OCULAR DRUG DELIVERY: AN OVERVIEW

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Abstract

Ocular drug delivery is one of the most fascinating and challenging tasks facing the Pharmaceutical researchers. One of the major barriers of ocular medication is to obtain and maintain a therapeutic level at the site of action for a prolonged period of time. The eye as a portal for drug delivery is generally used for local therapy against systemic therapy to avoid the risk of eye damage from high blood concentration of the drug, which is not intended.

Keywords: EYE, Ocular Inserts, Eye Infection, ophthalmic inserts.

1. Introduction:

‘VISION 2020, THE RIGHT TO SIGHT’, was the global initiative launched in the year 1999. It is estimated that, worldwide approximately 180 million people are visually impaired; of these between 40 and 45 million are blind. Even more compelling, it is estimated that the number of blind and visually impaired double by 2020, unless concerted action is undertaken to stem this toll. Glaucoma is the third leading cause of blindness worldwide and is responsible for about 52 million cases of blindness. \(^1\) (12.5\% based on the number legally blind persons in the population at a given time). It is an ocular disease caused by a progressive form of optic nerve damage associated with raised (≥21mm of Hg) intraocular pressure.\(^2,3\)

Most ocular treatments like eye drops and suspensions call for the topical administration of ophthalmically active drugs to the tissues around the ocular cavity. These dosage forms are easy to instill but suffer from the inherent drawback that the majority of the medication they contain 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 precorneal cavity by constant tear flow and lacrimo-nasal drainage. Therefore, the targeted tissues absorb a very small fraction of instilled dose. For this reason, concentrated solutions and frequent dosing are required for the instillation to achieve...
an adequate level of therapeutic effect. One of the new classes of drug delivery systems, polymeric film ocular drug delivery systems/ocular inserts, which are gaining worldwide accolade, release drugs at a pre-programmed rate for a longer period by increasing the pre-corneal residence time. Ocular inserts are composed of polymeric vehicle containing the drug and are mainly used for topical therapy.

2. Anatomy and Physiology of the Eye

The outermost layer of the globe of the eye or eyeballs is a tough pliable but non-stretchable structure that maintained in its shape by the internal pressure exerted by the aqueous and vitreous humor. Transverse section of the eye ball is shown in the figure 1.

The front part of the boundary layer is clear and colorless and is called cornea. The cornea contains no blood vessels but is richly supplied with nerve endings. The other part of the boundary layer of the eye is the sclera which is opaque and white in color and contains most of the blood vessels that nourish the anterior tissue of the eyeball.

The outer surface of the sclera is loosely covered by the conjunctival membrane which is continuous with the lining of the inner surface of the eyelids. The conjunctival and the corneal surfaces are continuously lubricated by a film of fluid secreted by the conjunctival and lacrimal glands. The lacrimal glands secrete tears, a clear watery fluid containing mineral salt, glucose and other lower molecular weight organic compounds and proteins.

Sebaceous glands on the margin of the eyelids secrete oily fluid which spreads over the tear film reducing the rate of evaporation from the exposed surface of the eye. The tear film in the eye is constantly being replenished; this process is assisted by blinking which spreads the film evenly over the surface of the eye and sweeps any excess fluid into the triangular lacrimal lake which lies at the angle of the inner junction of the eyelids. Excess tears are drained from the lacrimal lake into the lacrimal sac which is activated as a pump by blinking to drain the tears via the nasolacrimal duct into the nose. The turnover rate of nasolacrimal fluid is 16%. The eye ball is continually irrigated by a gentle steam of lacrimal fluid which prevents it from becoming dry and inflamed.

The lacrimal fluid in humans has a normal volume of 7 µl with ph 7.4 and if blinking does not occur, the volume can go up to 30 µl without spillage. It contains lysozyme which has bactericidal activity. The rate of blinking varies between 5 – 50 movements per minute. During blinking,
the eye lids are closed for a short period (about 0.30 seconds). The aqueous humor in humans has a volume approximately 300 µl. The film of fluid covering the eye maintains the optical efficiency of the cornea which must remain moist in order to function correctly, the composition of the precorneal film is complex and comprises of a three layered structure, a lipid outer layer, a watery middle layer, and a mucoid inner layer that is in contact with the corneal epithelium. figure 2.

