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Advancement and Tribulations in Ocular Drug Delivery.

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Abstract

Development of new drug candidates and novel delivery techniques for treatment of ocular diseases has recently accelerated. The field of ocular drug delivery is one of the most interesting and challenging endeavors facing the pharmaceutical scientist for past 10-20 years. In ophthalmic formulation to the eye like solutions, suspensions, and ointments are available in the market shows drawbacks such as increased precorneal elimination, blurred vision and high variability in efficiency. The major setback associated with the conventional dosage forms is the bioavailability of drug. In the last three decades to improve the bioavailability by common to adding viscosity-enhancing agents or mucoadhesive polymers into dosage formulations. To prevail over to conventional dosage formulations there were non-conventional technologies such as lipososme, niosome, microspheres, nanoparticle, implant, gene therapy and ocular inserts could be developed in pharmaceutical market. In this article, we have summarized the different types of commonly used ophthalmic formulations and compared the conventional formulations with the advanced formulation in many respects like their applicability, acceptance, characteristics and utility.

"Ocular drug delivery is one of the most interesting and challenging endeavours facing the pharmaceutical scientist...The anatomy, physiology and biochemistry of the eye render this organ exquisitely impervious to foreign substances...The challenge to the formulator is to outwit the protective barriers of the eye without causing permanent tissue damage...The ancient ophthalmic solutions, suspensions and ointment dosage forms are clearly no longer sufficient to combat some present virulent diseases..."

Keywords: Lipososme, Niosome, Microspheres, Implant, Gene Therapy and Ocular Inserts

Introduction

Many people suffer from a wide variety of ocular diseases, many of which lead to visual impairment and ocular blindness. Certain ocular diseases are quite rare, whereas others, such as cataracts, age-related macular degeneration (AMD), and glaucoma, are very common, especially in the aging population (Table 1). A rapid development of new technologies in ocular drug delivery and new drug candidates, including biologics, to treat these challenging diseases in the anterior and posterior segments of the eye have recently emerged [1]. For development of new drug candidates and novel delivery techniques for treatment of ocular diseases has recently accelerated. Controlled drug delivery to the eye is restricted due to these limitation imposed by the efficient protective mechanism. Ideal ocular drug delivery must be able to sustain the drug release and to remain in the vicinity of front of the eye for prolong period of time. Consequently it is imperative to optimize ocular drug delivery, one of the way to do so is by addition of polymers of various grades, development of viscous gel, development of colloidal suspension or using erodible or non erodible insert to prolong the precorneal drug retention. More efficient ocular delivery systems that have been commercialised recently and are still under evaluation aim at enhancing the drug bioavailability either by providing prolonged, sustained delivery to the eye or by facilitating transcorneal penetration.

Ocular Drug Absorption

Absorption of drugs takes place either through corneal or noncorneal routes. The noncorneal route involves absorption across the sclera and conjuctiva into the intraocular tissues. This route is, however, not productive as it restrains the entry of drug into aqueous humour. Maximum absorption thus takes place through cornea, which leads the drug into aqueous humour. The goal of oular drug delivery systems has traditionally been to maximize ocular drug absorption rather than to minimize systemic absorption [2,3].

Solutions are undoubtedly the most commonly used and accepted forms. They are relatively simple to make, filter and sterilise. The factors that must be taken into account while formulating aqueous solution include selection of appropriate salt of the drug substance, solubility, therapeutic concentration required, ocular toxicity, pKa, and the effect of pH on stability and solubility, tonicity, buffer capacity, viscosity, compatibility With other formulation ingredients as well as packaging components, choice of preservative, ocular comfort and ease of manufacturing. The stability of ophthalmic solutions and other dosage forms determine the shelf life and expiration dating of the product. Suspensions, while not as common as solutions, are

widely used for formulations involving anti-inflammatory steroids (for example prednisolone

