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# RECENT ADVANCES IN MUCOADHESIVE OCULAR DRUG DELIVERY SYSTEM: A REVIEW

**Seraj Alam Siddique[1]*, Bhagyashree Prabhat[2], Mohd Kalim[3] and Ankur Yadav[4]**

[1,3,4]Assistant Professor, Kanpur Institute of Technology and Pharmacy, Kanpur, U.P., India.

[2]Student, Department of Pharmacy, Radha Govind University, Ramgarh, Jharkhand, India.

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***Corresponding Author**
**Seraj Alam Siddique**
Assistant Professor, Kanpur Institute of Technology and Pharmacy, Kanpur, U.P., India.

## ABSTRACT

The current article has been mainly highlighted on the mucoadhesive drug delivery system that can be designed to shows prolonged retention at the site of application, providing a controlled rate of drug release for improved therapeutic outcome. For the application of dosage forms to mucosal surfaces which having many benefits to drug molecules not only for the oral route, which undergo acid degradation or extensive first-pass metabolism in the stomach. The main challenges in ocular drug delivery occurs due to unique anatomy and physiology of eye in comparison to other organs of the body. The conventional formulations like solution, suspensions and ointments having many demerits such as rapid precorneal elimination, high variability, drainage by gravity and absence of controlled release. Novel pharmaceutical ophthalmic formulations like in-situ gel, nanoparticle, liposome, nanosuspension, microemulsion, iontophoresis and ocular inserts have been developed in last three decades which provides increase in the solubility and bioavailability of the drug as a sustained and controlled manner to overcome these types of problems. There is a need to develop ocular drug delivery systems which gives sustained and controlled release for the treatment of chronic diseases and increase patient's and doctor's convenience to reduce the dosing frequency and invasive treatment. In this article, improvement of ocular drug delivery systems under clinical trials and in late experimental stage is reviewed.

**KEYWORDS:** Mucoadhesive, First-Pass Metabolism Bioavailability, Iontophoresis, Ocular Insert, In-situ gel, Nanoparticle, Liposome, Nanosuspension, Microemulsion Invasive Treatment.

## INTRODUCTION

Eye is the very important organ of body. It consist of epithelium, stroma and endothelium. The outermost that is epithelium is the rate limiting barrier for transcorneal diffusion of most hydrophilic drugs. The middle layer that is stroma act as diffusion barrier and it protects to highly lipophilic drugs. The last one that is endothelium is lipoidal in nature which does not protects transcorneal diffusion of most drugs. The traditional formulation like solution, suspension show disadvantages like rapid precorneal elimination, drainage by gravity, normal tear turnover, frequent instillation, enzymatic metabolism, nasolacrimal damage, conjunctival absorption and absence of controlled release. The traditional ocular formulation having very low residence time ranges between 5 and 25 minutes. When we apply the drug in eye, only 1-10% of the drug is absorbed into the eye and major amount of drug absorbed systemically which results in systemic side effects.[1,2]

There are various types of eye diseases that can affect the body and loss of vision as well. Therefore, many drug delivery systems are available and it is classified as traditional and new drug development system. For the treatment of various eye disorders, Eye is the very important organ of body. It consist of epithelium, stroma and endothelium. The outermost that is epithelium is the rate limiting barrier for transcorneal diffusion of most hydrophilic drugs. The middle layer that is stroma act as diffusion barrier and it protects to highly lipophilic drugs. The last one that is endothelium is lipoidal in nature which does not protects transcorneal diffusion of most drugs. The traditional formulation like solution, suspension show disadvantages like rapid precorneal elimination, drainage by gravity, normal tear turnover, frequent instillation, enzymatic metabolism, nasolacrimal damage, conjunctival absorption and absence of controlled release. The traditional ocular formulation having very low residence time ranges between 5 and 25 minutes. When we apply the drug in eye, only 1-10% of the drug is absorbed into the eye and major amount of drug absorbed systemically which results in systemic side effects.[1,2]

There are various eye diseases which can affect the body and loss of vision as well. They are classified as traditional and novel drug development system. Application of drugs to the eye, topical route is the most popular and well-accepted route of administration for the treatment of various eye disorders. The bioavailability and solubility of ophthalmic drugs is very poor due to efficient protective mechanisms of the eye. Various ocular delivery systems, such a ointments, suspensions, micro- and nanocarriers and liposomes, have been investigated

during the past two decades pursuing two main strategies: to increase the corneal permeability and to prolong the contact time on the ocular surface.[3] To remain in the vicinity of front of the eye for prolong period of time, Ideal ophthalmic drug delivery must be able to sustain the drug release. Development of viscous gel, colloidal suspension or using erodible or non-erodible insert to prolong the precorneal drug retention, an ideal ophthalmic drug delivery must be able to sustain the drug release by addition of polymers of various grades.[4] Bioadhesive systems utilized can be either microparticle suspension or polymeric solution. It is found that cornea offers more resistance to negatively charged compounds as compared to positively charged compounds.

Newer pharmaceutical ophthalmic formulation such as in-situ gel, nanoparticle, liposome, nanosuspension, microemulsion, iontophoresis and ocular inserts have been developed in last three decades that increase the bioavailability of the drug as a sustained and controlled manner to overcome these types of problems.

Eye pathologies involving the anterior segment of the eye are most often treated by topical instillation of aqueous solutions such as eye drops. Traditional dosage forms account for 90% of ophthalmic formulations, mainly due to their simplicity of formulation and excellent acceptance by patients. However, precorneal elimination caused by naso-lachrymal drainage and high tear fluid turnover remains the major drawback of these drug delivery systems for topical application.

