International Standard Serial Number (ISSN): 2249-6807

International Journal of Institutional Pharmacy and Life Sciences 9(6): November-December 2019

INTERNATIONAL JOURNAL OF INSTITUTIONAL PHARMACY AND LIFE SCIENCES

Pharmaceutical Sciences **Review Article……!!!**

Received: 10-10-2019; Revised: 19-11-2019; Accepted: 24-11-2019

OPHTHALMIC DRUG DELIVERY SYSTEM:- A REVIEW

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Keywords:

Nanoformulations, Retinal Diseases, Opthalmic Drugs

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ABSTRACT

The pharmacologist and formulation scientist faced the major challenge about ocular drug delivery.For the treatment of anterior segment disease the topical eye drop is most convenient and patient compliant route of drug administration .Delivery of drug to the targeted ocular tissues is restricted by various precornal ,dynamic and static ocular barriers. Also,therapeutic drug levels are not maintained for longer duration in target tissues.In the past two decades, ocular drug delivery research acceleratedly advanced towards developing a novel, safe and patient compliant formation and drug delivery devices , which may surpass these barriers and maintain drug level in tissues. Various nanoformulations have also been introduced for anterior segment ocular drug delivery. On the other hand, for posterior ocular delivery, and development of drug releasing devices. It is used for treating the chronic vitreoretinal diseases.

INTRODUCTION

The eye has unique anatomy and physiology it is a complex organ. The structure of eye can be divided into two main parts: anterior segment and posterior segment. Anterior segment of the eye occupies approximately one third while the remaining portion is occupied by the posterior segment. Tissues such as cornea, conjunctiva, aqueous humor, iris, ciliary body and lens make up the anterior portion. Back of the eye or posterior segment of the eye include sclera, choroid, retinal pigment epithelium, neural retina, optic nerve and vitreous humor.

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. Convention 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 marketed ophthalmic formulations are in the form of eye drops. These formulations mainly target the diseases in the anterior segment of the eye (2). Topical ocular medications do not reach the posterior segment of the eye. Posterior segment can be treated by high drug dosage regimen give intravenously or by intravitreal administration or implants or by periocular injection. 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 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 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 physiological 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 admistration. The active sites for the antibiotics, antiviral, and steroids are the infected or inflamed areas within the anterior as well as the posterior segment 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.

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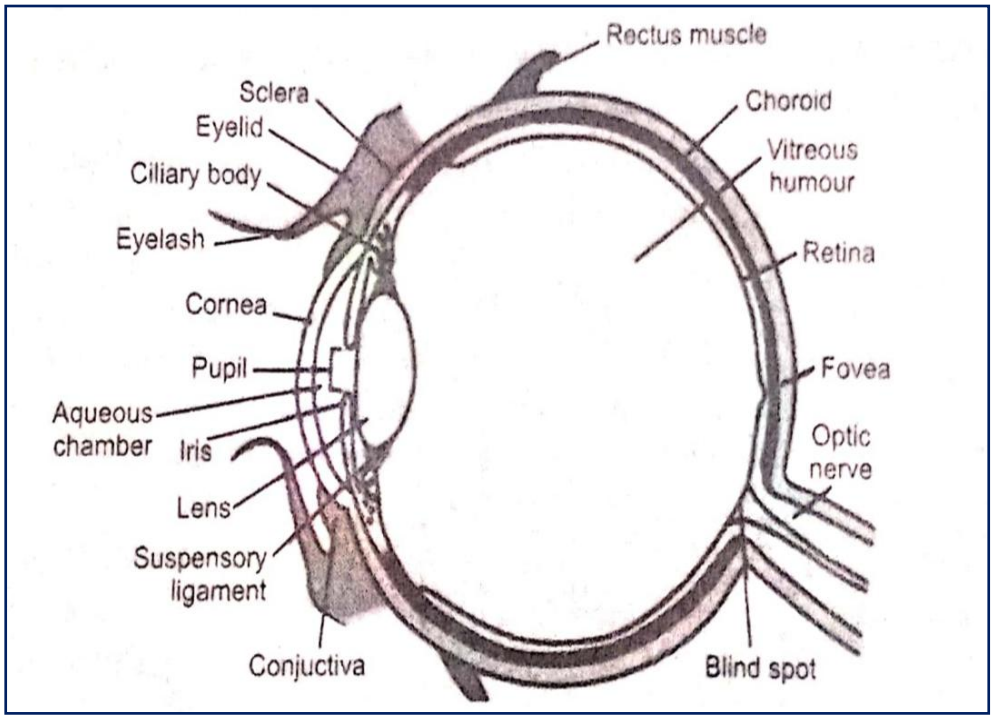