3. **Advantage of ocular drug delivery:**
   - Delivery of medication to the human eye is an integral part of medical treatment.53
   - Ocular preparations, including solutions, suspensions, and ointments, can be applied.54
   - Ocular preparations are Conventional dosage forms.
   - Generally, when it comes to patient safety, comfort, affordability, and ease of use, eye drops are superior to other forms of ocular drug delivery.56
   - Sustained drug release and prolonged therapeutic activity.
   - Novel drug delivery tool for chronic ocular diseases.
   - Site-specific targeting -surface modification with ligands.
   - Act as an inert carrier for ophthalmic drugs.

4. **Disadvantage of ocular drug delivery:**
   - Conventional dosage forms such as solutions, suspensions, and ointments have well-known disadvantages.55
   - Higher cellular permeability.

5. **Infections of the Eye**13,14
   - Diseases of conjunctiva and cornea may occur as a result of direct trauma, disorders of tearing, exposure to radiant energy, allergens, infectious agents, inflammatory, metabolic and neoplastic processes.13
   - Most bacterial conjunctival infections are caused by staphylococci, streptococci and pseudomonas species. Adenovirus infection is the leading cause of kerato conjunctivitis in adults.
   - Chronic amoebic ulcers of the cornea can occur in soft contact lens wearers, who have a break in the corneal epithelium. Debilitated patients can develop keratitis due to gram negative bacteria. The kerato conjunctivitis is often associated with corneal ulceration.
   - Many of the corneal and conjunctival diseases are due to immunological reactions. Interstitial keratitis and sclerosing keratitis are caused due to
sensitivity reactions of the corneal stroma. Bacterial allergies of the cornea follows topical administration of steroids and specific antibiotic therapy.

- Glaucoma is a large group of disorders with widely different clinical features in which the intraocular pressure (IOP) is too high which results in damage to the optic disc and visual field disturbances.

6. Most common eye problems:

- Eye Twitching (or Blepharospasm) – Despite being painless, eye twitching, a blinking disorder, can be very irritating and is a very common eye problem. Eye twitching is more often than not caused by stress, high caffeine levels, pink eye, fatigue, nervous system disorders, panic disorder, and/or staring at the television or computer for an extended period of time. Eye twitching may be experienced in both eyes, one of the eyes or under the eyes. Experts recommend resting and reducing causes of stress for treating mild eye twitching and medication, butox and surgery for severe eye twitching.

- Itchy (and Watery) Eyes – Itchy and watery eyes are usually caused by allergies or two types of allergic conjunctivitis; a). seasonal allergic conjunctivitis that causes itchy and watery eyes because of exposure to allergens (such as grass, weed, pollen, and certain types of trees) in spring or autumn, b). perennial allergic conjunctivitis that causes itchy and watery eyes all year long because of exposure to household allergens (such as mold, dust, pet dander and pet hair). Experts recommend taking over the counter oral antihistamines or over the counter antihistamines and decongestants in them or getting similar medication prescribed by an eye specialist for this common eye problem.

- Stye Eye Infection – An eye stye (also called hordeolum) is an infection because of blockage in the hair follicle of an eyelash that results in a small bump on the outside or inside the eye. Most of the time, an eye stye matures and heals in less than a week. Eye sties are caused by staphylococcal bacteria found in the nasal cavity that infects the glands causing it to swell and in some cases fill with pus. Experts recommend using a warm compress, gentle massage, antibiotics, ointments, eye drops and pills for treating this common eye problem if they are not healed within four to five days.
**Astigmatism** – another common eye problem, refers to a condition of the eyes in which patients find it hard to focus and objects (both near and far) appear blurred. In most cases, squinting or tilting the head one way or another seems to help improve the ability to focus. Astigmatism is caused by a de-shaped cornea (oblong instead of spherical) and results in two curves, a flat one and a steep one. Consequently, light is focused at two points instead of one, blurring your vision. Unless it is extreme, astigmatism can be addressed with prescription glasses or contact lenses. Moreover, contrary to popular belief soft contact lenses are also available in the market for astigmatism patients.