The eye-ball is an organ protected from exogenous substances and external stress by various barriers therefore, therapeutic drugs must be transported across several protective barriers regardless of which administration route is utilized, such as eye-drops, and sub-conjunctival, sub-tenon's and intravitreal injection and/or implant. For the treatment of the anterior segment of the eye (cornea, conjunctiva, sclera, anterior uvea), usually topical ocular eye-drops are used. An eye-drop, irrespective of the instilled volume, often eliminates rapidly within five to six minutes after administration, and only a small amount (1–3%) of an eye-drop actually reaches the intraocular tissue.[5] More than 75% of applied ophthalmic solution is lost via nasolachrymal drainage and absorbed systemically via conjunctiva, hence ocular drug availability is very low.[6] To increase ocular bioavailability and prolong the retention time on the ocular surface, various ophthalmic formulations such as viscous solutions, suspensions, emulsions, ointments, aqueous gels, and polymeric inserts have been investigated for topical application to the eye.

The bioavailability and solubility of ophthalmic drugs is very poor due to efficient protective mechanisms of the eye. Various ocular delivery systems, such a ointments, suspensions, micro- and nanocarriers, and liposomes, have been investigated during the past two decades pursuing two main strategies: to increase the corneal permeability and to prolong the contact time on the ocular surface.[3] Ideal ophthalmic drug delivery must be able to sustain the drug release and to remain in the vicinity of front of the eye for prolong period of time.[4] Bioadhesive systems utilized can be either microparticle suspension or polymeric solution. For small and medium sized peptides major resistance is not size but charge, it is found that cornea offers more resistance to negatively charged compounds as compared to positively charged compounds.

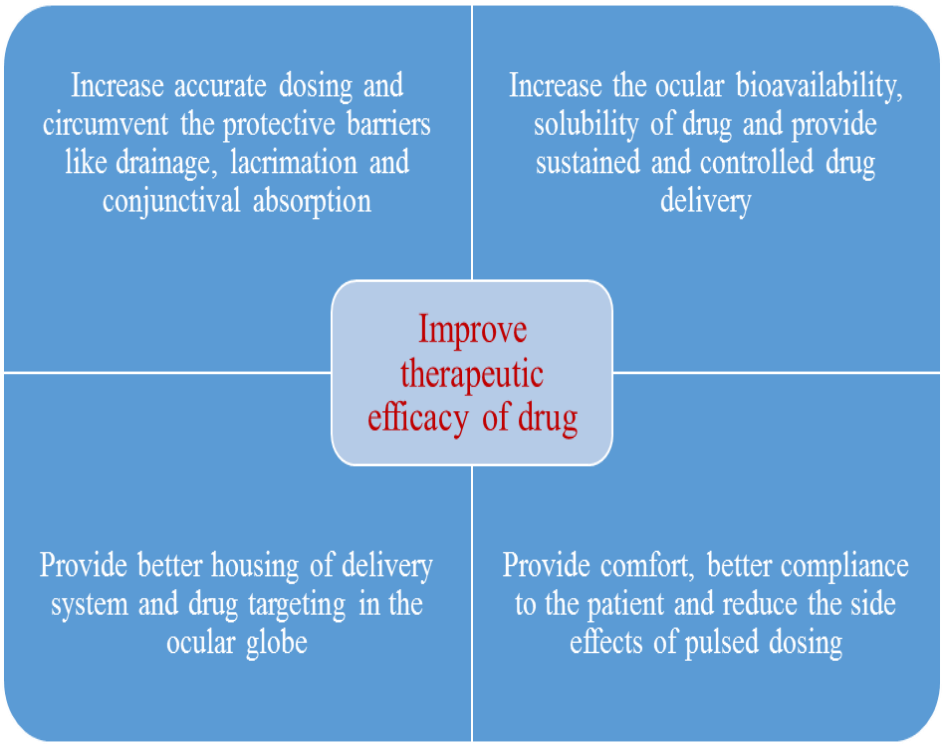
To increase the bioavailability of the drug as a sustained and controlled manner, newer pharmaceutical ophthalmic formulation such as in-situ gel, nanoparticle, liposome, nanosuspension, microemulsion, iontophoresis and ocular inserts have been developed in last three decades.

Eye pathologies involving the anterior segment of the eye are most often treated by topical instillation of aqueous solutions such as eye drops. Due to their simplicity of formulation and excellent acceptance by patients, traditional dosage forms account for 90% of ophthalmic formulations. However, precorneal elimination caused by naso-lachrymal drainage and high tear fluid turnover remains the major drawback of these drug delivery systems for topical application.

The eye-ball is an organ protected from exogenous substances and external stress by various barriers therefore, therapeutic drugs must be transported across several protective barriers regardless of which administration route is used. Topical ocular eye-drops are used for the treatment of the anterior segment of the eye such as cornea, conjunctiva, sclera, anterior uvea. An eye-drop, irrespective of the instilled volume, often eliminates rapidly within five to six minutes after administration, and only a small amount (1–3%) of an eye-drop actually reaches the intraocular tissue.[5] So it is very difficult to provide and maintain an adequate concentration of drug in the precorneal area. More than 75% of applied ophthalmic solution is lost via nasolachrymal drainage and absorbed systemically via conjunctiva, hence ocular drug availability is very low.[6] Various ophthalmic vehicles such as viscous solutions, suspensions, emulsions, ointments, aqueous gels, and polymeric inserts have been

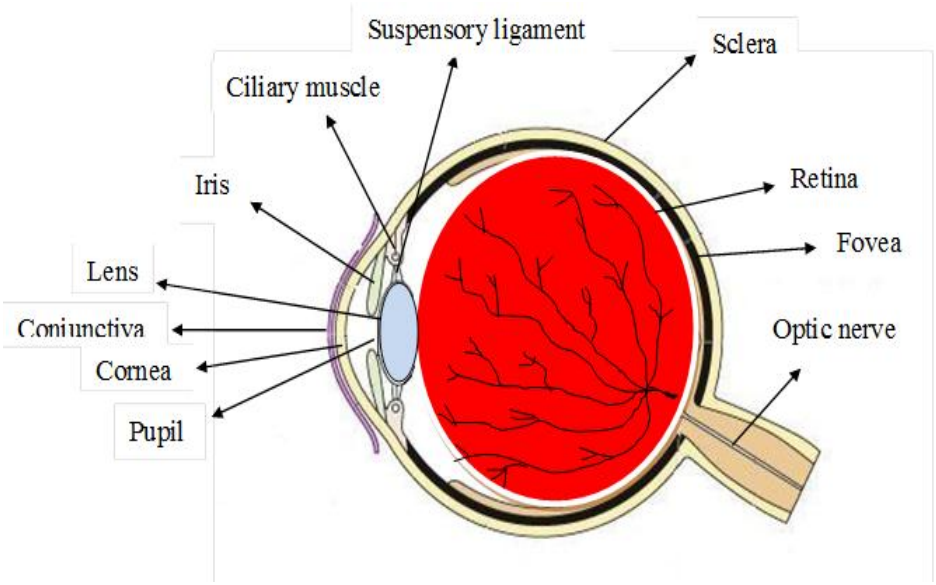
investigated for topical application to increase ocular bioavailability and prolong the retention time on the ocular surface.

