

Ophthalmic Drug Delivery System: Challenges and Approaches

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ABSTRACT

Promising management of eye ailments take off effective concentration of drug at the eye for sufficient period of time. Ocular drug delivery is hampered by the barriers protecting the eye. The bioavailability of the active drug substance is often the major hurdle to overcome. Conventional ocular dosage form, including eye drops, are no longer sufficient to combat ocular diseases. This article reviews the constraints with conventional ocular therapy, essential factors in ocular pharmacokinetics, and explores various approaches like eye ointments, gel, viscosity enhancers, prodrug, penetration enhancers, microparticles, liposomes, niosomes, ocular inserts, implants, intravitreal injections, nanoparticles, nanosuspension, microemulsion, *in situ*-forming gel, iontophoresis, and periocular injections to improve the ocular bioavailability of drug and provide continuous and controlled release of the drug to the anterior and posterior chamber of the eye and selected pharmacological future challenges in ophthalmology. In near future, a great deal of attention will be paid to develop noninvasive sustained drug release for both anterior and posterior segment eye disorders. Current momentum in the invention of new drug delivery systems hold a promise toward much improved therapies for the treatment of vision-threatening disorders.

Introduction

Ophthalmic drug delivery is one of the most interesting and challenging endeavors facing the pharmaceutical scientist. The anatomy, physiology, and biochemistry of the eye render this organ highly impervious to foreign substances. Drug delivery to the eye can be broadly classified into anterior and posterior segments [Figure 1]. Conventional systems like eye drops, suspensions, and ointments cannot be considered optimal in the treatment of vision-threatening ocular diseases.^[1] However, more than 90% of the marketed ophthalmic formulations are in the form of eye drops. These formulations mainly target the diseases in the anterior segment

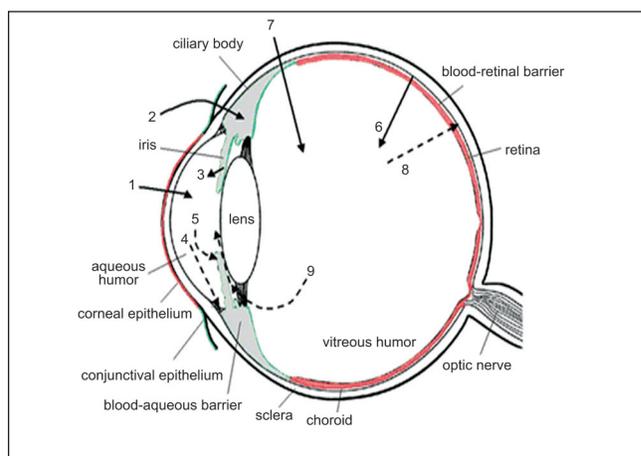


Figure 1: Schematic presentation of the ocular structure with the routes of drug kinetics illustrated^[4]

of eye.^[2] Topical ocular medications do not reach the posterior segment of the eye. Posterior segment (retina, vitreous, choroid) can be treated by high drug dosage regimen given intravenously or by intravitreal administration or implants or by periocular injections. Currently, the posterior segment drug delivery is a rapidly growing interest area in ophthalmic drug delivery.^[3]

The goal of pharmacotherapeutics is to treat a disease in a consistent and predictable fashion. A significant challenge to the

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formulator is to circumvent the protective barriers of the eye without causing permanent tissue damage. Development of newer, more sensitive diagnostic techniques and novel therapeutic agents continue to provide ocular delivery systems with high therapeutic efficacy. An assumption is made that a correlation exists between the concentration of a drug at its intended site of action and the resulting pharmacological effect. The specific aim of designing a therapeutic system is to achieve an optimal concentration of a drug at the active site for the appropriate duration. Ocular disposition and elimination of a therapeutic agent is dependent upon its physicochemical properties as well as the relevant ocular anatomy and physiology. A successful design of a drug delivery system, therefore, requires an integrated knowledge of the drug molecule and the constraints offered by the ocular route of administration. The active sites for the antibiotics, antiviral, and steroids are the infected or inflamed areas within the anterior as well as the posterior segments of the eye. A host of different tissues are involved, each of which may pose its own challenge to the formulator of ophthalmic delivery systems. Hence, the drug entities need to be targeted to many sites within the globe.

