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RESEARCH ARTICLE

RETINAL DRUG DELIVERY SYSTEM: CHALLENGES AND APPROACHES

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ABSTRACT

The scientists have faced major challenges in Ocular drug delivery system because of the unique anatomy and physiology of eye. In treating anterior segment diseases topical eye drop is the most convenient and patient compliant route of drug administration. There are two types of barriers in ocular drug delivery system: static and dynamic barrier. Static barrier includes cornea, sclera, retina and blood- retinal barriers while dynamic barrier includes choroidal and conjunctival blood flow, tear dilution and lymphatic clearance. These barriers influence the bioavailability of drugs. Current article reviews the manacles in conventional ocular therapy, indispensable factors in ocular pharmacokinetics. It also describes a variety of approaches such as eye ointments, gel, prodrug, intravitreal injections, viscosity enhancers, penetration enhancers, liposomes, microparticles, niosomes, ocular inserts, implants, nanoparticles, nanosuspension, microemulsion, in situ-forming gel, iontophoresis, and periocular injections to increase the ocular bioavailability of drug and provide controlled and continous release of the drug to the anterior and posterior chamber of the eye.

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INTRODUCTION

Ophthalmic drug delivery system is most interesting and challenging endeavors faced by the pharmaceutical scientist. The biochemistry, anatomy and physiology of the eye render this organ highly impermeable to foreign substances. Ophthalmic drug delivery system can be classified in to two segments such as anterior segment and posterior segment. Conventional systems like eye drops, ointments and suspensions cannot be measured in the treatment of vision threatening ocular diseases. 90% formulations are present in the form of eye drops. Eye drops are mainly used for the treatment of anterior segment of the eye. Topical medications do not cross the anterior segment of the eye. Posterior segment (retina, vitreous and choroid) is treated with high quantity of drug given intravenously or intravitreally or implants or by periocular injections. The goal of pharmacotherapeutics is to treat a disease in a consistent fashion. A major challenge is to circumvent protective barrier of the eye without causing tissue damage. Pharmacological actions depend on the drug concentration.

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The goal of therapeutic system is to achieve maximum concentration of drug at the active site in appropriate time period. Ocular drug disposition and elimination depends on the physicochemical property of the drug as well as ocular anatomy and physiology. The active site for the antibiotics, antiviral, and steroids are the infected and inflamed area in the anterior and posterior segment of the eye represent in figure 1. The need of the drug entities treatment to various site with globe (Patel P.B, 2011).

Common Eye Infections: The most common causative pathogens for eye infections are Bacterias. In addition, virus, fungus and protozoan also cause eye infections. Eyes are prone to a large number of diseases but more commonly found diseases are:

- Conjunctivitis.
- Blepharitis.
- Cataract.
- Keratitis.
- Glaucoma.
- Iritis (anterior uveitis) (Kumar K, 2013).

Physiological Considerations: The amount of absorption of an ophthalmic drug is severely limited by physiological constraints.

Along with the factors that bound ocular absorption of the impermeable corneal barrier. The cornea mainly consists of three membranes: epithelium, endothelium, and inner stroma which are the main absorptive barriers for ion transport process. The tight junctions of the corneal epithelium serve as a selective barrier for small molecule and stop the diffusion of macromolecules during the paracellular route. The stroma under the epithelium is a very hydrophilic layer making up 90% of the cornea. The corneal endothelium is responsible for maintaining normal corneal hydration. Obviously then, the more lipophilic drug is, the more resistance they will find crossing the stroma, the extra hydrophilic is the drug. These are the various physicochemical properties of the drug such as solubility, lipophilicity, molecular size and shape, charge and degree of ionization change the route and rate of permeation through the corneal membrane (Sampath K, 2012).

Pharmacokinetic considerations

These are main route for drug administration and elimination from the eye. The following various processes such as:

- Transcorneal penetration from the lachrymal fluid in to the anterior chamber.
- Noncorneal drug penetration across the conjunctiva and sclera in to the anterior uvea.
- Drug delivery from the blood stream through blood-aqueous barrier in to the anterior chamber.
- Removal of drug from the anterior chamber by the aqueous humor turnover to the trabecular meshwork and sclemm's canal.
- Drug removal from the aqueous humor into the systemic circulation across the blood-aqueous barrier.
- Drug delivery from the blood in to the posterior eye across the blood-retinal barrier.
- Intravitreal drug administration.
- Drug removal from the vitreous via posterior route across the blood-retina barrier.
- Drug removal from the vitreous via anterior route to the posterior chamber (Marmor M.F, 1985).

