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A RATIONAL APPROACH TO OCULAR DRUG DELIVERY SYSTEMS: A OVERVIEW

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ABSTRACT

In the earlier period, drug delivery to the eye has been limited to topical application, redistribution into the eye following systemic administration or directs intraocular/per ocular injections. These novel systems offer manifold advantages over conventional systems as they increase the efficiency of drug delivery by improving the release profile and also reduce drug toxicity. Ocular drug delivery has remained as one of the most taxing task for pharmaceutical scientists. The unique structure of the eye restricts the entry of drug molecules at the required site of action. Innovatory novel therapy for treatment of ocular diseases has emerged due to the recent advances in drug delivery approaches and material sciences. 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 periocular diseases and intraocular diseases. This review article briefly covers classification of ocular drug delivery systems and general outline with examples of various conventional and recent past time formulations for ophthalmic drug delivery. It also provides the limitations of conventional delivery with a view to find modern approaches like vesicular systems, nano technology, stem cell therapy as well as gene therapy, oligonucleotide and aptamer therapy, protein and peptide delivery, ribozyme therapy for treatment of various ocular diseases. The advanced drug delivery devices such as ocular insert, SODI, collagen shields, mini disc, liposomes, microspheres, nanoparticles and prodrugs, in spite of their

advantages demonstrated by extensive investigations and clinical tests, have not gained a wide acceptance by ophthalmologists.

Keywords: Physiology of eye, Ocular drug delivery, Ocular disorders, Advanced drug delivery etc.

INTRODUCTION

Ocular drug delivery has remained as one of the most taxing task for pharmaceutical scientists. The unique structure of the eye restricts the entry of drug molecules at the required site of action. Innovatory novel therapy for treatment of ocular diseases has emerged due to the recent advances in drug delivery approaches and material sciences. In the earlier period, drug delivery to the eye has been limited to topical application, redistribution into the eye following systemic administration or directs intraocular/per ocular injections. Conventional drug delivery systems; which include solutions, suspensions, gels, ointments and inserts, suffer with the problems such as poor drainage of instilled solutions, tear turnover, poor corneal permeability, nasolacrimal drainage, systemic absorption and blurred vision. Nanocarrier based approaches seem to be most attracting and are extensively investigated presently. it has been reported that particulate delivery system such as microspheres and nanoparticles; vesicular carriers like liposomes, niosomes pharmacosomes and discomes improved the pharmacokinetic and pharmacodynamic properties of various types of drug molecules. Emerging new controlled drug delivery systems such as dendrimers, microemulsions, muco-adhesive polymers, hydrogels, iontophoresis, collagenshelid, prodrug approaches have been developed for this purpose [1,2,3].

These novel systems offer manifold advantages over conventional systems as they increase the efficiency of drug delivery by improving the release profile and also reduce drug toxicity. The rapid progress of the biosciences opens new possibilities to meet the needs of the posterior segment treatments. The examples include the antisense and aptamer drugs for the treatment of cytomegalovirus (CMV) retinitis and age-related macular degeneration, respectively, and the monoclonal antibodies for the treatment of the age-related macular degeneration. Other new approaches for the treatment of macular degeneration include intravitreal small interfering RNA (siRNA) and inherited retinal degenerations involve gene therapy. This review article briefly covers general outline with examples of various conventional and recent past time formulations for ophthalmic drug delivery. It also provides the limitations of conventional delivery with a view to find modern approaches like vesicular

systems, nano technology, stem cell therapy as well as gene therapy, oligonucleotide and aptamer therapy, protein and peptide delivery, ribozyme therapy for treatment of various ocular diseases. The most commonly employed ophthalmic dosage forms are solutions, suspensions, and ointments. But these preparations when instilled into the eye are rapidly drained away from the ocular cavity due to tear flow and lacrimal nasal drainage. The newest dosage forms for ophthalmic drug delivery are: gels, gel-forming solutions, ocular inserts, intravitreal injections and implants. [4,5,6].

- Ocular drug delivery is useful to treat ophthalmic diseases and the drug enters the systemic circulation circumventing the hepatic first pass effect .
- This system is used to overcome all the disadvantages of conventional dosage forms like ophthalmic solutions which causes eye irritation which induces lacrimation.
- 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.

These drugs are meant for local therapy and not for systemic action.

- Miotics e.g. Pilocarpine Hcl
- Mydriatics e.g. Atropine
- Cycloplegics e.g. Atropine
- Anti-inflammatories e.g. Corticosteroids
- Anti-infectives (antibiotics, antivirals and antibacterials)
- Anti-glucoma drugs e.g. Pilocarpine Hcl
- Surgical adjuncts e.g. Irrigating solutions
- Diagnostic drugs e.g. Sodium fluorescein

ANATOMY OF EYE

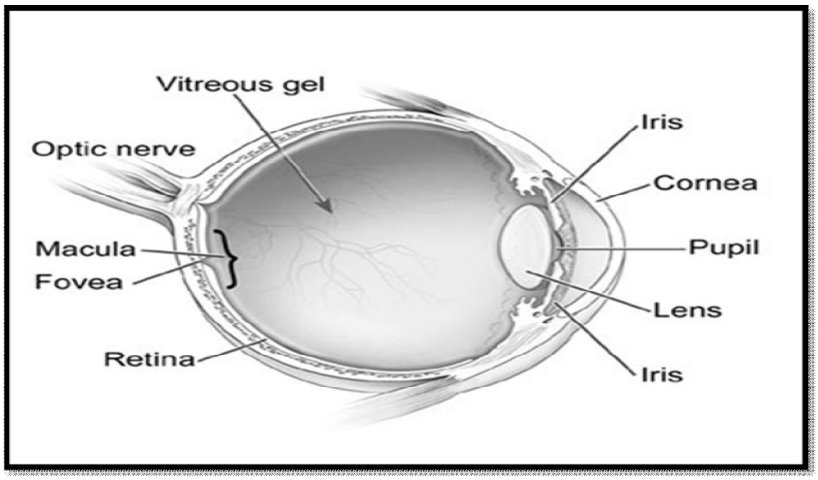


Fig 1 Anatomy of eye

The **sclera:** The protective outer layer of the eye, referred to as the "white of the eye" and it maintains the shape of the eye.