Physiological considerations

The extent of absorption of an ophthalmic drug is severely limited by physiological constraints. Among the factors that limit ocular absorption is the relatively impermeable corneal barrier. The cornea consists of three membranes: the epithelium, the endothelium, and inner stroma which are the main absorptive barriers. The epithelium facing the tears with lipophilic cellular layers acts as a barrier to ion transport. The tight junctions of the corneal epithelium serve as a selective barrier for small molecules and prevent the diffusion of macromolecules through the paracellular route. The stroma beneath the epithelium is a highly hydrophilic layer making up 90% of the cornea. The corneal endothelium is responsible for maintaining normal corneal hydration. Clearly then, the more lipophilic the drugs are, the more resistance they will find crossing the stroma. The more hydrophilic is the drug, the more resistant the epithelium; though the stroma and endothelium are limited in their resistance.

Physicochemical drug properties, such as lipophilicity, solubility, molecular size and shape, charge and degree of ionization affect the route and rate of permeation through the corneal membrane in the cul-de-sac.

Pharmacokinetic considerations

The main routes of drug administration and elimination from the eye have been shown schematically in Figures 1 and 2.

The numbers refer to following processes:^[4]

1. Transcorneal permeation from the lachrymal fluid into the anterior chamber,
2. Noncorneal drug permeation across the conjunctiva and sclera into the anterior uvea,
3. Drug distribution from the blood stream through blood-aqueous barrier into the anterior chamber,
4. Elimination of drug from the anterior chamber by the aqueous humor turnover to the trabecular meshwork and Schlemm's canal,
5. Drug elimination from the aqueous humor into the systemic circulation across the blood-aqueous barrier,
6. Drug distribution from the blood into the posterior eye across

7. the blood-retina barrier,
8. Intravitreal drug administration,
9. Drug elimination from the vitreous via posterior route across the blood-retina barrier, and
10. Drug elimination from the vitreous via anterior route to the posterior chamber.

Challenges in ophthalmic drug delivery system

The specific challenge of designing a therapeutic system is to achieve an optimal concentration of a drug at the active site for the appropriate duration to provide ocular delivery systems with high therapeutic efficacy. The anatomy, physiology, and barrier function of the cornea compromise the rapid absorption of drugs. Frequent instillations of eye drops are necessary to maintain a therapeutic drug level in the tear film or at the site of action. But the frequent use of highly concentrated solutions may induce toxic side effects and cellular damage at the ocular surface.

Poor bioavailability of drugs from ocular dosage forms is mainly due to the precorneal loss factors which include solution drainage, lacrimation, tear dynamics, tear dilution, tear turnover, conjunctival absorption, nonproductive absorption, transient residence time in the cul-de-sac, and the relative impermeability of the corneal epithelial membrane are the major challenges to anterior segment drug delivery following topical administration. Due to these physiological and anatomical constraints, only a small fraction of the drug, effectively 1% or even less of the instilled dose, is ocularly absorbed. To be clinically effective, topical formulation has to possess balance between lipophilicity and hydrophilicity with higher contact time.^[5]

Anterior segment delivery challenges

For ailments of the eye, topical administration is usually preferred over systemic administration, because before reaching the anatomical barrier of the cornea, any drug molecule administered by the ocular route has to cross the precorneal barriers. These are the first barriers that slow the penetration of an active ingredient 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 loss factors which are demonstrated in Figure 3

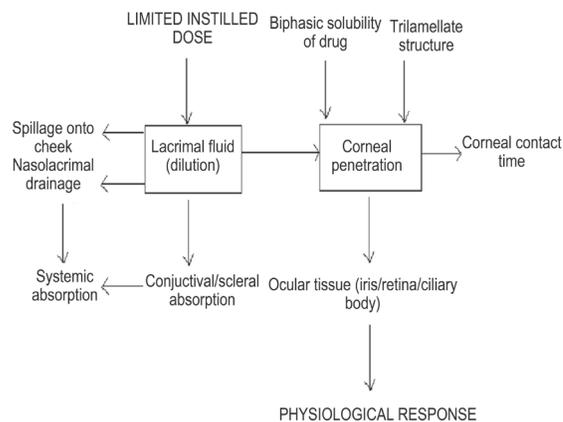


Figure 2: Flow chart of distribution of drug within ocular tissues after ophthalmic drug delivery