When the ophthalmic drug is applied topically it first gets mixed with lachrymal fluid. As the lachrymal fluid is produced continuously (0.5-2.2/~l/min), the contact time of the drug is short (1-2 min). Then, approximately half of the drug flows through the upper canaliculus and the other half, through the lower canaliculus into the lacrimal sac, which opens into the nasolachrymal duct. Drainage of lacrymal fluid during blinking (every 12s) towards the nasolachrymal duct induces a rapid elimination of conventional dosage forms. The drug is absorbed into the retina-choroid via an extracorneal or sclero-conjunctival route; the iris and ciliary body are presumably supplied via both the transcorneal and the extracorneal pathways (Bourlasis L, 1998).

Challenges in ophthalmic drug delivery system: The exact challenge of designing a therapeutic system is to achieve an optimal concentration of a drug at the active site for the suitable time to provide ocular delivery systems with high therapeutic efficacy. The anatomy, physiology, and barrier function of the cornea give and take the fast absorption of the drugs. Regular instillations of the eye drops are required to uphold a therapeutic drug level in the tear film or at the site of action.

Regular use of highly concentrated solutions may induce toxic side effects and cellular harm at the ocular surface. Poor bioavailability of the drug in ocular delivery system is mainly due to the precorneal defeat factors which include solution drainage, tear dynamics, lacrimation, tear turnover, tear dilution, conjunctival absorption, and transient residence time. The relative impermeability of the corneal epithelial membrane is the major challenges to anterior segment drug delivery following topical administration. These are the suitable constraints, used a minute fraction of the drug, effectively 1% or less of the instilled dose, and are ocularly absorbed. These are clinically successful; the topical formulation is maintaining the balance between lipophilicity and hydrophilicity with higher contact time (Patel P. B, 2011).

Anterior segment drug delivery challenges: For ailments of the eye, topical administration is usually chosen over systemic administration. Because when drug administered by ocular route, it has to cross the precorneal barrier before it reaches the anatomical barrier of the cornea. These are first barrier that slow the diffusion of an active constituent into the eye and consist of the tear film and the conjunctiva. Poor bioavailability of drugs from ocular dosage forms is mainly due to the precorneal defeat factors. Furthermore, frequent instillations of eye drops are essential to uphold a therapeutic drug level in the tear film or at the site of action. But the common use of highly concentrated solution may induce toxic side effects and cellular damage at the ocular surface (Steinfeld A, 2004).

Posterior segment drug delivery challenges: Topical ocular medications do not achieve the posterior segment drug targets because of the high efficiency of the blood-retinal barrier (BRB). The release of drugs to the posterior segment of ocular tissue is prohibited by the same factors that are responsible for the poor ocular bioavailability. In addition, the blood-retinal barrier bound the efficacy of the intravenous route in posterior drug delivery. The fixed junctions of the blood-retinal barrier restrict the entry of systemically administered drugs in to the retina. A high vitreal drug concentration is required in the treatment of posterior segment diseases. Blood-retinal barrier is selectively porous to extra lipophilic molecules mainly governs the entry of drug molecules into posterior segment of the eye. Frequently administration of drug leads to systemic side effect. Another challenge for posterior segment is to uphold the therapeutic drug concentration over prolonged periods and reduce the number of injections. Drug is eliminated via the anterior route, that is, to the aqueous humor then eliminated by the loss of the humor in the anterior chamber angle. Many drugs are also eliminated via posterior route through the blood-retinal barrier to the systemic circulation (Myles M. E, 2005).

Ideal characteristics of ophthalmic drug delivery system

These are the various ideal characteristics of ophthalmic drug delivery system such as

- Good corneal permeation
- Maximum ocular drug absorption through prolong contact time with corneal tissue.
- Simple instillation for the patient.
- Minimize the frequency of drug administration.
- Improve patient compliance.
- Decreases the toxicity and side effect.

