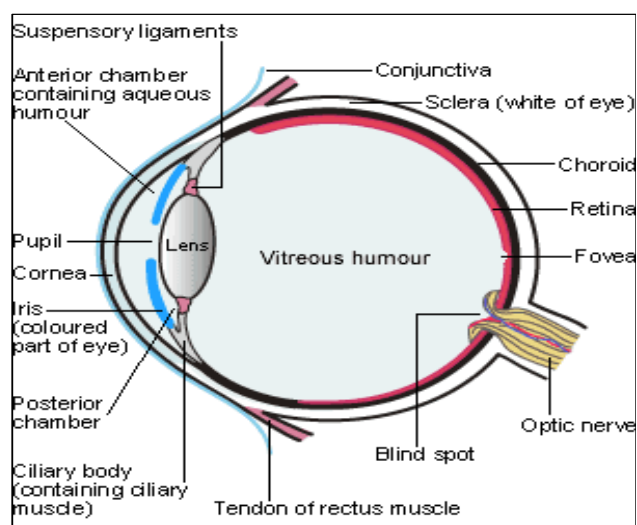


Figure: 1. Anatomy of Eye

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 posterior 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 [5].

The eye is constantly cleansed and lubricated by the lacrimal apparatus 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 reflex 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  $\mu$ l 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 [6].

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 [7].

#### 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 majorities are 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 intraocular infections: i.e. infections 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 spread of infection from the eye into 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 populations over the age of 40 have 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 [8].

Apart from these common problems of eye are cataract and macular degeneration [9] and sometimes diseases which may be of a systemic origin such as diabetes or hypertension effect the eye.

#### **OCULAR DRUG DELIVERY SYSTEMS:**

The necessary characters of ideal control release ocular drug delivery system are:

It should not induce a foreign-body sensation or long lasting blurring.

It should possess more local activity than systemic effects.

It must deliver the drug to the right place, i.e. in targeting the ciliary body.

It should be easy to self-administer.

The number of administrations per day should be reduced.

The primary approaches in the design of control release ocular drug delivery system attempt to slow down the drainage of drug by tear flow. The various formulations are explained as below.

#### **A. Ophthalmic Solutions of Drug Resinates:**

The first successful control release ophthalmic product for topical application using ion exchange resin technology for treatment of glaucoma was betaxolol ionic suspension (Betoptic S, 0.25%).

In this the drug is bound to Amberlite resin, a cationic exchange resin of sulphonic acid styrene vinyl copolymer. The solution is also having carbomer (Carbopol 934P) which acts as a viscosity enhancer which helps in increasing the residence time of product in eye [10].

#### **B. Viscous solutions and Hydrogels:**

The principle involved in the formulation of viscous solutions and hydrogels is addition of hydrocolloids to aqueous drug solutions. Commonly used polymers in these formulations are cellulose derivatives, carbomers, polysaccharides, polyvinyl alcohol, polyvinyl pyrrolidone and recently, hyaluronic acid. Gels permit longer residence time in the pre corneal area than viscous solutions. Hence, the drug solution that gels in the conjunctival cul-de-sac and it is more acceptable. Hence these formulations are referred to as in-situ gel forming systems [11].

The mechanisms which form sol to gel transition in the conjunctival pouch are due to change in pH, temperature, or due to change in ionic environment.

E.g. Timolol formulation based on the gellan gum undergoes sol to gel transition due to the ionic content of the tears.

#### **C. Mucoadhesive Formulations:**

Mucoadhesion is based on entanglement of no covalent bonds between polymers and mucous. Commonly used polymers in these formulations are many high molecular weight polymers with different functional groups like carboxyl, hydroxyl, amino and sulphate which are capable

of forming hydrogen bonds and not crossing biological membranes. These have been screened as possible mucoadhesive excipients in ocular delivery systems [3][10][12].

The Charged polymers i.e. both anionic and cationic polymers show better mucoadhesive capacity than the non-ionic ones.

Anionic polymers: Sodium alginate, Poloxamer, Carbomer, Sodium Carboxy Methoxy Cellulose.

Cationic polymers: Chitosan.

This formulation helps in increasing the residence time of drug in the eye.

