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A Review on Recent Studies and Advances in Ocular Drug Delivery System

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ABSTRACT

Ocular drug delivery is one of the most fascinating and challenging tasks facing the Pharmaceutical researchers. One of the major barriers of ocular medication is to obtain and maintain a therapeutic level at the site of action for prolonged period of time. Ocular drug delivery is hampered by the barriers protecting the eye. For the treatment of the anterior segment of the eye, various droppable products to prolong the retention time on the ocular surface have been introduced in the market. On the other hand, direct intravitreal implants, using biodegradable or non-biodegradable polymer technology, have been widely investigated for the treatment of chronic vitreo-retinal diseases. There is urgent need to develop ocular drug delivery systems which provide controlled release for the treatment of chronic diseases, and to reduce the dosing frequency and invasive treatment. Current momentum in the invention of new drug delivery systems hold a promise toward much improved therapies for the treatment of vision-threatening disorders.

Keywords: Ophthalmic drug delivery system, ocular barriers, conventional formulation, ocusert.

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INTRODUCTION

The eye can be broadly classified into two segments: anterior and posterior. Structural variation of each layer of ocular tissue can pose a significant barrier following drug administration by any route, i.e., topical, systemic, and periocular. For the treatment of the anterior segment of the eye (cornea, conjunctiva, sclera, anterior uvea), usually topical ocular eye-drops are used. An eye-drop, irrespective of the instilled volume, often eliminates rapidly within five to six minutes after administration, and only a small amount (1–3%) of an eye-drop actually reaches the intraocular tissue[1] .Thus, it is difficult to provide and maintain an adequate concentration of drug in the precorneal area. To improve ocular drug bioavailability, there is a significant effort directed towards new drug delivery systems for ophthalmic administration.

Ocular disorders

According to location of diseases, ocular disorders are grouped as periocular and intraocular.

A. Periocular disorders:

- **Blepharitis:** An infection of lid structures (usually by staphylococcus aureus) with concomitant seborrhoea, rosacea, a dry eye and abnormalities in lipid secretions.
- **Conjunctivitis:** The condition in which redness of eye and presence of a foreign body sensation are evident. There are many causes of conjunctivitis but the great majority are the result of acute infection or allergy.
- **Keratitis:** The condition in which patient have a decreased vision ,ocular pain, red eye, and often a cloud / opaque cornea .It is mainly caused by bacteria ,viruses, fungi etc.
- **Trachoma**: This is caused by the organism Chlamydia trachoma is; it is the most common cause of blindness in North Africa and Middle East.

B. Intraocular disorders: These conditions are difficult to manage and include intraocular infections: i.e. infections in the inner eye, including the aqueous humour, iris, vitreous humour and retina.

- **Glaucoma:** More than 2% of the population over age 40 years have this disorder in which an increased intraocular pressure greater than 22 mg Hg ultimately compromises blood flow to retina and thus causes death of peripheral optic nerves.

Routes of delivery

There are three main routes commonly used for administration of drugs to the eye [2] topical, intraocular and systemic. The topical route is the most common method to administer a medication to the eye .Introducing the drug directly to the conjuctival sac localizes drug effects, facilitates drug entry that is otherwise hard to achieve with systemic delivery and avoids first pass metabolism. The intraocular route is more difficult to achieve practically. Now research is concentrating on the development of intravitreal

injections and use of intraocular implants to improve delivery to eye. In systemic route, several studies have shown that some drugs can distribute into ocular tissues following systemic administration. Oral administration of carbonic anhydrase inhibitors including acetazolamide, methazolamide demonstrates the capacity of a systemic drug to distribute into the ciliary process of eye. To improve ocular drug bioavailability, there is a significant effort directed towards new drug delivery systems for ophthalmic administration. This should focus three representative areas of ophthalmic drug delivery systems: polymeric gels, colloidal systems, cyclodextrins and collagen shields. Hydrogels generally offer a moderate improvement of ocular drug bioavailability with the disadvantage of blurring of vision.

ADVANTAGES OF OCULAR DRUG DELIVERY SYSTEMS [3]

- Increased accurate dosing. To overcome the side effects of pulsed dosing produced by conventional delivery.
- To provide sustained and controlled delivery.
- To increase the ocular bioavailability of drug by increasing the corneal contact time.
- To circumvent the protective barriers like drainage, lacrimation and conjuctival absorption.
- To provide better housing of delivery system.

