



OCULAR DRUG DELIVERY SYSTEM: A REVIEW ON ITS RECENT ADVANCEMENT

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ABSTRACT

Ophthalmic drug delivery is one of the most interesting and challenging problem facing the pharmaceutical companies in the market. Low bioavailability of the drug is the main problem. Controlled drug delivery systems has many advantages over conventional dosage forms like improved drug bioavailability, reduced toxicity and decreased dosage frequency.^[8] In-situ-forming ophthalmic drug delivery systems can overcome the problems like Poor bioavailability of ophthalmic solutions caused by dilution and drainage from the eye. Different types of dosage forms such as nanoparticles, liposomes and microemulsions have been developed to improve the bioavailability of the drugs. Drug delivery can be affected by the Static barriers (different layers of cornea, sclera, and retina including blood aqueous and blood-retinal barriers), dynamic barriers (choroidal and conjunctival blood flow, lymphatic clearance, and tear dilution), and efflux pumps in conjunction. Newer research in ophthalmic drug delivery systems is carried out not only to extend the contact time of the vehicle at the ocular surface, but which at the same time slow down the removal of the drug. Identification of influx transporters on various ocular tissues and designing a transporter-targeted delivery of a parent drug has gathered momentum in recent years. This review focuses on recent development in conventional and non-conventional ophthalmic dosage formulation and products used for prolonged contact time of drugs with the cornea and increases their bioavailability.

KEYWORDS: Eye, Ocusert, Minidisk, liposomes, nanoparticles, eye drops.

INTRODUCTION

Eye is most important organ due to its drug disposition characteristics. The topical administration is usually preferred over systemic administration. Any drug molecule administered by the ocular route has to cross the precorneal barriers before reaching the anatomical barrier of the cornea. The medication, upon instillation, stimulates the protective physiological mechanisms, i.e., tear production, which exert a defense against ophthalmic drug delivery. Nasal cavity can eliminate topically applied drugs from the precorneal area because of its greater surface area and higher permeability of the nasal mucosal membrane.^[49]

Normal dropper used delivers about 50-75 μ l per drop and portion of these drops quickly drain until the eye is back to normal resident volume of 7 μ l. Very little drug is available to enter the cornea and inner tissue of the eye because of the drug loss. Actual corneal permeability of the drug is quite low and very small corneal contact time of the about 1-2 min in humans for instilled solution commonly less than 10%.^[45] Very little amount of the drug actually penetrates the cornea and reaches intraocular tissue.^[37] Most of ophthalmic drugs are administered topically in the form of eye drops, a dosage form consisting of buffered, isotonic, aqueous solution or

suspensions of the drug. Ophthalmic CDDS can be achieved by the preparations like gels, ointments, liposomes, micro and nanoparticles, microspheres and ocular minitables (MT) or films.^[34] By adding different the polymers of various grades viscous gel, colloidal suspension or erodible or non erodible insert can be used to increase the precorneal drug retention.^[9,35]

Physiology of eye.^[12,13,14]

The eye consists of transparent cornea, lens, and vitreous body. The aqueous humor in human is having volume of 300 μ l which fills the anterior chamber of the eye. The eye is constantly cleansed and lubricated by the lacrimal apparatus which consists of four structures:

1. lacrimal glands
2. lacrimal canals
3. lacrimal sac
4. nasolacrimal duct.

The lacrimal fluid secreted by lacrimal glands washes over the eye ball and is swept up by the blinking action of eye lids. The lacrimal fluid volume in humans is 7 μ l and is an isotonic aqueous solution of pH 7.4. The human eyes are divided into anterior and posterior segment as shown in figure.

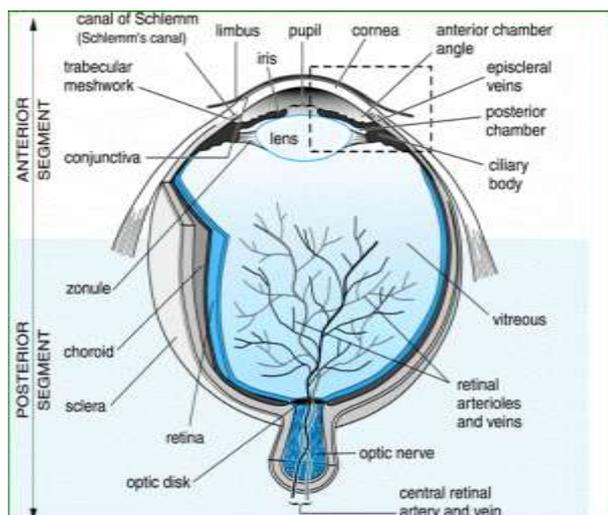


Fig 1: Structure of the eye.^[37]

Anterior Segment:^[34]

Anterior segment structure includes the cornea, limbus, anterior and posterior chambers, trabecular meshwork, schlemm's canal, iris, lens, zonule, and ciliary body.^[34]

