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Research Article

RECENT ADVANCES IN OPHTHALMIC DRUG DELIVERY SYSTEM

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ABSTRACT

In the present update on ocular drug delivery system, particulate carrier, the tremendous advances in ocular drug delivery system, the polymers used in particulate carriers for ocular dosage forms, the use of drug complexes and other technological advances are discussed. This review focuses on recent literature regarding mucoadhesive particulate dosage forms with special attention to in vivo studies.

Keywords: Ophthalmic drug delivery system, Mucoadhesive polymers, Particulate carriers

INTRODUCTION

Conventional eye drops currently account for more than 90% of the marketed ophthalmic formulations[1]. However, after instillation of an eye drop, typically less than 5% of the applied drug penetrates the cornea and reaches the intraocular tissues. This is due to the rapid and extensive precorneal loss caused by drainage and high tear fluid turnover. As a consequence, the typical corneal contact time is limited to 1 – 2 min and the ocular bioavailability is usually less than 10%[2].Various ocular delivery systems, such a ointments, suspensions, micro - and nanocarriers, and liposomes, have been investigated during the past two decades pursuing two main strategies: to increase the corneal permeability and to prolong the contact time on the ocular surface[3].

Anatomy and Physiology of Eye

In order to research and develop an effective ophthalmic delivery system, a good understanding of the anatomy and physiology of the eye (the globe) is necessary. Figure 1 shows a cross section through the human eye.

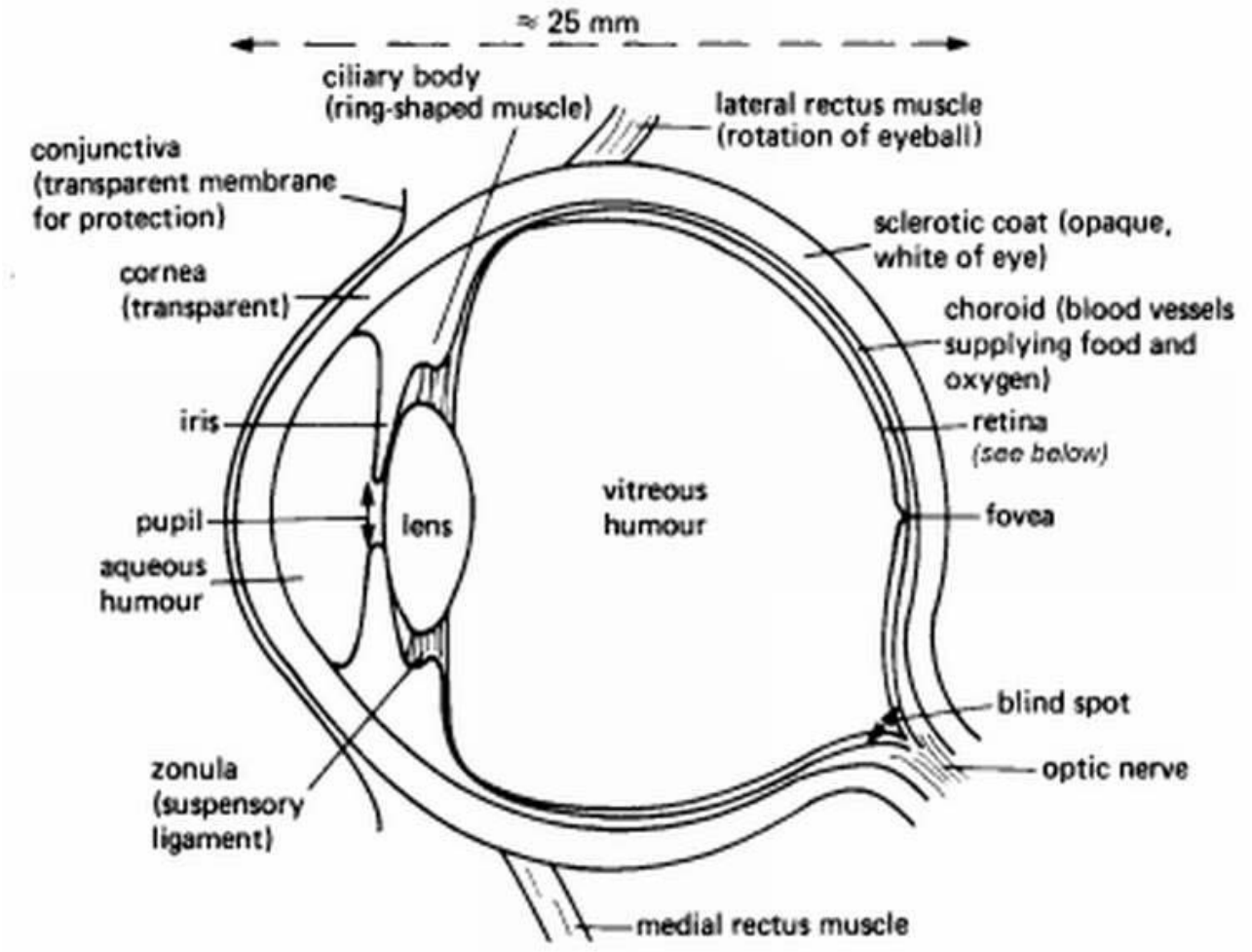

Fig. 1: Cross section of Eye

Precorneal tear film is corneal transparency and good visual function requires a uniform eye surface. This is achieved by the tear film, which covers and lubricates the cornea and the external globe. It is about 7 – 8 µ m thick and is the first structure encountered by topically applied drugs. The trilaminar structure of the tear film is shown in figure 2.