#### **D. Dispersed Systems:**

These are based on liposomes, nanoparticles or nanocapsules and the development of nano products was very challenging [13].

**1. Liposomes:** The potential advantages achieved with the liposomes are the control of the rate of encapsulated drug and protection of the drug from the metabolic enzymes present at the tear corneal epithelium interface.

Liposomes are vesicles composed of lipid membrane enclosing an aqueous volume. These structures are formed simultaneously when a matrix of phospholipids are agitated in an aqueous medium to disperse the two phases. Phospholipids commonly used are phosphotidylcholine, phosphotidylserine, phosphatidic acid sphingomyelins, and cardiolipins. They may be multilamellar vesicles or unilamellar depending upon the number of concentric alternating layers of phospholipid and aqueous phases [2].

They can be prepared by sonication of dispersion of phospholipids, reverse phase evaporation, solvent injection, detergent removal or calcium induced fusion. Lipophilic drugs are delivered to a greater extent to the ocular system by these liposomes. The drawbacks associated with the liposomes in ocular drug delivery are due to short shelf life, limited loading capacity and obstacles such as sterilization of the preparation.

**2. Nanoparticles:** This approach is considered mainly for the water soluble drugs. Nanoparticles are particulate drug delivery systems 10-1000 nm in the size in which the drug may be dispersed, encapsulated or absorbed. Nanoparticles for ophthalmic drug delivery were

mainly produced by emulsion polymerization. In this process a poorly soluble monomer is dissolved the continuous phase which may be aqueous or organic [3][13].

Polymerization is started by chemical initiation or by irradiation with gamma rays, ultraviolet or visible light. The emulsifier stabilizes the resulting polymer solution. The materials mainly used for the preparation of ophthalmic nanoparticles are poly alkyl cyano acrylates. The pH of the polymerization medium has to be kept below 3. After polymerization pH may be adjusted to the desired value. The drugs may be added, before, during or after the polymerization. The polymers used for the preparation of ophthalmic nanoparticles are rapidly bio-degradable. Hence the nanoparticles are very promising as targeted drug carriers to inflamed region of the eye.

**3. Pharmacosomes:** This term is used for pure drug vesicles formed by the amphiphilic drugs. Any drug possessing a free carboxyl group or an active hydrogen atom can be esterified (with or without a spacer group) to the hydroxyl group of a lipid molecule, thus generating an amphiphilic prodrug. The amphiphilic prodrug is converted to pharmacosomes on dilution with water. The pharmacosomes show greater shelf stability, facilitated transport across the cornea, and a controlled release profile [26].

#### **E. Ophthalmic-Inserts:**

Ophthalmic inserts are aimed at remaining for a 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 [14].

The advantages of these systems are:

- Ocular contact time is increased.
- Accurate dosing is possible.
- Constant and predictable rate of drug release can be achieved.
- Systemic absorption can be reduced and side effects can be reduced.
- Increased shelf life can be achieved. Better patient compliance.
- Targeting to internal ocular tissues can be done.

Some of the ophthalmic inserts are explained as follows:

#### **1. Non-erodible ocular insert:**

The Non-erodible ocular inserts include Ocusert, and Contact lens.

Ocusert was one of the earlier ocular inserts in use. The technology used in this is an insoluble delicate sandwich technology [15].

In ocusert the drug reservoir is a thin disc of pilocarpine-alginate complex sandwiched between two transparent discs of micro porous membrane fabricated from ethylene vinyl acetate copolymer [16].

The micro porous membranes permit the tear fluid to penetrate into the drug reservoir compartment to dissolve drug from the complex.

E.g. Alza-ocusert: In this Pilocarpine molecules are then released at a constant rate of 20 or 40  $\mu\text{g/h}$  for 4 to 7 days. Used in the management of glaucoma.

The use of pre-soaked hydrophilic contact lenses was used for ophthalmic drug delivery. Therapeutic soft lenses are used to aid corneal wound healing in patients with infection, corneal ulcers, which is characterized by marked thinning of the cornea.

An alternative approach to pre-soaked soft contact lenses in drug solutions is to incorporate the drug either as a solution or suspension of solid particles in the monomer mix [17].