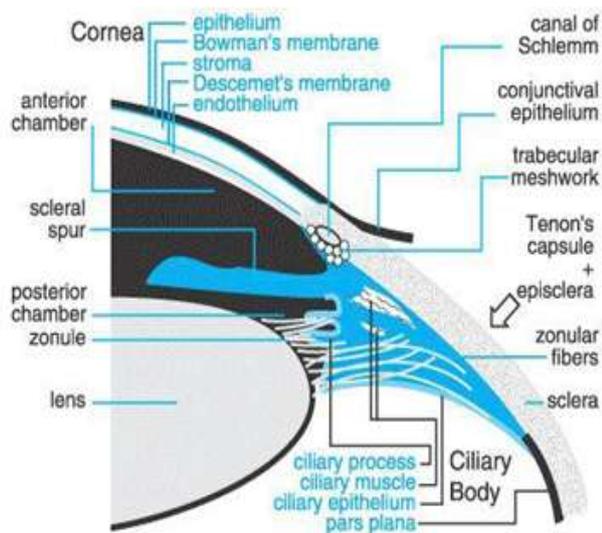


Figure 2: Anterior segment.^[36]

1. Cornea

It has an important optical function as it refracts light entering the eye which then passes through the pupil and onto the lens.^[35]

2. Iris

The iris is a thin circular contractile curtain located in front of the lens but behind the cornea. The iris adjust the size of the pupil to regulate the amount of light admitted into the eye.

3. Pupil

Pupil generally appears to be the dark "centre" of the eye, but can be more accurately described as the circular aperture in the centre of the iris through which light passes into the eye.

4. Lens

It is located behind the pupil of the eye and encircled by the ciliary muscles. It helps to refract light travelling through the eye. The lens focuses light into an image on the retina.^[27]

5. Ciliary Muscle

The ciliary muscle is a ring of striated smooth muscles in the eye's middle layer. Contraction and relaxation of the ciliary muscle alters the curvature of the lens.

6. Conjunctiva

The conjunctiva contributes to the formation of the tear film by way of secreting substantial electrolytes, fluid, and mucins.

7. Aqueous humor

The aqueous humor is a jelly-like substance located in the outer/front chamber of the eye. In human, the rate of aqueous humor turnover is approximately 1% - 1.5% of the anterior chamber volume per minute.^[30]

The Posterior Segment

The posterior segment comprises the vitreous, retina, sclera, choroid, and optic nerves.

1. Sclera

The sclera is the tough white sheath that forms the outer-layer of the ball. It is a firm fibrous membrane that maintains the shape of the eye as an approximately globe shape.

2. Retina

The retina is located at the back of the human eye. The retina may be described as the "screen" on which an image is formed by light that has passed into the eye via the cornea, aqueous humour, pupil, lens, and finally the vitreous humour before reaching the retina.

3. Vitreous Humour

The vitreous humour occupies approximately 80% of each eye in the human body. It is a perfectly transparent thin-jelly-like substance that fills the chamber behind the lens of the eye.^[11]

4. Optic nerve

The optic nerve is responsible for transmitting nerve signals from the eye to the brain. These nerve signals contain information on an image for processing by the brain.

5. Macula

The center of the retina is called the macula. The macula contains a high concentration of photoreceptor cells which convert light into nerve signals.

6. Choroid

It is a thin, highly vascular membrane that is dark brown in colour and contains a pigment that absorbs excess light and so prevents blurred vision.^[28]

Barriers to Restrict Intraocular Drug Transport

1. Tear

One of the precorneal barriers is tear film which reduces the effective concentration of the administered drugs due to dilution by the tear turnover^[36] (approximately 1 $\mu\text{L}/\text{min}$) and binding of the drug molecule to the tear proteins.^[34]

2. Cornea

The cornea consists of three layers; epithelium, stroma and endothelium, and a mechanical barrier to inhibit transport of exogenous substances into the eye.^[27]

3. Conjunctiva

Conjunctiva of the eyelids and globe is a thin and transparent membrane, which is involved in the formation and maintenance of the tear film. In addition, conjunctiva has a rich supply of capillaries and lymphatics^[30]

4. Sclera

The sclera mainly consists of collagen fibers and proteoglycans embedded in an extracellular matrix.^[10]

5. Choroid/Bruch's Membrane.^[28]

Choroid is one of the most highly vascularised tissues of the body to supply the blood to the retina. Its blood flow per unit tissue weight is ten-fold higher than in the brain^[37,38]

6. Retina

Elimination via the posterior route takes place by permeation across the retina. In intact retina, theoretically, the drugs in the subretinal fluid could either be absorbed by the sensory retinal blood vessels or transported across the RPE, where it may be absorbed into the choroidal vessels or pass through the sclera.

7. Blood-Retinal Barrier

Blood-retinal barrier (BRB) restricts drug transport from blood into the retina. BRB is composed of tight junctions of retinal capillary endothelial cells. The function of these endothelial vesicles has been described as endocytosis or transcytosis that may be receptor mediated or fluid phase.^[2]

Advantages of Ocular Drug Delivery Systems.^[15-18]

1. Easy convenience and needle free drug application without the need of trained personnel.
2. Assistance for the application, self medication, thus
3. improving patient compliances compared to parenteral routes.
4. Good penetration of hydrophilic, low molecular weight drugs can be obtained through the eye.
5. Rapid absorption and fast onset of action because of large absorption surface area and
6. High vascularisation. Ocular administration of suitable drug would therefore be effective in emergency therapy as an alternative to other administration routes.
7. Avoidance of hepatic first pass metabolism.

Disadvantages of Ocular Drug Delivery Systems.^[15-18]

1. The physiological restriction is the limited permeability of cornea resulting into low absorption of ophthalmic drugs.
2. A major portion of the administered dose drains into the lacrimal duct and thus can cause unwanted systemic side effects.
3. The rapid elimination of the drug through the eye blinking and tear flow results in a short duration of the therapeutic effect resulting in a frequent dosing regimen.