**Conjunctivitis** - Conjunctivitis (also known as pink eye) is a condition in which the conjunctiva, the mucus membrane lining the inside of your eye, experiences inflammation or swelling. Conjunctivitis is most common eye problem in school going children and is believed to be highly contagious. There are several types of conjunctivitis that is caused by various chemicals, viruses, bacteria, allergens, and/or foreign body in the eye. Some of the most common symptoms are; redness, itchiness, blurred vision, sensitivity to light, excessive tearing and discharge from the eyes that form a crust. Experts recommend taking antibiotic eye ointments or eye drops for treating conjunctivitis.

**Dry Eye Syndrome** – In dry eye syndrome, a common eye problem, your eyes feel dry and scratchy because of the inability of your tear ducts to produce the right quality and/or quantity of tears. Since it is attributed to lack of moisture in the eye, it should be treated properly. In case it is not treated effectively, dry eye syndrome is known to weaken vision and cause various types of eye infections. It is caused by hormonal changes, various medicines, continued use of contact lenses, chemical burns in the eye and various environmental factors. The most effective treatment options for dry eye includes using eye drops or having silicon plugs inserted in the tear ducts to hold moisture in the eye by preventing tears from falling out.

**Cataracts** – Cataracts, the most common eye problem, cause of blindness in people older than fifty five years of age, refers to a condition in which the eye’s lens in clouded or blurred. The lens of human eye is contained in a lens capsule in which
dead cells accumulate over time clouding it (partially or completely) disrupting the eyes ability to see clearly. Cataract is generally painless and is accompanied by the following symptoms; blurred vision, sensitivity to light, deteriorating night vision, double vision, rapid changes in eye sight prescription and blurred vision. In some cases, patients suffering from cataracts don’t need treatment as they remain small and negligible. In more severe cases, doctors recommend undergoing cataracts surgery that is the only effective way or restoring vision partially or completely.

- Retina Detachment – Cameras are manufactured on the principle of the retina that captures light and turns them into electronic impulses that are communicated to the brain that converts them into images allowing us to process them. Retina lies on top of the choroid, the tissue that provides nourishment to it. Retina detachment, a common eye problem, refers to a phenomenon in which it separates from the choroids. It is more common in patients suffering from myopia and is usually caused by trauma. Some of the treatment options for retina detachment are pneumatic retinopexy, cryotherapy and/or laser therapy.

7. Absorption of drugs in the eye:
The medicaments contained in products intended for administration to the surface of the eye may be required either to act at that surface or to penetrate through the surface structures to act within the interior of the eyeball.

1. Rapid solution drainage by gravity, induced lachrymation, blinking reflex, and normal tear turnover.

2. Loss of the drugs from the palpebral fissure (by spillage of the drug from the eye and its removal via nasolacrimal apparatus). Blinking: normal volume is 7 µl during blinking and 30 µl when blinking does not occur. (Drop volume = 50 µl). 70% of the administered volume is seen to be expelled from the eye by overflow.

3. Superficial absorption of drug into the conjunctiva and sclera and rapid removal by the peripheral blood flow.

4. Low corneal permeability In general:- Transport of hydrophilic and macromolecular drugs through scleral route-Lipophilic agents of low molecular weight follow trans corneal transport by passive diffusion and obey Fick's first law of diffusion:

\[ J = -D \cdot \frac{dCm}{dx} \]

\( J \) = The flux rate across the membrane
D = diffusion coefficient: The diffusion coefficient, as the molecular size of the drug
Cm = concentration gradient: As the drug solubility, the gradient, the driving force for drug entry into the aqueous humor

N.B the drug should have dual solubility (oil and water soluble to traverse the corneal epithelium (lipid barrier) then the aqueous humour. The drugs should be both oil and water soluble for the best therapeutic efficacy (Figure 3). 

