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Review Article

DEVELOPMENTS AND ADVANCED APPROACHES OF OPHTHALMIC DRUG DELIVERY SYSTEM: A REVIEW

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ABSTRACT

Ocular drug delivery has been a major challenge for scientists due to its unique anatomy and physiology which contains various types of barriers such as different layers of cornea, sclera and retina including blood aqueous and blood–retinal barriers, choroidal and conjunctival blood flow etc. These barriers cause a significant challenge for delivery of a drug alone or in a dosage form, the conventionally used dosage forms like eye drops, ointments. Delivery to the internal parts of the eye still remains troublesome due to the anatomical and protective structure of the eye. The newly developed particulate and vesicular systems like liposomes, pharmacosomes and discomes are useful in delivering the drug for a longer extent and helpful in reaching the systemic circulation. The most recent advancements of the ocular delivery systems provide the delivery of the genes and proteins to the internal structures which were once inaccessible and thus are of great importance in treating the diseases which are caused due to genetic mutation, failure in normal homeostasis, malignancy but also maintaining the physiological function of eye.

Keywords: Opthalmic drug delivery, Novel drug delivery, Occusert, Eye, Control drug delivery systems, Corneal permeability, Eye, Vesicular systems.

INTRODUCTION

Ocular drug delivery is one of the most interesting and challenging endeavors facing the pharmaceutical scientist for past 10-20 years. As an isolated organ, eye is very difficult to study from a drug delivery point of view. Despite these limitations, improvements have been made with the objective of maintaining the drug for an extended period. Recently, controlled and sustained drug delivery has become the standard in modern Pharmaceutical design and an intensive research have been undertaken in achieving much better drug product effectiveness, reliability and safety.

The eye is a sensory organ that converts light to an electric signal that is treated and interpreted by the brain. Briefly, the eye ball is covered by three layers: an outer fibrous protective layer (sclera and cornea), a middle vascular layer(choroid),and an inner nervous layer (retina). The cornea is a clear, transparent, thin avascular tissue that is composed of five layers: epithelium, bowmans's layer, stroma, Descemet's membrane and endothelium[1-5](fig.1). Eyes can get infections from bacteria, fungi or viruses. Eye infections can occur in different parts of the eye and can affect just one eye or both. Common eye infections are Conjunctivitis, Corneal ulcers & Endophthalmitis.

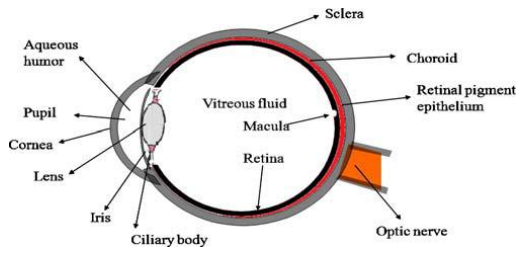


Fig. 1: Anatomy of the human eye

Drugs administered by instillation must penetrate the eye and do so primarily through the cornea followed by the non-corneal routes. These non-corneal routes involve drug diffusion across the conjunctiva and sclera and appear to be particularly important for drugs that are poorly absorbed across the cornea.

A. Corneal permeation

The permeation of drugs across the corneal membrane occurs from the precorneal space. Thus, the mixing and the kinetic behavior of drug disposition in tears have a direct bearing on efficiency of drug absorption into the inner eye. The productive absorption of most ophthalmic drugs results from diffusion process across corneal membrane. The efficiency of absorption process is a function of rate and extent at which the transport processes occur. The flux of any drug molecule across the biological membrane depends on the physicochemical properties of the permeating molecule and its interaction with the membrane. The extent to which the transport or absorption process occurs is also function of physiological mechanism of precorneal fluid drainage or turnover. In terms of transcorneal drug permeation, the cornea can be considered to consist of three primary layers (epithelium, stroma and endothelium). The epithelium and endothelium contain on the order of a 100 fold greater amount of lipid material than the stroma. Consequently, depending on the physicochemical properties of a diffusing drug, the resistance offered by the individual layers varies greatly. Epithelium, being lipoidal, represents a diffusion barrier offering high resistance to ionic or other aqueous soluble or polar species. In contrast, compounds with relatively low polarity encounter a greater diffusional resistance in the hydrophilic stroma layer. This frequently cited concept of drug permeation across the corneal membrane is referred to as ―differential solubility concept.