**Advantages of ocular drug delivery systems:**[7,8]




**Anatomy and Physiology of eye**[9,10,11]

The human eye is the very essential sense organ of the body and its structure and construction is very complex in comparison to other organs. The eye consists of the outer coat known as sclera and cornea, a middle layer or uveal coat and the inner coat or retina. The sclera is made of fibrous tissues shaped as segments of two spheres, the sclera and cornea. The external part of the eye is covered by the mobile tarsal part of the eyelids. They play role in distributing the tear fluid over the eye, providing an optically smooth surface over the cornea.




**(Physiology of eye)**

**Cul - de – sac:** The cul-de-sac normally holds 7 – 9 µ L of tear fluid, with the normal tear flow rate being 1.2 – 1.5 µ L/min. For determining the ocular bioavailability of a drug, the loss from the precorneal area by drainage, tear fluid turnover, and non-corneal absorption plays an important role in. Most of the topically applied drug is eliminated from the precorneal area within the first minute because the drainage rate is much faster than the ocular absorption rate.

**Cornea:** The cornea is a clear, transparent, non-vascular tissue to which the oxygen and nutrients are supplied by aqueous humour which is having high oxygen and same osmotic pressure as blood. It is composed of five layers: epithelium, Bowman's layer, stroma, Desceme's membrane and endothelium. It is covered by a thin epithelial layer continuous with the conjunctiva at the cornea-sclerotic junction. The main bulk of cornea is formed of criss-crossing layers of collagen and is bounded by elastic lamina on both front and back. Its posterior surface is covered by a layer of endothelium.

**Conjunctiva:** The conjunctiva is a thin transparent membrane, which lines the inner surface of the eyelids and is reflected onto the globe. At the corneal margin, it is structurally continuous with the corneal epithelium.

**Iris:** The iris is the visible coloured part of the eye and extends anteriorly from the ciliary body, lying behind the cornea and in front of the lens.

**Ciliary muscles:** The ciliary muscle is a ring-shaped muscle attached to the iris. It is important because its contraction and relaxation controls the shape of the lens.

**Lens:** The lens is the transparent biconvex structure situated behind the iris and in front of the vitreous. It plays an important role in the visual function of the eye and also enables accommodation together with the ciliary muscle. The lens is made up of slightly more than 30% protein (water - soluble crystalline) and therefore has the highest protein content of all tissues in the body. The lens receives its nutrients from the aqueous humour and its transparency depends on the geometry of the lens fibers.

**Retina:** The retina may be like a "screen" on which an image is formed by light that has passed into the eye through the cornea, aqueous humour, pupil, lens, then the hyaloids and finally the vitreous humour before reaching the retina. The retina possesses photosensitive elements (called rods and cones) that convert the light they detect into nerve impulses that are then sent onto the brain along the optic nerve.[71]

**Choroid:** The choroid layer is situated behind the retina and it absorbs the unused radiation.

**Sclera:** Around outside of the eye-ball, a tough white sheath called as sclera. It consists of a membrane that maintains the shape of the eye and gives the attachment to the extrinsic muscle of the eye.

**Optic nerve:** The optic nerve is the second cranial nerve and is responsible for vision. Approximately one million fibres transmitting information from the rod and cone cells of the retina by each nerve.

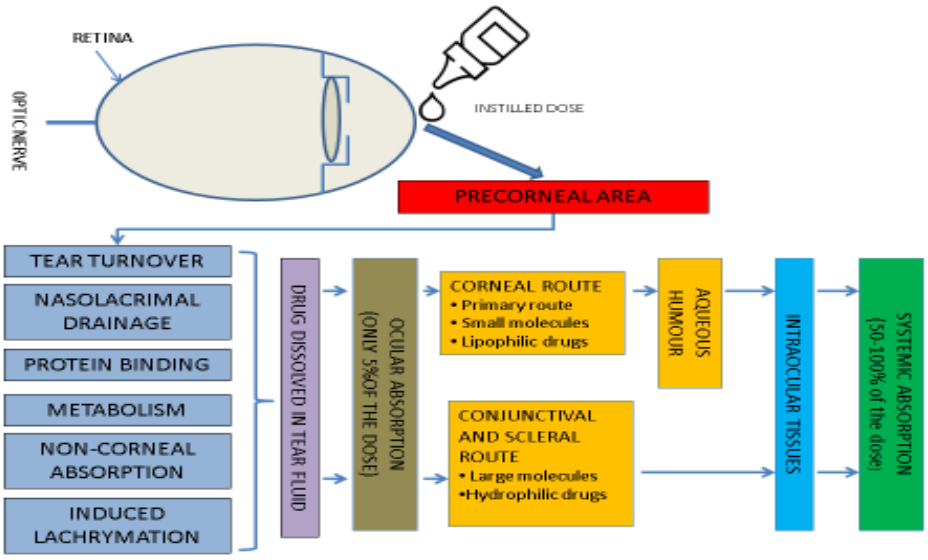
**Tear film:** A thin fluid layer is covered the exposed part of the eye known as precorneal tear film. The film thickness is about 3–10 Am and it is depend on the measurement method with the resident volume approximately 10 µl. The osmolality of the tear fluid is approx. 310– 350 mOsm/kg in normal eyes and it is maintained by the monovalent and divalent inorganic ions present in fluid such as Na+, K+, Cl-, HCO3 -, and proteins. The average pH of tears is about 7.4 (69). The diurnal patterns of pH changes the pH of tear, which a shift from acid to alkaline during the day. By the help of bicarbonate ions, proteins, and mucins, the buffer capacity of the tears fluid is determined. Tears possesses a non-Newtonian rheological behaviour with viscosity is about 3 mPas. The mean surface tension of tear film value is about 44 mN/m.[70]