8. Pharmacokinetic Consideration

Topical applied drugs which penetrate into the eye across the cornea first enter the aqueous humour and are then distributed to the surrounding tissues, i.e., iris ciliary body, lens, vitreous and choroid-retina. A summary of the drug deposition model in the eye after topical application is given in figure 4.

Corneal absorption is considered to be the major penetration pathway for topically applied drugs. There are two mechanisms for absorption across the corneal epithelium, transcellular and paracellular diffusion. Lipophilic drugs prefer the transcellular route while hydrophilic drugs penetrate primarily via the paracellular route.

The non-corneal route of absorption via the conjunctiva and the sclera is usually non-productive as most of the drug reaches the systemic circulation before gaining access to the intra-ocular tissues. As the surface area of the conjunctiva is much larger than that of the cornea and as the highly vascularised conjunctiva is more permeable, especially to larger hydrophilic molecules, drug loss through this route of absorption may be significant. Both transconjunctival absorption and absorption via the nasolacrimal duct are generally undesirable, not only because of the loss of drug into the systemic circulation, but also because of the possible systemic side effect. The volume of aqueous humor is topically about 0.3 ml, but the ocular volume of distribution for drugs is larger due to multicompartamental kinetics. Apparent volume of distribution (Vd) for ophthalmic drugs have been estimated from an intracameral injection and topical infusion data. Reported values for Vd are typically between 0.24 ml and 0.62 ml. Small values of Vd, suggest limited tissue distribution, possibly due to protein binding in aqueous humor.

As human studies are limited to non-invasive experiments, rabbits have been used as animal model for most ocular studies, as many pharmacokinetic parameters of the human and the rabbit eye are comparable (table 1).

9. Formulation approaches to improve Ocular Bioavailability
9.1. Conventional dosage forms

Conventional dosage forms such as solutions, suspensions and ointments account for almost 90% of the currently accessible ophthalmic formulation on the market.

- **Solutions**

  The reasons for choosing solutions over other dosage forms include their favorable cost advantage, the simplicity of formulation development and production and the high acceptance by patients. However, they also exhibit major drawbacks, such as the rapid and extensive precorneal loss, the high absorption via the conjunctiva and the nasolacrimal duct leading to systemic side effects, as well as increased instillation frequency resulting in low patient compliance.

- **Suspensions**

  Suspensions of the micronized drug (<10 µm) in a suitable aqueous vehicle are formulated, where the active compound is water insoluble, which is the case for most of the steroids. It is assumed that the drug particles remain in the conjunctival sac, thus promoting a sustained release effect. Topical ophthalmic suspensions have a number of limitations. They need to be adequately shaken before use to ensure correct dosing and the amount of drug required to achieve only a moderate increase in bioavailability is very high, rendering suspensions expensive in terms of their production costs. Moreover, the drug particles size plays a major role in the formulation process, with particles greater than 10 mm causing patient discomfort and therefore reflex tearing.

- **Ointments**

  Ointments generally consist of a dissolved or dispersed drug in an appropriate vehicle base. They are the most commonly used semisolid preparations as they are well tolerated, fairly safe and increase the ocular bioavailability of the drug. The instilled ointment breaks up into small oily droplets that remain in the cul-de-sac as a drug depot. The drug eventually gets to the ointment-tear interface due to the shearing action of the eye lids. Overall, ophthalmic ointments offer the following advantages: reduced dilution of the medication via the tear film, resistance to nasolacrimal drainage, and an increased precorneal contact time. However, oily viscous preparation for ophthalmic use (such as ointments) can cause blurred vision, matting of the eyelids, and may also be associated with discomfort by the patient as well as occasional ocular mucosal irritation.