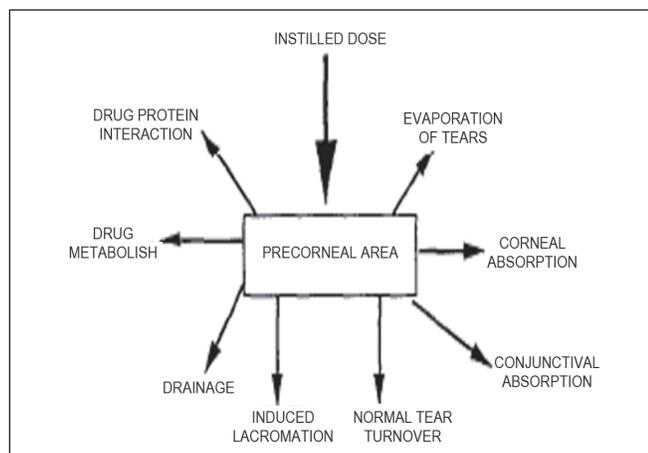


Figure 3: Precorneal factors that influence bioavailability of topically applied ophthalmic drugs

and Figure 4.

Moreover, frequent instillations of eye drops are necessary to maintain a therapeutic drug level in the tear film or at the site of action. But the frequent use of highly concentrated solutions may induce toxic side effects and cellular damage at the ocular surface.

Posterior segment delivery challenges

Topical ocular medications do not reach the posterior segment drug targets because of the high efficiency of the blood-retinal barrier (BRB). The delivery of drugs to the posterior segment of ocular tissue is prevented by the same factors that are responsible for the poor ocular bioavailability. In addition, the BRB limits the effectiveness of the intravenous route in posterior drug delivery.^[6]

The tight junctions of BRB restrict the entry of systemically administered drugs into the retina.^[7] High vitreal drug concentrations are required in the treatment of posterior segment diseases. BRB which is selectively permeable to more lipophilic molecules mainly governs the entry of drug molecules into posterior segment of the eye. This results in frequent administration of high amounts of drugs leading to systemic side effects.^[8]

Another challenge for posterior segment is to maintain the

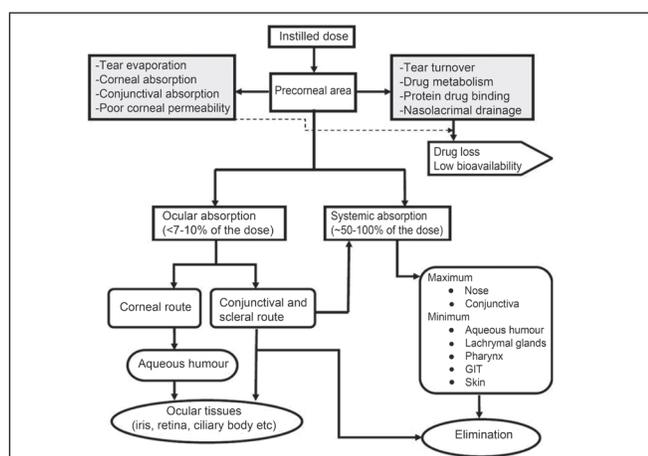


Figure 4: Fate of ophthalmic drug delivery system

therapeutic drug concentration over prolonged periods and minimize the number of injections. Drugs are eliminated via the anterior route, that is, to the aqueous humor and then eliminated by the outflow of the humor in the anterior chamber angle. Many drugs are also eliminated via posterior route through the blood-retina barrier to the systemic circulation.

Ideal characteristics of ophthalmic drug delivery system:^[9]

- Good corneal penetration.
- Maximizing ocular drug absorption through prolong contact time with corneal tissue.
- Simplicity of instillation for the patient.
- Reduced frequency of administration.
- Patient compliance.
- Lower toxicity and side effects.
- Minimize precorneal drug loss.
- Nonirritative and comfortable form (viscous solution should not provoke lachrymal secretion and reflex blinking).
- Should not cause blurred vision.
- Relatively nongreasy.
- Appropriate rheological properties and concentrations of the viscous system.