EXCIPIENTS USED IN OPHTHALMIC DRUG DELIVERY SYSTEMS [4]

The inactive ingredients in ophthalmic solutions are necessary to perform one or more the following functions

- Adjust concentration and tonicity,
- Buffer and adjust pH,
- Stabilize the active ingredients against decomposition,
- Increase solubility,
- Impart viscosity.

The use of unnecessary ingredients is to be avoided, and the use of ingredients solely to impart a colour, odour, or flavour is prohibited.

Buffer solutions

The pH and buffering of an ophthalmic solution is probably equal importance to proper preservation. The stability of most commonly used ophthalmic solutions is largely controlled by the pH of their environment. The stability of nearly all products can be enhanced by refrigeration. Except for those few in which a decrease in solubility and precipitation might occur. In addition to stability effect, pH adjustment can influence comfort, safety, and activity of the product. Ideally, would be buffered to a pH of 7.4, considered the normal physiological pH of tear fluid. The pH values of ophthalmic solutions are adjusted within the range to provide an acceptable shelf life. They are buffered adequately to maintain stability within the range for at least 2 years.

Reasons for buffering an ophthalmic solution

To prevent unwanted pH changes caused by hydroxyl ion release from the glass in which the solution is stored. In case of a pH-dependent degradation of the active principle, a buffer should be used for stabilization. In case of a pH dependent solubility, a buffer can be used to dissolve the required amount of drug. On the other hand there are also limitations to the use of buffers. First of all, the limited buffer capacity of the lachrymal fluid precludes the use of strong buffers outside the pH range of 6.8 -7.6. In addition, adherence to a pH as close to the physiological pH as possible is important for preventing local precipitations of the drug and minimizing deterioration after administration. For the formulation of eye drops, phosphate buffer of pH 7.4, used in an eye drop, was chosen as a starting point.

Tonicity and Tonicity adjusting agents

It should be adjusting the tonicity of an ophthalmic solution correctly. In compounding an eye solution, it is more important to consider the sterility, stability, and preservative. A range of 0.5% to 2.0% NaCl equivalency does not cause pain and a range of about 0.7%- 1.5% should be acceptable to most persons.

Common tonicity-adjusting ingredients:

- Sodium chloride
- Potassium chloride
- Buffer salts
- Dextrose
- Glycerine
- Propylene glycol
- Mannitol

Preservatives used in ophthalmic solutions [5]

All manufactured ophthalmic solutions be sterile preservatives included as a major component of all multiple-dose eye solutions for the primary purpose of maintaining that sterility in the opened product over it life time of its use. Packaging ophthalmic solutions in the popular plastic eye drop container has reduced, but not completely eliminated, the chances of inadvertent contamination. There can be a “suck-back” of an unreleased drop when pressure on the bottle is released. If the tip is allowed to touch a non-sterile surface, contamination may be introduced. The plastic eye drop container in order to minimise the hazards of contamination. The cross contamination hazard can be eliminated by the use of packages containing small volumes designed for single application only.

- Preservatives should not be used in a corneal storage media.
- Packaging for multidose no preserved preparations.
- Drug administered in dry form in offer no preserved choice for the formulator.

The choice of preservatives is limited only a few chemicals that have been found, to be safe and effective. They are

- Benzalkonium chloride
- Thimerosal
- Methyl and propyl paraben
- Phenyl ethanol
- Chlorhexidine
- Polyaminopropyl biguanide

MANUFACTURING ENVIRONMENT

Aside from drug safety, stability, efficacy and shelf-life consideration associated with tonicity, pH, and buffer capacity. The major design criteria of an ophthalmic solution are the additional safety criteria of sterility, preservation efficacy, and free from extraneous foreign particulate matter. These environmentally controlled must meet the requirement of class 100,000 space in all areas where open contain and closures are not exposed, or where product filling and capping operations are not taking place. Often there design criteria are coupled with laminar air flow concepts.

MANUFACTURING TECHNIQUES

Aqueous ophthalmic solutions are manufactured by methods that call for the dissolution of the active ingredient and all or portion of the excipients in to all or a portion of the water and sterilization of this solution by heat or by sterilizing filtration through sterile depth or membrane and filter receptacle. If complete at this point, such as previously sterilized solutions of viscosity-imparting agents, preservatives, and so on, and the batch is brought to final volume with additional sterile water.

EQUIPMENTS USED IN PREPARATION OF OPHTHALMIC PREPARATIONS

The design of equipment for use in controlled environment area follows similar principles, for the manufacture of sterile ophthalmic solutions. All tanks, valves, pumps, and piping must of the best available grade of corrosion stainless steel. This precaution is particularly important when laminar flow is used to control the immediate environment around the filling and capping operation. Some of the newer and more potent drugs, like the prostaglandins, which are produced at very low concentrations in the finished formulations, may require special precautions during compounding and processing in order to prevent loss of actives due to absorption adsorption to the walls of fill lines and or storage tanks.