Constrains of ocular delivery

The different barriers for ocular drug delivery is depicted in table 1.

Table 1: Barriers for the Ocular Delivery.

	Conjunctiva	Cornea	Sclera
Surface area (cm ²)	17.65 \pm 2.12	1.04 \pm 0.12	16-17
Thickness (mm)	-	0.57	0.4- 0.5
Structure composition	Mucus membrane Epithelium vasculature	5 layer	Collagen fiber a. Water b. Proteoglycans c. Elastic fibers d. Fibroblast

1. Drug loss from the ocular surface

After instillation, the flow of lacrimal fluid removes instilled compounds from the surface of the eye. Another source of non-productive drug removal is its systemic absorption instead of ocular absorption.^[42,43,44]

2. Lacrimal fluid-eye barriers

Corneal epithelium limits drug absorption from the lacrimal fluid into the eye. The corneal epithelial cells form tight junctions that limit the paracellular drug

permeation.^[30] In general, the conjunctiva is leakier epithelium than the cornea and its surface area is also nearly 20 times greater than that of the cornea.^[45,46]

3. Blood-ocular barriers

The eye is protected from the xenobiotic in the blood stream by blood-ocular barriers. The blood-eye barrier is composed of the endothelial cells in the uvea. This barrier prevents the access of plasma albumin into the

aqueous humor, and also limits the access of hydrophilic drugs from plasma into the aqueous humor.^[47,48]

Eye infections

Eyes can get infections from bacteria, fungi or viruses. Common eye infections are,

1. Corneal ulcers/ 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.

2. Endophthalmitis

It is severe form of intraocular inflammation involving ocular cavities & inner coats of eyeball. Mainly caused by the Streptococci, E.coli, Pseudomonas, etc.

3. Conjunctivitis

Conjunctivitis is swelling (inflammation) or infection of the membrane lining the eyelids (conjunctiva). It is mainly characterized by cellular infiltration and exudation. Staphylococcus aureus is the most common cause of bacterial conjunctivitis.

4. 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 under-surface of the upper eyelid and by non-specific inflammation. This is caused by the organism Chlamydia trachomatis.

5. Dry Eye

An inadequate volume of tears is produced if the composition of tears is changed, which results into the dry eye. Dry eye conditions are not just a cause for ocular discomfort where it also results in corneal damage.

Routes of Ocular Drug Delivery

There are several possible routes of drug delivery into the ocular tissues. The selection of the route of administration depends primarily on the target tissue.

1. Topical route

Typically topical ocular drug administration is accomplished by eye drops, but they have only a short contact time on the eye surface. The contact, and thereby duration of drug action, can be prolonged by formulation design.^[29]

2. Subconjunctival administration.^[36,37,38]

Traditionally subconjunctival injections have been used to deliver drugs at increased levels to the uvea. Currently this mode of drug delivery has gained new momentum for various reasons. The progress in materials sciences and pharmaceutical formulation have provided new exciting possibilities to develop controlled release formulations to deliver drugs to the posterior segment and to guide the healing process after surgery.

3. Intravitreal administration:

Direct drug administration into the vitreous offers distinct advantage of more straightforward access to the vitreous and retina. Delivery from the vitreous to the choroid is more complicated due to the hindrance by the RPE (Retinal Pigment Epithelium) barrier. Small molecules are able to diffuse in the vitreous but the mobility of large molecules, particularly positively charged, is restricted.^[40,41]

Mechanism of Ocular Drug Absorption

Drugs administered by instillation must penetrate the eye and do so primarily through the cornea followed by the non-corneal routes. These non-corneal routes involve drug diffusion across the conjunctiva and sclera.

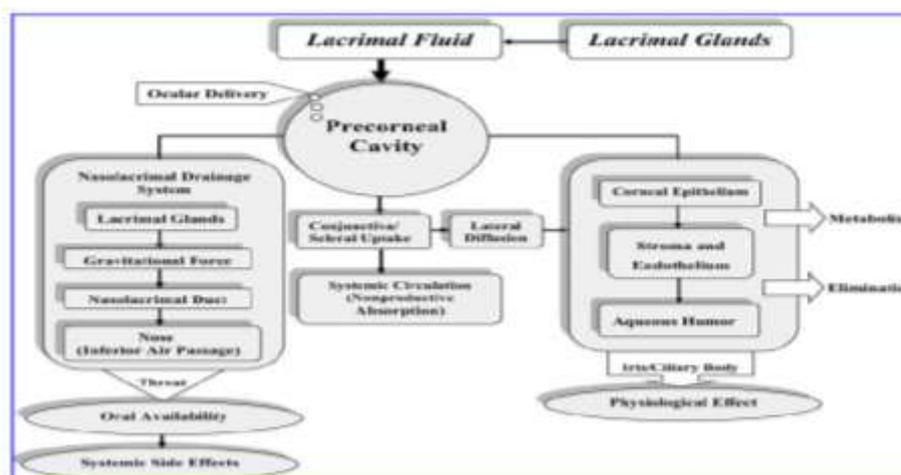


Figure 3: Ocular Drug Absorption.

Corneal permeation

The permeation of drugs across the corneal membrane occurs from the precorneal space. The productive

absorption of most ophthalmic drugs results from diffusional process across corneal membrane. The efficiency of absorption process is a function of rate and

extent at which the transport processes occur. In terms of transcorneal drug permeation, the cornea can be

considered to consist of three primary layers (epithelium, stroma and endothelium) as shown in figure 4.