Approaches in ophthalmic drug delivery system

The various approaches attempted in the early stages can be divided into two main categories: bioavailability improvement and controlled release drug delivery. The various approaches that have been attempted to increase the bioavailability and the duration of the therapeutic action of ocular drugs can be divided into two categories. The first one is based on maximizing corneal drug absorption and minimizing precorneal drug loss through viscosity and penetration enhancers, prodrug, gel, and liposomes. The second one is based on the use of sustained drug delivery systems which provide the controlled and continuous delivery of ophthalmic drugs, such as implants, inserts, nanoparticles, micro particulates, and colloid.^[10]

Traditional approaches like viscosity enhancers, gel, penetration enhancer, prodrug, liposomes improve the ophthalmic bioavailability of the drugs to the anterior segment of the eye. Various modern approaches like *in situ* gel, ocuserts, nanosuspension, nanoparticles, liposomes, niosomes, and implants improve the ophthalmic bioavailability of the drugs and controlled the release of the ophthalmic drugs to the anterior segment of the eye.^[11]

Moreover, approaches like intravitreal injections, iontophoresis, subconjunctival injection, and periocular route are used to deliver ophthalmic drugs to the posterior segment of the eye.

Approaches to improve ocular bioavailability

Viscosity enhancers

Viscosity-increasing polymers are usually added to ophthalmic drug solutions on the premise that an increased vehicle viscosity should correspond to a slower elimination from the precorneal area, which lead to improved precorneal residence time and hence a greater transcorneal penetration of the drug into the anterior chamber. It has minimal effects in humans in terms of improvement

in bioavailability. The polymers used include polyvinyl alcohol (PVA), polyvinylpyrrolidone (PVP), methylcellulose, hydroxyethyl cellulose, hydroxypropyl methylcellulose (HPMC), and hydroxypropyl cellulose.^[12]

Saettone *et al.*^[12] found that among PVA, HPMC, and PVP used for solutions of tropicamide at concentrations yielding the same viscosity of 20 cst, PVA was more effective. This is because of its adhesive properties and its capability to increase the thickness of the precorneal tear film. Saettone *et al.*^[13] indicated that the retention of drug in the precorneal tear film is not strictly related to the viscosity of the vehicle, but rather to the surface spreading characteristics of the vehicle and to the ability of a polymer to drag water as the vehicle spreads over the ocular surface with each blink.

Eye ointments

Ointments are usually formulated using mixtures of semisolid and solid hydrocarbons (paraffin) which have a melting or softening point close to body temperature and are nonirritating to the eye. Ointments may be simple bases, where the ointment forms one continuous phase, or compound bases where a two-phased system (e.g., an emulsion) is employed. The medicinal agent is added to the base either as a solution or as a finely micronized powder. Upon instillation in the eye, ointments break up into small droplets and remain as a depot of drug in the cul-de-sac for extended periods. Ointments are therefore useful in improving drug bioavailability and in sustaining drug release. Although safe and well-tolerated by the eye, ointments suffer with relatively poor patient compliance due to blurring of vision and occasional irritation.^[14]

Gel

Gel formation is an extreme case of viscosity enhancement through the use of viscosity enhancers which leads to slight prolonged precorneal residence time. It has advantage like reduced systemic exposure. Despite the extremely high viscosity, gel achieves only a limited improvement in bioavailability, and the dosing frequency can be decreased to once a day at most. The high viscosity, however, results in blurred vision and matted eyelids, which substantially reduce patient acceptability.

The aqueous gel typically utilizes such polymers as PVA, polyacrylamide, poloxamer, HPMC, carbomer, poly methylvinylether-maleic anhydride, and hydroxypropyl ethylcellulose. Swellable water-insoluble polymers, called hydrogel, or polymers having peculiar characteristics of swelling in aqueous medium give controlled drug delivery systems. The release of a drug from these systems occurs via the transport of the solvent into the polymer matrix, leading to its swelling. The final step involves the diffusion of the solute through the swollen polymer, leading to erosion/dissolution. Poly (acrylic acid) hydrogel has been reported to augment significantly the ocular bioavailability of tropicamide in humans, with respect to both a viscous solution and a paraffin ointment.^[15]

Pilopine HS[®] gel, commercialized in 1986 by Alcon, and more recently Merck's Timoptic-XE[®].

Prodrug

The principle of prodrug is to enhance corneal drug permeability through modification of the hydrophilicity (or lipophilicity) of the drug. Within the cornea or after corneal penetration, the prodrug is either chemically or enzymatically metabolized to the active parent compound. Thus, the ideal prodrug should not only have increased lipophilicity and a high partition coefficient, but it must

also have high enzyme susceptibility.^[16] Enzyme systems identified in ocular tissues include esterases, ketone reductase, and steroid 6-hydroxylase.^[17,18] Prodrug is considered as a new drug entity; so, extensive pharmacokinetic and pharmacologic information is required for proper design.