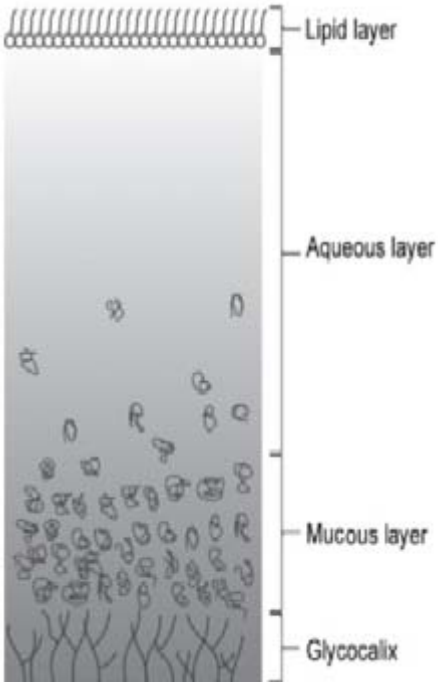

Fig. 2: Structure of the precorneal tear film

Nasolacrimal drainage system shown in figure 3 illustrates the nasolacrimal drainage system. The lacrimal gland, which is situated in the superior temporal angle of the orbit, is responsible for most of the tear fluid secretion. Secreted fluid is spread over the surface of the cornea during blinking and ends up in the punctual when the upper eye lid approaches the lower lid.

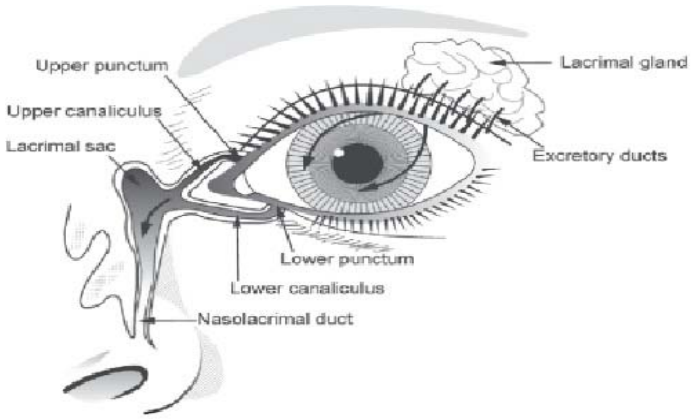

Fig. 3: The lacrimal system

The cul - de - sac normally holds 7 – 9 µ L of tear fluid, with the normal tear flow rate being 1.2 – 1.5 µ L/min. The loss from the precorneal area by drainage, tear fluid turnover, and non-corneal absorption plays an important role in determining the ocular bioavailability of a drug. As the drainage rate is much faster than the ocular absorption rate, most of the topically applied drug is eliminated from the precorneal area within the first minute[4].

The cornea is composed of five layers (see Figure 1): epithelium, Bowman's membrane stroma, Descemet ' s membrane, and endothelium. The epithelium is the outermost layer and consists of five to six cell layers. These can be subdivided into one to two outermost layers of flattened superficial cells with microvilli on their anterior surface enhancing the cohesion and stability of the tear film[5], two to three layers of polygonal wing cells, and a single layer of basal columnar cells, allowing for minimal paracellular transport[6].

The lens is the transparent biconvex structure situated behind the iris and in front of the vitreous. It plays an important role in the visual function of the eye and also enables accommodation together with the ciliary muscle. The lens is made up of slightly more than 30% protein (water - soluble crystalline) and therefore has the highest protein content of all tissues in the body[7]. The lens receives its nutrients from the aqueous humor and its transparency depends on the geometry of the lens fibers.

The blood ocular barriers can be divided into the blood aqueous barrier and the blood – retinal barrier. The blood – aqueous barrier is located in the anterior part of the eye and is formed by the endothelial cells of the blood vessels in the iris and the non pigmented cell layer of the ciliary epithelium[8]. The blood – retinal barrier can be found in the posterior part of the eye. It prevents toxic molecules, plasma components, and water from entering the retina. It also forms a barrier for passage of systemically administered drugs into the vitreous, typically resulting in only 1 – 2% of the drug's plasma concentration in the intraocular tissues[9].

Pharmacokinetic Considerations

After topical application of an ophthalmic solution, the solution is instantly mixed with the tear fluid and then spread over the eye surface. However, various precorneal factors such as the drainage of the instilled solution, induced lacrimation, normal tear turnover, non-corneal absorption, drug metabolism, and enzymatic degradation limit the ocular absorption by shortening the contact time of the applied drug with the corneal surface[10].

Formulation Considerations

Irritation of the eye following the use of an ocular delivery system can be induced by a number of factors, including the instilled volume, the pH, and the osmolality of the formulation, as well as by the drug itself. All these factors may induce reflex tearing and as a result increase lacrimal drainage.