Figure 1: The routes of drug kinetics illustrated.

PHYSIOLOGICAL CONSIDERATION

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 layer acts as a barrier to ion transport. the tight junction of the corneal epithelium serve as a selective barrier for small molecules and prevent the diffusion of macromolecules through the paracelluar 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 lipophilc 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.

PHARMACOKINETIC CONSIDREATION

The main routes of drug administration and elimination form the eye have been shown schematically in figures 1.

The number refer to following processes (4):

1) Transcorneal permeation permeation form the larchrymal fluid into the anterior chamber,
2) Noncorneal drug permeation across the conjunctiva and sclera into the anterior uvea,
3) Drug distribution form the blood stream through blood-aqueous barrier into the anterior chamber,
4) Elimination of drug form the anterior chamber by the aqueous humor turnover to the trabecular meshwork and sclemm'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 the blood-retina barrier,
7) Intravitreal drug administration,
8) Drug elimination from the vitreous via posterior route across the blood-retina barrier, and
9) Drug elimination from the vitreous via anterior route to the posterior chamber.

DELIVERY CHALLENGES IN OPTHALMIC DRUG 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 system with high therapeutic efficacy. The anatomy,physiological,and barrier function of the cornea compromise the rapid absorption of drugs. Frequent instillation 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 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 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 posses balance between lipophilicity and hydrophilicity with higher contact time (5).

ANTERIOR SEGMENTDELIVERY 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 administration by the ocular route has to cross the precorneal barrier. 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 drug from from ocular dosage forms is mainly due to the precorneal loss factors which are demonstrated in figure 2 and 3.

Moreover, frequent instillation 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 solution may induce toxic side effects and cellular damage at the ocular surface.