alcohol and acetate). In most ophthalmic suspension, the average particle size is less than 10 μm. The most efficient method of producing such particle size is by dry milling. However, we milling may be desirable for potentially explosive ingredients. Other methods of particle size reduction include micro-pulverization, grinding, and controlled precipitation. An ophthalmic suspension contains many inactive ingredients such as dispersing and wetting agents, suspending agents, buffers and preservatives. In case ointments are still being marketed for night time applications and where extended therapeutic actions are required [4, 5]. A major disadvantage of the ophthalmic ointments is that they cause blurred vision due to refractive index difference between the tears and the non-aqueous nature of the ointment and inaccurate dosing. This approach relies on vehicles containing polymers that adhere via non-covalent bonds to conjunctival mucin, thus ensuring contact of the medication with the precorneal tissues until mucin turnover causes elimination of the polymer Mucoadhesive polymers can provide a localized delivery of an active agent to a specific site in the body such as the eye. Such polymers have a property known as bioadhesion meaning attachment of a drug carrier to a specific biological tissue such as the epithelium and possibly to the mucosal surface of such tissues. These polymers are able to extend the contact time of the drug with the biological tissues and thereby improve ocular bioavailability. There are several bioadhesive polymers now available with varying degree of mucoadhesive performance Carboxymethylcellulose, Carbopol, Carbopol and hydroxypropyl cellulose [6].

Vesicular and Particulate

Liposomes and Niosomes

In recent years, vesicles have become the vehicle of choice in drug delivery. Lipid vesicles were found to be of value in immunology, membrane biology, diagnostic techniques, and most recently, genetic engineering. In vesicular dosage forms, the drug is encapsulated in lipid vesicles, which can cross cell membrane. Vesicles, therefore, can be viewed as drug carriers and as such they change the rate and extent of absorption as well as the disposition of the drug. Vesicular drug delivery systems used in ophthalmics broadly include liposomes and Niosomes.

Microspheres and Nanoparticles

Particulate polymeric delivery systems include microspheres and nanoparticles. The difference between these systems is based on their size. Particles in the micrometer size (>1 um) are called microspheres whereas those in the range of <1 μm are known as nanoparticles. This discrimination is useful because of their different biological and physicochemical behaviors. Although, there are no marketable sterile ophthalmic products based on these systems, their potential in the ocular field, particularly in delivering the drug to the back of the eye in the retinal space is quite exciting. These particles are either biodegradable such as polylactic acid (PLA) and polyglycolic acids (PLGA) or nonbiodegradable such as poly (alkyl cyanoacrylate), poly (butyl cyanoacrylate), isobutyl cyanoacrylate, cellulose acetate phthalate, poly (ethyl cyanoacrylate) and poly (hexadecyl cyanoacrylate). For retinal drug delivery biodegradable polymers are preferable and in most cases required. Both lactic acid and glycolic acids are biodegradable and they produced and eliminated by the body. These polymers decompose into carbon dioxide and water. The manufacture of sterile microspheres and nanoparticles is more complicated as compared to conventional dosage forms such as aqueous solutions and suspensions. Several manufacturing processes such as milling and homogenization techniques, supercritical fluid technology and emulsion technology been developed over the years [7,8].

Prodrugs

Prodrugs are chemical modifications of known pharmacological agents. These drugs, when administered to biological systems, are biotransformed to the parent compound. In the past, epinephrine has been routinely used to control ocular hypertension. However, due to its chemical structure, it does not have optimal ocular bioavailability characteristics.

A prodrug of epinephrine namely, dipivefrin (DPE) has been developed successfully for several years. Some key advantages of such prodrugs are (a) enhanced bioavailability (b) increased potency (c) lower dose (d) prolonged duration of action (e) reduce side effects and (f) enhanced chemical stability. The lipophilic nature of DPE responsible for its greater bioavailability in ocular

tissues. DPE at 0.1% concentration produces intraocular pressure lowering response which is clinically comparable to 2% epinephrine while showing greatly reduced ocular tolerance and no cardiovascular effects.