The **cornea:** The front portion of the sclera, is transparent and allows light to enter the eye. The cornea is a powerful refracting surface, providing much of the eye's focusing power.

The **choroid** is the second layer of the eye and lies between the sclera and the retina. It contains the blood vessels that provide nourishment to the outer layers of the retina.

The **iris** is the part of the eye that gives it color. It consists of muscular tissue that responds to surrounding light, making the **pupil,** or circular opening in the center of the iris, larger or smaller depending on the brightness of the light.

The **lens** is a transparent, biconvex structure, encased in a thin transparent covering. The function of the lens is to refract and focus incoming light onto the retina.

The **retina** is the innermost layer in the eye. It converts images into electrical impulses that are sent along the optic nerve to the brain where the images are interpreted.

The **macula** is located in the back of the eye, in the center of the retina. This area produces the sharpest vision.

The inside of the eyeball is divided by the lens into two fluid-filled sections.

The larger section at the back of the eye is filled with a colorless gelatinous mass called the **vitreous humor**. The smaller section in the front contains a clear, water-like material called **aqueous humor.**

The **conjunctiva** is a mucous membrane that begins at the edge of the cornea and lines the inside surface of the eyelids and sclera, which serves to lubricate the eye. [3,7].

A. DISEASES IN EYE

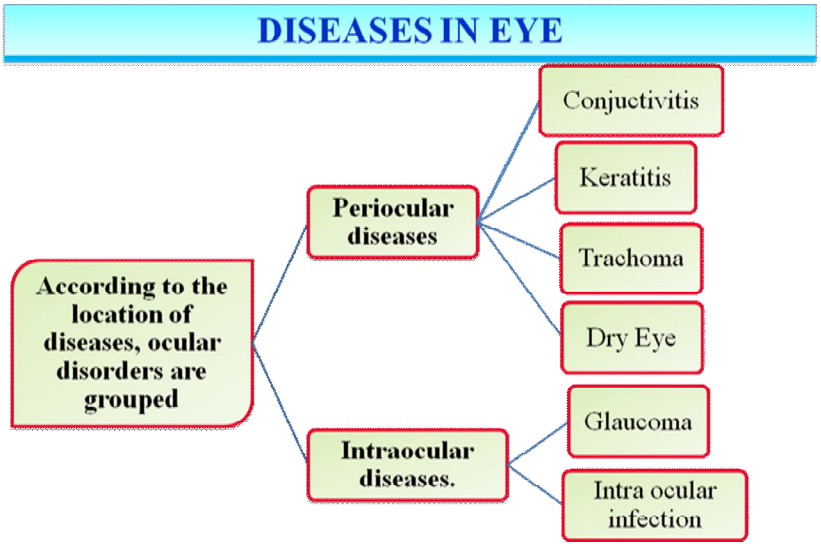


Chart of diseases in eye

DISEASES OF EYE [2,5,8,9].

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,

I) Periocular diseases

II) Intraocular diseases

The **periocular diseases** are explained as follows:

1. Conjuctivitis

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 majority are the result of acute infection or allergy. Bacterial conjunctivitis is the most common ocular infection.

2. 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.

3. 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.