9.2. Polymeric deliver systems

- **Viscosity enhancing polymers**

  In order to reduce the lacrimal clearance of
ophthalmic solutions, various polymers have been added to increase the viscosity of conventional eye drops, prolong precorneal contact time and subsequently improve ocular bioavailability of the drug. Among the range of hydrophilic polymers investigated in the area of ocular drug delivery are polyvinyl alcohol (PVA) and polyvinyl pyrrolidone (PVP), cellulose derivatives such as methylcellulose (MC) and polyacrylic acids (carbopols).

• **Mucoadhesive polymers**

Mucoadhesive polymers increase the contact time of a formulation with the tear film and simulate the continuous delivery of tears due to a high water restraining capacity. As such, they allow a decrease in the instillation frequency compared to common eye drops and are therefore useful as artificial tear products. In order to be an effective mucoadhesive excipients, polymers must show one or more of the following futures: strong hydrogen binding group, strong anionic charge, high molecular weight, sufficient chain flexibility, surface energy properties favoring spreading onto the mucus, and near zero contact angle to allow maximum contact with the mucin coat. The excipient, polymers must show one or more of the mucoadhesive various polymers are Hydroxypropyl methyl cellulose, Methyl cellulose, Polyvinyl alcohol, Polyvinyl pyrrolidone, Pectin, Chitosan, Polox.

• **In-situ gelling systems**

In situ gelling systems are viscous polymer-based liquids that exhibit sol-to-gel phase transition on the ocular surface due to change in a specific physic-chemical parameter (ionic strength, temperature or pH). They are highly advantageous over preformed gels as they can easily be instilled, but are capable of prolonging the residence time of the formulation on the surface of the eye due to gelling. The principal advantage of in-situ gelling systems is the easy, accurate and reproducible administration of a dose compared to the application of performed gels. Three methods have been employed to cause phase transition on the surface: change in temperature, pH, and electrolyte composition.

9.3. **Colloidal delivery systems**

Colloidal carriers are small particulate systems ranging in size from 100 to 1000 nm. As they are usually suspended in an aqueous solution, they can easily be administered as eye drops, thus avoiding the potential discomfort resulting from bigger particles present in ocular suspensions or from viscous or sticky preparations. The colloidal particles are preferable taken up by the corneal epithelium via endocytosis.
- **Nanoparticles**\(^\text{26}\)
Nanoparticles are defined as submicron-sized polymeric colloidal particles ranging from 10 to 1000nm, in which the drug can either be dissolved, entrapped, encapsulated or adsorbed. Depending on the preparation process, nanospheres or nanocapsules can be obtained. Diffusion of the drug from the oily core of the nanocapsule to the corneal epithelium seems to be more effective than diffusion from the internal more hydrophilic matrix of the nanospheres.

The most commonly used biodegradable polymers in the preparation of nanoparticulate systems for ocular drug delivery are poly-alkylcyanoacrylates, poly-e-caprolactone and poly-lactic-co-glycolic-acid copolymers.

- **Liposomes**\(^\text{27}\)
A liposomes consists of one or more concentric spheres bilayers separated by water compartments with a diameter ranging from 80 nm to 100 m. Due to their amphiphilic nature, liposomes can accommodate both lipophilic (due to the lipid bilayer) and hydrophilic (encapsulated in the central aqueous compartment) drugs. Liposomes are easy to prepare, exhibit versatile physical characteristic and are generally biodegradable, biocompatible and relatively non-toxic. However, their use is limited by instability (due to hydrolysis of the phospholipids), restricted drug-loading capacity, technical difficulties in obtaining sterile preparation and blurred vision due to their size and opacity. Depending on their lipid composition, they can have a positive, negative or neutral surface charge, which can have a great impact on their precorneal retention time.

- **Niosomes**\(^\text{28}\)
Niosomes are non-ionic surfactant vesicles, which exhibit the same bilayered structures as liposomes. However, they show improved chemical stability and lower production costs. They were also shown to increase the ocular bioavailability of hydrophilic drugs significance more than liposomes. This is due to the fact that the surfactant present in the niosomes act as penetration enhancers that remove the mucous layer from the ocular surface.