Controlled ocular drug delivery

Ocular insert

Ocular insert defined as sterile preparation with solid or semisolid consisting and whose size and sharp are especially designed for ophthalmic application. They offer several advantages as increase ocular residence, possibility of releasing drug at a slow constant rate, accurate dosing and increased shelf life with respect to aqueous solutions. Ocusert, pilocarpine ocular therapeutic system is the first product marketed by Alza incorporation USA from this category. Two types of Ocuserts are available in the market. Collegen shields used in animal models and in humans by Bloomfield et al. credits for first suggesting in 1977 and in 1978 use of collgen inserts as tear substitution and as delivery system for gentamicin. Saettone et al. evaluated series of commercially available polymers as possible material for the preparation of soluble, monolithic insert. Various polymers tried in ocular inserts were polyacrylic acid, polyvinyl alcohol, silicone elastomer, hydroxy propyl cellulose, ethyl cellulose cellulose acetate phthalate and polymethylacrylic acid, hyluronic acid [9, 10, 11].

These devices might present valuable advantages, such as:
• Increased ocular permanence with respect to standard vehicles, hence prolonged drug activity
and a higher drug bioavailability;
• Accurate dosing (theoretically, all of the drug is retained at the absorption site);
• Capacity to provide, in some cases, a constant rate of drug release;
• Possible reduction of systemic absorption, which occurs freely with standard eye-drops via the nasal mucosa;
• Better patient compliance, resulting from a reduced frequency of medication and a lower incidence of visual and systemic side effects;
• Possibility of targeting internal ocular tissues through non-corneal conjunctival scleral penetration routes; and
• Increased shelf life with respect to eye-drops due to the absence of water.
Ocular inserts have been developed in which the drug is delivered based on diffusional mechanisms. It delivers the drug at constant rate minimizing side effects by avoiding excessive absorption. One popular product is Ocusert which delivers pilocarpine.
Uses: This medication is a tear-like substance used in the treatment of dry eye syndromes.
How to Use: The inserts are to be properly placed in the eye once or twice daily as directed. Your doctor will demonstrate how to place the insert into the eye and how to remove it. Practice inserting and removing the insert while in the doctor's office so any questions you have can be answered.
Side Effects: Vision may be temporarily blurred or unstable for a period after applying the insert. Use caution if driving or performing duties requiring clear vision. Eye irritation or discomfort, sticking of eyelashes and sensitivity to bright light may occur when first using this medication. If these symptoms continue or become worse, inform your doctor. Notify your doctor immediately if you develop: itching, pain burning, and redness, swelling in or around the eyes, vision problems. If you notice other effects not listed above, contact your doctor or pharmacist.
Precautions: Tell your doctor if you have any of the following conditions: eye problems, any allergies. As with any medication, this should be used cautiously during pregnancy or while breast-feeding. Discuss the risks and benefits with your doctor.
Drug Interactions: Tell your doctor of any over-the-counter or prescription medication you may take. Do not start or stop any medicine without doctor or pharmacist approval.
Missed Dose: Each insert is to be used for a 24 hour period. If you forget to replace an insert, do it as soon as remembered. Do not "double-up" the dose to catch up.
Storage: Store at room temperature between 59 and 86 degrees F (15 and 30 degrees C) away from heat. Check the expiration date on the box and discard any expired medication.

Currently Available Insert for Ocular Drug Delivery System

Implants

Biodegradable Matrix Implants

Biodegradable Matrix implants are typically used to treat acute-onset diseases that require a loading dose followed by tapering doses of the drug during a 1-day to 6-month time period. They are most commonly made from the copolymers polylactic acid (PLA) and/or poly-lactic-glycolic acid (PLGA), The release of drug generally follows first-order kinetics with an initial burst of drug release followed by a rapid decline in drug levels. The advantage over a nonbiodegradable implant is that biodegradable implants do not require removal, as they dissolve over time [12]. Biodegradable implants also allow flexibility in dose and treatment from short duration (weeks) to longer duration (months to a year), depending on the polymer PLA/PLGA ratio, which is another benefit in tailoring drug delivery to disease progression, because dose and treatment requirements may change over time. Effective sustained delivery has been achieved using a variety of drugs: antiviral, antifungal, antimetabolic, immunosuppressive agents, and steroids. A biodegradable matrix implant consisting of PLGA and up to 700 μg dexamethasone (Posurdex) drug-delivery system (DDS) has been evaluated in patients with persistent macular edema in phase 2 trials.The implant releases dexamethasone for up to 6 months in nonclinical studies after insertion into the vitreous through an innovative special injector and does not disturb the clear media [13].