4. 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

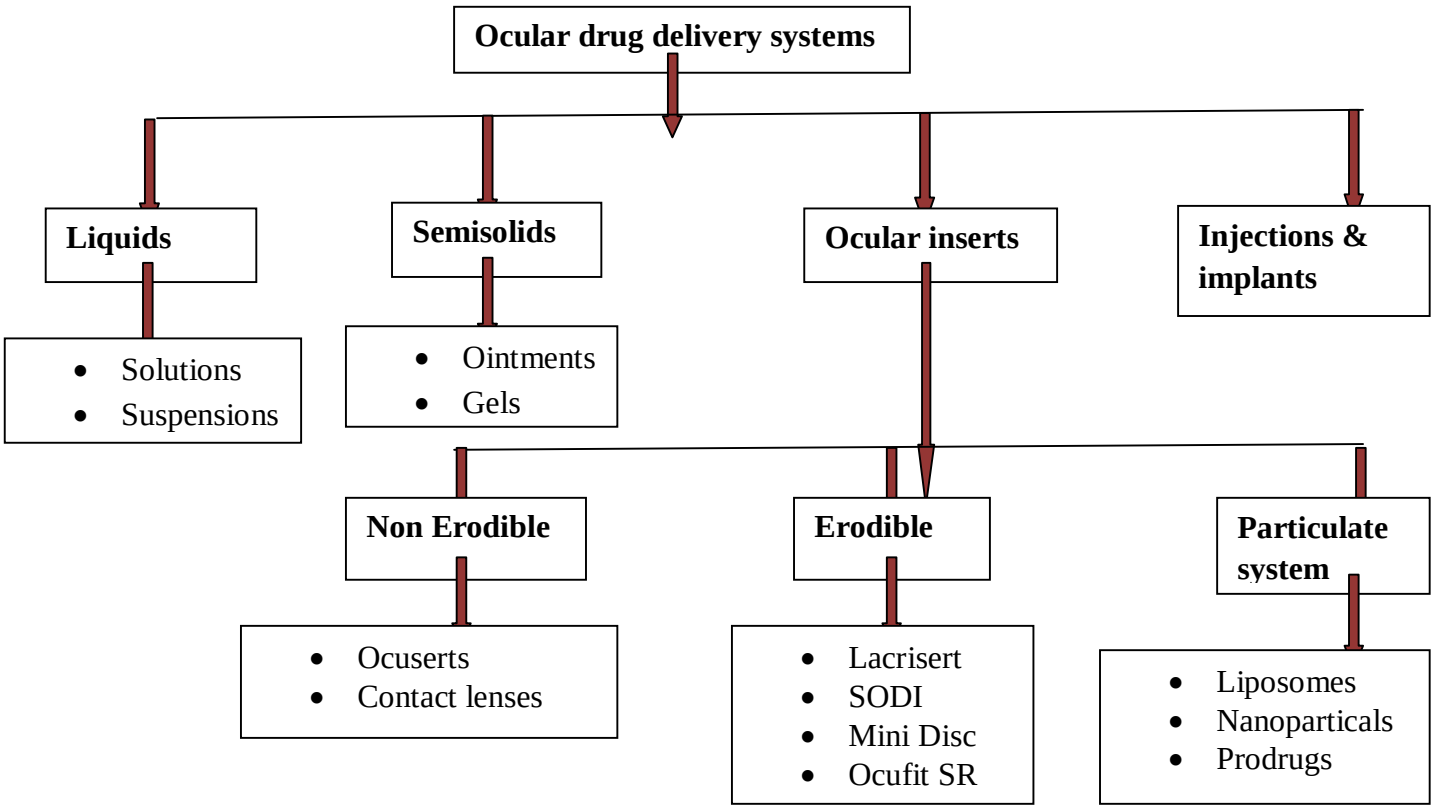
1.Intraocular infections

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.

2. Glaucoma

Considered to be one of the major ophthalmic clinical problems in the world. More than 2% of the population 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. Apart from these common problems of eye are cataract and macular degeneration and sometimes diseases which may be of a systemic origin such as diabetes or hypertension effect the eye.

CLASSIFICATION OF OCULAR DRUG DELIVERY SYSTEMS



A. LIQUIDS

1. Aqueous solutions

Today most of the topical ophthalmic preparations are in the form of aqueous 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, tonicity, viscosity,

buffering capacity, compatibility with formulation ingredients and effect of packaging components, choice of appropriate preservative, ocular comfort and dosing administration The designing of experiments and parameters must be conducted to achieve the optimum formulation. Corneal absorption enhancement can be achieved best by increasing solution concentration and viscosity, increasing contact time of formulation in the cornea film, appropriate pKa and offering optimal lipid solubility of drug. Commonly added viscosity enhancer agents to improve ocular bioavailability, these includes various synthetic polymers such as corboxymethyl cellulose, hydroxyl methylcellulose, polyvinyl alcohol, hydroxypropyl methylcellulose, and carbomers. Recently natural polymers have also been used to improve bioavailability of drugs. Examples of these polymers are hyaluronic acid (HA), guar gum, xylloglucan gum, Chitosan, gellan gum, pectin etc. The rheological characteristics of a polymer should be implicated the such as no adverse effects, contact time of dosage formulation and retention of dosage formulation ocular surface Aqueous ophthalmic solutions are generally manufactured by a process in which the dissolution of the active and other inactive ingredients (excipients/additives) after sterilization is achieved by application of heat or by sterile filtration. This prepared sterile solution may further be then mixed with other components such as sterilized solutions of viscosity – including agents and additives. The batch is made upto final volume with additional sterile water. e.g. Gentador-D (Gentamicin & dexamethasone sodium phosphate eye/ear drops). [2,6].

2. Suspensions[9, 10]

Ophthalmic suspensions products is another part of the ocular drug delivery system and have many distinct advantages over others formulation. Recently developed drugs are generally hydrophobic poor solubility in water and aqueous medium. Formulation offers a sterile, preserved, effective, stable and pharmaceutically elegant. Ophthalmic suspensions are more complex and challenging if compare with to ophthalmic (aqueous) solutions. The formulation of a ophthalmic suspension many problem occured such as nonhomogeneity of the dosage form, settling of particles, cake formation, aggregation of the suspended particles. The commercial ophthalmic products of should be effectively preserved on storage. To study the surface tension properties, such as wetting, particle size and interaction zeta potential, aggregation, sedimentation rate and rheological characterization of the formulation. Above all criteria are necessary for formulating an effective, elegant suspension ophthalmic formulation. Generally suspensions are kinetically stable at normal condition but thermodynamically unstable systems. If suspension keep undisturbed for a long duration of

time, can be lead to aggregation of particles, sedimentation, settling of particles and eventually forming caking.. But they are readily dispersible on hand shaking. Flocculation state of suspension the particles are held together in a loose open structure and the flocculated particles settle rapidly and for sediment. Relative properties of flocculated and deflocculated particles in suspension. e.g. Tobramycin Ophthalmic Suspensions).

Deflocculated

1. Rate of sedimentation is slow because each particle settles separately due to the particle size is minimal.
2. The sediment particle becomes very closely packed so that, a hard cake is formed due to repulsive forces between particles are overcome then is difficult to redisperse in media.
3. Generally suspensions have a pleasing appearance, due to the suspended material in solution form. The supernatant also remains cloudy on settling is remains in media.

Flocullated

1.Rate of sedimentation is high because particles settle as a floc, because a collection of particles.

2. Particle size of the suspension has a key role in physical stability and bioavailability.

The rate of sedimentation, agglomeration and resuspendability of suspensions are affected by particle size and bioavailability. In most ophthalmic suspension, the average particle size is less than 10 µm. Mostly the particle achieved by the efficient method is by dry milling and wet milling and other methods are also used of particle size reduction include micro-pulverization, grinding, and controlled precipitation. An ophthalmic suspension contains many inactive ingredients such as dispersing and wetting agents, suspending agents, buffers and preservatives. Wetting agents are used to decreases the contact angle between the solid surface and the wetting liquid. Generally ophthalmic suspension used suspending agents are includes cellulosic derivatives such as methyl cellulose, caboxy methyl cellulose, and hydroxyl propyl methyl cellulose, synthetic polymers such as carbomers, poloxamers, and polyvinyl alcohol. The selection of buffers and preservatives for suspension ophthalmic solutions in almost same as aqueous except that they must also be compatible with the flocculating systems [1].