Some examples of suitable prodrug include the antiviral medications ganciclovir and acyclovir. An acyl ester prodrug formulation of ganciclovir, a drug with a relatively low partition coefficient, substantially increased the amount of drug that can penetrate the cornea. This increased permeability was linearly correlated with increased susceptibility of the ganciclovir esters to undergo hydrolysis by esterases in the cornea.^[16]

Penetration enhancers

The transport characteristics across the cornea can be maximized by increasing the permeability of the corneal epithelial membrane.^[19,20] The stratified corneal epithelial cell layer is a 'tight' ion-transporting tissue, because of the high resistance of 12 to 16 kΩcm² being exhibited by the paracellular pathway. So, one of the approaches used to improve ophthalmic drug bioavailability lies in increasing transiently the permeability characteristics of the cornea with appropriate substances known as penetration enhancers or absorption promoters. It has disadvantages like ocular irritation and toxicity.

The transport process from the cornea to the receptor site is a rate-limiting step, and permeation enhancers increase corneal uptake by modifying the integrity of the corneal epithelium.^[21] Inclusion of these agents such as cetylpyridinium chloride,^[22] ionophore such as lasalocid,^[23] benzalkonium chloride,^[24] Parabens,^[20] Tween 20, saponins,^[25] Brij 35, Brij 78, Brij 98, ethylenediaminetetraacetic acid, bile salts,^[26] and bile acids (such as sodium cholate, sodium taurocholate, sodium glycodeoxycholate, sodium taurodeoxycholate, taurocholic acid, chenodeoxycholic acid, and ursodeoxycholic acid), capric acid, azone, fusidic acid, hexamethylene lauramide, saponins,^[27] hexamethylene octanamide, and decylmethyl sulfoxide^[28] in different formulations have shown a significant enhancement in corneal drug absorption.

Liposomes

Liposomes are the microscopic vesicles composed of one or more concentric lipid bilayers, separated by water or aqueous buffer compartments. Liposomes possess the ability to have an intimate contact with the corneal and conjunctival surfaces, which increases the probability of ocular drug absorption.^[29] This ability is especially desirable for drugs that are poorly absorbed, the drugs with low partition coefficient, poor solubility, or those with medium to high molecular weights.^[30] The behavior of liposomes as an ocular drug delivery system has been observed to be, in part, due to their surface charge. Positively charged liposomes seem to be preferentially captured at the negatively charged corneal surface as compared with neutral or negatively charged liposomes. It is droppable, biocompatible, and biodegradable in nature. It reduced the toxicity of the drug. It provides the sustained release and site-specific delivery. Liposomes are difficult to manufacture in sterile preparation. It has limitation like low drug load and inadequate aqueous stability.

Schaeffer *et al.* worked on indoxole and penicillin G and reported that liposome uptake by the cornea is greatest for positively charged liposomes and least for neutral liposomes, suggesting that the

initial interaction between the corneal surface and liposomes is electrostatic adsorption.^[31]

Niosomes

Niosomes are bilayered structural vesicles made up of nonionic surfactant which are capable of encapsulating both lipophilic and hydrophilic compounds. Niosomes reduce the systemic drainage and improve the residence time, which leads to increase ocular bioavailability. They are nonbiodegradable and nonbiocompatible in nature. In a recent approach to deliver cyclopentolate, niosomal formulation was developed. It released the drug independent of pH, resulting in significant enhancement of ocular bioavailability. Niosomal formulation of coated (chitosan or carbopol) timolol maleate exhibited significant IOP lowering effect in rabbits as compared with timolol solution.^[32]

Nanoparticles/nanospheres

These are polymeric colloidal particles, ranging from 10 nm to 1 µm, in which the drug is dissolved, entrapped, encapsulated, or adsorbed.^[33] Encapsulation of the drug leads to stabilization of the drug. They represent promising drug carriers for ophthalmic application.^[34] They are further classified into nanospheres (small capsules with a central cavity surrounded by a polymeric membrane) or nanocapsules (solid matricial spheres). Marchal-Heussler *et al.*^[35] found that the nanocapsules show a better effect than the nanospheres, probably because the drug (betaxolol, carteolol) is in a unionized form in the oily core and can diffuse at a greater rate into the cornea. Several authors^[36] suggest that the better efficiency of nanocapsules is due to their bioadhesive properties, resulting in an increase in the residence time and biological response. Hence, it improved the ocular bioavailability of the drug and reduced dosing frequency. Alonso *et al.*^[37] have also reported that the nanoparticles of poly-ε-caprolactone containing cyclosporin show a better corneal absorption with respect to the oily solution of the drug.