Figure 4: Corneal Membrane Depicting Various Barriers to Drug Absorption Non-corneal permeation.^[37]

Naso-lacrimal drainage system

The nasolacrimal drainage system consists of three parts: the secretory system, the distributive system and the excretory system. The secretory system consists of basic secretors that are stimulated by blinking and temperature change due to tear evaporation and reflex secretors that have an efferent parasympathetic nerve supply and secrete in response to physical or emotional stimulation.

The excretory part of the nasolacrimal drainage system consists of: the lacrimal puncta, the superior, inferior and common canaliculi; the lacrimal sac; and the nasolacrimal duct. The tears are largely absorbed by the mucous membrane that lines the ducts and the lacrimal sac; only a small amount reaches the nasal passage as shown in figure 5.^[50]

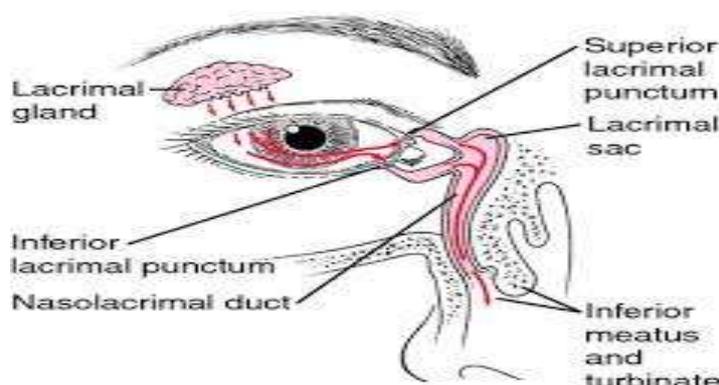


Figure 5: Nasolacrimal Drainage [50]

Factors affecting intraocular bioavailability includes.

- 1) lacrimal fluids.
- 2) Efficient naso-lacrimal drainage.
- 3) Interaction of drug with proteins of lacrimal fluid.
- 4) Dilution with tears.
- 5) Corneal barriers.
- 6) Physicochemical properties of the drugs.
- 7) Active ion transport at cornea.
- 8) Limited & poor corneal permeability.

Classification of ocular drug delivery system:

1. Type -I.
2. Type-II.

Type-I are divided into different types:

1. Drug Delivery Systems to Anterior Segment of the eye:

1. Eye-Drops.
2. Contact Lens.
3. Cul-de sac Inserts.
4. Punctal Plugs.

Subconjunctival/Episcleral Implants.

2. Drug Delivery Systems to Posterior Segment of the eye:

1. Intravitreal Implants (e.g.-Duraser Technology System)
2. Injectable Particulate Systems (RETAAC, Cortiject, Visudyne).
3. Eye-Drops.

3. Physical Devices

1. Iontophoresis.
2. Micro-Electromechanical Intraocular Drug Delivery Device.

Type-II are divided into different type

1. Conventional delivery systems:

1. Eye Drops.
2. Ointment and Gels.
3. Ocuserts and Lacrisert.

2. Vesicular system

1. Liposomes.
2. Niosomes and Discomes.
3. Pharmacosomes.

3. Control delivery systems

1. Implants.
2. Iontophoresis.
3. Dendrimer.
4. Cyclodextrin.
5. Contact lenses.
6. Collagen Shield.
7. Microemulsion.
8. Nanosuspensions.
9. Microneedle.
10. Prodrugs.
11. Penetration Enhancers.
12. Mucoadhesive Polymers.
13. Phase Transition Systems/Insitu gel system.

4. Particulates (nanoparticles and microparticles)

5. Advanced delivery system:

1. Cell Encapsulation.
2. Gene Therapy.
3. Stem cell Therapy.
4. Protein and Peptide therapy.
5. Scleral Plug therapy.
6. siRNA therapy.
7. Oligonucleotide therapy.

Ophthalmic formulations

1. Solutions

A sterile homogeneous solution dosage form have many advantages over the other dosage such as formulation, including the easily commercially capability produce on large scale manufacture. There are various factors that must be consider during the formulating aqueous solution includes selection of appropriate salt of the drug, solubility in solvents, therapeutic systemic effect, ocular toxicology, pKa of formulation, and the effect of pH of the formulation. Others stability parameters includes such as solubility, the solubility and stability, and corneal permeability of the drugs which are depends on pH of the formulation, solubility, tonicity, viscosity, buffering capacity, compatibility with formulation ingredients and effect of packaging components.

2. Suspensions

Ophthalmic suspensions are more complex and challenging if compare with to ophthalmic (aqueous) solutions. The formulation of an ophthalmic suspension many problems occurred such as nonhomogeneity of the dosage form, settling of particles, cake formation, aggregation of the suspended particles.

3. Eye Ointments.^[19]

Ointments are the semi-solid preparations intended for external application. They are usually formulated using mixture of semisolid and solid hydrocarbons (paraffin) which have a melting or softening point close to the body

temperature and are nonirritating to the eye. 35 Ointments are useful in improving the drug bioavailability and in sustaining drug release.

4. Aqueous Gel

Aqueous gel (hydrogels) consists of high molecular weight, cross linked polymers that form a three dimensional network in water. Gels permit longer residence time in the precorneal area then viscous solution.