- Reduce the pre corneal drug loss.
- Should not cause blurred vision.
- Relatively nongreasy.
- Appropriate rheological properties and concentrations of the viscous system (Gadbey R. E, 1979).

Approaches in ophthalmic drug delivery system: The approaches attempted in the early stages can be divided into two main categories: the first one is the bioavailability enhancement and second is the controlled release drug delivery. These approaches can be used to enhance the bioavailability. The duration of therapeutic effect of ocular drug can be divided into two categories: The first one is based on maximizing corneal drug absorption and reduces the precorneal drug loss through viscosity and penetration enhancers, prodrug, gel, and liposome. The second one is based on the use of sustained drug delivery system which provides the controlled and regular delivery of ophthalmic drug, such as inserts, nanoparticles, micro particulate implants, and colloid. Conventional approaches like viscosity enhancer, gel, diffusion enhancer, prodrug, and liposome enhance the ophthalmic bioavailability of the drugs to the anterior segment of the eye. Various current approaches like in situ gel and implants enhance the ophthalmic bioavailability of the drug and controlled the release of the ophthalmic drugs to the anterior segment of the eye. Furthermore; approaches like intravitreal injections, iontophoresis, subconjunctival injections, and periocular route are used to deliver ophthalmic drugs to the posterior segment of the eye (Patel P.B, 2011).

Approaches to improve ocular bioavailability

Eye ointments: These are usually ready by using a mixture of semisolid and solid hydrocarbons (paraffin) which have a melting and softening point near body temperature and are nonirritating to the eye. Ointment may be simple bases, where the ointment forms one is the continous phase, or mix bases where a two phase system such as emulsion. The medicinal substance is added in the base in the form of solution or as a finely micronized powder. Ointments break up in to minute droplets and remain as a depot of the drug for complete periods. These are useful in enhance drug bioavailability and in sustaining drug release. Ointment are safe and well-tolerated by the eye, ointment suffer with comparatively reduced patient compliance due to blurring of vision and irritation (Raghava S, 2004 and Ashaben P, 2013). The batter bioavailability of drugs from ointment bases is because of several factors likes: (i) higher effective concentration (ii) inhibition of dilution by the tears (iii) increased tissue contact time and resistance to nasolachrymal drainage (Shell J, 1984).

Gel: This formulation is a case of viscosity improvement through the use of viscosity enhancers which lead to slight prolonged precorneal residence time. Gel based system has reduced systemic exposure. Due to high viscosity, gel attains an enhancement in bioavailability, and the dosing frequency can be reducing to once a day. High viscosity gel while, result is blurred and matted eyelids, which significantly decreases the patient acceptability. Aqueous gel naturally utilizes such polymer as polyvinylalcohal (PVA), polyacrylamide, poloxamer, HPMC, carbomer, poly methylvinylethermaleic anhydride, and hydroxypropyl ethyl cellulose. Swellable water insoluble polymers, called hydrogel or polymer having irregular characteristics of swelling in aqueous medium provide controlled drug delivery systems. The discharge of drug from these systems occur using transport of the solvent into the polymer matrix most important to its swelling. The final step involves the dispersion of the solute during the swollen polymer, leading to dissolution (Ali M, 2017).

Penetration enhancers: The transfer individuality across the cornea can be maximized by raising the permeability of the corneal epithelial membrane. The stratified corneal epithelial cell layer is a tight ion transporting tissue. One of the approaches used to develop ophthalmic drug bioavailability lies in raising rapidly the permeability characteristics of the cornea with suitable substances known as penetration enhancers or absorption promoters. These are disadvantages like ocular irritation and toxicity. The transport of drug from cornea to receptor site is a rate-limiting step. The penetration enhancer increases the corneal uptake by changing the integrity of the corneal epithelium. Addition of these agents such as cetyloyridinium chloride, benzalkonium chloride, ionophore (Such as lasalocid), Tween 20, Parabens, saponins, brij 35, brij 78, brij 98, ethylenediaminetetraacetic acid, bile salt, and bile acids (Such as sodium cholate, taurocholic acid), capric acid, fusidic acid, azone, saponins, hexamethylene octanamide, and decylmethyl sulfoxide in different formulation have shown a significant improvement in corneal drug absorption (Gadbey R.E, 1979).