PACKAGING MATERIALS

Eye drops have been packaged almost entirely in a plastic dropper bottle. The designed plastic dropper bottle is convenience of use by the patient, decreased contamination potential, lower weight, and lower cost. The plastic bottle has the dispensing tip as an integral part of the package. The plastic bottle and dispensing tip is

made of low density polyethylene (LDPE) resin. The LDPE resins used are compatible with a very wide range of drugs and formulation components. The plastic dropper bottles are also permeable to water. The disadvantage is their sorption, leaching and permeability characteristics. This can be achieved by using a resign containing an opacifying agent such as titanium dioxide, by placing an opaque sleeve over the containers. If the drug is light sensitive, additional package protection may be required. Use of an ETO(ethylene oxide) sterilized PE, PP and/or PET container to improve the stability of an aqueous pharmaceutical composition, in particular to improve the stability of a composition being susceptible to oxidative degradation.

ASSESSMENT OF PERFORMANCE OF OPHTHALMIC FORMULATIONS

Pharmacokinetics

Rabbits

Assessment of the performance of a modified-drug-release dosage form relies upon changes in bioavailability. When dealing with systemically administered dosage forms, kinetic studies of plasma levels are the basic tool to establish bioavailability. Needless to say, plasma levels are irrelevant to assess ocular bioavailability of topically administered ophthalmic drugs. However, assessment of the performance of a modified-release ophthalmic drug delivery system is based upon pharmacokinetic and/or pharmacodynamic studies. There is a long history of invasive studies (e.g., aqueous humor levels) in animals, mainly in albino rabbits. This is because the rabbit is a very convenient animal in which to assess transcorneal penetration as a function of various factors such as salt, pH, adjuvants, etc. The rabbit and human eye do exhibit some similarities; the cornea is very similar in both species (but for the absence of Bowman's membrane in rabbits) and the aqueous humor composition is very similar in both species. However, essentially, rabbits and humans were not created equal in terms of eye physiology16. Rabbits blink only a few times per hour whereas humans blink 15–20 times per minute. Tear turnover is approximately 7% per minute in rabbits, compared to 16% in humans. The rabbit has a third eyelid—the nictitating membrane. This structure does not exist in humans. Also, the drainage rate constant is approximately 0.545/min in rabbits and three times larger, approximately 1.545/min in humans. In general, therefore, the respective precorneal parameters between rabbit and human are dissimilar. This means that formulation modified to change their behaviour in the front of the cornea can act differently in the two species. It is possible to obtain aqueous humor samples from patients implications. However, it provides a unique opportunity to compare aqueous humor levels obtained in humans versus those obtained in rabbits. It is interesting to note that data published for the drug dorzolamide tend to conclude that the transcorneal penetration is quite similar in the two species [6-7]

Humans

Clearly, human studies that assess the performance of a modified-release ophthalmic drug delivery system rely essentially on non invasive methods. Precorneal

disposition can be studied using tear sampling and measurement of tear levels of the drug(s). It should be noted, however, that such a procedure can induce excessive blinking and tear production in subjects sensitive to the sampling pipette, and therefore induce a bias in the results. Moreover, when dealing with formulations that do not mix rapidly with tear film, one can sample of tear levels of the drug(s). It should be noted, however, that such a procedure can induce excessive blinking and tear production in subjects sensitive to the sampling pipette, and therefore induce a bias in the results. Moreover, when dealing with formulations that do not mix rapidly with tear film, one can sample a small piece of the formulation itself, thus making the assay results from such a sample meaningless [8-12].

Pharmacodynamics

Drug pharmacodynamics are used when pharmacokinetic properties cannot be employed [13]. Some biological responses, such as miosis, mydriasis, intraocular pressure, and bactericidal activity, are easy to assess quantitatively, whereas the appreciation of leakage from the retinal vessels is by far more difficult. It is mandatory when using pharmacological activity as a measurement of changes in bioavailability not to overlook the need to be in the linear part of the dose-response curve .Otherwise, even with a change in Cmax, the response will plateau and nothing can be deduced from the experiment [14].