4. Eye Drops^[19]

Drugs which are active at eye or eye surface are widely administered in the form of Solutions, Emulsion and Suspension. Various properties of eye drops like hydrogen ion concentration, osmolality, viscosity and instilled volume can influence retention of a solution in the eye.

5. Ointment and Gels^[19]

Prolongation of drug contact time with the external ocular surface can be achieved using ophthalmic ointment vehicle and enhancing ocular bioavailability of drugs. But, the major drawback of this dosage form like, blurring of vision and matting of eyelids can limits its use.

7. Ophthalmic-Inserts

Ophthalmic inserts are aimed at remaining for a long period of time in front of the eye.^[45] These solid devices are intended to be placed in the conjunctival sac and to deliver the drug at a comparatively slow rate.

The Advantages of these systems are

1. Ocular contact time is increased.
2. Accurate dosing is possible.
3. Constant and predictable rate of drug release can be achieved.
4. Systemic absorption can be reduced and side effects can be reduced.
5. Increased shelf life can be achieved
6. Better patient compliance.
7. 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 Ocuser, and Contact lens. Ocuser is a multilayer structure consisting of a drug containing core surrounded on each side by a layer of copolymer membranes through which the drug diffuses at constant rate. Ocular insert (Ocuser) are sterile preparation that prolong residence time of drug with a controlled release manner and negligible or less affected by nasolacrimal damage.^[28] In ocuser 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.^[2] The microporous membranes permit the tear fluid to penetrate into the drug reservoir

compartment to dissolve drug from the complex eg. 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 rate of

drug diffusion is controlled by the polymer composition, the membrane thickness and the solubility of the drug. It is shown in figure 7.

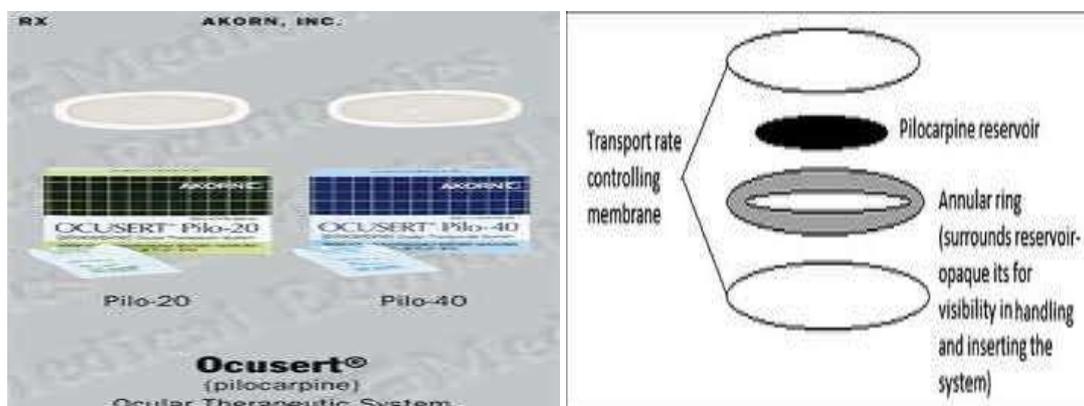


Fig 6: Ocuserts.

2. Erodible ophthalmic insert

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

a. Lacisert:^[19,20,32]

Lacisert is a sterile rod shaped device for the treatment of dry eye syndrome and keratitis sicca and was

introduced by Merck, Sharp and Dohme in 1981. They act by imbibing water from the cornea and conjunctiva and form a hydrophilic film which lubricates the cornea. Preservatives are not used in lacisert preparation.^[42] It weighs 5 mg and measures 12.7 mm in diameter with a length of 3.5 mm. Lacisert is useful in the treatment of keratitis.^[37] It dissolves in 24 hours.



Fig 7: Lacisert.

b. SODI:^[19,20,32]

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-vinylpyrrolidone and ethylacrylate. [37] It weighs about 15-16 mg. It is used in the treatment of glaucoma and trachoma. It is inserted into the inferior cul-de-sac and get wets and softens in 10-15 seconds. [29] 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.



Fig 8: SODI.

Advantages of SODI

1. Once a day treatment of glaucoma & trachoma.
2. Single dose application replaces 4-12 eye drops instillation or 3-6 application of ointments.

c. Minidisc:^[19,20]

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 pre-polymer- α - ψ -bis (4-methacryloxy) butyl-n-poly-

dimethyl -siloxane. Minidisc can be hydrophilic or hydrophobic to permit extend release of both water soluble and insoluble drugs. It can release drug upto 170 hr.

8. Liposomes

Liposomes are biocompatible and biodegradable lipid vesicles made up of natural lipids and about 25–10 000 nm in diameter. They are having an intimate contact with the corneal and conjunctival surfaces which is desirable for drugs that are poorly absorbed, the drugs with low partition coefficient, poor solubility and thus increases the probability of ocular drug absorption.^[46]

9. Niosomes and Discomes:^[16,19,20]

The major limitations of liposomes are chemical instability, oxidative degradation of phospholipids, cost and purity of natural phospholipids. To avoid this niosomes are developed as they are chemically stable as compared to liposomes and can entrap both hydrophobic and hydrophilic drugs. Non-ionic surface active agents based discoidal vesicles known as (discomes) loaded with timolol maleate were formulated and characterized for their *in vivo* parameters. Discomes may act as potential drug delivery carriers as they released drug in a sustained manner at the ocular site.^[47]