Prodrug

Prodrug is to improve corneal drug permeability through change the hydrophilicity and lipophilicity characteristic of the drug. Within the cornea or after corneal penetration, the prodrug is either chemically or enzymatically metabolized to the active substances. Therefore, ideal prodrug should not only have improved lipophilicity and a high partition coefficient, but it must also have high enzyme susceptibility. Enzyme systems recognized in ocular tissues include esterase, ketone reductase, and steroid 6-hydroxylase. Prodrug is considered as a new drug entity; so broad pharmacokinetic and pharmacologic information is required for proper design. Some suitable examples of prodrug include the antiviral medications ganciclovir and acyclovir. An acyl ester prodrug formulation of ganciclovir, a drug with a comparatively low partition coefficient, significantly increased the amount of drug that can penetrate the cornea. Enhance the permeability was linearly linked with improved susceptibility of the ganciclovir esters to undergo hydrolysis by esterase in the cornea (Sultana Y, 2006).

Viscosity enhancers: Viscosity enhancer polymers is usually added in ophthalmic drug solutions on the principle that an increased vehicle viscosity. Should correspond to a slower removal from the preocular area, which lead to enhanced precorneal residence time, and hence a greater transcorneal diffusion of the drug into the anterior segment of the eye. It has minimum effect in terms of enhancement in bioavailability. Polymers used include polyvinyl alcohol (PVA), polyvinylpyrrolidone (PVP), methylcellulose, hydroxyethylcellulose, hydroxypropyl methylcellulose (HPMC) and hydroxypropylcellulose. PVA was more effective. This is because of its adhesive properties and its capability to enhance the thickness of the precorneal tear film. Indicated that the retention of drug in the precorneal tear film is not strictly linked to the viscosity of the vehicle, and the capability of a polymer to drug water as the vehicle spreads over the ocular surface with each bink (Gadbey R.E, 1979).

Table 1. Available ocular product

Sr. No.	Dosage Form	Active Pharmaceutical Ingredient	Company Name
1.	Eye Drop	Fluorometholone and Neomycin Sulphate	Cipla
2.	Eye Ointment	Ciprofloxacin	FDC
3.	Eye Gel	Dexpanthenolum	Bausch & Lomb

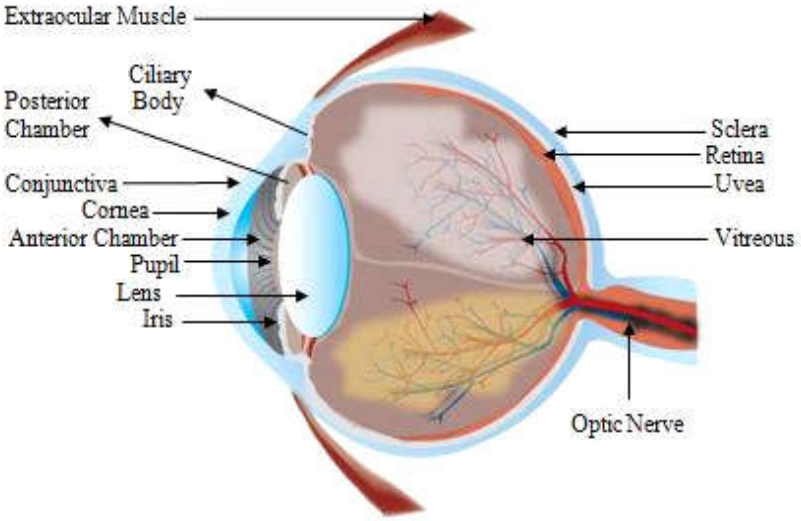

Figure 1. Schematic presentation of the ocular structure with the routes of drug kinetics illustrated

Liposomes: These are microscopic vesicles composed of one or more concentric lipid bilayers, separated by water or aqueous buffer compartments. These are posses the ability to have an intimate contact with the corneal conjunctival surfaces, which improve the probability of ocular drug absorption. The ability is particularly desirable for drugs that are poorly absorbed, the drugs with low partition coefficient, low solubility, or those with medium to high molecular weights. Positively charged liposomes appear to be preferentially captured at the negatively charged corneal surface as compared with neutral or negatively charged liposomes. These are biodegradable and biocompatible in nature. It reduced the drug toxicity, and provides the sustained release and site specific delivery. These are difficult to manufacture in sterile preparation. It is limitation like drug load and inadequate aqueous stability (Peyman G.A, 1995).