Mechanism of controlled sustained drug release into the eye [15-20]

1. The corneal absorption represents the major mechanism of absorption for the most conventional ocular therapeutic entities.
2. Passive Diffusion is the major mechanism of absorption for nor-erodible ocular insert with dispersed drug.
3. Controlled release can further regulated by gradual dissolution of solid dispersed drug within this matrix as a result of inward diffusion of aqueous solution. The existing ocular drug delivery systems are thus fair and inefficient. The design of ocular system is undergoing gradual transition from an empirical to rational basis; Interest in the broad areas of ocular drug delivery has increased in recent years due to an increased understanding of a number of ocular physiological process and pathological conditions. The focus of this review is the approaches made towards optimization of ocular delivery systems by

- Improving ocular contact time
- Enhancing corneal permeability

FORMULATION APPROACHES

Qualities of a Modified-Release Ophthalmic Drug Delivery System: A well-designed modified release ophthalmic drug delivery system must:

- Deliver the active ingredient to the right place, i.e., high conjunctival levels are Useless when targeting the ciliary body.

- Improve the ratio of local activity versus systemic effects.
- Reduce the number of installations per day, once-a-day being considered the optimal goal, although some can consider twice daily is a better insurance against a forgotten administration.
- Be easy to self-administer.
- Not induce a foreign-body sensation, longlasting blurring, or a very bad after taste.Not rely on "exotic" ingredients like new chemical entities or difficult-to-source
- Excipients (unless this is a key element).Preferably, excipients should have a drug master file and history of safe use for humans.

Table 1: shows various Types of polymers used in ocular drug delivery

S.no.	Polymer	Adhesive performance
1.	Carboxy methyl cellulose	Excellent
2.	Carbopol	Excellent
3.	Carbopol and Hydroxypropyl cellulose	Good
4.	Carbopol and Ex55	Good
5.	Polyacrlamide	Good
6.	Polycarbophil	Excellent
7.	Gelatin	Fair
8.	Dextran	Good
9.	Pectin	Poor
10.	Acaia	Poor

Dosage Form	Drug	Preparation	Merits	Demerits
Ophthalmic Solutions	Olopatadine Moxicillin	Patanol eye drops Mezol eye drops	convenienence of ease administration	Unsustained action Loss of drug by drainage
Ophthalmic suspensions	Nepafenac Triamcinoline acetonaide	Nevanac suspension Trisence suspension	Patient compliance Best for drugs with slow Dissolution	Drug properties decides performance
Ophthalmic ointments	Gatifloxacin Keturolac trometame	Gatiflo	Flexibility in drug choice Improved drug stability	Sticking of eye lids Blurred vision
Ophthalmic gels	Norethindrone and Ethinylestradiol Oxybutynin chloride	Brevicon Gelnique	Comfortable Less blurred vision than Gels	No rate control on diffusion Matted eyes
Ophthalmic erodible Inserts	Pilocarpine Gentacin	Ethicon Vitrasert	Sophisticated and effective Flexibility in drug type and dissolution rate	Patient discomfort Requires patient insertion
Ophthalmic non erodible Inserts	Pilocarpine	Pilo-20 and pilo-40 Ocusert	Controlled rate of release Prolonged delivery	Patient discomfort Irritation to eye

Table 2: Shows Various available marketed preparations

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BARRIERS TO RESTRICT INTRAOCULAR DRUG TRANSPORT

Tear [21-23]

One of the precorneal barriers is tear film which reduces the effective concentration of the administrated drugs due to dilution by the tear turnover (accelerated clearance, and binding of the drug molecule to the tear proteins. In addition the dosing volume of instillation is usually whereas the size of cul-de-sac is only. The excess volume may spill out on the cheek or exit through the nasolacrimal duct.

Cornea [24]

The cornea consists of three layers; epithelium, stroma and endothelium, and a mechanical barrier to inhibit transport of exogenous substances into the eye. Each layer possesses a different polarity and a rate-limiting structure for drug permeation. The corneal epithelium is of a lipophilic nature, and tight junctions among cells are formed to restrict paracellular drug permeation from the tear film. The stroma is composed of an extracellular matrix of a lamellar arrangement of collagen fibrils. The highly hydrated structure of the stroma acts as a barrier to permeation of lipophilic drug molecules. Corneal endothelium is the innermost monolayer of hexagonal-shaped cells, and acts as a separating barrier between the stroma and aqueous humor. The endothelial junctions are leaky and facilitate the passage of macromolecules between the aqueous humor and stroma.

Conjunctiva

Conjunctiva of the eyelids and globe is a thin and transparent membrane, which is involved in the formation and maintenance of the tear film. In addition, conjunctiva or episclera has a rich supply of capillaries and lymphatics [25-27] therefore, administrated drugs in the conjunctival or episcleral space may be cleared through blood and lymph. The conjunctival blood vessels do not form a tight junction barrier, which means drug molecules can enter into the blood circulation by pinocytosis and/or convective transport through paracellular pores in the vascular endothelial layer.