Modified version of niosomes is the so called discomes, which vary from the conventional niosomes in size and shape. The larger size of the vesicles (12-60 m) prevents their drainage into the nasolacrimal drainage systems. Furthermore, their disc like shape provides them with a better fit in the cul-de-sac of the eye.

**9.4. Other delivery approaches**
- **Cyclodextrins**\(^\text{29}\)
Cyclodextrins are a group of homologous
cyclic oligosaccharides with a hydrophilic outer surface and a lipophilic cavity in the center. Their initial aim was to increase the solubility of lipophilic drugs by forming inclusion complexes. Cyclodextrins complexation generally results in improved wetability, dissolution, solubility, and stability in solutions as well as reduced side effects. It is assumed that cyclodextrin themselves are too large and hydrophilic to penetrate biological membranes. However, they act as penetration enhancers by assuring a high drug concentration at the corneal surface, from where the drug then partitions into the ocular tissues. Therefore, the improvement of ocular bioavailability seems to be limited by the very slow dissociation of the complexes in the precorneal tear fluid.

- **Ocular inserts**

Ophthalmic inserts are solid devices intended to be placed in the conjunctival sac to deliver the drug at a comparatively slow rate. They are composed of polymeric support containing drugs. The inserts can be useful for topical or systemic therapy. The main objective of ophthalmic inserts is to increase the contact time between the preparation and conjunctival tissue to ensure a sustained release suited for topical or systemic treatment. The inserts placed in the cul-de-sac or on the cornea represents one of the possibilities to reach the increased residence time. These devices present the advantage of avoiding a pulsed release due to multiple applications.

10. **Ocular Inserts (Ophthalmic Inserts)**

The name “Inserts” was derived from the Latin word “inserere”, which means “to introduce”. Historically the first solid medication precursors of the present insoluble inserts were described in the 19th century. It consists of squares of dry filter paper impregnated with drug solution. Small sections were cut and applied under the eye lid.

Ocular inserts are defined as sterile preparations, with a thin, multilayered, drug-impregnated, solid or semisolid consistency devices placed into cul-de-sac or conjunctival sac and whose size and shape are especially designed for ophthalmic application. The inserts can be used for topical or therapy. Ocular inserts as ocular sustained release drug delivery system.

The development of newer, more sensitive diagnostic techniques and therapeutics agents renders urgency to the development of maximum successful and advanced ocular drug delivery systems. These dosage forms give only marginally maximum sustained drug-eye contact than eye drop solutions and do not yield a constant drug bioavailability. Repeated
medications are still required throughout the day. The conventional ocular dosage forms for the delivery of drugs are:

1. Eye drops (solution, suspension)
2. Ophthalmic Ointments

The eye drop dosage form is easy to install but suffers from the inherent drawback that most of the instilled volume is eliminated from the pre-corneal area resulting in a bioavailability ranging from 1-10% of total administrated dose. The poor bioavailability and rapid pre-corneal elimination of drugs given in eye drops is mainly due to conjunctival absorption, rapid solution drainage by gravity, induced lachrymation, blinking reflex, low corneal permeability and normal tear turnover. Because of poor ocular bioavailability, many ocular drugs are applied in high concentrations. This cause both ocular and systemic side-effects, which is often related to high peak drug concentrations in the eye and in systemic circulation. The frequent periodic instillations of eye drops are necessary to maintain a continuous sustained therapeutic drug level. This gives the eye a massive and unpredictable dose of medication.

**Objective:** Increase the contact time between the preparation and the conjunctival tissue to ensure a sustained release suited to topical or systemic treatment.

**Advantages:**
- Increasing contact time and thus improving bioavailability.
- Possibility of providing a prolong drug release and thus a better efficacy.
- Reduction of systemic side effects and thus reduced adverse effects.
- Reduction of the number of administrations and thus better patient compliance.