Nanosuspension

This can be defined as sub-micron colloidal system which consists of poorly water-soluble drug, suspended in an appropriate dispersion medium stabilized by surfactants. Nanosuspension usually consists of colloidal carriers like polymeric resins which are inert in nature. Nanosuspension improves the ocular bioavailability of the drug by prolonging the contact time. Charge on the surface of nanoparticles facilitates its adhesion to the cornea. Cloricromene (AD6) was formulated in nanosuspension by using Eudragit RS100 and RL100. AD6-loaded Eudragit retarded nanoparticles suspension offered a significant edge in enhancing the shelf life and bioavailability of the drug.^[38]

Microemulsion

Microemulsion is stable dispersions of water and oil, facilitated by a combination of surfactant and co-surfactant in a manner to reduce interfacial tension. Microemulsion improves the ocular bioavailability of the drug and reduces frequency of the administration. These systems are usually characterized by higher thermodynamic stability, small droplet size (~100 nm), and clear appearance.^[39] An oil in water system consisting of pilocarpine using lecithin, propylene glycol, PEG 200 as surfactant/co surfactants, and isopropyl myristate as the oil phase has been designed, which is nonirritating to the rabbit animal model. Such formulations often

provide sustained drug release, thereby reducing frequency of the drug administration. Potential toxicity of higher concentration of surfactant/co-surfactant, selection of the surfactant/co-surfactant, and aqueous/organic phase affects its stability.

In situ-forming gel

The droppable gels are liquid upon instillation, and they undergo a phase transition in the ocular cul-de-sac to form a viscoelastic gel, and this provides a response to 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 gels include pH, temperature, and ionic strength. Examples of potential ophthalmic droppable gels reported in the literature include gelling triggered by a change in pH - CAP latex^[40,41] cross linked polyacrylic acid and derivatives such as carbomers and polycarbophil, gelling triggered by temperature change - poloxamers^[40,41] methyl cellulose and Smart Hydrogel™, gelling triggered by ionic strength change - Gelrite^[42] and alginate.^[43]

Approaches to provide controlled and continuous ocular drug delivery

Microparticles

Microparticles are drug-containing, micron-sized polymeric particles suspended in a liquid medium. Drugs can be physically dispersed in the polymer matrix or covalently bound to the polymer backbone.^[44] Upon topical instillation, the particles reside in the ocular cul-de-sac, and the drug is released from the particles through diffusion, chemical reaction, and/or polymer degradation. Microparticles improve precorneal residence time, which leads to continuous and sustain release of the drug. Hence, improved ocular bioavailability of the drug and reduced dosing frequency. It causes irritation to the eye because of the large particle size.

Biodegradation, bioadhesion, and biocompatibility are the desired properties for the fabrication polymers of ophthalmic microparticles. The following are examples of published biodegradable microparticles, in which the *in vivo* efficacy performance is reportedly superior to that of the corresponding conventional dosage forms:

- Microspheres of methylprednisolone chemically linked to hyaluronate esters;^[45]
- Pilocarpine-loaded albumin or gelatin microspheres;^[46]
- Acyclovir-loaded chitosan microspheres.^[47]

Betoptic® S is on the US market. By binding betaxolol to ion-exchange resin particles, Betoptic® S retards drug release in the tear and enhances drug bioavailability. Betoptic® S 0.25% is bioequivalent to Betoptic solution 0.5% in lowering intraocular pressure. By reducing the drug strength by half and slowing down the drug-release rate in tears, Betoptic® S significantly improves the ocular comfort of Betoptic solution.^[48]

Ocular inserts

The ocular inserts overcome this disadvantage by providing with more controlled, sustained, and continuous drug delivery by maintaining an effective drug concentration in the target tissues and yet minimizing the number of applications. It reduces systemic adsorption of the drug. It causes accurate dosing of the drug. It has disadvantages like patient incompliance, difficulty with self-

insertion, foreign body sensation, and inadvertent loss from the eye. A number of ocular inserts were prepared utilizing different techniques to make soluble, erodible, nonerodible, and hydrogel inserts [Table 1].