The conjunctival lymphatics act as an efflux system for the efficient elimination from the conjunctival space. Recently, it has been reported that at least 10% of a small molecular weight hydrophilic model compound (sodium fluorescein), administered in the subconjunctival space, is eliminated via the lymphatics within the first hour in rat eyes [39]. Therefore, drugs transported by lymphatics in conjunction with the elimination by blood circulation can contribute to systemic exposure, since the interstitial fluid is returned to the systemic circulation after filtration through lymph nodes.

Sclera [28-30]

The sclera mainly consists of collagen fibers and proteoglycans embedded in an extracellular matrix. Scleral permeability has been shown to have a strong dependence on the molecular radius; scleral permeability decreases roughly exponentially with

molecular radius. Additionally, the posterior sclera is composed of a looser weave of collagen fibers than the anterior sclera and the human sclera is relatively thick near the limbus (0.53 ± 0.14 mm), thin at the equator (0.39 ± 0.17 mm), and much thicker near the optic nerve (0.9–1.0 mm). Thus, the ideal location for transscleral drug delivery is near the equator at 12–17 mm posterior to the corneoscleral limbus. Hydrophobicity of drugs affects scleral permeability; increase of lipophilicity shows lower permeability; and hydrophilic drugs may diffuse through the aqueous medium of proteoglycans in the fiber matrix pores more easily than lipophilic drugs. Furthermore, the charge of the drug molecule also affects its permeability across the sclera. Positively charged compounds may exhibit poor permeability due to their binding to the negatively charged proteoglycan matrix.

Choroid/Bruch's Membrane [31-34]

Choroid is one of the most highly vascularized tissues of the body to supply the blood to the retina. Its blood flow per unit tissue weight is ten-fold higher than in the brain. In addition the choroidal capillary endothelial cells are fenestrated and, in humans, are relatively large in diameter (20–40 micro meter) An Optical Coherence Tomography (OCT) can noninvasively measure the thickness of retina and choroid. Using an OCT, it has been shown, choroidal thickness becomes thinner with age. In addition, chorioretinal diseases including with pigment epithelial detachment central serous chorioretinopathy age-related choroidal atrophy and high myopia affect choroidal thickness. In contrast, Bruch's membrane (BM) causes thickening with age. These changes cause increased calcification of elastic fiber increased cross-linkage of collagen fibers and increased turnover of glycosaminoglycans. In addition, advanced glycation end products and lipofuscin accumulate in BM. Thickness changes of choroid and BM might affect drug permeability from subconjunctiva or episcleral space into the retina and the vitreous.

Retina [35-38]

The drugs in the vitreous are eliminated by two main routes from anterior and posterior segments. All drugs are able to eliminate via the anterior route. This means drugs can diffuse across the vitreous to the posterior chamber and, thereafter, eliminate via aqueous turnover and uveal blood flow. Elimination via the posterior route takes place by permeation across the retina. One of the barriers restricting drug penetration from the vitreous to the retina is the internal limiting membrane The ILM separates the retina and the vitreous, and is composed of 10 distinct extracellular matrix proteins. Although a previous study using primates has suggested that molecules exceeding 100 kDa cannot cross the retinal layers into the subretinal space, it has been confirmed by immunohistochemical analysis, a full-length, humanized, anti-vascular endothelial growth factor (VEGF) monoclonal antibody composed of 214 amino acids with a molecular weight of 149 kDa, injected into the vitreous cavity, can penetrate through the sensory retina into retinal pigment epitheliums (RPE), subretinal and choroidal space, in monkey and rabbit. In addition, nanometer-sized particles whose mean diameter is below 200 nm can penetrate across the sensory retina into RPE after intravitreal injection in rabbit. In intact retina, theoretically, the drugs in the subretinal fluid could either be absorbed by the sensory retinal blood vessels or transported across the RPE, where it may be

absorbed into the choroidal vessels or pass through the sclera. Drug transport across the RPE takes place both by transcellular and paracellular routes. The driving forces of outward transport of molecules from the subretinal spaces are hydrostatic and osmotic, and small molecules might transport through the paracellular inter-RPE cellular clefts and by active transport through the transcellular route.