**Classification of Ocular Inserts:**
1. Insoluble ophthalmic inserts
   - Diffusion inserts
   - Osmotic inserts
   - Soft Contact lenses
2. Soluble ophthalmic inserts
3. Bioerodible ophthalmic inserts

**1. Insoluble ophthalmic inserts:**
- **Diffusion Inserts:** The diffusion inserts are composed of a central reservoir of drug enclosed in specially designed semi-permeable or micro porous membrane which allows the drug to diffuse from reservoir at precisely determined rate. The drug release from such system is controlled by lacrimal fluid penetrating through the membrane until a sufficient internal pressure is reached to drive the drug out of the reservoir. The drug delivery rate is controlled by diffusion through the membrane, which one can be
controlled.\textsuperscript{39} 

- **Osmotic Inserts:** The osmotic inserts are generally compared to a central part surrounded by a peripheral part.\textsuperscript{40} The first central part can be composed of a single reservoir or of two distinct compartments. It is composed of a drug with or without an additional osmotic solute dispersed through a polymeric matrix, so that the drug is surrounded by the polymer as discrete small deposits.\textsuperscript{41} In the second case, the drug and the osmotic solutes are placed in two separate compartments, the drug reservoir being surrounded by an elastic impermeable membrane and the osmotic solute reservoir by a semi permeable membrane. The second peripheral part of these osmotic inserts comprises in all cases a covering film made of an insoluble semi permeable polymer.\textsuperscript{42} The tear fluid diffuse into peripheral deposits through the semi permeable polymeric membrane wets them and induces their dissolution. The solubilized deposits generate a hydrostatic pressure against the polymer matrix causing its rupture under the form of apertures. Drug is then released through these apertures from the deposits near the surface of the device which is against the eye, by the sole hydrostatic pressure.\textsuperscript{43} This corresponds to the osmotic part characterized by zero order drug release profile.

- **Soft Contact lens:** These are shaped structure made up of a covalently crosslinked hydrophilic or hydrophobic polymer that forms a three-dimensional network or matrix capable of retaining water, aqueous solution or solid components.\textsuperscript{44} When a hydrophilic contact lens is soaked in a drug solution, it absorbs the drug, but does not give a delivery as precise as that provided by other non-soluble ophthalmic systems. The drug release from such a system is generally very rapid at the beginning and then declines exponentially with time. The release rate can be decreased by incorporating the drug homogeneously during the manufacture\textsuperscript{45} or by adding a hydrophobic component. Contact lenses have certainly good prospects as ophthalmic drug delivery systems.\textsuperscript{46} 

2. **Soluble ophthalmic inserts**

Soluble inserts correspond to the oldest class of ophthalmic inserts. They offer the great advantage of being entirely soluble so that they do not need to be removed from their site of application thus, limiting the interventions to insertion only.\textsuperscript{47} 

Types 

- Based on natural polymers e.g. collagen.
- Based on synthetic or semi synthetic polymers.
The therapeutic agents is preferably absorbed by soaking the insert in a solution containing the drug, drying and rehydrating it before use on the eye. The amount of drug loaded will depend upon the amount of binding agent, upon the concentration of the drug solution into which the composite is soaked, as well as the duration of the soaking.48

The soluble ophthalmic inserts containing synthetic/semi synthetic polymers offers the additional advantages of being generally of a simple design.

a) Based on products well adopted for ophthalmic use.

b) Easily processed by conventional methods – slow evaporating extrusion, compression or injection molding.

The release of the drug from such system is by penetration of tears into the insert which induces release of the drug by diffusion and forms a gel layer around the core of the insert, this external gelification induces the further release, but still controlled by diffusion. The release rate, J, is derived from Fick’s law yields the following expression.49

\[ J = \frac{A}{D} kCS \ L \]

When A - Surface area of the membrane.

K – Diffusion coefficient of the drug

L – Membrane thickness

CS – Drug solubility in water

D – Diffusion coefficient of the Ocuserts membrane.