Implants

The goal of the intraocular implant design is to provide prolonged activity with controlled drug release from the polymeric implant material. Intraocular administration of the implants always requires minor surgery. In general, they are placed intravitreally, at the pars plana of the eye (posterior to the lens and anterior to the retina).^[51,52] Although this is an invasive technique, the implants have the benefit of (1) by-passing the blood-ocular barriers to deliver constant therapeutic levels of drug directly to the site of action, (2) avoidance of the side effects associated with frequent systemic and intravitreal injections, and (3) smaller quantity of drug needed during the treatment. The ocular implants are classified as nonbiodegradable and biodegradable devices. Nonbiodegradable implants can provide more accurate control of drug release and longer release periods than the biodegradable polymers do, but the nonbiodegradable systems require surgical implant removal with the associated risks. The ocular implants are summarized in Table 2.

With implants, the delivery rate could be modulated by varying

Types	Description
Erodible inserts	The fabrication polymer is hydrophobic but biodegradable. Drug is released through the erosion of the surface of the insert.
Soluble inserts	The fabrication polymer is hydrophilic and water soluble. Drug release characteristics: Diffusion control for soluble drugs Dissolution control for less soluble drugs
Hydrophilic but water insoluble Inserts	The fabrication polymer is hydrophilic but water-insoluble. Drug release characteristics: Diffusion control for soluble drugs Dissolution control for less soluble drugs
Inserts using osmotic system	A polymeric matrix in which the drug is dispersed as discrete small domains. Upon placement in the cul-de-sac, tears are imbibed into the matrix because of an osmotic pressure gradient created by the drug, where upon the drug is dissolved and released.
Membrane-controlled diffusional inserts	The drug core is surrounded by a hydrophobic polymer membrane; this controls the diffusion of the drug from the core to the outside.

Registered name	Active substance	Mode of administration
Vitrasert [®]	Ganciclovir	Surgical implantation at the pars plana
Retisert [®]	Fluocinolone acetonide	Surgical implantation at the pars plana
Medidur [®]	Fluocinolone acetonide	Injected in the vitreous cavity
Posurdex [®]	Dexamethasone	Injected or through small incision at the pars plana
Surodex [®]	Dexamethasone	Placed underneath the scleral flap

polymer composition. Implants can be in the form of solid, semi-solid, or particulate-based delivery systems.^[53] Drug release from polylactic acid, polyglycolic acid, and polylactic-co-glycolic acid usually follows three phases of drug release which constitute an initial burst, a middle diffusive phase, and a final burst of the drug. It is an alternative to repeated injections, because they increase half-life of the drug and may help to minimize peak plasma level; they might improve patient acceptance and compliance.

It has disadvantages like side effects: the insertion of these devices is invasive and with associated ocular complications (retinal detachment and intravitreal hemorrhage for intravitreal implant). The nonbiodegradable requires surgery to harvest the device once it is depleted of the drug (risk of ocular complications). The biodegradable implants have a final uncontrollable 'burst' in their drug release profile.^[53]

Approaches to posterior segment drug delivery

Intravitreal injections

This method involves injection of drug solution directly into vitreous via pars plana using a 30G needle which improve drug absorption over systemically and topically delivered agents. It leads to drug delivery to the target sites of the eye. It has more safety drug delivery to the posterior segment of the eye than systemic administration (no systemic toxicity). Unlike other routes, intravitreal injection offers higher drug concentrations in vitreous and retina. Elimination of drugs following intravitreal administration depends on their molecular weight.^[54] Though intravitreal administration offers high concentrations of drugs in retina, it is associated with various short-term complications such as retinal detachment, endophthalmitis, and intravitreal hemorrhages.^[55] Moreover, patients need to be carefully monitored in intravitreal injections.

It has disadvantages like injections display first-order kinetics (this rapid rise may cause difficulties with toxicity, and drug efficacy can diminish as the drug concentration falls below the targeted range), injections have short half-life (few hours), and should be administered repeatedly, side effects which include pain caused by repeated injections, discomfort, increased IOP, intraocular bleeding, increased chances for infection, and the possibility of retinal detachment; the major complication for intravitreal injection is endophthalmitis, poor acceptance by patients.

Iontophoresis

Ocular iontophoresis has gained significant interest recently due to its noninvasive nature of delivery to both anterior and posterior segment. Iontophoresis is a noninvasive method of transferring ionized drugs through membranes with low electrical current.^[56,57] The drugs are moved across the membranes by two mechanisms: migration and electro-osmosis.