The polymerization is then carried out to fabricate the contact lenses. This technique is promising longer release up to 180 h as compared to pre-soaked contact lenses.

Disadvantages of these non-erodible ocular inserts are Complexity and difficulty of usage is noticed particularly in self administration. Tolerability in the eye is poor, due to rigidity, size or shape [18]. Foreign body sensation and they are to be removed at the end of the dosing period.

## 2. Erodible ophthalmic insert:

The marketed devices of erodible drug inserts are Laciserts, SODI, and Minidisc.

(a) Lacisert: It is a sterile rod shaped device made up of hydroxyl propyl cellulose without any preservative is used for the treatment of dry eye syndromes. It weighs 5 mg and measures 12.7 mm in diameter with a length of 3.5 mm [19].

Lacisert is useful in the treatment of keratitis whose symptoms are difficult to treat with artificial tear alone. It is inserted into the inferior fornix where it imbibes water from the conjunctiva and cornea, forms a hydrophilic film which stabilizes the tear film and hydrates and lubricates the cornea. It dissolves in 24 hours [3].

(b) Sodi: Soluble Ocular Drug Insert is a small oval wafer developed for cosmonauts who could not use eye drops in weightless conditions. It is sterile thin film of oval shape made from acrylamide, N vinyl pyrrolidone and ethyl acrylate called as ABE. It weighs about 15-16 mg [3].

It is used in the treatment of glaucoma and trachoma. It is inserted into the inferior cul-de-sac and gets wets and softens in 10-15 seconds. After 10-15 min the film turns into a viscous polymer mass, after 30-60 minutes it turns into polymer solutions and delivers the drug for about 24 hours [20].

(c) Minidisc: The minidisc consists of a contoured disc with a convex front and concave back surface in the contact with the eyeball. It is like a miniature contact lens with a diameter of 4-5 mm.

The minidisc is made up of silicone based prepolymer- $\alpha$ - $\psi$ -bis (4-methacryloxy) butyl Polydimethyl siloxane. Minidisc can be hydrophilic or hydrophobic to permit extend release of both water soluble and insoluble drugs.

3. New Ophthalmic Drug Delivery System: The New Ophthalmic Drug Delivery System (NODDS) is a method of presenting drugs to the eye within a water soluble drug loaded film. It provides accurate, reproducible dosing in an easily administered preservative free form [21].

These systems were developed with two primary objectives:

a. To provide a sterile, preservative-free, water soluble, drug loaded film to the eye

b. It serves as a unit-dose formulation for the delivery of a precise amount of drug to the ocular surface.

The basic design of NODDS consists of three components: Water soluble, drug-loaded film (flag) attached via thin, water soluble membrane film, to Thicker, water-soluble, handle film.

All the three films are made using the same grade of polyvinyl alcohol (PVA) in aqueous medium, but at three different concentrations.

The NODS is approximately 50 mm in length, 6 mm in width, the flag (drug loaded film) is semi circular in shape and has an area of 22 sq mm and a thickness of 20  $\mu\text{m}$  and a total weight of 500  $\mu\text{g}$  of which 40% can be drug.

On contact with the tear film in the lowerconjunctival sac, the membrane quickly dissolves releasing the flag into the tear film. The flag hydrates allowing diffusion and absorption of the drug. For easy handling the handle film is sandwiched between the paper strips before the whole unit is sealed in a moisture free pouch. By this system an eight fold greater bioavailability was observed compared to the conventional eye drop [22].

4. Bio adhesive Ophthalmic Drug Inserts: These are soluble inserts made of synthetic and semi synthetic polymers. They are composed of ternary mixture of hydroxyl propyl cellulose, ethyl cellulose and carbomer (Carbapol 934P) [21][23].

These are developed to overcome the drawback of available inserts which are sometimes displaced or expelled by eyeball movements. These are rod shaped inserts obtained by the extrusion of a dried homogeneous powder mixture composed of the polymeric vehicle and the active compound using a specially designed ram extruder.

Release of the drug from BODI takes place by two phases: Initial penetration of tear 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 corresponds to a slower release rate, but which is still controlled by a diffusion mechanism.