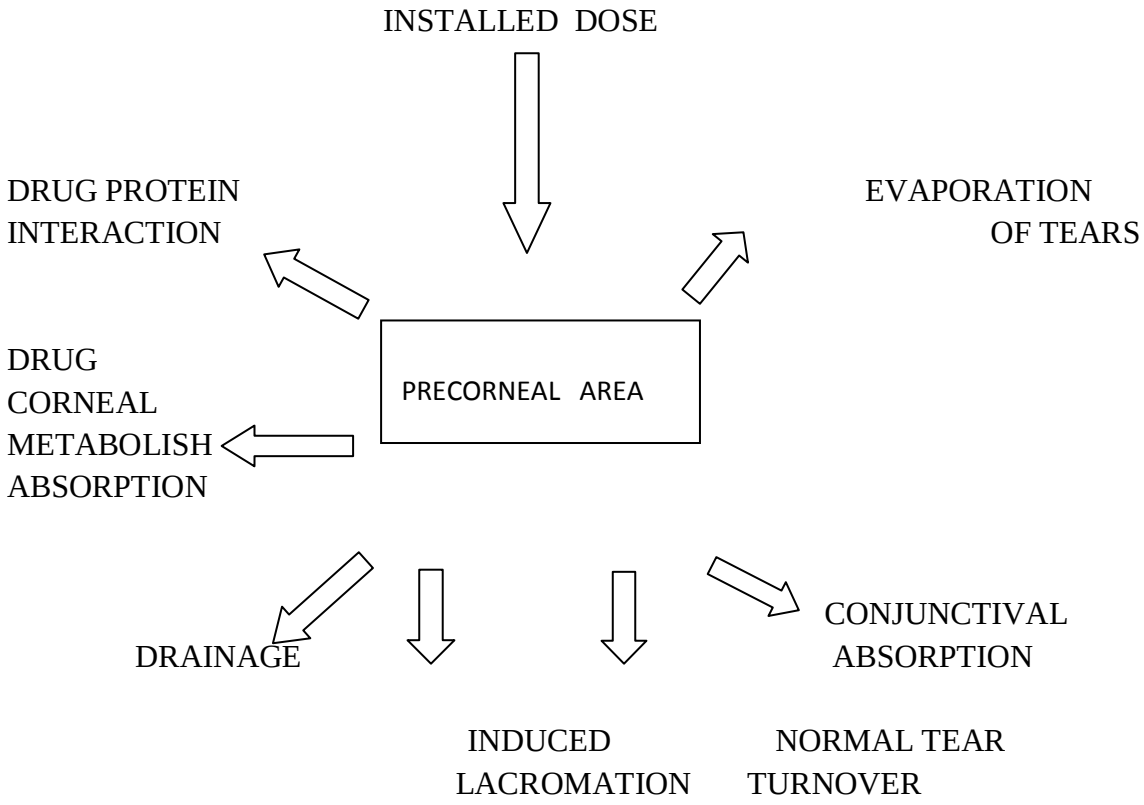

Figure 2: Precorneal factors that influence bioavailability of topically applied ophthalmic drugs.

POSTERIOR SEGMENT DELIVERY CHALLENGES

Topical ocular medication 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 junction of BRB restrict the entry of systemically administered drug 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 amount of drugs leading to systemic side effects (8).

Another challenge for posterior segment is to maintain the therapeutic drug concentration periods and minimize the number of injection. 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