Niosomes: These are bilayered vesicles made up of nonionic surfactant. Which are capable of encapsulating both lipophilic and hydrophilic substances. Niosomes reduced the systemic drainage and improve the residence time, which lead to enhance the ocular bioavailability. These are nonbiocompatiable and nonbiodegradable in nature. These are used to deliver cyclopentolate, niosomal formulation was developed. It releases the drug independent of pH, resulting significant improvement of ocular bioavailability. Niosomal formulation coated with carbopol and chitosan polymer (Peyman G.A, 1995).

Nanosuspension: This is defined as sub-micron colloidal systems which consist of poorly water-soluble drug, suspended in an appropriate dispersion medium stabilized with surfactants. These are usually consists of colloidal carriers like polymeric resins which are inert in nature. These are improving the ocular bioavailability of the drug by increase the residence time. Charge on the surface of nanoparticles facilitates adhesion to the cornea (Leucuta S.E, 1989). Nanosuspension technology can be better utilized for drug compounds with high energy content, which rather them insoluble in either organic (lipophilic) or hydrophilic media. Since these carriers do not irritate cornea, iris or conjunctiva, they act as an inert carrier for ophthalmic drugs (Harikumar S, 2011).

Microemulsion: This is stable dispersions of water and oil facilitated by a combination of surfactant and co-surfactant in a way to decrease interfacial tension. Microemulsion enhances the ocular bioavailability of the drug and reduced frequency of the administration. This system is usually characterized by higher thermodynamic stability, small droplets size (100 nm), and clear appearance. Oil and water system consisting of pilocarpine drug using lecithin, propylene glycol (surfactant), PEG 200 (co-surfactant), and isopropyl myristate as the oil phase has been designed. It is nonirritating to the eye. Such some formulations provide sustained drug release, thereby reducing the frequency of drug administration (Leucuta S.E, 1989).

Nanoparticles / Nanospheres: Nanospheres are providing colloidal particles, ranging from 10 nm to 1 mm, in which the drug is dissolved, entrapped, adsorbed or encapsulated. Encapsulated drug leads to stabilization of the drug. Nanospheres are used as drug carriers for ophthalmic application. These are further classified into nanospheres (small capsules with a central cavity surrounded by a polymeric membrane) or nanocapsules (solid metrical spheres). Nanocapsules show a better effect then the nanospheres, nanocapsule is due to their bioadhesive properties, resulting in enhancing the residence time and biological response. It enhances the ocular bioavailability of the drug and reducing dosing frequency (Peyman G.A, 1995).

In Situ-Forming gel: A droppable gel is present in liquid form and they involve phase transition process in to the form a viscoelastic gel, and this provides environmental changes.

It improves the patient acceptance. It prolongs the residence time and improves the ocular bioavailability of the drug. Parameters that can change and trigger the phase transition of droppable gel include pH, temperature, and ionic strength (Ali M, 2017).

Approaches to provide controlled and continous ocular drug delivery microparticles: These are drug-containing, micron-sized polymeric particles suspended in a liquid medium. Drug can be dispersed in the polymer matrix or covalently bound to the polymer backbone. Ahead topical instillation, the particles exist in the ocular drug delivery system. And discharge the drug from the particles through distribution, chemical reaction and/or polymer degradation. Microparticles enhance the precorneal residence time, which leads to continous and sustained release of the drug. Hence, enhance the ocular bioavailability of the drug and reduced the dosing frequency. Biodegradation, bioadhesion, and biocompatibility are preferred properties for the manufacture of polymers using ophthalmic microparticles. The following example, such as

- Microspheres of methylprednisolone chemically linked to hyaluronate esters.
- Pilocarpine-loaded albumin or gelatin microspheres.
- Acyclovir-loaded with chitosan microspheres (Peyman G.A, 1995).