**Routes of ocular drug delivery:** There are a no. of routes of drug delivery into the ocular tissues. The selection of the route of drug administration depends primarily on the target tissue. Design of the dosage can play a major role on the resulting drug concentrations and on the duration of drug action.

**Topical ocular:** Typically topical ocular drug administration is achieved by eye drops, but they have very short contact time on the eye surface. The contact time and duration of drug action can be increased by formulation design such as gels, deifying formulations, ointments, and inserts.[12] During the short contact of drug on the corneal surface it partitions to the epithelium and in the case of lipophilic compounds it remains in the epithelium and it is released in very slow manner from the corneal stroma and further goes to the anterior chamber.[13] After 20–30 min. of eye drop administration, the peak concentration in the anterior chamber is reached, but this concentration is typically two orders of magnitude lower than the instilled concentration even for lipophilic compounds.[14] From the aqueous humour the drug has an easy access to the iris and ciliary body, where the drug may bind to melanin. Melanin containing drug may produce a reservoir which is released gradually to the surrounding cells, thereby prolonging the drug activity. Drug is eliminated from the aqueous humour by two main mechanisms: by aqueous turnover through the chamber angle and Sclemm's canal and by the venous blood flow of the anterior uvea.[15] The first mechanism which is having a rate of about 3µl/min and this convective flow is independent of the drug. Elimination by the uveal blood flow, on the other hand, depends on the drug's ability to penetrate across the endothelial walls of the vessels. For this reason, clearance from the anterior chamber is faster for lipophilic in comparison to hydrophilic drugs. The clearance of lipophilic drugs from eye can be in the range of 20–30 µl/min. So that most of drug elimination takes place through uveal blood flow. Half-life of drugs in the anterior chamber is typically short and it is about an hour. In the ocular tissues, volumes of distribution is very difficult to determine due to the slow equilibration of drug. The estimates in rabbits range from the volume of aqueous humour (250 µl) up to 2 ml.[12] Some part of topically administered drugs may absorb across the bulbar conjunctiva to the sclera and further to the uvea and posterior segment. The role of this non-corneal route of absorption depends on the drug properties. By this route, more hydrophilic and larger molecules may absorb. The relative contribution of the non-corneal is more eminent because they have particularly poor penetration across the cornea. Delivery across the conjunctiva and further to the posterior segment would be desirable, but unfortunately the penetration is clinically insignificant.

**Sub-conjunctival administration:** To the uvea reason of eye Sub-conjunctival injections have been used to deliver drugs at increased level. This route of drug administration have gained a very much popularity. The types of progress play a major role in pharmaceutical formulation which provided new exciting possibilities to develop controlled release formulations to deliver drugs to the posterior segment and to guide the healing process after surgery (e.g. glaucoma surgery). Secondly, the development of new therapies for macular degeneration (antibodies, oligonucleotides) must be delivered to the retina and choroid.[16,17] Sub-conjunctival injection drug must penetrate across sclera which is more permeable in comparison to the cornea. As earlier mention that the scleral permeability is not dependent on drug lipophilicity.[18] Even more interesting is the surprisingly high permeability of sclera to the large molecules of even protein size.[19] Therefore it seems very feasible to deliver drugs across sclera to the choroid. The drug delivery to the retina is more complicated, because in this case the drug must across the choroid layer and RPE. The role of blood flow in eye is very well characterize and so that there are good reasons to believe that drugs may be cleared significantly to the blood stream in the choroid region. Pitkänen et al. suggested that RPE is tighter barrier that sclera for the permeation of hydrophilic compounds.[18]

**Intravitreal administration:** Direct drug administration into the vitreous chambers provides a great advantage of more access to the vitreous and retina. It should be noted, however, that delivery from the vitreous to the choroid is more complicated due to the hindrance by the RPE barrier. Small molecules are able to diffuse rapidly in the vitreous but the mobility of large molecules, particularly positively charged, is restricted.[20] Likewise, the mobility of the nanoparticles is highly dependent on the structure due to which it provides controlled release. After intravitreal injection the drug is eliminated by two main routes: anterior and posterior.[21,22] All compounds are able to use the anterior route. This means drug diffusion across the vitreous to the posterior chamber and, thereafter, elimination via aqueous turnover and uveal blood flow. Drugs can be administered to the vitreous chamber by controlled release formulations such as liposomes, microspheres, implants to prolong the drug activity. This requires adequate passive permeability or active transport through these types of barriers. For these reasons, large molecular weight and water-solubility tend to prolong the half-life in the vitreous.[23,24]




**Drug delivery to anterior segment of the eye:**

The cornea is composed with the sclera, joining it at the limbus. It is convex in shape and is approximately 1 mm thick at the periphery, thinning to about 0.5 mm at the center. The cornea is normally clear, avascular and in a state of relative dehydration. The cornea which having negatively charged, is more permeable to cations in compare to anions at physiological pH. Physiologically, the cornea can be divided into four layers. These are given below:

- The Bowman's layer, unlike the epithelium, does not regenerate after injury or disease and heals with a scar.
- The stroma, which constitutes 90% of corneal thickness is comprised mainly of collagen fibers and heals with a scar.
- The Decemet's membrane is a transparent and elastic membrane.
- The endothelium is a single cell-layer thick, and regulates corneal dehydration through a sodium-potassium pump, essential for maintaining transparency.[25]