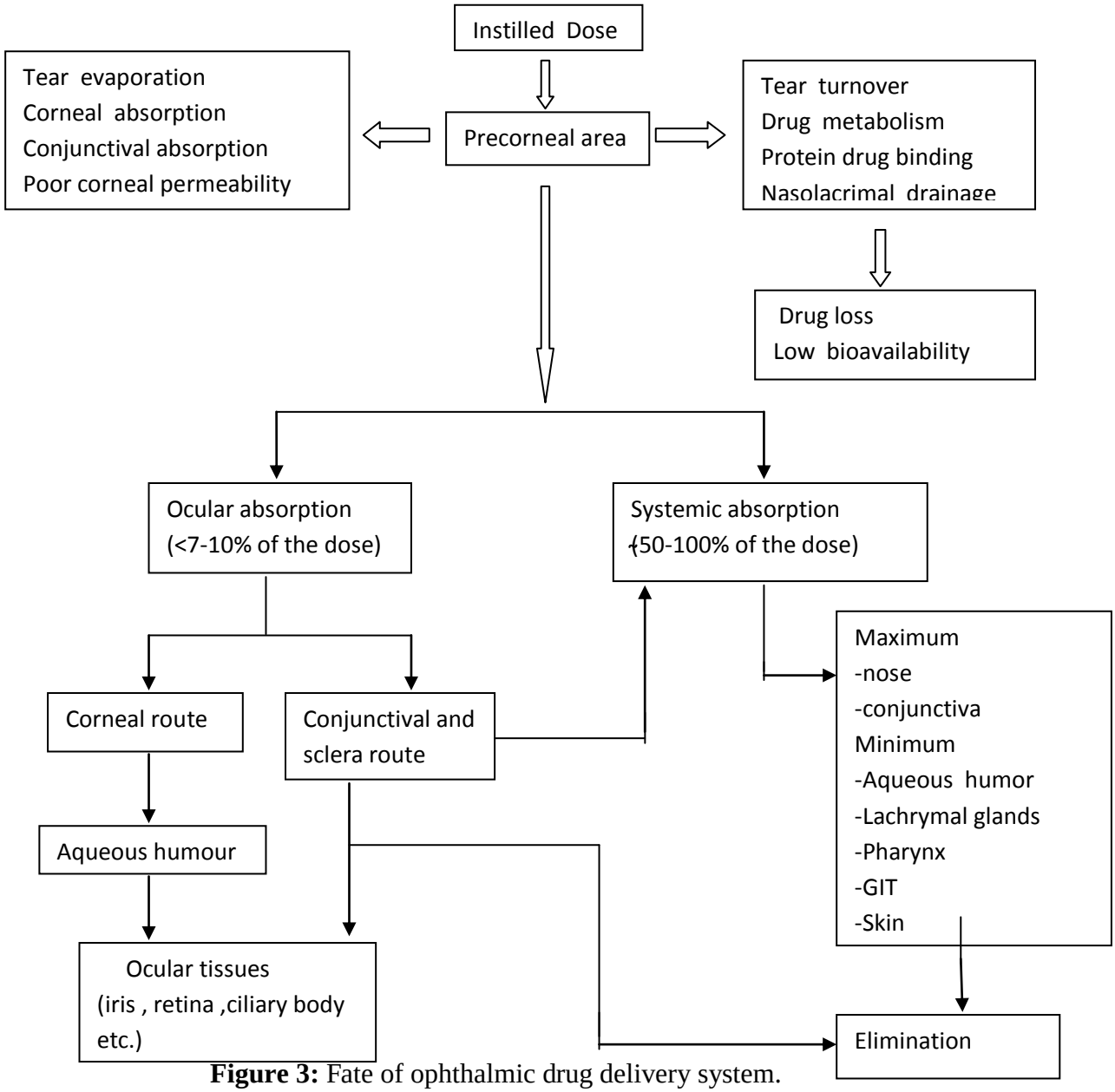

Figure 3: Fate of ophthalmic drug delivery system.

IDEAL CHARACTERISTICS OF OPTHALMIC 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 effect.
- Minimize precorneal drug loss.
- Nonirritative and comfortable form .

- Should not cause blurred vision.
- Relatively nongreasy.
- Appropriate rheological properties and concentration of the viscous system.

APPROACHES IN OPTHAMIC DRUG DELIVERY SYSTEM

The various approaches attempted in the early stage 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 therapeutical action of ocular drugs can be divided into two categorise. The first one is based on maximizing corneal drug absorption and minimizing precorneal drug loss through viscosity and penetration enhancer, 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, nanoparticle, 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, nanosuspention, nanopartical, liposome, 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 intravitral injection, iontophoresis, subconjunctival injection, and periocular route are used to deliver ophthalmic drug to the posterior segment of the eye.

APPROACHES TO IMPROVE OCULAR BIOAVAILABIITY

Viscosity enhancers

Viscosity-increasing polymers are usually added to ophthalmic drug solution on the premise that an increased vehicle viscosity should correspond to a slower elimination from the preocular 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 bioavailabilty.the polymers used include polyvinyl alcohol, polyvinylpyrrolidone, methylcellulose, hydroxyethyl cellulose, hydroxypropyl methylcellulose, and hydroxpropyl cellulose (12).

Found that among PVA,HPMC, and PVP used for solution of tropicamide at concentrations yielding the same viscosity of 20 cst, PVP was more effective. This is because of its adhesive properties and its capability to increase the thickness of the preconeal 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 vehical and to the ability of a polymer to drug water as the vehicle spreads over the ocular surface with each blink.

Eye Ointments

Ointments are usually formulated using mixture of semisolid and solid hydrocarbon which have a melting or softening point close to body temperature and are nonirritating to the eye. Ointments may be simple bases, where a two-phased system 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 periods. Ointment are therefore useful in 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, ointment suffer with relative poor patient compliance due to blurring of vision and occasional irritation (14).

Gel

Gel formation is an extreme case of viscosity enhancer 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 eyelied, which substantically reduce patient acceptability.