According to Kaur and Smitha , the optimum lipophilicity for corneal absorption is found in drugs with an n - octanol – water partition coefficient between 10 and 100. Cationic drugs permeate the cornea more easily than anionic compounds, which are repelled by the negative charge of the mucin layer on the ocular surface as well as the negatively charged pores present in the corneal epithelium[10]. Finally, the molecular size of the drug has an effect on the corneal absorption. The normal pH of the tear fluid is 7.4. Ocular formulations should ideally be formulated between pH 7.0 and 7.7 to avoid irritation of the eye. However, in most cases the pH necessary for maximal solubility or stability of the drug is well outside this range.

Chrai et al. determined the influence of drop size on the rate of drainage of a solution instilled into the conjunctival sac of rabbits. The observations were reported with other dosage forms such as suspensions and liposomes[11].

Formulation Approaches to Improve Ocular Bioavailability

One of the major problems encountered with topical administration is the rapid precorneal loss caused by nasolacrimal drainage and high tear fluid turnover, which leads to drug concentrations of typically less than 10% of the applied drug.

Polymeric Delivery Systems

Polymeric Gels

Viscosity - enhancing polymers, which simply increase the formulation viscosity, resulting in decreased lacrimal drainage and enhanced bioavailability; mucoadhesive polymers, which interact with the ocular mucin, therefore increasing the contact time with the ocular tissues; and in situ gelling polymers, which undergo sol - to – gel phase transition upon exposure to the physiological conditions present in the eye. Viscosity enhancing polymers reduce the lacrimal clearance (drainage) of ophthalmic solutions, various polymers have been added to increase the viscosity of conventional eye drops, prolong precorneal contact time, and subsequently improve ocular bioavailability of the drug[12,13]. Among the range of hydrophilic polymers investigated in the area of ocular drug delivery are polyvinyl alcohol (PVA) and polyvinyl pyrrolidone (PVP), cellulose derivates such as methylcellulose (MC), and polyacrylic acids (carbopols).

It has a great influence on the rheological properties of viscous ocular dosage forms and consequently the bioavailability of the incorporated drug[14]. Newtonian systems do not show any real improvement of bioavailability below a certain viscosity and blinking becomes painful, followed by reflex tearing, if the viscosity is too high[15] . While the viscosity of Newtonian systems is independent from the shear rate, non - Newtonian pseudo plastic or so called shear - thinning systems exhibit a decrease in viscosity with increasing shear rates.

Mucoadhesive Polymers

The most commonly used bioadhesives are macromolecular hydrocolloids with numerous hydrophilic functional groups capable of forming hydrogen bonds (such as carboxyl, hydroxyl, amide, and sulfate groups). Hui and Robinson were the first to demonstrate the usefulness of bioadhesive polymers in improving the ocular bioavailability of progesterone[16].

Saettone et al. [evaluated a series of bioadhesive dosage forms for ocular delivery of pilocarpine and tropicamide and found hyaluronic acid to be the most promising mucoadhesive polymer[17]. However, according to Park and Robinson, polyanions are better than polycations in terms of binding and potential toxicity. In general, both anionic and cationic charged polymers demonstrate better mucoadhesive properties than nonionic polymer, such as cellulose derivates or PVA [18].

Conventional Dosage Forms

Conventional dosage forms such as solutions, suspensions, and ointments account for almost 90% of the currently accessible ophthalmic formulations on the market[19].

However, there are also significant disadvantages associated with the use of conventional solutions in particular, including the very short contact time with the ocular surface and the fast nasolacrimal drainage, both leading to a poor bioavailability of the drug. Various ophthalmic delivery systems have been investigated to increase the corneal permeability. The reasons behind choosing solutions over other dosage forms are their favorable cost advantage, the simplicity of formulation development and production, and the high acceptance by patients[20]. However, there are also a few drawbacks, such as rapid and extensive precorneal loss, high absorption via the conjunctiva and the nasolacrimal duct leading to systemic side effects, as well as the increased installation frequency resulting in low patient compliance.

Some of these problems have been encountered by addition of viscosity - enhancing agents such as cellulose derivates, which are believed to increase the viscosity of the preparation and consequently reduce the drainage rate. The use of viscosity enhancers will be discussed later in this section.

***In Situ* Gelling Systems**

In situ gelling systems are viscous polymer - based liquids that exhibit sol - to - gel phase transition on the ocular surface due to change in a specific physicochemical parameter (ionic strength, temperature, pH, or solvent exchange). Formulations containing in situ gelling system for ocular drug delivery approaches are listed in Table 1. Polymers that may undergo sol - to - gel transition triggered by a change in pH are cellulose acetate phthalate (CAP) and cross - linked poly acrylic acid derivates such as carbopols, methacrylates and polycarbophils. CAP latex is a free - running solution at pH 4.4 which undergoes sol - to - gel transition when the pH is raised to that of the tear fluid. This is due to neutralization of the acid groups contained in the polymer chains, which leads to a massive swelling of the particles. The use of pH – sensitive latex nanoparticles has been described by Gurny et al. Carbopols have apparent pKa value in the range of 4 – 5 resulting in rapid gellation due to rise in pH after ocular administration.