The conjunctiva is a thin transparent membrane which produces mucus that lines and lubricates the surface of the eye, the important vascularization of the conjunctiva is responsible for the elimination of a significant proportion of active ingredients into the systemic circulation.[26] The iris stroma, is composed of connective tissue that extends from the ciliary body stroma. The aqueous humor is a clear watery fluid that occupies the anterior and posterior chambers between the posterior surface of the cornea and anterior lens. It is secreted by the ciliary body at the posterior chamber, is directed into the anterior chamber

through the pupil and is drained by the trabecular meshwork and Schlemm's canal. Its role is to provide nutrients, remove waste from avascular tissues and regulate the intraocular pressure that maintains the convex shape of the cornea.[25]

The crystalline is a transparent biconvex lens, located behind the iris separating the aqueous and the vitreous humor. It is composed of fibers from epithelial cells. It is characterized by its plasticity and its ability to change the curvature radius and refractive index, allowing active control of light penetration.

The ciliary body is a thin vascular middle layer of the eye which is situated between the sclera and the retina. It also possesses the ciliary muscle, which changes the shape of the lens when the eye focuses on an object, and the ciliary processes responsible for the secretion of aqueous humor.[26]

The lachrymal apparatus (Figure 2) is the physiologic system containing the orbital structures for tear production and drainage. It consists of the lachrymal gland, which secretes the tears that form a tear film covering the conjunctiva and cornea.[25]

**Table 1: Current and Future drugs in clinical trials for anterior DDSS.**

| Active ingredient | Brand name | Dosage form | Release-controlling excipient | Target Indication | Developmental stage |
|---|---|---|---|---|---|
| Azithromycin | AzaSite® | Eye-drops | Polycarbophil | Bacterial conjunctivitis | Launched |
| Azithromycin/ Dexamethasone (ISV-502) | AzaSite Plus™ | Eye-drops | Polycarbophil | Blepharoconjunctivitis | P3 |
| Bromfenac (ISV-303) | - | Eye-drops | Polycarbophil | Post cataract surgery | P1/2 |
| Timolol maleate | Rysmon® TG | Eye-drops | Methylcellulose | Glaucoma | Launched |
| Betaxolol | Betoptic S® | Eye-drops | Amberlite® IRP-69 | Glaucoma | Launched |
| Tobramycin/ Dexamethasone | TobraDex® ST | Eye-drops | Xanthan gum | Blepharitis | Launched |
| Timolol maleate | Timoptic-XE® | Eye-drops | Gellan gum | Glaucoma | Launched |
| - | Cationorm® | Eye-drops | Cationic emulsion | Mild dry eye | Launched |
| Cyclosporine (NOVA22007) | - | Eye-drops | Cationic emulsion | Dry eye Vernal keratoconjunctivitis | P3 P2/3 |
| Ketotifen | - | Soft contact | - | Allergic conjunctivitis | P3 |

| | | | | | |
|---|---|---|---|---|---|
| | | lens | | | |
| Latanoprost | - | Puctal plug | - | Glaucoma | P2 |
| Bimatoprost | - | Puctal plug | - | Glaucoma | P2 |
| Cyclosporine (LX201) | - | Episcleral implant | Silicone | Aeratoconjunctivitis | P3 |
| Latanoprost | - | Subconjunctival insert | PLGA/PVA | Glaucoma | P1 |
| Dexamethasone phosphate (EGP-437) | EyeGate II® | Iontophoresis | - | Dry eye<br>Anterior uveitis | P3<br>P2 |

**Drug delivery to posterior segment of the eye:**

The retina is the innermost eye tissue. It is a thin transparent membrane that adheres to the choroid through one of its layers: the retinal pigment epithelium. On its inner surface, it is in contact with the vitreous. The retina comprises two layers: an outer layer (pigment epithelium) and an inner layer (neuro-epithelium) where the functions of light reception and transmission are located. The vitreous is a transparent, colorless and gelatinous mass, its volume composed of 99% water, and constitutes two thirds of the eyeball.[25]

The choroid is a richly pigmented membrane located at the posterior of the uvea. Oxygen and nourishment are provides to the outer layers of the retina by choroid layer of eye. The choroid contributes to the thermal equilibrium and intraocular pressure (IOP) of the eyeball.[72]

The sclera covers four fifths of the posterior external part of the globe and has a protective function. It is a fibrous tissue, strong and durable, that protects the globe, in particular its sensory elements.[26]

**Table 2: Current and Future drugs in clinical trials for posterior DDSS.**

| Active ingredient | Brand name | Dosage form | Release-controlling excipient | Target Indication | Developmental stage |
|---|---|---|---|---|---|
| Ganciclovir | Vitrasert® | IVT, implant | EVA/PVA | CMV retinitis | Launched |
| Fluocinolone acetonide | Retisert® | IVT, implant | Silicone/PVA | Posterior uveitis | Launched |
| Fluocinolone acetonide | Iluvien® | IVT, implant | Polyimide/PVA | DME<br>Wet AMD | P3<br>P2 |
| Dexamethasone | Ozurdex® | IVT, implant | PLGA | CRVO<br>BRVO<br>Posterior uveitis | Launched |
| Brimonidine | - | IVT, implant | PLGA | Dry AMD<br>RP | P2<br>P1/2 |

| | | | | | |
|---|---|---|---|---|---|
| Triamcinolone acetonide | I-vation™ TA | IVT, implant | PMMA/EVA | DME | P2 |
| CNTF (NT-501) | - | IVT, implant | Semipermeable membrane/ARPE-19 | RP<br>Dry AMD | P2/3<br>P2 |
| Triamcinolone acetonide (IBI-20089) | - | IVT, injection | Oil | CRVO<br>BRVO | P1 |
| Triamcinolone acetonide (RETAAC) | - | IVT, injection | PLGA | DME | P1/2 |
| Corticosteroid prodrug (NOVA-63035) | Cortiject® | IVT, injection | Emulsion | DME | P1 |
| Verteporfin | Visudyne® | IV, injection | Liposome | Wet AMD | Launched |
| Difluprednate | Durezol™ | Eye-drops | Emulsion | DME | Off-label |