B. Non-corneal permeation

Primary mechanism of drug permeation is the sclera is likely to be diffusion across the intercellular aqueous media in the case of structurally similar corneal stroma. Therefore the possibility of partitioning mechanism cannot be eliminated. Although like cornea, the conjunctiva is composed of an epithelial layer covering an underlying stroma, the conjunctival epithelium offers substantially less resistance than the corneal epithelium[6].

Advantages of Ocular Drug Delivery Systems

Various advantages of ocular drug delivery system are given below.

- Easy convenience and needle free drug application without the need of trained personnel assistance for the application, self medication, thus improving patient compliances compared to parenteral routes.
- Good penetration of hydrophilic, low molecular weight drugs can be obtained through the eye.
- Rapid absorption and fast onset of action because of large absorption surface area and high vascularisation. Ocular administration of suitable drug would therefore be effective in emergency therapy as an alternative to other administration routes.
- Avoidance of hepatic first pass metabolism and thus potential for dose reduction compared to oral delivery.

Disadvantages

Various disadvantages of ocular drug delivery system are given below.

- The physiological restriction is the limited permeability of cornea resulting into low absorption of ophthalmic drugs.
- A major portion of the administered dose drains into the lacrimal duct and thus can cause unwanted systemic side effects.
- The rapid elimination of the drug through the eye blinking and tear flow results in a short duration of the therapeutic effect resulting in a frequent dosing regimen[7,8].

Various problems encountered in poor bioavailability of the eye installed drugs are

- Binding by the lachrymal proteins
- Drainage of the instilled solutions
- Lachrimation and tear turnover
- Limited corneal area and poor corneal
- Metabolism
- Non-productive absorption/adsorption
- Tear evaporation and permeability[9](fig.2)

To enhance the amount of the active substances reaching the target tissue or exerting a local effect in the cul de sac, Numerous strategies were developed to increase thec (fig.3) by prolonging the contact time between the drug and cornea/ conjunctival epithelium such as muco adhesive polymers, hydro gel insitu gelling system, colloidal system like nanoparticles, microspheres, vesicular system, dendrimers, solid dosage forms ocular inserts, iontophorosis and many recent developments[10].

Routes of ocular drug delivery

There are several possible routes of drug delivery into the ocular tissues. (Figure 2) The selection of the route of administration depends primarily on the target tissue.

A. Topical route

Typically topical ocular drug administration is accomplished by eye drops, but they have only a short contact time on the eye surface. The contact, and thereby duration of drug action, can be prolonged by formulation design (e.g. gels, gellifying formulations, ointments, and inserts).

B. Subconjunctival administration

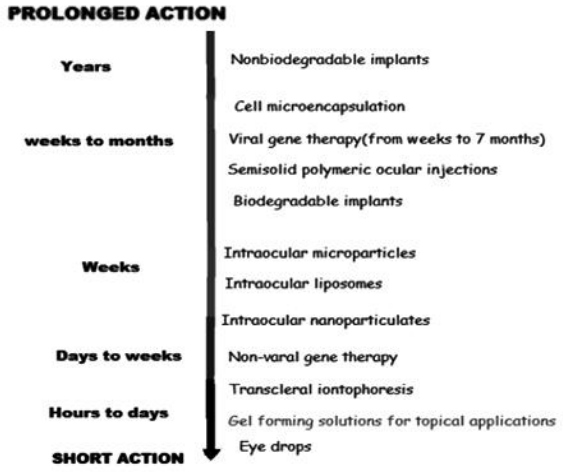
Traditionally subconjunctival injections have been used to deliver drugs at increased levels to the uvea. Currently this mode of drug delivery has gained new momentum for various reasons. The progress in materials sciences and pharmaceutical formulation have provided new exciting possibilities to develop controlled release formulations to deliver drugs to the posterior segment and to guide the healing process after surgery.

C. Intravitreal administration

Direct drug administration into the vitreous offers distinct advantage of more straightforward access to the vitreous and retina. It should be noted; however that delivery from the vitreous to the choroid is more complicated due to the hindrance by the RPE (Retinal Pigment Epithelium) barrier. Small molecules are able to diffuse rapidly in the vitreous but the mobility of large molecules, particularly positively charged, is restricted[11].