Non biodegradable (Reservoir) Implants

Non biodegradable Reservoir implants are typically made with a pelleted drug core surrounded by nonreactive substances such as silicon, ethylene vinyl acetate (EVA), or polyvinyl alcohol (PVA); these implants are nonbiodegradable and can deliver continuous amounts of a drug for months to years. One of the first reservoir implants to gain Food and Drug Administration (FDA) approval was Vitrasert ganciclovir intraocular implant for treatment of cytomegalovirus retinitis in patients with acquired immunodeficiency .The Vitrasert implant is fixed and it releases the drug for 5 to 8 months.

Advanced ocular drug delivery

Gen delivery and Scleral Plug

Technologies for drug, gene delivery for the treatment of diseases of the back of the eye. It will integrate the topics of nanotechnology; current and emerging drug and gene delivery systems; and smart delivery strategies to address current challenges and future opportunities in treating blinding diseases. With the identification of new therapeutic agents such as siRNA, miRNA and gene therapies, the need for the development of novel delivery systems also escalates. Several nucleic acid therapies may fail due to the lack of availability of appropriate delivery systems that can:
Protect the therapeutic agent from degradation by nucleases,
Allow enhanced cellular entry,
Minimize off-target effects,
Offer prolonged delivery in treating chronic retinal disorders.
Most blinding diseases progress over several decades, therefore even with successful protein therapeutic agents, frequent injections throughout several years might be detrimental to retinal health. This limitation can potentially be overcome through the development of long-term delivery approaches for protein drugs.
The entrapment of immunologically isolated cells with hollow fibres or microcapsules before their administration into the eye is called Encapsulated Cell Technology (ECT) which enables the controlled, continuous, and long-term delivery of therapeutic proteins directly to the posterior regions of the eye. Along with tissue engineering, gene therapy approaches stand on the front line of advanced biomedical research to treat blindness arising from corneal diseases, modified human RPE cells secretes ciliary neurotrophic factor into the vitreous humour of the patients' eyes. ECT can potentially serve as a delivery system for chronic ophthalmic diseases like neuroprotection in glaucoma, anti-angiogenesis in choroidal neovascularization, anti-inflammatory factors for uveitis. Several kinds of viruses including adenovirus, retrovirus, adeno-associated virus, and herpes simplex virus, have been manipulated for use in gene transfer and gene therapy applications

Scleral plug can be implanted using a simple procedure at the pars plana region of eye, made of biodegradable polymers and drugs, and it gradually releases effective doses of drugs for several months upon biodegradation. The release profiles vary with the kind of polymers used, their molecular weights, and the amount of drug in the plug. The plugs are effective for treating vitreoretinal diseases such as proliferative vitreoretinopathy, cytomegalovirus retinitis responds to repeated intravitreal injections and for vitreoretinal disorders that require vitrectomy [14,15].

Conclusion

Nonstop progress in the understanding of principles and processes leading ocular drug absorption and disposition and continuing technological advances have surely brought some improvements in the efficacy of ocular drug delivery systems. However, ocular drug delivery still faces the challenges enunciated by (Lee and Robinson) several years ago. The most widely developed drug delivery system is represented by the conventional and non-conventional ophthalmic formulations to polymeric nanoparticle, microemulsions, implant, and ocular inserts. At present very few new ocular drug delivery systems have been commercialized in which them ocular inserts have been mostly used. In future 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 and the system should be both comfortable and easy to use.