10. Pharmacosomes.^[16,19,20]

This term is used for pure drug vesicles formed by the amphiphilic drugs. 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.^[48]

11. Iontophoresis:^[19,21]

In Iontophoresis direct current drives ions into cells or tissues. For Iontophoresis the ions of importance should be charged molecules of the drug. Positively charged of drug are driven into the tissues at the anode and vice versa. Ocular iontophoresis delivery is not only fast, painless and safe but it can also deliver high concentration of the drug to a specific site.^[4]

12. Dendrimer

Dendrimers can successfully used for different routes of drug administration and have better water-solubility, bioavailability and biocompatibility. The residence time of the solutions containing dendrimers with carboxylic and hydroxyl surface groups is generally more.^[6]

14. Collagen Shield

Collagen shield basically consist of cross linked collagen, fabricated with Foetal calf skin tissue and developed as a corneal bandage to promote wound healing.

Topically applied antibiotic conjugated with the shield is used to promote healing of corneal ulcers. Tear fluid makes these devices soft and form a thin pliable film

which is having dissolution rate up to 10, 24 or 72 hours. It has good structural stability, good biocompatibility and biological inertness.^[49]

15. Microemulsion

Microemulsion is dispersion of water and oil stabilized using surfactant and cosurfactant to reduce interfacial tension and usually characterized by small droplet size (100 nm), higher thermodynamic stability and clear appearance. Optimization of these components results in significant improvement in solubility of the drug molecule e.g. indomethacin, chloramphenicol for eye diseases.

16. Nanoparticles.^[24,25]

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. The materials mainly used for the preparation of ophthalmic nanoparticles are polyalkylcyanoacrylates. The drugs may be added, before, during or after the polymerization.

17. 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 an extent that after corneal penetration or within the cornea they are either chemically or enzymatically metabolized to the active parent compound.^[18,19]

18. Penetration Enhancers.^[16,18]

Transport of drug across the cornea is increased by increasing the permeability through corneal epithelial membranes. For such purpose Penetration enhancers can be used. Examples of enhancers include actin filament inhibitors, surfactants, bile salts, chelators, and organic compounds.

19. Phase Transition Systems/Insitu gel system:^[19,21,22,23]

Phase transition of the formulation from the liquid form to the gel or solid phase occurs when these systems instilled into the cul-de-sac of eye lead to increase the viscosity of a drug formulation in the precorneal region results in increased bioavailability, due to slower drainage from the cornea. These systems can be influenced by pH, temperature or by ion activation.

20. Gene Therapy

Along with tissue engineering, gene therapy approaches stand on the front line of advanced biomedical research to treat blindness arising from corneal diseases, which are second only to cataract as the leading cause of vision loss. Several kinds of viruses including adenovirus, retrovirus, adeno-associated virus, and herpes simplex virus, have been manipulated for use in gene transfer and gene therapy applications.

21. Stem cell Therapy

Emerging cell therapies for the restoration of sight have focused on two areas of the eye that are critical for visual function, the cornea and the retina. The most successful ocular application has been the use of limbal stem cells, transplanted from a source other than the patient for the renewal of corneal epithelium. The sources of limbal cells include donors, autografts, cadaver eyes, and (recently) cells grown in culture. Stem-cell Therapy has demonstrated great success for certain maladies of the anterior segment.

22. Protein and Peptide therapy

Delivery of therapeutic proteins/ peptides has received a great attention over the last few years. The intravitreal injection of ranibizumab is one such example. However; several limitations such as membrane permeability, large size, metabolism and solubility restrict their efficient delivery must be taken into the consideration. Ocular route is not preferred route for systemic delivery of such large molecules.

Pharmaceutical requirement

1. Tonicity and Tonicity Adjusting Agents

Lacrimal fluid is isotonic with blood, having an isotonicity value corresponding to that of a 0.9% sodium chloride solution. Ideally, an ophthalmic solution should have this isotonicity value. A common tonicity-adjusting ingredient includes NaCl, KCl, buffer salts, dextrose.

2. PH Adjustment and Buffers

The pH and buffering of an ophthalmic solution is probably of equal important to proper preservation. In addition to stability effects, pH adjustment can influence comfort, safety, and activity of the product. Ideally, every product would be buffered to a pH of 7.4, considered the normal physiological pH of tear fluid.

3. Stabilizers

Stabilizers are ingredients added to a formula to decrease the rate of decomposition of the active ingredients. Antioxidants are the principal stabilizers added to some ophthalmic solutions, primarily epinephrine and other oxidizable drugs. Ascorbic acid and acetylcysteine, sodium bisulfite, 8-hydroxyquinolone, and isoascorbic acid are other commonly used antioxidants.

4. Surfactant

The use of surfactants is greatly restricted in formulating ophthalmic solutions. Several nonionic surfactants are used in relatively low concentrations. Those principally used are the sorbitan ether esters of oleic acid (Polysorbate or tween 20 and 80) and polyoxyl 40 stearate.

5. Viscosity-Imparting Agent

Polyvinyl alcohol, methylcellulose, HPMC, hydroxyethyl-cellulose, and carbomers are commonly used to increase the viscosity of ophthalmic solution and suspensions. Although they reduce surface tension

significantly, their primary benefit is to increase the ocular contact time, thereby decreasing the drainage rate and increase drug bioavailability.