Gellan gum is an anionic polysaccharide which undergoes phase transition under the influence of an increased ionic strength. In fact, the gel strength increases proportionally with the amount of mono - or divalent cations present in the tear fluid[21].

As a consequence, the usual reflex tearing, which leads to a dilution of common viscous solutions, further enhances the viscosity of gellan gum formulations due to the increased amount of tear fluid and thus higher cation concentration[22].

Table 1: Formulation containing *in situ* gelling system

Drug	Formulation	Polymers
Pilocarpine	In situ gelling system	Pluronic F127, MC, HPMC
Timolol	In situ gelling system	Pluronic F127, MC, HPMC, CMC
Doxorubicin	In situ gelling system	Chitosan/glycerophosphate
Indomethacin	In situ gelling system	Gellan gum
Pefloxacinmesylate	In situ gelling system	Gelrite®
Sezolamide	In situ gelling system	Gelrite®
Ciprofloxacin HCl	In situ gelling system	Poloxamer/ Hyaluronic acid

Colloidal Delivery Systems

Colloidal carriers are small particulate systems ranging in size from 100 to 400 nm. As they are usually suspended in an aqueous solution, they can easily be administered as eye drops, thus avoiding the potential discomfort resulting from bigger particles present in ocular suspensions or from viscous or sticky preparations[23].

Nanoparticles

Nanoparticles have been among the most widely studied particulate delivery systems over the past three decades. They are defined as sub micrometer - sized polymeric colloidal particles ranging from 10 to 1000 nm in which the drug can be dissolved, entrapped, encapsulated, or adsorbed[24]. Depending on the preparation process, nanospheres or nanocapsules can be obtained.

The first nanoparticulate delivery system studied was Piloplex, consisting of pilocarpine ionically bound to poly (methyl) methacrylate – acrylic acid copolymer nanoparticles[25]. Klein et al. found that a twice - daily application of piloplex in glaucoma patients was just as effective as three to six instillations of conventional pilocarpine eye drops. However, the formulation was never accepted for commercialization due to various formulations - related problems, including the non biodegradability, local toxicity, and difficulty of preparing a sterile formulation.

The most commonly used biodegradable polymers in the preparation of nanoparticulate systems for ocular drug delivery are poly – alkyl cyano acrylates, poly - ε - caprolactone, and polylactic - co - glycolic acid copolymers. Marchal - Heussler et al. compared the three particulate delivery systems using anti glaucoma drugs including betaxolol and cartechol. Results showed that poly - ε - caprolactone (nanospheres and nanocapsules) exhibited the highest pharmacological activity [26].

In general, nanocapsules displayed a much better effect than nanospheres probably due to the fact that the active compound was in its un- ionized form in the oily core and could diffuse faster into the cornea. Diffusion of the drug from the oily core of the nanocapsule to the corneal epithelium seems to be more effective than diffusion from the internal, more hydrophilic matrix of the nanospheres [27]. The major limiting issues for the development of nanoparticles include the control of particle size and drug release rate as well as the formulation stability.

Liposomes

Liposomes were first reported by Bangham in the 1960s and have been investigated as drug delivery systems for various routes ever since then. A liposome or so - called vesicle consists of one or more concentric spheres of lipid bilayers separated by water compartments with a diameter ranging from 80 nm to 100 μ m. Owing to their amphiphilic nature, liposomes can accommodate both lipohilic (in the lipid bilayer) and hydrophilic (encapsulated in the central aqueous compartment) drugs . According to their size, liposomes are classified as either small unilamellar vesicles (SUVs) (10 – 100 nm) or large unilamellar vesicles (LUVs) (100 – 300 nm). If more than one bilayer is present, they are referred to as multilamellar vesicles (MLVs). Depending on their lipid composition, they can have a positive, negative, or neutral surface charge.

Liposomes are potentially valuable as ocular drug delivery systems due to their simplicity of preparation and versatility in physical characteristics. However, their use is limited by instability (due to hydrolysis of the phospholipids), limited drug - loading capacity, technical difficulties in obtaining sterile preparations, and blurred vision due to their size and opacity .

In addition, liposomes are subject to the same rapid precorneal clearance as conventional ocular solutions, especially the ones with a negative or no surface charge [28]. There have been several attempts to use liposomes in combination with other newer formulation approaches, such as incorporating them into mucoadhesive gels or coating them with mucoadhesive polymers. Bochot et al. developed a novel delivery system for oligonucleotides by incorporating them into liposomes and then dispersing them into a thermo sensitive gel composed of poloxamer 407. They compared the in vitro release of the model oligonucleotides pdT16 from simple poloxamer gels (20 and 27% poloxamer) with the ones where pdT16 was encapsulated into liposomes and then dispersed within the gels. They found that the release of the oligonucleotides from the gels was controlled by the poloxamer dissolution, whereas the dispersion of liposomes within 27% poloxamer gel was shown to slow down the diffusion of pdT16 out of the gel[29].

Niosomes

In order to circumvent some of the limitations encountered with liposomes, such as their chemical instability, the cost and purity of the natural phospholipids, and oxidative degradation of the phospholipids, niosomes have been developed. Niosomes are nonionic surfactant vesicles which exhibit the same bilayered structures as liposomes. Their advantages over liposomes include improved chemical stability and low production costs. Moreover, niosomes are biocompatible, biodegradable, and non-immunogenic[30]. They were also shown to increase the ocular bioavailability of hydrophilic drugs significantly more than liposomes. This is due to the fact that the surfactants in the niosomes act as penetrations enhancers and remove the mucous layer from the ocular surface.