Interests of novel ophthalmic drug delivery

Ophthalmic drug delivery is one of the most interesting and challenging endeavors facing the pharmaceutical scientist[12]. The landscape of ophthalmic drug delivery is highly competitive and rapidly evolving. New classes of pharmaceuticals and biologics are fueling the demand for novel drug delivery. The main aim of pharmacotherapeutics is the attainment of effective drug concentration at the site of action for the sufficient period of time to elicit a response. Most of the formulation efforts aim at maximizing ocular drug absorption through prolongation of the drug residence time in the cornea and conjunctival sac, as well as to slow drug release from the delivery system and minimize precorneal drug loss. Various ophthalmic formulations and their residence time period in the ocular cavity are given below[13](Figure)



CONVENTIONAL DELIVERY SYSTEMS

Liquids

Eye drops/lotion- Eye drops may be solutions or suspensions and are comparatively convenient, safe, immediately active and acceptable to patients. An eye drops is sterile, contains a preservative (if not singly used only), is isotonic, has a pH of about 7.4 for the patient comfort and has a limited shelf life after opening (if used more than one time). Eye lotions are isotonic, sterile solutions for the irrigation of the eye, usually as a single use first aid treatment. Polymers are frequently added to ophthalmic solutions and suspensions in order to increase the viscosity of the vehicle, this prolongs contact with the cornea, so that enhancing bioavailability. Generally, the high molecular weight hydrophilic polymers those are unlikely to cross the biological membrane. They include poly vinyl alcohol, hyaluronic acid, dextran, gellan, methylcellulose, hydroxymethylcellulose[14,15].

Eye Ointments

Ointments are the semi solid preparations intended for external application. They are usually formulated using mixture of semisolid and solid hydrocarbons (paraffin) which have a melting or softening point close to the body temperature and are nonirritating to the eye. Ointments are useful in improving the drug bioavailability and in sustaining drug release. Ointments suffer with relatively poor patient compliance due to blurring of vision. So, they are often used as night time medication[16].

Ocuserts and Lacrisert

Ocular insert (Ocusert) are sterile preparation that prolong residence time of drug with a controlled release manner and negligible or less affected by nasolacrimal damage. Inserts are available in different varieties depending upon their composition and applications. Lacrisert is a sterile rod shaped device for the treatment of dry eye syndrome and keratitis sicca and was introduced by Merck, Sharp and Dohme in 1981. They act by imbibing water from the cornea and conjunctiva and form a hydrophilic film which lubricates the cornea[17].

Vesicular System

Liposomes

Liposomes are biocompatible and biodegradable lipid vesicles made up of natural lipids and about 25–10 000 nm in diameter.

They are having an intimate contact with the corneal and conjunctival surfaces which is desirable for drugs that are poorly absorbed, the drugs with low partition coefficient, poor solubility or those with medium to high molecular weights and thus increases the probability of ocular drug absorption[18].The corneal epithelium is thinly coated with negatively charged mucin to which the positive charged surface of the liposomes may bind[19].Liposomes containing GCV were formulated by a reversed phase evaporation method and in vivo pharmacokinetic evaluation was performed in a rabbit Recent Perspectives in Ocular Drug Delivery 1203 model. Permeability of GCV solution was compared with the liposomal formulation containing GCV. Transcorneal permeability and area under the curve (AUC) were was 3.9 and 1.7 fold higher than the solution. Ocular tissue distribution was higher in the sclera, cornea and vitreous humor from liposomal formulation[20].

Niosomes and Discomes

The major limitations of liposomes are chemical instability, oxidative degradation of phospholipids, cost and purity of natural phospholipids. To avoid this niosomes are developed as they are chemically stable as compared to liposomes and can entrap both hydrophobic and hydrophilic drugs. They are non toxic and do not require special handling techniques. Niosomes are nonionic surfactant vesicles that have potential applications in the delivery of hydrophobic or amphiphilic drugs. Vyas and co workers reported that there was about 2.49 times increase in the ocular bioavailability of timolol maleate encapsulated in niosome as compared to timolol maleate solution. Non-ionic surface active agents based discoidal vesicles known as (discomes) loaded with timolol maleate were formulated and characterized for their *in vivo* parameters. *In vivo* studies showed that discomes released the contents in a biphasic profile if the drug was loaded using a pH gradient technique.