B. SEMISOLIDS

1. Ointment [9]

Prolongation of drug contact time with the external ocular surface can be achieved using ophthalmic ointment vehicle but, the major drawback of this dosage form like, blurring of vision and matting of eyelids can limits its use. Pilopine HS gel containing pilocarpine was used to provide sustain action over a period of 24 hours. A number of workers reported that ointments and gels vehicles can prolong the corneal contact time of many drugs administered by topical ocular route, thus prolonging duration of action and enhancing ocular bioavailability of drugs.e.g. Neosporin Eye Ointment.

2. Gel and Bioadhesive gel

There are many different marketed formulation adhesions depending upon the environment of the eye for prolonging effectiveness of the drug at the site of the administration (eye). Adhesion as a process is defined as the ‘‘fixing” of two surfaces to one another .Thus bioadhesion is the binding of a natural or synthetic polymer to a biological substrate such as a mucous layer, the term mucoadhesion is often used . Mucoadhesion has been mostly used to promote a simple way of achieving site of action drug delivery by the incorporation of mucoadhesive hydrophilic polymers within ophthalmic formulations along with the active pharmaceutical ingredient (API). The API from the formulation will be released close to the site of action with a consequent incrment of bioavailability. While mucoadhesive drug delivery systems provides a means of enhancing retention time at defined sites of application, if systemic uptake occurs the use of mucoadhesive polymers will not prove to effective distribution of the API. Chitosan (CS) a cationic polysaccharide that has widely being used in ophthalmic preparations. Interactions of suitable mucoadhesive natural and synthetic polymers with mucins were evaluated from biological substances. Interactions between the mucous layer and the eye tissues, an increase in the precorneal residence time of the formulation was observed. [9,11].

C. OCULAR INSERTS[12, 13,14].

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. [1,14,15].

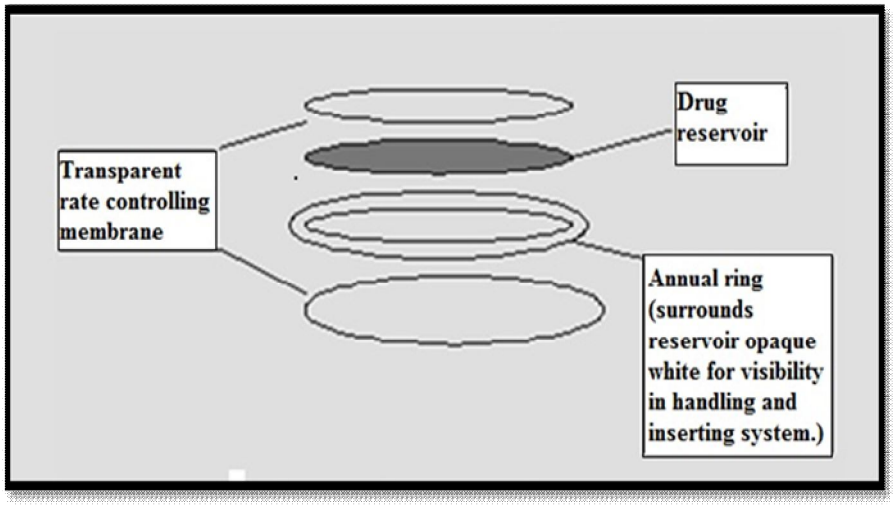
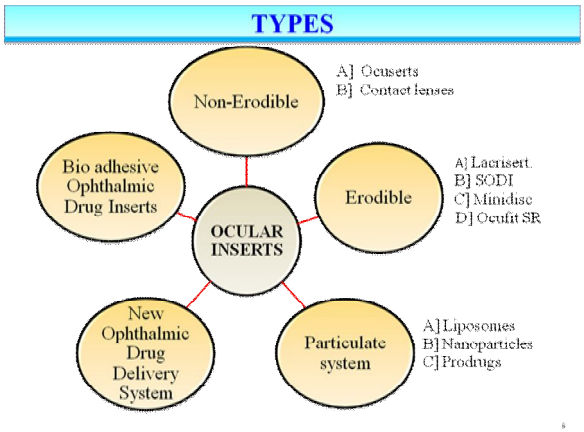


Fig. no 2 Schemetic Diagram of Opthalmic insert

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 Better patient compliance.
6. Targeting to internal ocular tissues can be done.

Types of ocuserts [13,16,17]



Types of ocular insert

I) Non-Erodible Ocular Insert[17,18]

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

1. **Ocusert**

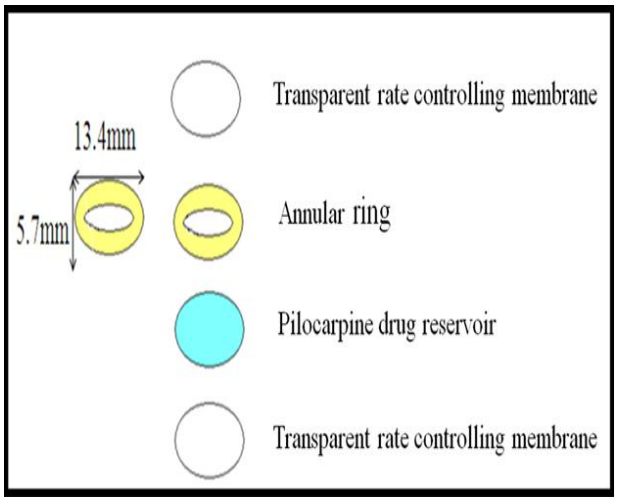


Fig 3 Ocusert

One of the earlier ocular inserts in use. The technology used in this is an insoluble delicate sandwich technology . 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. 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 µg/h for 4 to 7 days. Used in the management of glaucoma [3].

2. Contact lenses

The use of pre-soaked hydrophilic 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 . 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 [11].

Disadvantages

1. Non-erodible ocular inserts are Complexity and difficulty of usage is noticed particularly in self administration.
2. Tolerability in the eye is poor, due to rigidity, size or shape.
3. Foreign body sensation and they are to be removed at the end of the dosing period.