The aqueous gel typically utilizes such polymers as PVA, polyacrylamide, poloxamer, HPMC, carbomer, poly methyvinylethermaleic anhydride, and hydroxypropyl ethylcellulose. Swellable water insoluble polymers, called hydrogel, or polymers having peculiar characteristics of swelling in aqueous medium give controlled drug delivery system. The release of drug from these system 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 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 of the drug. Within the corneal 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 enzume susceptibility (16). Enzyme system identified in ocular tissue include esterases, ketone redutase, and steroid 6-hydroxylase (17,18).

Prodrug is considered as a new drug entity; so, extensive pharmacokinetic and pharmacological information is required for proper design.

Some examples of suitable prodrug include the antiviral medications gaanciclovir, a drug with a relatively low partition coefficient, substantially increased permeability was linearly correlated with increased susceptibility of the ganciclovir esters to undergo hydrolysis by esterases in the corneal (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 corea epithelial cell layer is a 'tight' ion-transporting tissue, because of the high resistance of 12 to16k$\tilde{\Omega}cm$ 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 form the cornea to the receptor site is a rate-limiting step, and permeation enhancers increase cornea uptake by modifying the integrity of the cornea epithelium (21). Inclusion of these agents such as cetylpyridinium chloride(22), ionophore such as lasalocid(23), benzalkonium chloride(24), paraben(20), Tween 20 , saponins(25), Brij 35,Brij78, Brij98, ethylenediaminetetraactic acid, bile salts(26), and bile acids, capric acid, azone, fusidic acid, lauramide, saponins (27), hexamethylene octanamide, and decylmethyl sulfoxide(28) in different formulations have shown a significant enhancement in cornea drug absorption.

Liposomes

Liposome are the microscopic vesicles composed of one or more concentric lipid bilayers, separated by water or aqueose buffer compartments. Liposome posses the ability to have an intimate contact with the cornea and cojunctival surface, which increases the probability of ocular drug that are poorly 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 liposome seem to be preferentially captured at the negatively charged liposomes. It is droppable, biocompatible, and biodegradable in nature. It reduced the toxicity of the drug. It provide 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 liposome, suggesting that the initial interaction between the corneal surface and liposome 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 lead to incrase 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. Niosomes formulation of coated timolol maleate exhibited significant IOP lowering effect in rabbits as compared with timolol solution (32).

Nanoparticles/nanospheres

These are polymeric colloidal particle, ranging from 10nm to 1mm, 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 carrier for ophthalmic application (34). They are further classified into nanospheres or nanocapsules. Marchal –Heussler et al (35).found that the nanocapsules show a better effect than the nanospheres, probably because the drug 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 bioavailability of the drug and reduced dosing frequency. Alonso et al(37). Have also reported that the nanoparticles of poly-e-caprolactone containing cyclosporin show a better corneal absorption with respect to the oily solution of the drug.

Nanosuspension

This can be defined as sub-micro colloidal system which cocsists 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 inter in nature. Nanosuspension improves the ocular bioavailability of the drug by prolonging the contact time. Charge on the surface of nanoparticle facilitates its adhesion to the cornea. Cloricromene was formulated in nanosuspension by using eudragit RS100 and RL100. AD6-loaded Eudragit retarded nanoparticles suspention offered a significant edge in enhancing the shelf life and bioavailbility of the drug(38).

Microemulsion

Microemulsion is stable dispersion of water and oil, facilitated by a combination of surfacctant 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 themodynamic stability, small droplet size, and clear appearance(39). An oil in water system consisting of pilocarpine using lecithin, propylene glycol, PEG 200 as surfactant/co surfactant, 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-polyoxamers(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

Microparticle are drug-containing, micro-sized polymeric particle suspended in a liquid medium. Drug can be physically dispersed in the polymer matrix or convalently bound to the polymer backbone(44). Upon topical instillation, the particles reside in the ocular cul-de-sac, and the drug is relased form the paticles through diffusion, chemical reaction,and/or polymer degradation. Microparticle improve precorneal residencetime, which leads to continuous and the drug and reduced dosing frequency. It causes irritation to the eye because of 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 example of published biodegradable

microparticle, in which the in vivo efficacy performance is reportedly superior to that of the corresponding conventional dosage form:

- Microspheres of metylprednisolone chemically linked to hyaluronate esters(45);
- Pilocarpine-loaded albumin or gelatin microspheres(46);
- Acyclovir-loaded chitonsan microspheres(47).