Microemulsions

Microemulsions (MEs) are colloidal dispersions composed of an oil phase, an aqueous phase, and one or more surfactants. They are optically isotropic and thermodynamically stable and appear as transparent liquids as the droplet size of the dispersed phase is less than 150 nm. One of their main advantages is their ability to increase the solubilization of lipophilic and hydrophilic drugs accompanied by a decrease in systemic absorption. Moreover, MEs are transparent systems thus enable monitoring of phase separation and/or precipitation. In addition,

MEs possess low surface tension and therefore exhibit good wetting and spreading properties.

While the presence of surfactants is advantageous due to an increase in cellular membrane permeability, which facilitates drug absorption and bioavailability[31].Caution needs to be taken in relation to the amount of surfactant incorporated, as high concentrations can lead to ocular toxicity. In general, nonionic surfactants are preferred over ionic ones, which are generally too toxic to be used in ophthalmic. Surfactants most frequently utilized for the preparation of MEs are poloxamer, polysorbate, and polyethylene glycol derivatives[32].

Similar to all other colloidal delivery systems discussed above it was hypothesized by numerous research teams that a positive charge (provided by cationic surfactants [33] would increase the ocular residence time of the formulation due to electro static interactions

with the negatively charged mucin residues. However, toxicological studies contradicted this assumption regarding the ocular effects, and so far there has been no publication demonstrating a distinct beneficial effect of charged surfactants incorporated into MEs. Microemulsions can be classified into three different types depending on their microstructure: oil - in - water (o/w ME), water - in - oil (w/o ME), and bicontinuous ME. They have been investigated by physical chemists since the 1940s but have only gained attention as potential ocular drug delivery carriers within the last two decades.

The potential application of o/w lecithin MEs for ocular administration of timolol, in which the drug was present as an ion, pair with octanoate. The ocular bioavailability of the timolol ion pair incorporated into the ME was compared to that of an ion pair solution as well as a simple timolol solution. Areas under the curve for the ME and the ion pair solution respectively were 3.5 and 4.2 times higher than that of the simple timolol solution. A prolonged absorption was achieved using the ME with detectable amounts of the drug still present 120 min after instillation. In addition, in vitro and in vivo evaluations were performed. The tested MEs showed favorable physicochemical parameters and no ocular irritation as well as a prolonged pilocarpine release *in vitro* and *in* vivo[34].

Beilin et al. demonstrated a prolonged ocular retention of a sub micrometer emulsion (SME) in the conjunctival sac using a fluorescent marker (0.01% calcein) as well as the miotic response of New Zealand Albino rabbits to pilocarpine [35]. They found that the fluorescence intensity of calcein in SME was significantly higher than that of a calcein solution at all time points.

Development, and Manufacturing that w/o MEs undergo phase transition into lamellar liquid crystals (LCs) upon aqueous dilution by the tears, prolonging the precorneal retention time due to an increase in the formulation ' s viscosity. HET - CAM studies revealed no ocular irritancy by the excipients used. Ocular drainage was evaluated via γ - scintigraphy and demonstrated a significantly higher precorneal retention of the tested microemulsions compared to an aqueous solution[36].

The use of MEs in ocular delivery is very attractive due to all the advantages offered by these formulations. They are thermodynamically stable and transparent, possess low viscosity, and thus are easy to instill, formulate, and sterilize (via filtration).

Moreover, they offer the possibility of reservoir and/or localizer effects. All these factors, in addition to the ones previously mentioned, render MEs promising ocular delivery systems.

Table 2: Colloidal ocular drug delivery system

Drug	Formulation	Polymer
Pilocarpine	Nanoparticles	Gelatin
Hydrocortisone	Nanoparticles	Albumin
Pilocarpine	Nanoparticles	Albumin methacrylate acrylic acid copolymer (Piloplex)
Betaxolol	Nanoparticles	Poly - ε - caprolactone (PECL), polyIsobutyl cyanoacrylate (PLGA)
Carteolol	Nanoparticles	Poly - ε - caprolactone (PECL)
Ciclosporine	Nanoparticles	Chitosan
Indomethacine	Nanoparticles	Chitosan - and poly - L - lysine coated poly - ε – caprolactone
Aciclovir	Nanoparticles	PEG - coated PLA nanospheres
Ibuprofen	Nanoparticles	Eudragit RS100
Gentamicin	Microspheres	Eudragit RS100 and RL100
Piroxicam	Microspheres	Pectin ,Albumin
Pilocarpine	Liposomes	Carbopol - coated liposomes
Timolol	Niosomes	Chitosan - and carbopol – coated Niosomes
Retinol	Microemulsions	Tween 60 and 80, soy bean lecithin, triacetin, PG
cyclosporine	NLC	Polyethylene glycol Monostearate
Diclofenac sodium	liposome	Phosphatidylserine Chitosan
acetazolamide	niosome	span 60 ketamine HCl injection, cholesterol
flurbiprofen	Nanostructured lipid carrier	Chitosan Oligosaccharides

Other Delivery Approaches

Many other ocular delivery approaches have been investigated over the past decades, including the use of prodrugs, penetration enhancers, cyclodextrins, as well as different types of ocular inserts shown in table 3.