Ocular iontophoresis is classified into transcorneal, corneoscleral, or trans-scleral iontophoresis,^[56] the latter being the most interesting option. The sclera has larger surface area than the cornea (about 17 cm² vs 1.3 cm²), high degree of hydration, low number of cells, and it is permeable to large molecular weight compounds. Trans-scleral delivery allows drug transfer to the posterior segment. It is noninvasive method and easy to use. It has ability of modulate dosage (less risk of toxicity), a broad applicability to deliver a broad range of drugs or genes to treat several ophthalmic diseases in the posterior segment of the eye, and good acceptance by patients. It may combine with other drug delivery systems. It has disadvantage

like no sustained half-life, requires repeated administrations, side effects include mild pain in some cases, but no risk of infections or ulcerations, risk of low patient compliance because the frequent administrations that may be needed.

OcuPhor™ system has been designed with an applicator, dispersive electrode, and a dose controller for transscleral iontophoresis (DDT).^[58] This device releases the active drug into retina-choroid as well. A similar device has been designed called Visulex™ to allow selective transport of ionized molecules through sclera. Examples of antibiotics successfully employed are gentamicin, tobramycin, and ciprofloxacin, but not vancomycin because of its high molecular weight.^[59] Successful delivery was obtained with dexamethasone and with antisense ODNs.^[60] A number of antibiotics, including gentamicin, cefazolin, ticarcillin, amikacin, and vancomycin have been successfully delivered into the vitreous of rabbit eyes. Transscleral iontophoresis of steroids (dexamethasone and methyl prednisolone), amikacin, gentamicin, and other drugs was also reported.^[61,62]

Periocular route

It has been considered as the most promising and efficient route for administering drugs to posterior eye segment. Periocular refers to the region surrounding the eye. Drug solutions are placed in close proximity to the sclera, which results in high retinal and vitreal concentrations. It has advantages like improved drug absorption over systemically and topically delivered agents, more safety drug delivery to the posterior segment of the eye than systemic administration (no systemic toxicity), drug delivery to the target sites of the eye. Injections display first-order kinetics (this rapid rise may cause difficulties with toxicity, and drug efficacy can diminish as the drug concentration falls below the targeted range).^[63]

Ghate *et al.* studied the pharmacokinetics of sodium fluorescein following periocular administration in rabbits. The study concluded that administration of drug via subtenon injection resulted in the highest and sustained vitreous concentration of sodium fluorescein compared with retrobulbar and subconjunctival routes.^[64]

Future consideration

In future, much of the emphasis will be given to achieve noninvasive sustained drug release for eye disorders in both segments. A clear understanding of the complexities associated with tissues in normal and pathological conditions, physiological barriers, and multicompartmental pharmacokinetics would greatly hasten further development in the field.

An ideal system should be able to achieve an effective drug concentration at the target tissue for an extended period of time, while minimizing systemic exposure. In addition, the system should be both comfortable and easy to use. Patient acceptance will continue to be emphasized in the design of future ophthalmic drug delivery systems. A reasonable strategy to circumvent the drawbacks of individual technologies is to combine technologies. Reported examples include liposomes and nanoparticles in droppable gels and liposomes and nanoparticles coated with bioadhesive polymers.

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

1. The ocular bioavailability must be increased from less than 1% to 15–20% of the administered dose.
2. Most of the currently marketed ocular drugs were initially developed for nonocular applications, hence their low or

nonspecificity. So, there is a need to develop new drug candidates primarily intended for ocular use.

3. Further studies to fully exploit the potential of noncorneal routes, especially for ionic/water-soluble moieties and also drug molecules with a preferential corneal absorption (and minimum absorption through nasal mucosa), should be explored.
4. Appropriate 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 provide new smart technologies to augment ophthalmic drug delivery.

Conclusion

Effective treatment of ocular diseases is a formidable challenge for scientists in the field, especially because of the nature of diseases and presence of the ocular barriers especially in posterior ocular segments. Over last several years, attempts have been made to improve ocular bioavailability through manipulation of product formulation such as viscosity and application of mucoadhesive polymers. Thus far, these approaches to prolong corneal contact time have led to modest improvement in ocular bioavailability. Consequently, it seems logical to consider nonconventional approaches such as nanotechnology, microspheres, liposomes, appropriate prodrug *in situ* forming gel, and iontophoresis for effective delivery and to further enhance ocular absorption and reduce side effects.

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