II) Erodible Ophthalmic Insert

The solid inserts absorb the aqueous tear fluid and gradually erode or disintegrate.The drug is slowly leached from the hydrophilic matrix.They quickly lose their solid integrity and are squeezed out of the eye with eye movement and blinking. Do not have to be removed at the end of their use.

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

1. Lacisert [19]

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. 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.

2. 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-vinylpyrrolidone and ethylacrylate called as ABE. 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. 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 24hours [18,19].

3. Minidisc [9]

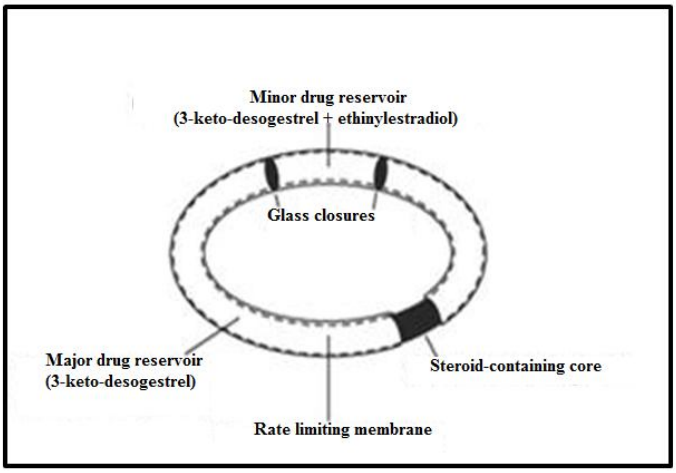


Fig 4:Minidisc

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 4-5mm. The minidisc is made up of silicone based prepolymer-α-ψ-bis (4-methacryloxy) butyl polydimethyl siloxane. Minidisc can be hydrophilic or hydrophobic to permit extend release of both water soluble and insoluble drugs.

4. Ocufit SR

It is a sustained release, rod shaped device made of silicone elastomer . It is designed to fit the shape and size of the human conjunctivalfornix. Accordingly, it does not exceed 1.9 mm in diameter and 25-30 mm in length, although smaller sizes for children and newborn babies are planned.e.g. Acetal SR Clamp.

III) Particulate System

1. Liposomes [20]

Liposomes are biocompatible and biodegradable lipid vesicles made up of natural lipids and about 25–10 000 nm in diameter.11 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 or those with medium to high molecular weights and thus increases the probability of ocular drug absorption.The corneal epithelium is thinly coated with negatively charged mucin to which the positive charged surface of the liposomes may bind.

2. Niosomes and Discomes [2]

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. They are non toxic and do not require special handling techniques.

Niosomes [21]

Nonionic surfactant vesicles that have potential applications in the delivery of hydrophobic or amphiphilic drugs. Vyas and co workers reported that there was about 2.49 times increase in the ocular bioavailability of timolol maleate encapsulated in niosome as compared to timolol maleate solution.

Discomes [9]

Non-ionic surface active agents based discoidal vesicles loaded with timolol maleate were formulated and characterized for their in vivo parameters. In vivo studies showed that discomes released the contents in a biphasic profile if the drug was loaded using a pH gradient technique. Discomes may act as potential drug delivery carriers as they released drug in a sustained manner at the ocular site.

3. 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 continous phase which may be aqueous or organic. 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 polyalkylcyanoacrylates. 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.[22]

4. 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. The partition coefficient of ganciclovir found to be increased using an acyl ester prodrug, with substantially increased the amount of drug penetration to the cornea which is due to increased susceptibility of the ganciclovir esters to undergo hydrolysis by esterase in the cornea.[23]

IV) New Ophthalmic Delivery System

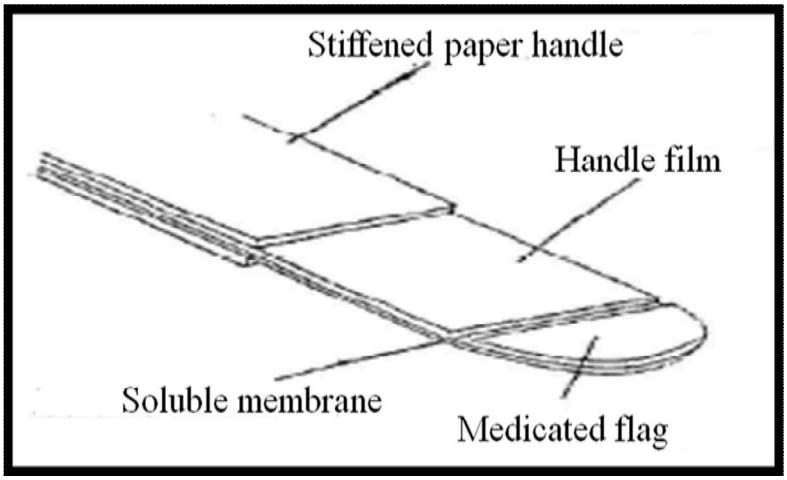


Fig 5 New ophthalmic drug delivery system

The NODS originally patented by Smith and Nephew npharmaceuticals Ltd., is a method of delivering the drug to the eye with in water soluble, drug loaded film. It provides for accurate, reproducible dosing in an easily administered preservative free form. The drug is incorporated into a water soluble polyvinyl alcohol film. Each NODS consists of a drug loaded film or (flag) attached to a handle film by means of thin membrane. The NODS is approximately 50 mm in length, 6 mm in width, the flag is semicircular in shape and has an area 22 mm2 and a thickness of 20µm and a total weight of 500 µg of which 40% can be drug. On contact with the tear film in the lower conjunctival sac, the membrane quickly dissolves releasing the flag into the tear film. Delivers precise amount of drug to the eye through water soluble drug loaded film. It provides accurate, reproducible dosing in easily administered preservative free form.[24,25]

V) 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).These are developed to overcome the drawback of available inserts which are sometimes displaced or expelled by eyeball movements. These are rod shaped inserted 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

1. 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.