In addition, iontophoresis, which is an active drug delivery approach utilizing electrical current of only 1 – 2 mA to transport ionized drugs across the cornea, offers an effective, noninvasive method for ocular delivery. Iontophoresis is the process in which direct current drives ions into cells or tissues. When iontophoresis is used for drug delivery, the ions of importance are charged molecules of the drug[37]. If the drug molecules carry a positive charge, they are driven into the tissues at the anode; if negatively charged, at the cathode. Ocular iontophoresis offers a drug delivery system that is fast, painless and safe; and in most cases, it results in the delivery of a high concentration of the drug to a specific site. Increased incidence of bacterial keratitis, frequently resulting in corneal scarring, offers a clinical condition that may benefit from drug delivery by iontophoresis. Iontophoretic application of antibiotics may enhance their bactericidal activity and reduce the severity of disease; similar application of anti-inflammatory agents could prevent or reduce vision threatening side effects[38,39]. But the role of iontophoresis in clinical ophthalmology remains to be identified.

Another more recent approach is the use of dendrimers in ocular therapy. Dendrimers are synthetic spherical molecules named after their characteristic treelike branching around a central core with a size ranging from 2 to 10 nm in diameter [40]. So far, PAMAM (polyamidoamine) has been the most commonly studied dendrimer system for ocular use [41].

Prodrugs

Prodrugs are pharmacologically inactive derivates of drug molecules that require a chemical or enzymatic transformation into their active parent drug. To be effective, an ocular prodrug should show an appropriate lipophilicity to facilitate corneal absorption, posses sufficient aqueous solubility and stability to be formulated as an eye drop, and demonstrate the ability to be converted to the active parent drug at a rate that meets therapeutic needs[42].

Prodrugs were introduced into the area of ocular drug delivery about 25 years ago[43], and steroids were probably the first ones to be utilized as prodrugs. However, the concept of prodrugs was not fully exploited until the introduction of dipivefrin (epinephrine prodrug) in the late 1970s.

Penetration Enhancers

The transport process across the corneal tissue is the rate - limiting step in ocular drug absorption. Increasing the permeability of the corneal epithelium by penetration enhancers is likely to enhance the drug transport across the corneal tissues and therefore improve ocular bioavailability of the drug.

Penetration enhancers act by increasing the permeability of the corneal cell membrane and/or loosening the tight junctions between the epithelial cells, which primarily restrict the entry of molecules via the paracellular pathway. Classes of penetration enhancers include surfactants, bile salts, calcium chelators, preservatives, fatty acids, and some glycosides such a saponin.

Surfactants are perceived to enhance drug absorption by disturbing the integrity of the plasma membranes. When present at low concentrations, surfactants are incorporated into the lipid bilayer, leading to polar defects in the membrane, which change the membrane's physical properties. When the lipid bilayer is saturated, micelles start to form, enclosing phospholipids from the membranes, hence leading to membrane solubilization[44].

Cyclodextrins complexation generally results in improved wettability, dissolution, solubility, and stability in solution as well as reduced side effects[45].

Cyclodextrins improve chemical stability, increase the drug's bioavailability, and decrease local irritation. However, the improvement of ocular bioavailability seems to be limited by the very slow dissociation of the complexes in the precorneal tear fluid.

Ocular Inserts

Solid ocular dosage forms such as films, erodible and non erodible inserts, rods, and shields have been developed to overcome the typical pulse - entry - type drug release associated with conventional ocular dosage forms.

A number of ocular inserts using different techniques, namely soluble, erodible, non erodible, and hydrogel inserts with polymers such as cellulose derivates, acrylates, and poly (ethylene oxide), have been investigated over the last few decades.

Sasaki et al. prepared non degradable disc - type ophthalmic inserts of β - blockers using different polymers. They found that inserts made from poly (hydroxypropyl methacrylate) were able to control the release of tilisolol hydrochloride[46].

Numerous studies have also been performed on soluble collagen shields. Collagen shields are fabricated from porcine sclera tissue, which has a similar collagen composition to that of the human cornea. Drug loading is typically achieved by soaking the collagen shield in the drug solution prior to application. Designed to slowly dissolve within 12, 24, or 72 h, collagen shields have attracted much interest as potential sustained ocular drug delivery systems over the last years[47,48].