Discomes may act as potential drug delivery carriers as they released drug in a sustained manner at the ocular site[21].

Pharmacosomes

This term is used for pure drug vesicles formed by the amphiphilic drugs. Any drug possessing a free carboxyl group or an active hydrogen atom can be esterified (with or without a spacer group) to the hydroxyl group of a lipid molecule, thus generating an amphiphilic prodrug. The amphiphilic prodrug is converted to pharmacosomes on dilution with water. The pharmacosomes show greater shelf stability, facilitated transport across the cornea, and a controlled release profile[22].

Control Delivery Systems

Implants

Implants have been widely employed to extend the release in ocular fluids and tissues particularly in the posterior segment. Implants can be broadly classified into two categories based on their degradation property

(1) biodegradable

(2) non-biodegradable.

With implants, the delivery rate could be modulated by varying polymer composition. Implants can be in the form of solid, semi-solid or particulate based delivery systems. These implants have been applied in the treatment of diseases affecting both anterior and posterior segments of the eye. The diseases include anterior segment disorders like glaucoma filtering surgery and posterior segment disorders like proliferative vitroretinopathy, CMV retinitis, endophthalmitis, and posterior capsule opacification.

Iontophoresis

In Iontophoresis direct current drives ions into cells or tissues. For iontophoresis the ions of importance should be charged molecules of the drug. Positively charged of drug are driven into the tissues at the anode and vice versa. Ocular iontophoresis delivery is not only fast, painless and safe but it can also deliver high concentration of the drug to a specific site. Iontophoretic application of antibiotics in eye not only increases their bactericidal activity but also reduce the severity of disease. Similarly application of anti-inflammatory agents can reduce vision threatening side effects[23,24].

Dendrimer

Dendrimers can successfully used for different routes of drug administration and have better water-solubility, bioavailability and biocompatibility. Vandamme and co workers have developed and evaluated poly (amidoamine) dendrimers containing fluorescein for controlled ocular drug delivery. They determined the influence of size, molecular weight and number of amine, carboxylate and hydroxyl surface groups in several series of dendrimers. The residence time was longer for the solutions containing dendrimers with carboxylic and hydroxyl surface groups[25].

Cyclodextrin

Cyclodextrins (CDs) are cyclic oligosaccharides capable of forming inclusion complexes with many guest molecules.23 CD complexes are reported to increase corneal permeation of drugs like dexamethasone, dexamethasone acetate, cyclosporine and pilocarpine resulted in higher bioavailability than the conventional eye drops. This complexation of CD does not interrupt the biological membrane compared to conventional permeation enhancer like benzalkonium chloride. Due to inclusion, the free drug is not available, so drugs with inherent irritant properties can be successfully delivered by this approach. CD molecules are inert in nature and were found to be non irritant to the human and animal eye[26].

Contact lenses

Water soluble drugs soaked in drug solutions can be absorbed through Contact lenses. The drug saturated contact lenses are placed in the eye which releases the drug in eye for a long period of time. For prolongation of ocular residence time of the drugs, hydrophilic contact lenses can be used. Greater penetration of fluorescein has been reported by Bionite lens made from hydrophilic polymer (2-hydroxy ethyl methacrylate) in human[27].

Collagen Shield

Collagen shield basically consist of cross linked collagen, fabricated with foetalcalf skin tissue and developed as a corneal bandage to promote wound healing. Topically applied antibiotic conjugated with the shield is used to promote healing of corneal ulcers. Tear fluid makes these devices soft and form a thin pliable film which is having dissolution rate up to 10, 24 or 72 hours. Because of its structural stability, good biocompatibility and biological inertness, collagen film proved as a potential carrier for ophthalmic drug delivery system. Collagen ophthalmic inserts are available for delivery of pilocarpine to the eye[28].