2. The external gelification induces the second period, which corresponds to a slower release rate, but which is still controlled by a diffusion mechanism.

VI) Other Drug Delivery System

1. Iontophoresis

Iontophoretic technique is used to depth penetration of topically applied drug loaded nanoparticles Iontophoresis is a method for enhancing charged drug penetration into anterior and posterior ocular structures, by using a low electric current. The mechanisms of drug penetration are followed by iontophoresis of electro repulsion elecroosmosis and current-induced tissue damage . However, each drug has to be evaluated for its penetration capacity and pharmacokinetically profile, due to different physicochemical properties of the drug molecules. This novel approach of charged nanoparticles iontophoresis can benefit from: (1) deep penetration, regardless of drug's ionic activity strength and diffusion capacity in ocular tissues, (2) controlled and sustained release of the drug for better therapeutic activity, (3) targeting to a specific desired tissue and lacalised tissues.

Advantages

- Increases the bioavailability and decreases the adverse effects.
- Iontophoresis of charged nanoparticles as drug carriers, providing a long duration therapeutic activity.
- Topical ophthalmic preparation and easy to apply.
- Good drug penetration to the anterior and posterior segments of the eye by topically.
- May combine to other drug delivery system.
- Good acceptance by the patients.

2. Microemulsion [23,24,25]

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.28 Selection of aqueous phase, organic phase and surfactant/cosurfactant 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.

3. Microneedle

As an alternative to topical route Researchers have developed microneedle to deliver drug to posterior segment. The extent of lateral and transverse diffusion of sulforhodamine was reported to be similar across human cadaver sclera. Microneedle had shown prominent in vitro penetration into sclera and rapid dissolution of coating solution after insertion while in vivo drug level was found to be significantly higher than the level observed following topicaldrug administration like pilocarpine.

4. Phase Transition Systems/Insitu gel system

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. A sol to gel system with mucoadhesive property to deliver the steroid fluorometholone to the eye was prepared by Middleton and Robinson.

D. INJECTIONS AND IMPLANTS[13]

1. Injections

This method has been used for decades to deliver a variety of drugs including steroids for treating ocular inflammation and AMD. Intravitreal administration of triamcinolone acetonide (TA) has been widely used in ophthalmology for decades for the treatment of diabetic retinopathy, uveitis, pseudophakic cystoid macular edema, choroidal neovascularization associated with AMD, and macular edema associated with central retinal vein occlusion. is the most commonly used formulation for off-label intravitreal use. Unfortunately, there have been reports of sterile endophthalmitis and vision loss, thought to be related to the preservative and/or dispersion agent. Injectable therapies are also given by periocular routes including subconjunctival, retrobulbar, peribulbar, and posterior sub-Tenon injections. The subconjunctival route is an attempt to minimize dosing frequency while maintaining a sustained drug delivery to the anterior and posterior segment during a prolonged period of time. Hydrophilic drugs, which penetrate through the sclera, are more effective when given by the subconjunctival route, because they do not have to penetrate the conjunctival epithelium. One problem with this route of administration is reflux of the drug from Tenon space.

2. Ocular Implants

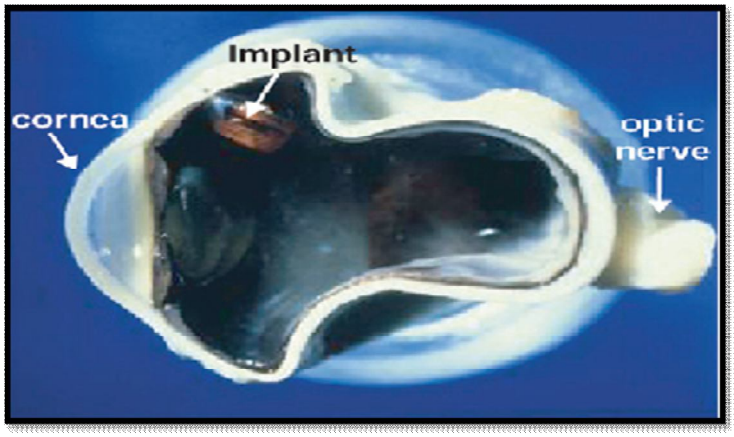


Fig 6 Ocular Implants

Ocular implants have many advantages over more traditional methods of drug administration to the eye, including delivering constant therapeutic levels of drug directly to the site of action and bypassing the blood–brain barrier. Release rates are typically well below toxic levels, and higher concentrations of the drug are therefore achieved without systemic side effects. In general, subconjunctival implantation is used for anterior-segment diseases, whereas intravitreal and suprachoroidal methods are typically used to treat posterior-segment diseases.

Site of Ocular implants

1. Subconjunctival implants

Subconjunctival implants are inserted through a small incision in the conjunctiva and placed in contact with the sclera. Intrascleral devices, implanted in a small scleral pocket at one-half the total scleral thickness, place the drug closer to its site of action than conventional transcleral devices, making it more useful for treatment of posterior-segment diseases with less systemic absorption of the drug than subconjunctival or peribulbar injections.

2.Intravitreal implants

Intravitreal placement of ocular implants has the advantage of delivering a drug directly to target tissues of the posterior segment. The implant is inserted into the vitreous through a sclerotomy site or injected with an applicator, which has the advantage of no sutures with needle delivery. The site of implantation is commonly over the pars plana, which is anterior to the insertion of the retina and posterior to the lens, and this is the area least likely to damage those structures.