6. Vehicle

Ophthalmic drops are, with few exceptions, aqueous fluids using purified water USP as the solvent. All ophthalmic drops must be rendered sterile. When oils are used as vehicle in ophthalmic fluids, they must be of the highest purity. Vegetable oils such as olive oil, castor oil, and sesame oil have been used extemporaneous compounding.

Evaluation of ocular drug delivery systems

Ocular drug delivery systems are evaluated by various methods.

IN-VITRO evaluation methods

A number of approaches are used by different workers to conduct in-vitro evaluation of controlled ocular drug delivery systems. These include bottle method, modified rotating basket/ paddle method and flow through apparatus.etc.

1. Bottle method

In this method, dosage forms are placed in the culture bottles containing phosphate buffer at pH 7.4. The culture bottles are shaken in a thermostatic water bath at 37°C. A sample of medium is taken out at appropriate intervals and analyzed for drug contents.

2. Diffusion method

An appropriate simulator apparatus is used in this method. Drug solution is placed in the donor compartment and buffer medium is placed in the receptor compartment. An artificial membrane or goat cornea is placed in between donor and receptor compartment. Drug diffused in receptor compartment is measured at various time intervals.

3. Modified rotating basket method

In this method, dosage form is placed in a basket assembly connected to a stirrer. The assembly is lowered into a jacketed beaker containing buffer medium. The temperature of system is maintained at 37°C. A sample of medium is taken out at appropriate time intervals and analyzed for drug content.

4. Modified rotating paddle apparatus

In this method, diffusion cells (those that are used for analysis of semi-solid formulations) are placed in the flask of rotating paddle apparatus. The buffer medium is placed in the flask and paddle is rotated at 50 rpm. The entire unit is maintained at 37±0.5° C. Aliquots of samples are removed at appropriate time intervals and analyzed for drug content.

5. Flow through devices

A constant fluid circulation apparatus is used as a flow through device. The apparatus consist of a glass

dissolution cell, a continuous duty oscillating pump, a water bath and a reservoir. The dosage form is placed in the reservoir of the dissolution medium. The whole assembly is maintained at the temperature of 37°C. The dissolution medium is circulated through the apparatus. Sampling of medium is done at various time intervals and analyzed for drug content.^[45]

IN-VIVO evaluation methods

Rabbit is used as an experimental animal because of a number of anatomical and physiological ocular

similarities. drug concentration in various eye tissues eg. lens, cornea, iris, ciliary body, retina sclera, aqueous and vitreous humor is measured for the pharmacokinetic studies in rabbits. the intraocular pressure of the eye is measured with a tonometer. ocular pharmacokinetic studies can also be carried out by tear fluid sampling, which is a non-invasive technique. To withdraw aqueous humour, rabbits are anaesthetized with ketamine and aqueous humour about 2 ml is withdrawn from the anterior chamber.^[47]

MARKETED OPHTHALMIC PRODUCTS

Table 2: Marketed ophthalmic products.

Brand Name	Drug	Dosage Form	Use
Acivir eye	Acyclovir	Ointment	For eye infection
Acuvaill	Ketorolac tromethamine	Eye solution	Cataract surgery
Alocril	Nedocromil	Eye solution	Allergic conjunctivitis
Chloromycetin	Chloramphenicol palmitate	Ointment	In conjunctivitis and eye inflammation
Ciplox	Ciprofloxacin	Eye drops	In eye infection and conjunctivitis
Dexcin	Dexamethasone	Eye drops	In eye infection
Dichol	Carbachol	Sterile solution and prefilled syringes	In ophthalmic surgery
Elestat	Epinastine solution	Eye solution	Allergic conjunctivitis
Geltear	Carbomer	Bioadhesive gel	As a lubricant, in burning, irritated and dried eye
Ocupol	Polymixin-B	Eye drops and ointment	In bacterial infection, corneal ulcer
Ozurdex	Dexamethasone	Ocular implant	Retinal vein occlusion
Pred forte	Prednisolone acetate	Suspension	As anti allergic and anti inflammatory
Refresh classic	Artificial tear fluid	Single use vials	Relieves dry and irritated eyes
Refresh tears	Hydroxypropyl methylcellulose	Eye drops	In dryness of eye and eye lubricant
Restasis	Cyclosporine	Emulsion	In dry eye
Timolol xe	Timolol maleate	In situ gel	For dried eye and keratoconjunctivitis
Zymaxid	Gatifloxacin	Solution	Bacterial conjunctivitis

RECENT ADVANCES

1. Implantable silicone rubber devices

It is a drug delivery device used for the hydrophobic drugs eg:- BCNU (1,3 -bis (2- chloro ethyl)-1-nitroso urea), an intraocular malignancy agent. The device

consists of 2 sheets of silicone rubber glued together only at the edges with silicone adhesive. A tube of the same material extends from device. The device released BCNU at a constant rate about 200-400 mcg / hr.

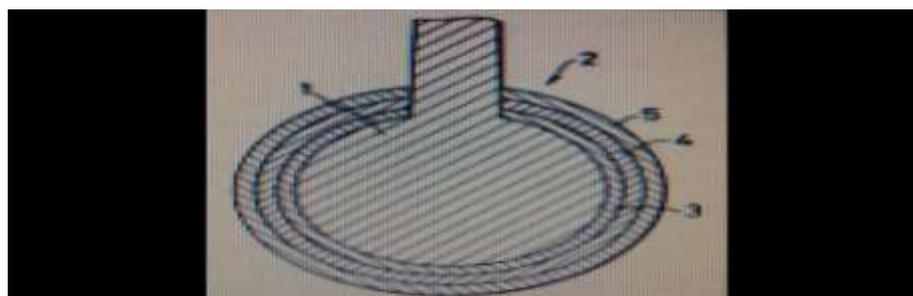


Fig 9: Diagram of the implantable silicone rubber device.