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Table 1 Leading causes of visual impairment and ocular discomfort

S.No	Disease	Number of Patients
1	Cataract	6–19% of patients older than 43 years
2	Age-related macular	11–28% of patients older than 65 years
3	Glaucoma	1–4% of patients older than 45 years
4	Diabetic retinopathy	71–90% of diabetics older than 10 years
5	Dry eye	50–60 million (10–15% of U.S. population)
6	Ocular allergy	~25% of U.S. population

Table 2 Approaches Developed On Ocular Drug Delivery

S. NO	DOSAGE FORMS	ADVANTAGES	DISADVANTAGES
1.	Polymeric solutions	Increased residence time Increased corneal penetration of drug	Rapid initial drainage rate Bioavailability is valid in animals but minimal in humans.
2.	Phase transition systems	Gel at physiological pH comfortable, Less blurred vision than ointment	No rate control on diffusion Matted eyelids after use
3.	Suspensions	Patient compliance, Best for drugs with slow dissolution.	Drug properties decide performance Loss of both solution and suspended solid.
4.	Ointments	Flexibility in drug choice Improved drug stability	Drug choice limited by partition co-efficient No true sustaining effect
5.	Ocular penetration enhancers	Increased bioavailability of peptides & proteins	Physiochemical properties of the drug Tissue irritation and damage
6.	Emulsions	Prolonged release of drug from vehicle Enhanced pulsed entry	Patient non compliance Blurred vision Possible oil entrapment

7.	Bioadhesives	Increased corneal contact time	Water soluble polymers face the disadvantage of having a short half - life.
8.	Collagen shields	Simple and convenient Drug concentration achieved higher levels in the cornea and aqueous humour	Discomfort Application of shield requires to anesthetize the cornea
9.	Nanoparticles	Patient acceptance Prolonged sustained release of drug	Rapid disappearance from tear poor Costly and technological difficulties.
10.	Vesicular systems (such as liposomes, niosomes, pharmacosomes,)	No tissue irritation & drainage. Patient compliance Prolonged sustained release of drug. Biocompatible & increased residence	Limited drug loading Unstable due to hydrolysis of phospholipids Costly and technological difficulties.

Table 3: Currently Available Insert for Ocular Drug Delivery System

Drug	Types of insert	Transporter
Anti glaucoma		
Timolol	Soluble	HPC,EudragitsRS100
Timolol	Soluble/Bioerodible	HPC;PVA;Carbopol
Timolol and prodrug of Timolol	Soluble/ Bioerodible	HPC;PVA;Carbopol
Timolol	Soluble	HPMC
Pilocarpine	Soluble	HPC/D-Lactose , EudragitsRS100
Pilocarpine	Soluble	PVA,XG,HPMC, EudragitsRS100
Pilocarpine	Soluble	MC,Alginate
Pilocarpine	Soluble	HA,HAE
Pilocarpine	Soluble	HPC,PVM/MA
Pilocarpine	Bioerodible	PVMMA
Pilocarpine	Bioerodible	Gelatin
Pilocarpine	Insoluble (Contact Lens)	HEMM/EGDM
Pilocarpine	Insoluble (Contact Lens)	TEGDMA/MM
Pilocarpine	Insoluble (Osmotic)	Ethylene vinyl acetate
Pilocarpine	Insoluble	
Anti Bacterial Chloramphenicol	Soluble	PVA
Tobramycine /Chloramphenicol	Soluble	Collagen
Tetracycline /Chloramphenicol	Insoluble (Contact Lens)	PMM
Gentamicin	Soluble	Collagen
Gentamicin	Soluble	Collagen
Gentamicin	Soluble	HPC,EC, Carbopol
Gentamicin	Bioerodible	Gelatin
Erythromycine	Soluble	Copolymers of Nvinylpyrrolidone
Antiviral Idoxuridine	Bioerodible	Polypeptide
Trifulurothymidine	Soluble	Collagen
Antiinflammatory Dexamethasone	Soluble	PVA,HPC,EC,CAP,Eudragit
Dexamethasone	Soluble	Collagen
Dexamethasone	Bioerodible	Gelatin
Perdnisolone acetate	Soluble	Collagen
Perdnisolone	Insoluble (Contact Lens)	HEM, N vinylpyrrolidone