Classification of Ocular implants [13,20]

1. Nonbiodegradable (Reservoir) Implants

Reservoir implants are typically made with a pelleted drug core surrounded by nonreactive substances such as silicon, ethylene vinyl acetate (EVA), or polyvinyl alcohol (PVA); these implants are nonbiodegradable and can deliver continuous amounts of a drug for months to years. One of the first reservoir implants to gain Food and Drug Administration (FDA) approval was Vitrasert ganciclovir intraocular implant for treatment of cytomegalovirus retinitis in patients with acquired immunodeficiency. The Vitrasert implant is fixed at the pars plana and projects into the vitreous cavity; it releases the drug for 5 to 8 months and must be replaced. Complications in humans include vitreous hemorrhage, retinal detachment, and endopthalmitis. Delivery of large-molecular-weight compounds has been relatively unsuccessful when incorporated into reservoir implants.

One exception is encapsulated cell technology (ECT), which is a cell-based delivery system that can be used to deliver therapeutic agents to the eye. Genetically modified cells are packaged in a hollow tube of semipermeable membrane, which prevents immune-cell entry and allows nutrients and therapeutic molecules to diffuse freely across the membrane. Two ends of the polymer section are sealed, and a titanium loop is placed on the anchoring end, which is implanted at the pars plana and anchored to the sclera.

2. Biodegradable Matrix Implants

Matrix implants are typically used to treat acute-onset diseases that require a loading dose followed by tapering doses of the drug during a 1-day to 6-month time period. They are most commonly made from the copolymers polylactic- acid (PLA) and/or poly-lactic-glycolic acid (PLGA), which degrade to water and carbon dioxide. The rate and extent of drug release from the implant can be decreased by altering the relative concentrations of lactide (slow) and glycolide (fast), altering the polymer weight ratios, adding additional coats of polymer, or using hydrophobic, insoluble drugs. The release of drug generally follows first-order kinetics with an initial burst of drug release followed by a rapid decline in drug levels. The advantage over a nonbiodegradable implant is that biodegradable implants do not require removal, as they dissolve over time. Biodegradable implants also allow flexibility in dose and treatment from short duration (weeks) to longer duration (months to a year), depending on the polymer PLA/PLGA ratio, which is another benefit in tailoring drug delivery to disease progression, because dose and treatment requirements may change over time.

ADVANCED DELIVERY SYSTEM

1. 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. Topical delivery to the eye is the most expedient way of ocular gene delivery. However, the challenge of obtaining substantial gene expression following topical administration has led to the prevalence of invasive ocular administration.Retroviral vectors have been widely used due to their high efficacy; however, they do not have the ability to transduce nondividing cells, leads to restrict their clinical use. The advanced delivery systems that prolong the contact time of the vector with the surface of the eye may enhance transgene expression, thereby facilitate non-invasive administration [1,22]

2. 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.Current strategy for management of ocular conditions consists of eliminating the injurious agent or attempting to minimize its effects. 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.

3. Protein and Peptide therapy

Delivery of therapeutic proteins/ peptides has received a great attention over the last few years. The intravitreous injection of ranibizumab is one such example. The designing of optimized methods for the sustained delivery of proteins and to predict the clinical effects of new compounds to be administered in the eye, the basic knowledge of Protein and Peptide is required.However, several limitations such as membrane permeability, large size, metabolism and solubility restrict their efficient delivery. A number of approaches have been used to overcome these limitations. Poor membrane permeability of hydrophilic peptides may be improved by structurally modifying the compound, thus increasing their membrane

permeability. Ocular route is not preferred route for systemic delivery of such large molecules. Immunoglobulin G has been effectively delivered to retina by trans scleral route with insignificant systemic absorption.

4. Scleral Plug therapy

Scleral plug can be implanted using a simple procedure at the pars plana region of eye, made of biodegradable polymers and drugs, and it gradually releases effective doses of drugs for several months upon biodegradation. The release profiles vary with the kind of polymers used, their molecular weights, and the amount of drug in the plug. The plugs are effective for treating vitreoretinal diseases such as proliferative vitreoretinopathy, cytomegalovirus retinitis responds to repeated intravitreal injections and for vitreoretinal disorders that require vitrectomy.

5.Oligonucliotide therapy

Oligonucleotide (ON) therapy is based on the principle of blocking the synthesis of cellular proteins by interfering with either the transcription of DNA to mRNA or the translation of mRNA to proteins. Among several mechanisms by which antisense molecules disrupt gene expression and inhibit protein synthesis, the ribonuclease H mechanisms is the most important. A number of factors have been determined to contribute to the efficacy of antisense ON. One primary consideration is the length of the ON species. Lengths of 17–25 bases have been shown to be optimal, as longer ONs have the potential to partially hybridize with nontarget RNA species. Biological stability is the major barrier to consider when delivering both DNA and RNA oligonucleotides to cells. Protection from nuclease action has been achieved by modification of phosphate backbones, sugar moiety, and bases.