Blood-Retinal Barrier [39-42]

Blood-retinal barrier (BRB) restricts drug transport from blood into the retina. BRB is composed of tight junctions of retinal capillary endothelial cells and RPE, called iBRB for the inner and oBRB for the outer BRB, respectively. The function of iBRB is supported by Müller cells and astrocytes. The retinal capillary endothelial cells are not fenestrated and have a paucity of vesicles. The function of these endothelial vesicles has been described as endocytosis or transcytosis that may be receptor mediated or fluid phase requiring adenosine triphosphate. A close spatial relationship exists between Müller cells and retinal capillary vessels to maintain the iBRB in the uptake of nutrients and in the disposal of metabolites under normal conditions. Müller cells are known to support neuronal activity and maintain the proper functioning of the iBRB under normal conditions. They are involved in the control and homeostasis of K+ and other ions signaling molecules, and in the control of extracellular pH.

Dysfunction of Müller cells may contribute to a breakdown of the iBRB in many pathological conditions, such as diabetes. Müller cells enhance the secretion of under hypoxic and inflammatory conditions. In vitro study has shown that induced occluding phosphorylation and ubiquitination causes trafficking of tight junction and leads to increased retinal vascular permeability. The astrocytes originate from the optic nerve and migrate to the nerve fiber layer during development. They are closely associated with the retinal capillary vessels and help to maintain the capillary integrity. Astrocytes are known to increase the barrier properties of the retinal vascular endothelium by enhancing the expression of the tight junction protein and modifying endothelial morphology. Following systemic drug administration, drugs can easily enter into the choroid since choroid is highly vascularized tissue compared to retina.

The choriocapillaris are fenestrated resulting in rapid equilibration of drug molecules present in the bloodstream with the extravascular space of the choroid. Therefore, restricts further entry of drugs from the choroid into the retina. RPE is a monolayer of highly specialized hexagonal-shaped cells, located between the sensory retina and the choroid. The tight junctions of the RPE efficiently restrict intercellular permeation into the sensory retina.

DRUG DELIVERY SYSTEMS TO ANTERIOR SEGMENT OF THE EYE

Eye-Drops [43-44]

To prolong the retention time of topically applied drugs, anterior DDSs for eye-drops utilizing interaction between drug carrier (excipients) and physiological environment of cornea and/or subconjunctiva are being developed. Durasite Alameda, is

based on a polycarbophil aqueous solution. Polycarbophil is polyacrylic acid cross-linked with divinyl glycol, and forms hydrogen-bonding with the mucus, and corneal and conjunctival epitheliums, which are all negatively charged, to extend the effects of drug to several hours. A broad-spectrum antibiotic, azithromycin ophthalmic solution, formulated with Durasite for the treatment of bacterial conjunctivitis was launched in the United States in 2007. This utilizes Durasite, a combination of azithromycin and dexamethasone AzaSite Plus™, InSite Vision Inc.), for the treatment of blepharoconjunctivitis and is currently in Phase III. Bromfenac in DuraSiteis in Phase I/II to reduce inflammation and pain after ocular surgery. Methylcellulose (MC) has a lower critical solution temperature (LCST) at approximately 50 °C, and sol-gel phase transition occurs. Since the temperature of ocular surface is 32–34 °C, LCST needs to be lower to gel MC solution at ocular surface quickly after instillation as eye-drops. In general, high concentration of electrolytes leads to salting-out and gelation of MC. Wakamoto Pharmaceutical Co., Ltd. (Tokyo, Japan) has developed temperature-responsive eye-drops formulated timolol maleate for glaucoma therapy (Rysmon® TG) available in Japan, using combinations of MC, sodium citrate and polyethylene glycol, which can act by lowering LCST of MC.

A strong cationic ion exchange resin, Amberlite IRP-69 is polystyrene sulfonic acid resin cross-linked with divinyl benzene. Betoptic S marketed from 1990 (Alcon Laboratories, Inc., Fort Worth, TX, U.S.), whose active ingredient is betaxolol for glaucoma therapy, is consisted of this resin. Positively charged betaxolol is bound to the negatively charged sulfonic acid groups in the resin. When betaxolol-bound resin is applied to the eye, the cationic ions such as Na+ or K+ in the tearfluid induce the release of betaxolol molecules from resin matrix into the tear film and lead to betaxolol penetration across the cornea.

TobraDex ST (Alcon Laboratories, Inc.), a combination of tobramycin 0.3% and DEX 0.05%, has been launched as an anti-inflammatory and anti-infective formulation for blepharitis. It improves the suspension formulation characteristics and quality, tear film kinetics, and tissue penetration using xanthan gum, an anionic polysaccharide with repeating unit of two D-glucose, two D-mannose and one D-glucuronic acid residues. The xanthan gum forms an ionic interaction with tobramycin to decrease the viscosity of the suspension compared with that normally expected from xanthan gum. The xanthan gum-tobramycin interaction reduces sedimentation of DEX particles and improves suspension characteristics.