Microemulsion

Microemulsion is dispersion of water and oil stabilized using surfactant and cosurfactant to reduce interfacial tension and usually characterized by small droplet size (100 nm), higher thermodynamic stability and clear appearance. Selection of aqueous phase, organic phase and surfactant/cosurfactant systems are critical parameters which can affect stability of the system. Optimization of these components results in significant improvement in solubility of the drug molecule e.g. indomethacin, chloramphenicol for eye diseases[29].

Nanosuspensions

Nanosuspensions have emerged as a promising strategy for the efficient delivery of hydrophobic drugs because they enhanced not only the rate and extent of ophthalmic drug absorption but also the intensity of drug action with significant extended duration of drug effect. For commercial preparation of nanosuspensions techniques like media milling and highpressure homogenization have been used. The higher drug level in the aqueous humour was reported using Eudragit nanosuspensions for the ophthalmic controlled delivery of ibuprofen[30].

Microneedle

As an alternative to topical route Researchers have developed microneedle to deliver drug to posterior segment. The extent of lateral and transverse diffusion of sulforhodamine was reported to be similar across human cadaver sclera. Microneedle had shown prominent in vitro penetration into sclera and rapid dissolution of coating solution after insertion while in vivo druglevel was found to be significantly higher than the level observed following topical drug administration like pilocarpine[31].

Prodrugs

The ideal Prodrugs for ocular therapy not only have increased lipophilicity and a high partition coefficient, but it must also have high enzyme susceptibility to such an extent that after corneal penetration or within the cornea they are either chemically or enzymatically metabolized to the active parent compound. The partition coefficient 138 of ganciclovir found to be increased using an acyl ester prodrug, with substantially increased the amount of drug penetration to the cornea which is due to increased susceptibility of the ganciclovir esters to undergo hydrolysis by esterases in the cornea[32].

Penetration Enhancers

Transport of drug across the cornea is increased by increasing the permeability through corneal epithelial membranes. For such purpose Penetration enhancers can be used. Examples of enhancers include actin filament inhibitors, surfactants, bile salts, chelators, and organic compounds. Selection of enhancer is critical due to unique characteristics and great sensitivity of the corneal conjunctival tissues. Penetration enhancers themselves can penetrate the eye and may lead to unknown toxicological complications e.g., benzalkonium chloride(BAC) was found to accumulate in the cornea for days[33].

Mucoadhesive Polymers

They are basically macromolecular hydrocolloids with plentiful hydrophilic functional groups, such as hydroxyl, carboxyl, amide and sulphate having capability for establishing electrostaticinteractions. A mucoadhesive drug formulation for the treatment of glaucoma was developed using a highly potent beta blocker drug, levobetaxolol (LB) hydrochloride and partially neutralized poly acrylic acid (PAA). Complexes were prepared with varying degrees of drug loading, such that the same PAA chain would have free -COOH groups for mucoadhesion along with ionic complexes of LB with COO- groups. Thin films of the complexes dissociated to release the drug by ion exchange with synthetic tear fluid[34].