F. Corneal collagen shields: Collagen is a structural protein that can be applied safely to the body for medical purpose. The creation of collagen shield has provided a means to promote wound healing and perhaps more importantly to deliver a variety of modifications to the cornea and other ocular tissues.

The preparation of collagen shields includes extraction of the collagen and moulding of collagen into a contact lens configuration. The shields are 14.5 mm in diameter with a 9 mm base curve and thickness of 0.15-0.19 mm. The shields are sterilized by gamma irradiation then dehydrated and individually packaged for storage. Drugs can be incorporated into collagen matrix during manufacture absorbed into the shields in the eye. As the shield dissolves

**Table 1: Ocular inserts devices** [29, 30]

Name	Description
Soluble ocular drug Insert	Small oval wafer, composed of soluble copolymers consisting of acrylamide, N-venyl pyrrolidone and ethyl acetate soften on insertion
New ophthalmic drug delivery system	Medicated solid polyvinyl alcohol flag that is attached to a paper covered with handle. On application, the flag detaches and gradually dissolves, releasing the drugs
Collagen shields	Erodible disc consist of cross-link porcine scleral collagen
Ocusert	Flat, flexible elliptical insoluble device consisting of two layers, enclosing a reservoir, use commercially to deliver Pilocarpine for 7 days
Minidisc or ocular therapeutic	system 4-5 mm diameter contoured either hydrophilic or hydrophobic disc
Lacrisert	Rose shape device made from Hydroxy propyl cellulose use for the eye syndrome as an alternative to tears
Bioadhesive ophthalmic eye inserts	Adhesive rods based on a mixture of Hydroxy propyl cellulose, ethyl cellulose, Poly acrylic acid cellulose phthalate
Dry drops	A preservative free of hydrophilic polymer solution that is freeze dried on the tip of a soft hydrophobic carrier strip, immediately hydrate in tear strip
Gelfoam	Slabs of Gelfoam impregnated with a mixture of drug and cetyl ester wax in chloroform

the drug is released gradually in the tear film and into the aqueous humor. The simplicity of use and the convenience afforded by shields make them an attractive delivery device [3].

G. Implants: Scleral and vitreal implants are developed for treatment of endophthalmitis. Implants made from poly lactide/glycolide polymers can result in drug release over 5-6 month period without the need for replacement.

H. Iontophoresis: In iontophoresis, direct current drives ions into the cell or cells or tissues. Ocular iontophoresis delivery is not only fast, painless and safe, but it can also deliver high concentrations of the drug to a specific site. Iontophoretic application of antibiotics in eye not only increases their bactericidal activity but also reduces the severity of disease. Similarly, application of anti-inflammatory agents can reduce vision threatening side effects [24][25].

I. Dendrimer: Dendrimers can successfully used for different routes of drug administration and have better water-solubility, bioavailability and biocompatibility. Vandamme and co workers have developed and evaluated poly(amidoamine) dendrimers containing fluorescein for controlled ocular drug

J. Prodrugs: The ideal Prodrugs for ocular therapy not only have increased lipophilicity and a high partition coefficient, but it must also have high enzyme susceptibility to such delivery system. Collagen ophthalmic inserts are available for delivery of pilocarpine to the eye [27].

Surfactant systems are critical parameters which can affect stability of the system. Optimization of these components results in significant improvement in solubility of the drug molecule e.g. indomethacin, chloramphenicol for eye diseases [28]

## CONCLUSIONS

Ocular drug delivery systems provide local as well as systemic delivery of drugs. A substantial amount of work has been carried out to develop new drug delivery systems which are efficient in delivering accurate and precise doses with minimum toxic effects. The novel advanced delivery systems offer more protective and effective means of the therapy for nearly inaccessible diseases. Nonstop progress in the understanding of principles and processes leading ocular drug absorption and disposition and continuing technological

advances have surely brought some improvements in the efficacy of ocular drug delivery systems. At present very few new ocular drug delivery systems have been commercialized in which their ocular inserts have been mostly used. In future an ideal system should be able to achieve an effective drug concentration at the target tissue for an extended period of time, while minimizing systemic exposure and the system should be both comfortable and easy to use.

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