The viscosity increases after mixing with tears as the interactions between xanthan gum and tobramycin are interrupted by pH and the ionic content of tears. The enhanced viscosity leads longer retention and improves the ocular bioavailability of the drugs. *In situ* gelation occurs in the presence of mono- and divalent cations including Ca2+, Mg2+, K+ and Na+. Timoptic-XE formulated using gellan gum, is on the market, and shows administration once a day is equally effective in lowering intraocular pressure (IOP) as the equivalent concentration of simple eye-drops of aqueous solution of timolol maleate is a cationic emulsion, based on electrostatic attraction that occurs between the oily droplets of a positively-charged emulsion loaded with active ingredient, and negatively charged ocular surface.

Therefore, Novasorb® improves solubility and absorption of lipophilic drugs, reduces the number of instillation times and side effects, leading to better efficacy and compliance. Cationorm®, which is composed of only cationic emulsion without any active ingredients, has been launched for mild dry eye. NOVA22007, a cationic emulsion incorporated cyclosporine, has completed Phase III studies for dry eye and Phase II/III studies for vernal keratoconjunctivitis.

Contact Lens [45-49]

Soft contact lens-based DDSs have been investigated by several approaches: (1) Soak and absorption of drug solution; (2) piggyback contact lens combined with a drug plate or drug solution; (3) surface-modification to immobilize drugs on the surface of contact lenses; (4) incorporation of drugs in a colloidal structure dispersed in the lens; (5) ion ligand-containing polymeric hydrogel; and (6) molecularly imprinting of drugs.
The soft contact lens based drug delivery devices are being developed by the following two companies, but details have not been disclosed. Vistakon Pharmaceuticals, LLC (Philadelphia, PA, has completed a multicenter Phase III clinical trial for a contact lens presoaked to release an antihistamine drug, ketotifen, to prevent allergic conjunctivitis in contact lens wearers. SEED Co., Ltd. (Tokyo, Japan) and Senju Pharmaceutical Co., Ltd. (Osaka, Japan) have co-developed a disposable soft contact lens to release incorporated sodium cromoglicate for one day. They have announced clinical trials for allergic conjunctivitis in Japan will be conducted in 2010.

Cul-de sac Inserts [50]

Ocusert provides uniform controlled release (20 or 40 microgram/hour for 7 days) of pilocarpine as an ocular hypotensive drug, and has been commercialized in 1974. Ocusert® consists of two outer layers of ethylene-vinyl acetate copolymer (EVA), and an inner layer of pilocarpine in alginate gel within di-(ethylhexyl)phthalate for a release enhancer, sandwiched between EVA layers. However, Ocusert® has not become widely used because of unsatisfactory IOP control due to various causes, including difficulty of inserting the device, ejection of the device from eye, and irritation during insertion.
Lacrisert® (Aton Pharma, Inc., Lawrenceville, NJ, U.S.) is a rod-shaped, water-soluble cul-de-sac insert composed of hydroxypropyl cellulose without preservatives and other ingredients (1.27 mm diameter, 3.5 mm long), and is indicated in moderate to severe dry eye syndrome.[119] Lacrisert® has not been applied as a drug delivery carrier as yet.
Although previously many inserts including collagen shield, Ocufit SR®, New Ophthalmic Delivery System, and Minidisc ocular therapeutic system have been developed, there are no further activities at present. The commercial failure of inserts might be attributed to psychological factors including the reluctance to abandon the traditional droppable formulations, and occasional ejection from the eye observed in the case of Ocusert.

Punctal Plugs [51-53]

To prolong the retention time and increase absorption and efficacy after instillation of eye-drops, inhibition of drainage through nasolacrimal system using punctal

plug into the pancta is a long-standing approach. Efficacy of an ocular hypotensitive agent in eye-drops in conjunction with punctual occlusion by punctual plug has been evaluated. Although punctal occlusion significantly decreased approximately 2 mmHg of IOP in the plugged eyes ($p < 0.001$), it was not concluded that this IOP decrease is clinically significant.