2. Implantable drug delivery pumps

It is an osmotic mini pump (ALZET) which releases drug at constant rate with a pumping duration of up to 2 weeks.

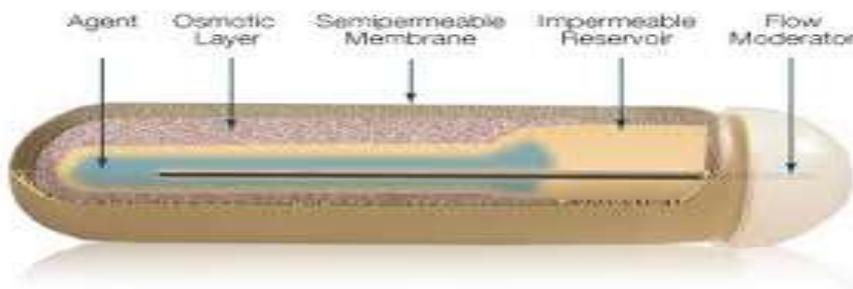


Fig 10: Implantable drug delivery pump.

2. Punctal plug

The punctal plugs are placed in the tear duct (punctum) to release a variety of drugs. Currently it is used in the treatment of glaucoma & ocular hypertension.



Fig 11: Design of the punctual plug.

3. Replenish mini pump

It is micro-electro chemical system that delivers continuous or bolus-targeted drugs to both the anterior & posterior segments. It is refillable drug (via 31 gauge needle) that capable of storing & delivering upto 12 months.

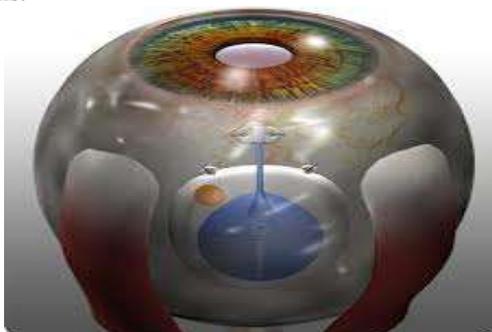


Fig 12: Design and the position of the replenish mini pump.

4. Odtx

It is non-biodegradable implant that is comprised of multiple sealed reservoirs containing individual doses of drugs. This implant is injected into the vitreous fluid for its action. In this, the drug is released by creating an opening via laser.



Fig 13 : Design of the Odtx.

6. I-vation

It is a solid triamcinolone acetate implant, which can deliver drug upto 24 months. The phase 1 showed positive outcome and the phase 2 terminated before completion. It also has polysaccharide based matrix for protein delivery (eureka duet).



Fig 14: Design of the I-vation.

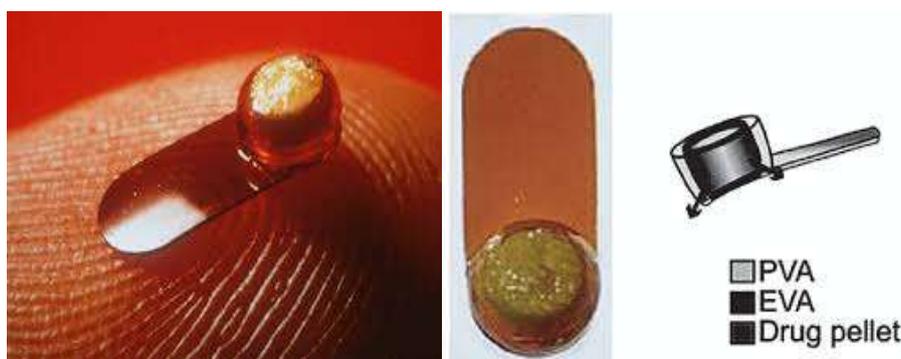


Fig 15: Design of the Vitrasert.

CONCLUSION

Ocular drug delivery systems provide local as well as systemic delivery of the drugs. The latest available targeted drug delivery systems focus on the localised delivery of the drugs as well as certain macromolecular substances like proteins, genes like DNA, siRNA to the internal parts of the eye. Ophthalmic drug delivery system is the field in which most of the researchers are taking challenges to combat various problems related to this delivery. The primary requirement of a successful controlled release product focuses on increasing patient compliance which the Insitu gels offer. Exploitation of polymeric Insitu gels for controlled release of various drugs provides a number of advantages over conventional dosage forms. This type of dosage forms are used now a day in combat glaucoma, dry eye syndrome, Sjogren's syndrome and trachoma.

Currently, very few new ophthalmic drug delivery systems have been commercialized in which their ocular inserts have been mostly used. Patient acceptance is very important for the design of any comfortable ophthalmic drug delivery system. Major improvements are required in each system like improvement in sustained drug release, large scale manufacturing and stability. 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.

6. Vitrasert

Vitrasert are approved by the FDA. These devices are solid sustained release device, typically made up of PLGA and they are capable of delivering drug for upto 30 months. Eg: retisert (flucinolone acetonide-chronic non infectious uveitis and ganci clovir-retinitis).

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