The soluble insert made of cellulose derivatives can be sterilized by exposure to gamma radiation without the cellulose components being altered.50 A decreased release rate is obtained by using a component of the matrix a polymer normally used for enteric coatings47 or by introducing a suitable amount of hydrophobic polymer capable of diminishing the tear fluid penetration and thus of decreasing the release of the drug without modifying the solubility of the insert when added in proper proportion.

3. Bioerodible ophthalmic inserts

The biodegradable inserts are composed of material homogeneous dispersion of a drug included or not into a hydrophobic coating which is substantially impermeable to the drug. They are made of the so-called biodegradable polymers.51 Successful biodegradable materials for ophthalmic use are the poly (orthoesters) and poly (orthocarbonates). The release of the drug from such a system is the consequence of the contact of the device with the tear fluid inducing a superficial diversion of the matrix.52

The use of solid ophthalmic devices will certainly increase owing to the development of new polymers, the emergence of new drugs having short biological half-lives or systemic side effects.
and the need to improve the efficacy of ophthalmic treatment by ensuring an effective drug concentration in the eye over an extended period of time.19

11. Conclusion:
Most conventional ophthalmic dosage forms are simplistic. It is usual that watersoluble drugs are delivered through topical administration in an aqueous solution, and water insoluble drugs are administered topically, as an ointment or aqueous suspension.

The bioavailability of traditional ocular drug delivery systems such as eye drops is very poor because eye is protected by a series of complex defense mechanisms that make it difficult to achieve an effective drug concentration within the target area of the eye. Many approaches have been developed to solve the problem in recent decades, of which colloidal drug delivery system has been paid much attention.

Bibliography:


Figure 1: Schematic cross section of human eye and cornea

Figure 2: Schematic illustration of the nasolacrimal drainage system

Drug delivery in ocular therapeutics is a challenging problem.

- Poor Bioavailability
- Protective Mechanisms (Short residence time)
  - Blinking
  - Reflex Lacrimation
  - Nasolacrimal Drainage
- Anatomy of the eye
  - Barrier properties of the cornea
**Figure 3:** Schematic illustration of the drug delivery in ocular therapeutic

![Schematic illustration of the drug delivery in ocular therapeutic](image)

**Figure 4:** Schematic illustration of ocular disposition of topically applied ocular formulation.

**Table 1:** Comparison of pharmacokinetics factors between the rabbit and the human eye.  18

<table>
<thead>
<tr>
<th>Pharmacokinetic factors</th>
<th>Human</th>
<th>Rabbit</th>
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<tbody>
<tr>
<td>Bowman’s membrane</td>
<td>Present</td>
<td>Partially absent</td>
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<tr>
<td>Nictitating membrane</td>
<td>Absent</td>
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<td><strong>Spontaneous blinking rate</strong></td>
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<td>1.6</td>
<td>0.55</td>
</tr>
<tr>
<td>pH of aqueous humour</td>
<td>7.1-7.3</td>
<td>8.2</td>
</tr>
<tr>
<td>Aqueous humour volume (mL)</td>
<td>0.1-0.25</td>
<td>0.25-0.3</td>
</tr>
<tr>
<td>Aqueous humour turnover rate (µL/min)</td>
<td>2-3</td>
<td>3-4.7</td>
</tr>
<tr>
<td>Protein content of aqueous humour (mg/ml)</td>
<td>30</td>
<td>0.5</td>
</tr>
<tr>
<td>Corneal thickness (mm)</td>
<td>0.52-0.54</td>
<td>0.35-0.45</td>
</tr>
<tr>
<td>Corneal diameter (mm)</td>
<td>11-12</td>
<td>15</td>
</tr>
<tr>
<td>Corneal surface area (cm²)</td>
<td>1.04</td>
<td>1.5-2.0</td>
</tr>
<tr>
<td>Ratio of conjunctival and corneal surface</td>
<td>17</td>
<td>9</td>
</tr>
</tbody>
</table>