QLT Inc. (Vancouver, Canada) and Vistakon Pharmaceuticals, LLC have individually developed punctal plugs as DDSs for latanoprost and bimatoprost, respectively. QLT Inc. has reported Phase II data for a punctual plug containing a latanoprost dose of 44 microgram, 81 microgram, and two different release rates of 95 microgram. A retention rate based on available data from 185 eyes with 12 weeks of follow-up in conjunction with previous studies was 81%, but a dose-response for IOP reduction was not observed. QLT Inc. plans a clinical trial of punctal plug containing an antihistamine drug, olopatadine, for the treatment of allergic conjunctivitis.

The Phase II results of punctal plug containing bimatoprost conducted by Vistakon Pharmaceuticals, LLC has also shown no dose-response

Subconjunctival/Episcleral Implants [54-56]

LX201 (Lux Biosciences Inc., Jersey City, NJ, U.S.) is a silicone matrix episcleral implant designed to deliver cyclosporine A to the ocular surface for one year. The implant is flat on the bottom in contact with the episclera, and the top is rounded, in contact with anterior surface. LX201 is available in two different lengths of 0.5 and 0.75 inches. Each implant is 0.08 inches wide and 0.04 inches high. In preclinical studies using rabbits and dogs, the episcleral cyclosporine implant delivered continuously potentially therapeutic cyclosporine levels to the lacrimal gland, and showed efficacy in a model of keratoconjunctivitis. Phase III study of LX201 to prevent corneal transplant rejection is now ongoing.

An episcleral implant developed by 3T Ophthalmics (Irvine, CA, U.S.) is also composed of silicone and looks like a tiny bathtub, less than 1.0 cm long. It can be re-filled with drugs in any form, such as a solution, gel or matrix. In animal studies using model compound (sodium fluorescein), the episcleral implant facilitates diffusion of fluorescein through the sclera, leading to high levels in the retina and posterior vitreous, and tissue levels are markedly increased compared with periocular injection of the same amount of fluorescein. At present, 3T Ophthalmics plans to enter clinical r IOP reduction. trials for retinoblastoma in the near future.

A subconjunctival insert containing latanoprost (Latanoprost SR insert) in Phase I clinical study developed by Pfizer, Inc. (New York, NY, U.S.) is composed of a poly (DL-lactide-*co*-glycolide) (PLGA) tube containing a latanoprost-core. One end of the tube is capped with an impermeable polymer, silicone, and the other end is capped with a permeable polymer, polyvinyl alcohol (PVA). Latanoprost is released across the PVA-end and its release rate is regulated by an internal diameter of PLGA tube. Duration of latanoprost release is designed for 3–6 months.

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Table3 shows: Various types of drugs used for ophthalmic diseases

S.No	Disease	Product	Brand name	Mfg by	Dosage form
1.	Inflammation	Ketorolac,diclofenac	ACUVAIL	Allergan	Eye drops
2.	Inflammation	Chloramphenicol,pilocorpin hcl	VOLTARIN	Novartis	Eye drops
3.	Infection	Ganciclovi,gatifloxacin	CHLOPTIC	Allergan	Eye drops
4.	Miotics	Dexamethasone,Laxobetolol hcl	PILOPINI	Alcon	Gel
5.	Viral	Flurometholone	ZIRGAN	Alliance	Gel
6.	Infection	Azithromycin,Bipostatin	ZYMAR	Allergan	Eye drops
7.	Inflammation	Besifloxacin,Betaxolol	TOBRADEX	Alcon	Eye ointment
8.	Glaucoma	Ciprofloxacin	BETAXON	Alcon	Eye drops
9.	Inflammation	Ciprofloxacin	FML	Allergan	Suspension
10.	Conjunctivitis		AZASITE	Catalent	Eye drops
11.	Conjunctivitis		BIPREVE	Ista	Eye drops
12.	Conjunctivitis		BESIVANCE	Bausch	Suspension
13.	Glaucoma		BETAXOLOL	Alocon	Eye drops
14.	Infection		CILOXIN	Alocon	Eye drops
15.	Conjunctivitis		CILOXIN	Alocon	Eyeointment

CONCLUSION

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, especially to the posterior segment of the eye. Due to transparent ocular mediums, intraocular tissues (vitreous and retina) are relatively easy to be observed without invasion, and various administration approaches including intravitreal or subretinal injection/implantation could be developed. In addition to Lucentis (monoclonal antibodies), since the eye-ball is a closed organ, novel therapeutic molecules such as an antisense oligonucleotide for cytomegalovirus retinitis, an aptamer or a small interfering RNA for neovascular AMD, have been investigated in human eye before their applications for systemic diseases. Therefore more challenging approaches might be applicable in the ophthalmic field. Drug delivery via ophthalmic route has proved significant advancement for future perspectives.

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