Phase Transition Systems/Insitu gel system

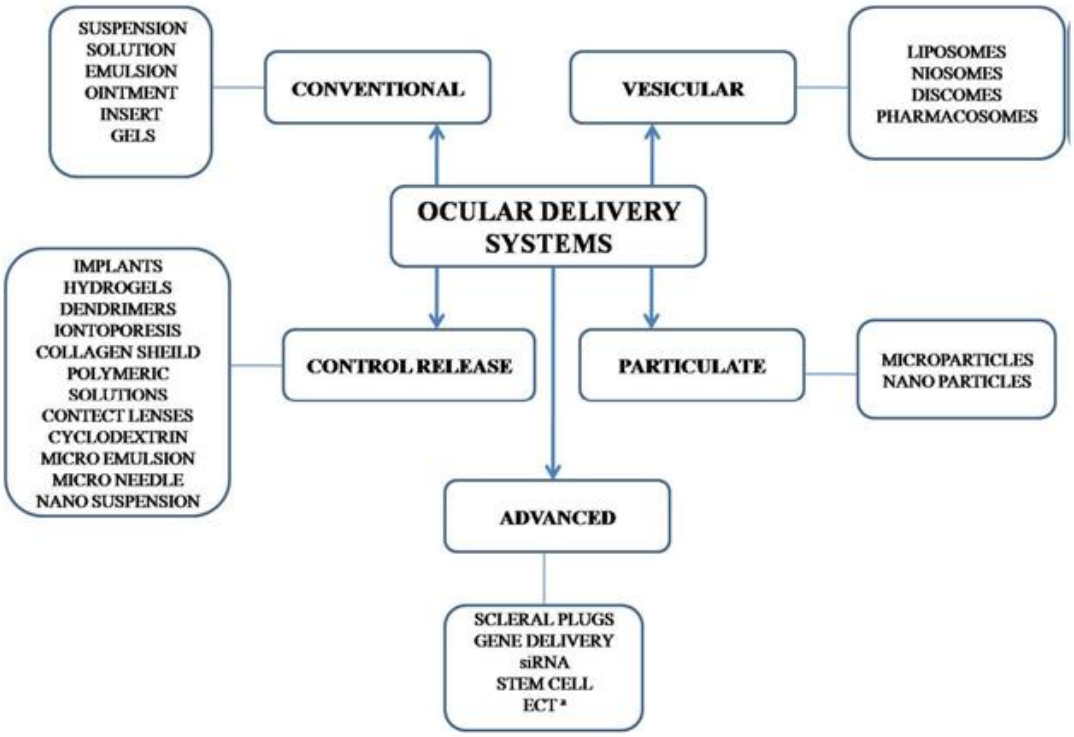
Phase transition of the formulation from the liquid form to the gel or solid phase occurs when these systems instilled into the cul-de-sac of eye lead to increase the viscosity of a drug formulation in the precorneal region results in increased bioavailability, due to slower drainage from the cornea. These systems can be influenced by pH, temperature or by ion activation. A sol to gel system with Mucoadhesive property to deliver the steroid fluorometholone to the eye was prepared by Middleton and Robinson[35].

Particulates (nanoparticles and microparticles)

Microspheres and Nanoparticales

These are the promising drug carriers for ophthalmic applications; the drug absorption is enhanced significantly in the eye in comparison to eye drop solution owing to the much slower ocular elimination rate of particles. Smaller particles are better tolerated by the patients than longer particles therefore nanoparticles may represent very comfortable ophthalmic prolonged action delivery systems However, albumin microspheres reportedly cause adverse in suppressing corneal inflammation reaction in the eye[36].

The maximum size limit for microparticles for ophthalmic administration is about 5-10 mm above which a scratching feeling in the eye can result upon ocular instillation. That is why microspheres and nanoparticles are promising drug carriers for ophthalmic application. Nanoparticles are prepared using bioadhesive polymers to provide sustained effect to the entrapped drugs. An optimal corneal penetration of the encapsulated drug was reported in presence of bioadhesive polymer chitosan. Similarly Poly butyl cyanoacrylate nanoparticles,containing pilocarpine into collagen shields, showed greater retention and activity characteristics with respect to the controls[37].



Advanced Delivery System

Cell Encapsulation

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. The polymer implant containing genetically modified human RPE cells secretes ciliary neurotrophic factor into the vitreous humour of the patient's eyes[38].

Gene Therapy

Along with tissue engineering, gene therapy approaches stand on the front line of advanced biomedical research to treat blindness arising from corneal diseases, which are second only to cataract as the leading cause of vision loss. Several kinds of viruses including adenovirus, retrovirus, adeno-associated virus, and herpes simplex 140 virus, have been manipulated for use in gene transfer and gene therapy applications[39]. Topical delivery to the eye is the most expedient way of ocular gene delivery.

Stem cell Therapy

Emerging cell therapies for the restoration of sight have focused on two areas of the eye that are critical for visual function, the cornea and the retina. Current strategy for management of ocular conditions consists of eliminating the injurious agent or attempting to minimize its effects.The most successful ocular application has been the use of limbal stem cells, transplanted from a source other than the patient for the renewal of corneal epithelium[40].

Protein and Peptide therapy

Delivery of therapeutic proteins/ peptides has received a great attention over the last few years. The intravitreous injection of ranibizumab is one such example. The designing of optimized methods for the sustained delivery of proteins and to predict the clinical effects of new compounds to be administered in the eye, the basic knowledge of Protein and Peptide is required[41].