**Factors limiting ocular bioavailability of drugs**

**Tears:**

Secreted from the lachrymal gland, tears play a very important role in maintaining normal eye function. Tears of healthy people are composed of water, electrolytes, lipids, proteins, glucose and mucins, while in some disease states additional components can be found, such as inflammatory mediators, antigens and cytokines. Tears form a thin film that covers, hydrates and protects the ocular surface, as well as improving the quality of the retinal image by smoothing out irregularities in the cellular surface. The tear film consists of three layers: the outermost lipid layer (0.1 μm in thickness secreted by meibomian glands), a middle aqueous layer (7–10 μm in thickness), and the innermost mucous layer (0.2–1.0 μm in thickness). However, while these properties make tears an essential component of normal ocular function, they have a negative effect on ocular drug bioavailability.[71] Indeed, given that the cul-de-sac can transitorily contain about 30 μL and that normal human tear volume is estimated at roughly 7 μL, a considerable diluting effect can be attributed to tears, which means that it is essential to modulate the concentration of drugs administrated via this route.

Moreover, tears are characterized by a high turnover rate (restoration time of 2–3 min), thus limiting ocular residence time for a drug (5–6 min before being completely washed away) and consequently minimizing the period during which the drug can penetrate the ocular tissues. This effect of tear turnover rate on drug delivery is also greatly dependent on molecular characterization. Indeed, various types of commonly used ophthalmic drugs are

alkaloids or other weak bases which are chemically unstable in neutral or alkaline solution. Accordingly, the pH of the solution is adjusted by the manufacturer the acid side to maintain stability in storage. Such preparations, examples of which include pilocarpine and epinephrine, produce irritation immediately upon instillation, which greatly increases lacrimation and dilution. To minimize this effect, the solutions are generally not buffered to the lower pH. So, the loss through drainage is lesser with drug formulations approximating the pH of tears (pH = 7.4).[27]

Another factor with negative consequences for drug bioavailability is that tears contain proteins and mucins that bind to drug molecules, thereby reducing the effective concentration of drug in contact with the cornea. Since tears possesses buffering agents in the form of carbonic acid and weak organic acids which considerable volume compared to the usual volume of ocular drug instilled, they can be expected to modify the extent of drug ionization and thus its bioavailability.

**Conjunctiva:**

Constituted of mucus tissue, the conjunctiva contributes to the lubrication and protection of the eye by producing mucus and antimicrobial peptides. The conjunctiva is highly vascularized and plays an important role as a protective barrier on the ocular surface since tight junctions are present on the apical surface of its cells. In fact, it is considered as a non-productive route with respect to ocular drug administration, since drug penetrating the conjunctiva is thought to reach general blood circulation rather than intraocular segments. In addition to the conjunctiva, the naso-lachrymal duct is known to contribute to the systemic absorption of locally distilled drug. For certain anterior segment pathologies, this may be enough to produce an effect, as exemplified by the choice of intraocular pressure lowering drugs. However, this systemic absorption represents a restrict application to posterior segment, since the intraocular drug levels achieved are often below effective concentrations. For this reason, drug administration via the subconjunctival route is increasing seen as a promising way to enhance the efficacy of topical drug application.[25]

**Cornea:**

The cornea is the anterior layer of the eye, composed principally of epithelium, stroma and endothelium. In addition to its protective effect on ocular tissue, the cornea refracts light, accounting for approximately two-thirds of the eye's total optical power. Corneal layer represents a mechanical barrier which restrict from absorption of drug molecules. Due to their

high lipid content, the epithelium and the endothelium are considered as a barrier to the passage of hydrophilic molecules. The presence of tight junctions between the corneal epithelial cells restricts paracellular drug permeation and so that limiting corneal permeability to hydrophilic and ionized molecules. On the other hand, the stroma, which is constituted by an extracellular matrix consisting of a lamellar arrangement of collagen fibrils, is characterized by a high water content that makes this layer impermeable to lipophilic molecules. Therefore the corneal epithelium at a greater extent and stroma represent a barrier to the permeation of macromolecules which having a size less than 50,000 Da can diffuse into the stroma.[28] The corneal endothelium is a single-cell layer constituting the innermost part of the cornea, which is in direct contact with the aqueous humor. This layer has been shown to play a major role in transporting substances from the aqueous humor to the stroma. Since phospholipids are the major components of the corneal endothelium, this part of the cornea is known to be permeable to lipophilic molecules and nearly impermeable to ionized molecules. Overall, it would appear that in order to penetrate through these three layers, molecules should have an amphiphilic nature characterized by the presence of hydrophilic and lipophilic properties in the same structure.

**Sclera:**

Continuous with the cornea, the sclera maintains the shape of the eye globe, offering resistance to internal and external forces, and provides a support for extraocular muscle insertions. The sclera is essentially composed of an extracellular matrix consisting of collagen fibrils and glycoproteins. This structure suggests that the permeability of this layer is comparable to that of the corneal stroma. It is easily permeable to hydrophilic substances. Nevertheless, the molecular radius and geometry and charge of a drug molecule are reported to affect their permeation through this layer. Indeed, the sclera is reported to be more permeable both for small and negatively charged molecules; positively charged molecules are difficult to trap by the negatively charged glycoproteins present in the sclera.[25]

**Blood-ocular barriers:**

The term “blood-retinal barrier” refers to the tight junctions between retinal capillary endothelial cells and the tight junctions between retinal pigment epithelial cells, the inner and the outer components of the blood retinal barrier, respectively. Due to its anatomic position, it restricts access by therapeutic agents from the blood to the posterior segment of the eye.[67]

The aqueous humor is secreted into the posterior chamber and then flows into the anterior chamber, crossing the iris diaphragm.[68]

**Key approaches to improve ocular bioavailability:**

Most current improvements are intended to increase the corneal residence time of the drug and so that increase intracorneal diffusion, by modifying the active ingredient or by using excipients.