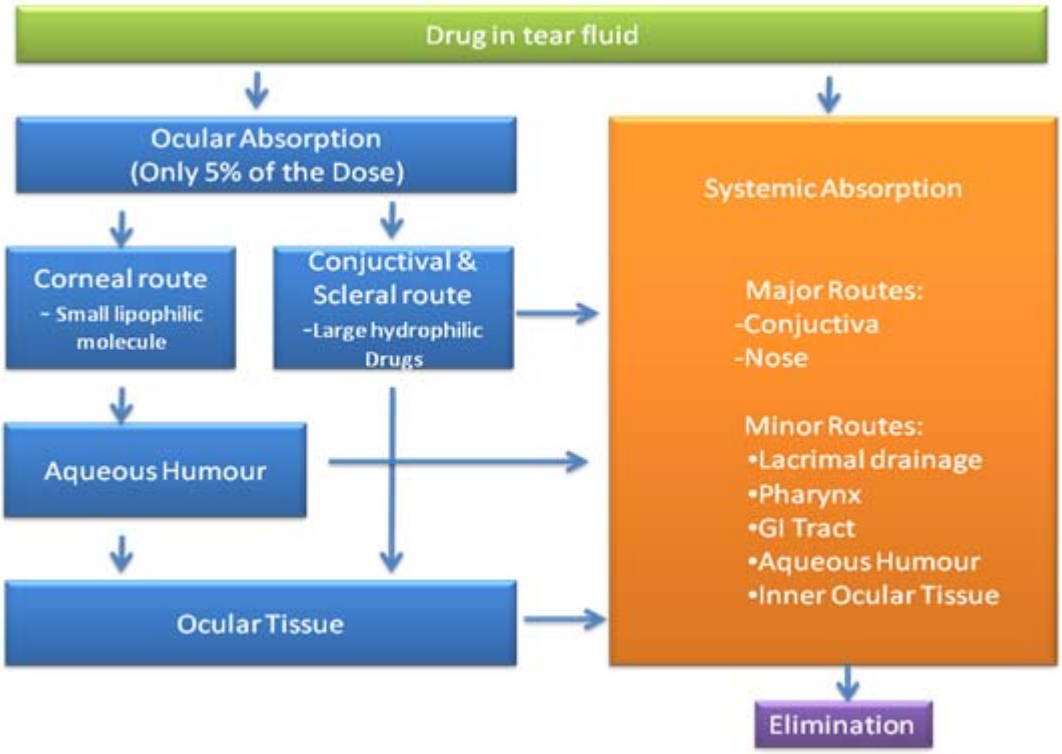

Figure 1: Ocular Drug Absorption

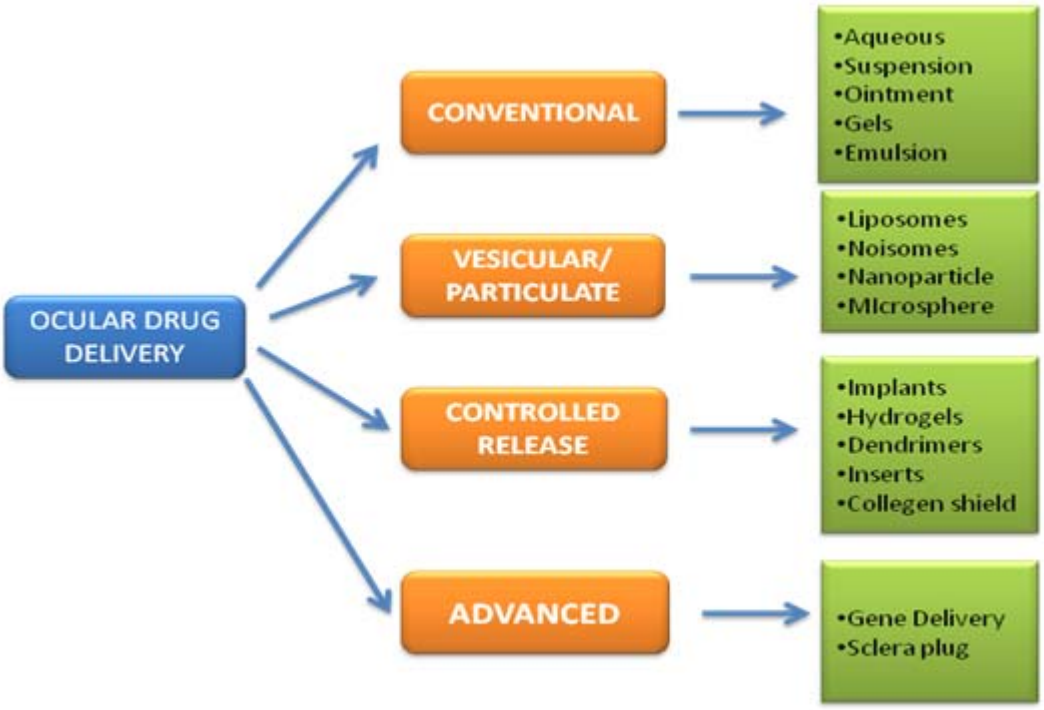

Figure 2: Advance Approaches to Ocular Drug Delivery System