Betopic S is on the US market. By binding betaxolol to ion exchange resin particle,

Betopic S retards drug release in the tear and enhances drug bioavailability. Betopic 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 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

Implants

The goal of the intraocular implant design is to provide prolonged activity with controlled drug release form 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 (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 level of drug directly to the site of action, (2) avoidance of the side effects associated with frequent systemic and intravitreal injection,and (3) smaller quantity of drug needed during the treatment. The ocular implants are classified as nonbiodegrable 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 system require surgical implant removal with the associated risks. The ocular implants are summarized in with implants, the delivery rate could be modulated by varying

Table 1: Various types of ophthalmic inserts(49,50)

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 drug 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, tear 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 form the core to the outside.

Table 2: Description of current and potential ophthalmic implants(53)

Registered name	**Active substance**	**Mode of administration**
Viteasert	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	Dexanethasone	Injected or through small incision at the pars plana.
Surodex	Dexanethasone	Placed underneath the sclera flap.

Polymer composition. Implants can be in the form of solid, semi soild, or particulate-based delivery systems(53). Drug release from polylactic acid, polyglycolic acid, and polylactic-co-glycolic acid usually follows three phase of drug release which constitute an initial burst, a

middles 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 complication.

It has disadvantages like side effect: the insertion of these devices is invasive and with associated ocular complication . the nonbiodegradable requires surgery to harvest the device once it is deplected of the drug. 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 .unlike other routes, intravitreal injection offers higher drug concentration in vitreous and retina. Elimination of drugs following intravitreal administration depends on their molecular weight(54). Though intravitreal administration offer high concentrations of drugs in retina, it is associated with various short-term complication such as retina detachment, endophthalmitis, and intravitreal hemorrhages(55). Moreover , patients need to be carefully monitored in intravitreal injection.

It has disadvantages like injction display first-order kinetics, injections have short half-life, and should be administered repeatedly, side effects which include pain caused by repeated injections, discomfort, increased IOP, intraocular bleeding, increased chances for injection, and the possibility of retinal detachment; the major complication for intravitreal injection is endophalmitis, poor acceptance by patients.

Iontophoresis

Ocular iontophoresis has gained significant interest recently due to its nonivasive nature of delivery to both anterior and posterior segment. Iontophoresis is a noninvasive method of transferring ionized drugs are through membranes with low electrical current(56,57). The drugs are moved across the membranes by two mechanism: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, high degree of hydration,low nmber of cells, and it is permeable to large molecular weight compounds. Trans sclera delivery allows drug transfer to the posterior segment.it is noninvasive method and easy to use. It has abilityof modulate dosage, 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 drg delivery system. 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 ulceration, risk of low patient compliance because the frequent administration that may be needed .

Ocuphor, system has been designed with an applicator, dispersive electrode, and a dose controller for transscleral iontophoresis(58). This device releases the active drug into retina-choroid as well. A similar devise 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 antisebse 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, amikacin, gentamicin, and other drugs was also reported(61,62).

Periocular route

It has been considered as the most promising and efficient route for administration 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 viteral concentration. 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, drug delivery to the target sites of the eye. Injections display first-order kinetic(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 subconjunctive routes(64).

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

pordrug in situ forming gel, and iontophoresis for effective delivery and to futher enhance ocular absorption and reduce side effects. Drug delivery to targeted ocular tissues has been a major challenge to ocular scientist, for decades. Administration of drug solutions as topical drop with conventional formulations was associated with certain drawbacks which initiated the introduction of different carrier system for ocular delivery. Tremendous efforts are being put into ocular research towards the development of safe and patient compliant novel drugs delivery strategies. Currently, researchers are thriving hard to improve in vivo performance of conventional formulations.

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