**Prodrug strategies:**

To improve bioavailability and reduce adverse drug reactions, a prodrug strategy can often be used to enhance drug lipophilicity, reducing the effect of the permeability barrier. Prodrug strategies can be employed for many purposes including enhancing solubility, improving the shelf life of a drug or stabilizing a drug both chemically and metabolically.[64,65,66] These strategies can facilitate formulation efficacy as exemplified by the case of dipivefrine (Propine®), an ester prodrug of epinephrine, which is 600 times more lipophilic and thus offers a 17-fold increase in permeation across the cornea compared with epinephrine, leading to a 10 times higher intracorneal concentration of epinephrine than the parent molecule.[29]

Another example is latanoprost, the prodrug of latanoprost acid, which because of the isopropylester group, enhances tolerance and penetration of drug at a lower dose. This prodrug strategy is also attractive for administering drugs with a narrow therapeutic index[30,31] UNIL088, a water-soluble prodrug of Cyclosporine was developed via an ester linkage which is converted into the parent drug by chemical or enzymatic hydrolysis of the terminal ester group. The solubility of UNIL088 in isotonic phosphate buffer solution pH 7 is approximately 25,000 times higher than that of Cyclosporine.[32,73,74] Acyl ester prodrugs of acyclovir and ganciclovir (GCV) have been shown to increase drug passage across the corneal barrier. Apparent permeation of the valerate ester prodrug of GCV is six times higher than the parent drug across the cornea.[33]

**Novel application of excipients:**

**Use of cyclodextrins:** The use of cyclodextrins (CDs) in ophthalmic drug delivery systems is recent which appears in the early 1990s. CD complexations are used to improve drug solubility and stability in solution and to reduce local irritation.[62] Therefore a no. of eye drop products containing CDs have already been registered in Europe, such as chloramphenicol (Clorocil® – Edol), diclofenac (Voltaren Ophthalmic® – Novartis) and indomethacin

(Indocid® –Merck Sharp & Dohme-Chibret). Conventional or traditional penetration enhancers which play a major role such as benzalkonium chloride (BAC) obstruct the ophthalmic barrier in which CDs solubilize the lipophilic active ingredient by formation of complex resulting in increased drug penetration into the eye and so that increasing drug availability at the lipophilic eye surface.[61] However in some reported studies, the use of CDs is used to enhance drug bioavailability, while in other studies, addition of CDs results in decreased bioavailability. Such alternative results could be due to inappropriate CD dosage. To reach optimum bioavailability, some 15% or less CDs should be added to aqueous eye drop solutions to solubilize the lipophilic water-insoluble drug.[34] Adding CDs in large quantities will decrease bioavailability by retaining the drug molecules in the aqueous tear fluid,[35] Loftsson and Stefansson,[36] reported the effect of CD concentration on the permeation potential of the lipophilic water-insoluble drug dexamethasone, using an aqueous CD solution containing 0.5% (w/v) dexamethasone through a semi-permeable cellophane membrane. Dexamethasone was in suspension at a CD concentration below 5% but in solution at higher CD concentrations. The results obtained showed that at low CD concentrations, when the drug was in suspension, the flux of the drug increased with increasing CD concentration. At higher CD concentrations, when the entire drug was in solution, the flux decreased with increasing CD concentration. So to provide maximum permeation, enough CD is added to the vehicle to solubilize the entire drug resulting provide a better bioavailability.[63]

Saari et al.[37] compared the effect of 0.7% dexamethasone-CD eye drops applied once daily with 0.1% dexamethasone sodium phosphate applied three times a day for post-cataract inflammation. Twenty cataract patients who underwent pharmacoemulsification and intraocular lens implantation were randomly divided into two postoperative treatment groups. By practical application, results shows that 0.7% dexamethasone CD eye drops applied once daily is a more effective postoperative anti-inflammatory medication than 0.1% dexamethasone sodium phosphate applied three times a day. Three weeks after the operation, the mean best-corrected visual acuity was normal and there were no significant differences between the two test groups. No side effects were observed and compliance was good in both groups. There is a practical application that the 0.7% dexamethasone-CD eye drops were applied once daily, making the patient compliance more likely.

Recently a study was carried out by Sigurdsson et al.[38] to determine the relative concentration of dexamethasone in CDs following topical and systemic absorption in the rabbit eye. For example, distinguish between topical and systemic absorption, 0.5% dexamethasone-CD eye drops were applied to one of the rabbit eyes and not to the contralateral eye (control). The investigators concluded that after topical application, while absorption is greater in the anterior segment, a significant amount of drug reaches posterior segment tissue, like retina and vitreous humor.

Singh et al.[39] filed a patent on an ophthalmic formulation containing an antibiotic drug: linezolid using a CD as a solubilizer. A preservative-free solution containing 5% of linezolid was prepared and compared with a suspension composed of 5% linezolid, 4% sodium citrate, 1% soya lecithin and 0.1% povidone. Both the above formulations were administered to rabbit eyes to assess the concentration of linezolid in the lachrymal fluid, cornea and conjunctiva 1 h after application. Histological analysis and lachrymal fluid analysis showed that higher levels of linezolid absorption in the ocular tissues were achieved with the solubilized formulation than with the suspension.