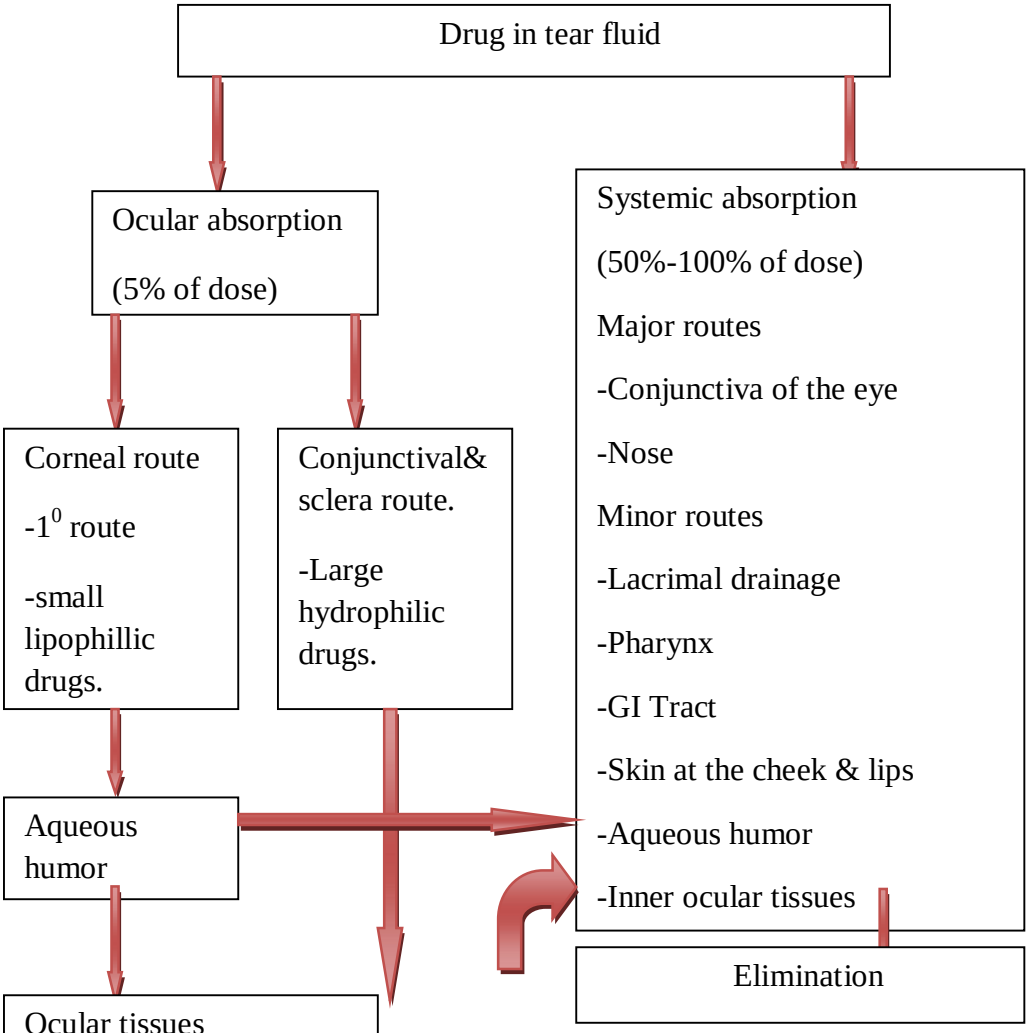
6. Aptamer [25]

Aptamers are oligonucleotide ligands that are used for high-affinity binding to molecular targets.They are isolated from complex libraries of synthetic nucleic acid by an iterative process of adsorption, recovery, and reamplification. They bind with the target molecules at a very low level with high specificity. One of the earliest aptamers studied structurally was the 15 mer DNA aptamer against thrombin, d(GGTTGGTGTGGTTGG). Pegaptanib sodium is an RNA aptamer directed against VEGFb165, where VEGF isoform primarily responsible for pathological ocular neovascularization and vascular permeability.

7. Ribozyme therapy

RNA enzymes or ribozymes are a relatively new class of single-stranded RNA molecules capable of assuming three dimensional conformations and exhibiting catalytic activity that induces site-specific cleavage, ligation, and polymerization of nucleotides involving RNA or DNA. They function by binding to the target RNA moiety through Watson-Crick base pairing and inactivate it by cleaving the phosphodiester backbone at a specific cutting site. A disease named, Autosomal dominated retinitis pigmentosa (ADRP) is caused by mutations in genes that produce mutated proteins, leading to the apoptotic death of photoreceptor cells. Lewin and Hauswirth have worked on in the delivery of ribozymes in ADRP in rats shows promise for ribozyme therapy in many other autosomal dominant eye diseases, including Glaucoma [26].

Mechanism of ocular absorption[9]



General pathway of ocular absorption

General pathway of ocular absorption

Corneal and Non-Corneal Routes of Absorption

The mechanical and chemical barrier functions of the cornea control the access of exogenous substances into the eye, thereby protecting intraocular tissues. The human cornea measures approximately 12 mm in diameter and 520 µm in thickness, and consists of five layers; epithelium, basement membrane (Bowman's layer), stroma, Descemet's membrane, and endothelium. The human corneal epithelium is a stratified, squamous, non-keratinized epithelium, 50 µm in thickness. It is composed of 2-3 sheets of flattened superficial cells, wing cells, and a single sheet of columnar basal cells. The tightest monolayer is made by the outer superficial epithelial cells which display tight junction complexes (Zonulae occludens). These tight junctions seal the superficial cells, building a diffusion barrier in the surface of the epithelium. In contrast, the basal cells are separated by 10–20 nm intercellular spaces. The wing and basal cells communicate via gap junctions allowing the intercellular communication of small molecules. Compared to the stroma and endothelium, the corneal epithelium represents a rate-limiting barrier which hinders permeation of hydrophilic drugs and macromolecules. The stroma and Descemet’s membrane cover the inner endothelial cells. These cell layers contain macula adherens and are more permeable than the epithelium. The stroma displays an hydrophilic nature due to an abundant content of hydrated collagen, which prevents diffusion of highly lipophilic agents[11].

CONCLUSION

Ocular drug delivery systems provide local as well as systemic delivery of the drugs. The novel advanced delivery systems offer more protective and effective means of the therapy for the nearly inaccessible diseases or syndromes of eyes. Self medication is also possible no need for the experts, irrespective of having several drawbacks like loss of drug by tear and lachrymal fluid, need of frequent administration and poor bioavailability. The advanced drug delivery devices such as Ocular Insert, SODI, Collagen shields, Mini disc, Liposomes, Microspheres, Nanoparticles and Prodrugs, in spite of their advantages demonstrated by extensive investigations and clinical tests, have not gained a wide acceptance by ophthalmologists. The most widely developed drug delivery system is represented by the conventional and non-conventional ophthalmic formulations to polymeric hydrogels, nanoparticle and nanosuspensions, microemulsions, iontophorosis and ocular inserts. Currently, very few new ophthalmic drug delivery systems have been commercialized in which them ocular inserts have been mostly used. Traditional liquid and semi-solid

medications, to price factors and to occasional therapeutic failures (e.g. unnoticed=expulsion from the eye, membrane rupture ,etc.). The manufacturers of ocular dosage forms appear to show a continued preference for dropper-dispensed medications.

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