Implants: The objective of the intraocular implant design is to give prolong action with sustained drug delivery system from the polymeric implant material. Intraocular implant is required in minor surgery. In general, they are placed intravitreally in the eye. The implants have the benefit of (i) Cross the blood ocular barriers to deliver constant therapeutic levels of the drug. (ii) Minimize the side effects associated with frequent systemic and intravitreal injection. (iii) Required small quantity of drug during the treatment. Ocular implants are classified as nonbiodegradable and biodegradable devices. Nonbiodegradable implants provide accurate control of drug release and long duration of release then the biodegradable polymers (Anita K, 2010).

Ocular inserts: Ocular inserts provide more controlled, sustained, and continous drug delivery by maintaining an effective drug concentration in the target tissues. It decreases the systemic absorption of the drug. It causes accurate dosing of the drug. A number of ocular inserts were equipped using various techniques to make soluble, hydrogel, nonerodible, and erodible inserts (Anita K, 2010).

Approaches to posterior segment drug delivery

Iontophoresis: Ocular iontophoresis has gained significant interest because of its non-invasive nature of delivery to both anterior and posterior segment of the eye. This is a noninvasive method of transfer the ionized drug through membranes. The drugs are moved across the membranes by two mechanisms: migration and electro-osmosis (Sultana Y, 2006).

Periocular route: Periocular route is the most important route for administering drugs to posterior eye segment. Periocular is the region near the eyes. Drug solutions are applied in close proximity to the sclera, which result in high retinal, vitreal concentrations. These are advantages like increase the drug absorption over systemically and topically delivered agents. This delivery is safe to the posterior segment of the eye ball, then the systemic administration (no systemic toxicity), drug delivery to the target site of the eye. Injection show first order kinetics (rapidly increase the drug level may cause the drug toxicity) (Sultana Y, 2006).

Intravitreal injections: In this method, the injection of drug solution is directly injected into vitreous through pars plana utilizing a 30G needle which increases the drug absorption over topically and systemically delivered agents. This process is use to targeted drug delivery system. It has more safety drug delivery to the posterior segment to the eye then systemic administration (no systemic toxicity). Different other routes, intravitreal injection give high drug concentrations in vitreous and retina. Elimination of drug depends on its molecular weight. Intravitreal injection produces high drug concentrations in retina. Furthermore patients require to be carefully monitored in intravitreal injections. These are disadvantages like injection show first order kinetic (rapidly increase the drug level may cause the drug toxicity) (Sultana Y, 2006).

Future Aspects: In future, a lot of the emphasis will be given to attain noninvasive sustained drug release for eye disorders in both segments. An ideal system is supposed to attain an effective drug concentration at the target tissue for an extended period of time, while reducing the systemic exposure. In addition, the system should be both easy to use and comfortable. Patient acceptance will continue to be an important factor in designing future ophthalmic drug delivery systems. A reasonable approach to avoid the drawbacks of individual technologies is to combine the technologies. The reported examples include liposomes and nanoparticles coated with bioadhesive polymers and liposomes and nanoparticles in droppable gels.

The future challenges which could be faced by topical ocular drug delivery systems are as follows:

- The ocular bioavailability must be enhanced from less than 1% to 15–20%.
- Most of the currently marketed ocular drugs were initially developed for non ocular applications, resulting in no specificity. So, it is required to develop new drug candidates for ocular use.
- Suitable design and packaging of these delivery systems needs further research.

There are several scientific and technological advances that are driving the progress in this field. Especially the advances in nanotechnology and biomaterials science may present new smart technologies to enhance ophthalmic drug delivery (Joshi A, 1994). These are the various ocular products available in the market represent in table 1.

Conclusion

The extensive work has been done in ocular drug delivery system. It has been intended, to extend the residence time of topically applied drugs in the corneal and conjunctiva section. Some new approaches such as liposome, nanoparticles, collagen shield, ocular inserts, in situ activated gel formation, non corneal route of ocular drug diffusion, and nanoparticles-based polymeric solutions and gels are being developed by the pharmaceutical science to increase the residence time of the drugs. Patient acceptance is very important for the design of

any comfortable ophthalmic drug delivery system. Major Improvements are required in each system like improvement in sustained drug release, large scale manufacturing and stability.

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