In a recent reported patent, Loftsson and Stefansson,[40] developed an aqueous suspension which is comprising a therapeutic agent, a CD and water. This drug delivery system was suitable for the treatment of both posterior and anterior segment conditions. The particles in suspension were able to dissolve in tears within 24 h, being in the range of 10 nm to 1 mm. For example a comparison between dexamethasone formulated in a methylated β-CD solution and a γ-CD suspension. Analysis of the rabbit's ocular tissues showed that drug concentrations from the suspension group were higher in the sclera and optic nerve than those from the solution group, while drug delivery into the cornea, aqueous humor, iris-ciliary body, and lens was more efficient from the solution than from the suspension.[80]

More recently, Ito et al.[41] investigated the effect of disulfiram solution containing 2-hydroxypropyl-β-CD (2 HP-β-CD) and hydroxypropylmethylcellulose (HPMC) on intraocular pressure (IOP) in experimentally induced ocular hypertension in rabbits. They found that 2 HP-β-CD and HPMC increase the solubility of disulfiram and thereby improve its poor water solubility. They demonstrated that the instillation of disulfiram eye drops had an IOP-reducing effect in rabbits with experimentally induced hypertension, probably due to suppression of nitric oxide production.[81]

**Penetration enhancers:**

Another idea which is very helpful in improving drug permeability through corneal epithelial membrane consists with the use of penetration enhancers (also called absorption promoters or accelerants) which penetrates into the cornea to decrease barrier resistance. Penetration enhancers transiently increase the permeability characteristics of the ocular tissues.[59]

Most agents are surfactants which can changes the physical properties of cell membranes, e.g. by removal of phospholipids or membrane solubilization, whereas EDTA loosens the tight junctions between the superficial epithelial cells, facilitating paracellular transport. Sasaki et al. demonstrated that EDTA, taurocholic acid and capric acid significantly increased the corneal permeability of hydrophilic β-blocking agents in rabbits, without local toxicity. Only with saponin was a slight irritation observed after instillation. However, further investigations of the in vivo penetration behavior of β blockers are necessary and a safety assessment of absorption promoters is required before their use in clinical trials.[42] Furthermore, the addition of a penetration enhancer to the vehicle of an ophthalmic solution makes it possible to reduce the size of the drop and so that it provide a better ocular absorption of poorly absorbed drugs, increasing bioavailability, provided the penetration enhancer does not induce local irritation and/or is not cytotoxic to the ocular tissues.

In fact, the nature of the corneal conjunctival tissues possesses great caution in the selection of enhancers because they can penetrate into the eye and therefore lead to unknown toxicological complications.[58] EDTA was found to reach the iris-ciliary body in concentrations high enough to alter the permeability of the blood vessels in the uveal tract, indirectly accelerating drug removal from the aqueous humor.[43] Bile salts and surfactants reported that it causes irritation of the eye mucosa.[35] Therefore, these penetration enhancers offers various advantages for improvement of bioavailability, they may be responsible for tissue irritation and damage.

**Mucoadhesive polymers:**

These mucoadhesive polymers are used most of the times in various ophthalmic drug delivery systems and it is given following.[44,45,45,46,47,48,49]

**A) Polyacrylic acid:**

**a) Corbopol:** Cross linked polymer like polyacrylic acid is having excellent mucoadhesive properties which is very helpful in significant increase in ocular bioavailability. Carbopol

934 P is high cross linked water swellable acrylic polymer which having molecular weight approximately 3000000 Dalton and it is very useful in pharmaceutical industry.[75] Park Robinson and Ponchel et al. reported that poly acrylic acid react with functional group of mucus glycol protein by carboxylic group. As earliar mention that precorneal residence of carbopol solution found to be greater than that of PVA solution.[50,51]

Saettone et al. carried out much experiment with pilocarpine, the poly acrylic acid (5%w/v) carbopol 941P form a stable precorneal film and with less solubility.[52] Weinreh et al. found that suspension beta hexabol base on the poly acrylic acid provided a more constant release of betaxol that its solution.[53] Thermos et al. evaluated ocular bioavailibity of timolol in isoviscous solution of PVA (PAA and timolol PAA salt). The result suggested that PAA polymer produce lower ocular concentration in comparison of PVA resulting slower the release of timolol and longer retention of vehicle in cunjuctivital sac by mucoadhesion.

The use of carpool in ocular drug delivery having following advantages and disadvantages and it is given following.

Gel prepared for ophthalmic administration using carbopol are more comfortable than solution, or soluble inserts though they are instilled like ointment less blurring of vision occurred as compare to ointment. However, demerits are no rate control on drug instability which resulting to matted lids.[54]

**b) Polycarbophil:** Polycarbophil is cross linked poly acrylic acid polymer which is insoluble in water but it swells and can hold large quantity of water. Carbophil cross linked with divinyl glycol that give good bioadhesion in comparison to conventional non bioadhesive suspension.[55]

**B) Carboxymethyl cellulose:** Sodium CMC is having excellent mucoadhesive properties. Ophthalmic gel formulation using NaCMC, PVP and corbopol on the in-vivo studies on the gel showed diffusion coefficient in corbopol 940 1%> NaCMC 3%> PVP 23%. Recent research reported that adhesive strength increases as molecular weight increases up to 100000 Da.[56,57]

## CONCLUSION

The eye is one of the most complex and unique organs in the human body as previously mentioned in this review.

Many successes has been made to anterior DDSs for prolonging retention time and reducing dosing frequency. There should be an additional needs in this field might be to improve patient's and doctor's compliance.

On the other hand, many implantable sustained and controlled DDSs for chronic vitreoretinal diseases in which using biodegradable or non-biodegradable polymers, are being developed. So to minimize side-effects during long-term drug use, a beneficial posterior drug delivery strategies, which results to external environment changes and/or disease-oriented pathophysiological signals, are needed. Due to transparent ocular mechanism, intraocular tissues (vitreous and retina) are relatively easy to be observed without invasion, and there are a no. of administration approaches for delivery including intravitreal or subretinal injection/implantation could be developed. In addition to Lucentis® (monoclonal antibodies), as already known that the eye-ball is a closed organ, a newer therapeutic molecules such as an antisense oligonucleotide for cytomegalovirus retinitis, an aptamer or a small interfering RNA for neovascular AMD, have been identified in human eye before their applications for systemic diseases. So there are more challenging approaches might be applicable in the ophthalmic field. In fact, we should further consider the most efficacious combinations of optimal drugs, dose, route, and drug release pattern (sustained-release, pulsatile-release, or controlled-release responding to a trigger) according to the pathophysiology and progressive courses of the targeted disease.

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