Table 3: Other Approaches for Ocular Drug Delivery

Drug	Formulation	Polymer
Epinephrine	Prodrug	Dipivalyl epinephrine
Pilocarpine	Prodrug	*O, O'* (Xylylene)bispilocarpic acid esters
Ganciclovir	Prodrug	Ganciclovir acyl ester
Cromoclycin	Penetration enhancers	EDTA
Atenolol,	Penetration enhancers	Polyoxyethylene alkyl ethers (Brij), bile salts
Chloramphenicol, diclofenac, cyclosporin	Penetration enhancers	Cyclodextrins
Sufonamide carbonic anhydrase inhibitors	Penetration enhancer	Hydroxy propyl beta cyclodextrin
Pilocarpine nitrate	Penetration enhancer	Hydroxy propyl beta cyclodextrin
Ciprofloxacin	Cyclodextrins	Hydroxypropyl - β - cyclodextrin
Pilcarpine	Ocular insert	Mixtures of polyvinyl alcohol, glycerylbehenate, xanthan gum, jota carrageenan; Eudragit®RS, RL for coating.
Oxytetracycline HCL	Ocular insert	Medical grade silicone elastomers and rubbers
Fluorescein,	Ocular inserts	HPMC lyophilisate on carrier strip
Gentamicin	Ocular inserts	CAP, carbomer, HPMC, HPC, EC
Ofloxacin	Ocular inserts	PEO 200, 400, 900, and 2000 [163] PEO 400, Eudragit L100 [164] PEO 900, PEO 2000, chitosan - thiolated PAA
Ciprofloxacin	Ocular inserts	Sodium alginate, Eudragit, polyvinyl acetate
Pradofloxacin	Ocular inserts	Hydrogel coating on thin metallic wire (OpthaCoil

CONCLUSION

Although conventional eye drops still represent about 90% of all marketed ophthalmic dosage forms, there have been significant efforts towards the development of new drug delivery systems. Only a few of these new ophthalmic drug delivery systems have been commercialized

over the past decades, but research in the different areas of ocular drug delivery has provided important impetus and dynamism, with the promise of some new and exciting developments in the field.

An ideal ophthalmic delivery system should be able to achieve an effective drug concentration at the target site for an extended period of time while minimizing systemic side effects. In addition, the system should be comfortable and easy to use, as the patient ' s acceptance will continue to play an important role in the design of future ocular formulations. All delivery technologies mentioned in this chapter hold unlimited potential for clinical ophthalmology. However, each of them still bears its own drawbacks. To circumvent these, newer trends are directed toward combinations of the different drug delivery approaches. Examples for this include the

incorporation of particulates into in situ gelling systems or coating of nanoparticles with mucoadhesive polymers. These combinations will open new directions for the improvement of ocular bioavailability, but they will also increase the complexity of the formulations, thus increasing the difficulties in understanding the mechanism of action of the drug delivery systems.

Many interesting delivery approaches have been investigated during the past decades in order to optimize ocular bioavailability, but much remains to be learned before the perfect ocular drug delivery system can be developed.