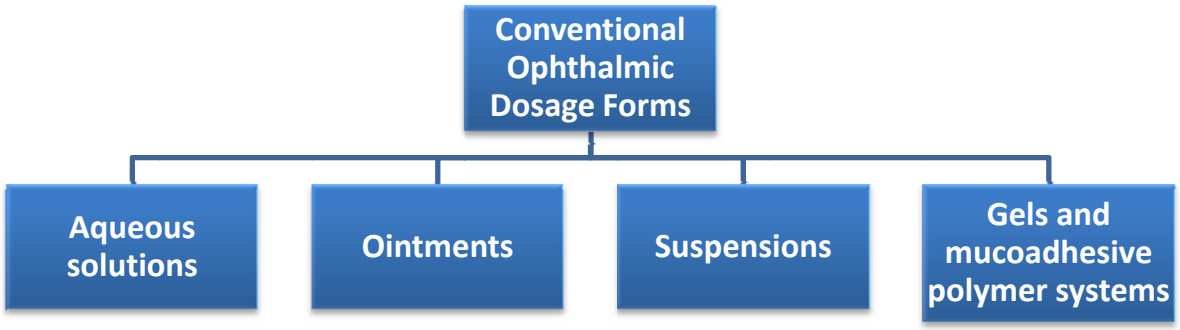

Figure 3: Convectional Ophthalmic Dosage Form

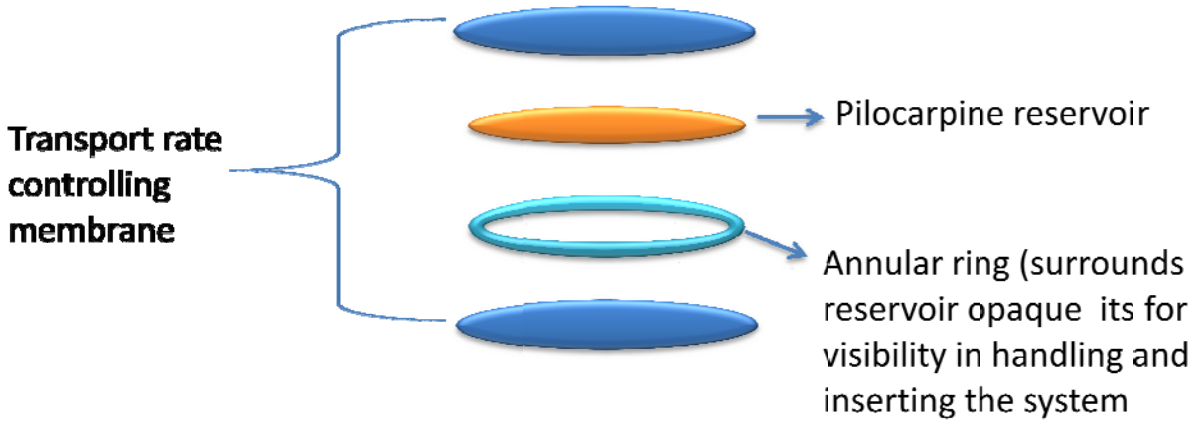

Figure 4: Ocular Insert