MARKETED OPTHALMIC PRODUCTS

Brand Name	Drug	Dosage forms	Use
Dichol	Carbachol	Sterile solution and prefilled syringes	In ophthalmic surgery
Refresh Tears	Hydroxy propyl methyl cellulose	Eyedrops	In dryness of eye and as eye lubricant
Restasis	Cyclosporine	Emulsion	In dry eye
Refresh Classic	Artificial tear fluid	Single use vials	Relieves dry and irritated eyes
Ciplox	Ciprofloxacin	Eyedrops	In eye infection and conjunctivitis
Geltear	Carbomer	Bio-adhesive gel	As a lubricant in burning, irritated and dried eye
Timolol xe	Timolol maleate	Insitu gel	For dried eye and Keratoconjunctivitis
Acivir eye	Acyclovir	Ointment	For eye infection
Ocupol	Polymixin B	Eye drops and ointment	In bacterial infection, corneal ulcer
Pred Forte	Prednisolone acetate	Suspension	As anti allergic and anti-inflammatory
Chloromycetin	Chloramphenicol palmitate	Ointment	In conjunctivitis and eye inflammation
Betnisol N	Betamethasone	Eye drop	In eye infection
Dexcin	Dexamethasone	Eye drop	In eye infection

CURRENT TRENDS AND FUTURE CHALLENGES

The most exciting opportunities in controlled drug delivery lie in the arena of responsive delivery systems to deliver a drug precisely to a targeted site. Much of the development of novel materials in controlled drug delivery is focusing on the preparation and use of these responsive polymers with specifically designed macroscopic and microscopic structural and chemical features.

Small, ocular solid dosage forms, in particular gel-forming mini-tablets and erodible inserts, show interesting in vivo performances and allow for therapeutic levels to be obtained over an extended period of time in the tear film and anterior chamber. Sustained release can be modulated by the composition and manufacturing procedure. Mucoadhesive mini-tablets or insert are promising ocular drug delivery systems to treat external and intraocular eye infections and diseases that require frequent eye drops instillation in order to maintain therapeutic drug levels. The new biomaterials, tailor-made copolymers have excellent potential for drug delivery but the formulations based on them have still to go a long way to find their path in actual clinical practice. Successful development of these novel formulations will obviously require assimilation of a great deal f emerging information about the chemical nature and physical structure of these new materials. However the attempts based on these principles are surely a route to better drug bioavailability through the stubborn sites (as eye) for drug delivery.

Challenges for effective front of the eye (FOTE) drug delivery include somehow minimizing the use of preservatives in the drug solution being applied, and avoiding excess eye drop solution being drained through the nasolachrymal duct with potential systemic absorption into the circulatory system. Currently available devices for improving FOTE drug delivery using eye drops include the Visine pure tears single drop dispenser, which contains no preservatives.

The Pfizer Xal-ease FOTE drop delivery device which encloses a traditional eye drop bottle and the Autosqueeze and Autodrop devices developed in the UK, with Royal national Institute for the Blind, which clip into bottles of the eye drop. Recent innovations in FOTE drug delivery devices include the Eye-Instill produced by Med-Instill Inc., which have one way valve to ensure multiple dosings of sterile, preservative free drug solution and the OptiMyst device, which dispenses medication as a mist rather than as a drop. The latter provides much less medication per dose, below blink and lachrymation thresholds.

The VersiDoser TM drug delivery system under development by Mystic pharmacueticals, Inc., holds the near term potential for setting new standard for effective FOTE drug delivery. The VersiDoser platform utilizes the pack with Novel multidose delivery device that dispenses the drug into the eye in a predictable manner irrespective of the orientation of the device and the eye. These devices are capable of the self administered precision dosing in the 12-15µl range and provide automatic dose counters. Preservative free packaging and ergonomic design will significantly enhance compliance, ease of use and therapeutic benefits for elderly and pediatric patients[42].

CONCULSION

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. An ideal therapy should maintain effective levels of drug for the longer duration following a single application. Drug delivery by topical and intravitreal routes cannot be considered safe, effective and patient friendly.Designing these innovative techniques has given an unprecedented momentum for their protection by intellectual rights. In future, much of the emphasis will be given to achieve non-invasive 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.

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