REFERENCES

1. Bourlais Le, Sado PA, Needham T, Leverge R. Ophthalmic drug delivery systems Recent advances. Prog. Ret. Eye Res 1998; 17 (1): 33 –58.
2. Bourlais Le, Treupel – Acar, Sado PA, LevergeR. New ophthalmic drug delivery systems. Drug Dev Ind Pharm 1995; 21(1): 19 – 59
3. Jarvinen K, Jarvinen T, Urtti A. Ocular absorption following topical delivery. Adv Drug Deliv Rev 1995; 16 (1): 3 – 19.
4. Sasaki H, Yamamura K, Mukai T, Nishida K, Nakamura J, Nakashima M. Enhancement of ocular drug penetration. Crit Rev Ther Drug Carrier Syst 1999;16(1): 85 – 146
5. Jumbe NL, Miller MH. Ocular drug transfer following systemic drug administration , in Mitra , A. K. , Ed., Ophthalmic Drug Delivery Systems .2nd ed., Marcel Dekker NewYork 2003 ;109 – 133 .
6. Urtti A, Salminen L. Animal pharmacokinetic studies in Mitra , A. K. Ed. Ophthalmic Drug Delivery Systems , Marcel Dekker , New York 1993; 121 – 136
7. Stjernschantz J. and Astin M. Anatomy and physiology of the eye. Physiological aspectsof ocular drug therapy , in Edman , P. , Ed., Biopharmaceutics of Ocular Drug Delivery , CRC Press , Boca Raton, FL 1993; 1 – 25 .
8. Hornof M, Toropainen E, Urtti, A. Cell culture models of the ocular barriers, Eur J Pharm Biopharm 2005; 60 (2): 207 – 225 .
9. Duvvuri S, Majumdar S, Mitra AK. Drug delivery to the retina: Challenges and opportunities, Expert Opin Biol Ther 2003; 3(1): 45 – 56.
10. Kaur I P, Garg A, Singla AK, Aggarwal D. Vesicular systems in ocular drug delivery: An overview. Int J Pharm.2004; 269 (1): 1 – 14
11. Chrai S S, Robinson J R. Ocular evaluation of methylcellulose vehicle in albino rabbits ,
12. J Pharm Sci 1974; 63(8): 1218 – 1223.
13. Ludwig A, van Haeringen N J, Bodelier V M, Van Ooteghem M. Relationship between precorneal retention of viscous eye drops and tear fluid compositions. Int Ophthalmol 1992; 16 (1): 23 – 26 .
14. Greaves J L, Olejnik O, Wilson C G. Polymers and the precorneal tear film , STP Pharma Sci 1992; 2: 13 – 33
15. Park H, Robinson JR. Mechanisms of mucoadhesion of poly (acrylic acid)hydrogels , Pharm Res 1987; 4 (6): 457 – 464.
16. Van Ooteghem M. Factors influencing the retention of ophthalmic solutions on the eyesurface. Ophthalmic Drug Delivery: Biopharmaceutical, Technological and Clinical Aspects, Vol. 11, Livinia, Padova. 1984; 7 – 17.
17. Hui HW and J. R. Robinson, "Ocular delivery of progesterone using bioadhesive polymer", Int J Pharm 1985; 26:203-213.
18. Saettone MF, Giannaccini B, Ravecca S, La Marca F, and Tota G. (1984), Polymer effects on ocular bioavailability — The influence of different liquid vehicles on the mydriatic response of tropicamide in humans and in rabbits. Int. J. Pharm; 20 (1 – 2) : 187 – 202.
19. Park H, Robinson, JR. Mechanisms of mucoadhesion of poly(acrylic acid) hydrogels .Pharm Res 1987; 4 (6): 457 – 464.
20. Lang JC. Ocular drug delivery conventional ocular formulations, Adv. Drug Deliv Rev 1995; 16 (1): 39 – 43.
21. Fitzgerald P, Wilson CG. Polymeric systems for ophthalmic drug delivery , in Dimitriuitra S. , Ed., Polymeric Biomaterials , Marcel Dekker , New York 1994 , pp.373– 398 .
22. Gurny R, Ibrahim H, Buri P. The development and use of in situ formed gels, triggered by pH , in Edman , P. , Ed., Biopharmaceutics of Ocular drug Delivery 1993 , CRC Press, Boca Raton, FL , pp. 81 – 90.
23. Rathore KS, Insitu gelling ophthalmic drug delivery system: an overview. IJPPS 2010; 2,(4): 30-34.
24. Mainardes RM, Urban MCC, Cinto PO, Khalil NM. Colloidal carriers for ophthalmic drug delivery. Curr Drug Targets 2005; 6 (3): 363 – 371.
25. Kreuter J. Nanoparticles as bioadhesive ocular drug delivery systems in Lenaerts V and Gurny R. , Eds., Bioadhesive Drug Delivery Systems CRC Press , Boca Raton, FL 1990 ; 203 – 212.
26. Ludwig A. The use of mucoadhesive polymers in ocular drug delivery. Adv Drug Deliv Rev 2005; 57 (11): 1595 – 1639.
27. MarchalHeussler L, Sirbat D, Hoffman M, Maincent P. Poly(epsilon -caprolactone) nanocapsules in carteolol ophthalmic delivery. Pharm Res1993 ; 10 (3):386 – 390 .
28. Kaur, IP, Kanwar M. Ocular preparations: The formulation approach. Drug Dev Ind Pharm.2002; 28 (5): 473 – 493.32 – 46.
29. Nagarsenker MS, Londhe VY, Nadkarni GD. Preparation and evaluation of liposomal formulations of tropicamide for ocular delivery. Int J Pharm.1999; 190 (1):63 – 71.
30. Bochot A, Fattal E, Grossiord JL, Puisieux F, Couvreur P. Characterizatio of a new ocular delivery system based on a dispersion of liposomes in a thermosensitive gel. Int J Pharm 1998; 162 (1 – 2): 119 – 127.
31. Carafa M, Santucci E, Lucania G. L idocaine - loaded non - ionic surfactant vesicles: Characterization and in vitro permeation studies. Int J Pharm 2002; 231 (1):21– 32.
32. Schmalfuss U, Neubert R, Wohlrab W. Modification of drug penetration into human skin using microemulsions. J Controlled Release 1989 ; 46 (3):279 – 285.
33. Attwood D, Kreuter J, Ed, Colloidal Drug Delivery Systems, Marcel Dekker , New York , 1994; 31 – 71.
34. Benita S, Levy MY. Submicron emulsions as colloidal drug carriers for intravenous administration: Comprehensive physicochemical characterization. J Pharm Sci 1993; 82 (11): 1069 – 1079.
35. Radomska A, Dobrucki R. The use of some ingredients for microemulsion preparation containing retinol and its esters. Int J Pharm.2000; 196 (2): 131 – 134.
36. Beilin M, Bar Ilan A, Amselem S, Schwarz J, Yogev A, Neumann R. Ocular retentiontime of submicron emulsion (SME) and the miotic response to pilocarpine delivered in SME . Invest Ophthalmol Vis Sci1995; 36 (4): 166.
37. Rootman DS, Jantzen JA, Gonzalez JR, Fischer MJ, Beuerman R, Hill JM. Pharmacokinetics and safety of transcorneal iontophoresis of tobramycin in the rabbit. Invest Ophthalmol Vis Sci 1988; 29:1397-401.
38. Callegan MC, Hobden JA, O'Callaghan RJ, Hill JM. Ocular drug delivery: A comparison of transcorneal iontophoresis to corneal collagen shields. Int J Pharma 1995; 123:173-9.
39. Nagarsenkar MS, Vaishali Y, Londhe, Nadkarni GD. Preparation and evaluation of liposomal formulations of tropicamide for ocular delivery. Int J Pharma 1999;190:63- 71.
40. EsfandR, Tomalia DA. Poly (amidoamine) (PAMAM) dendrimers: From biomimicry to drug delivery and biomedical applications. Drug Discov Today 2001; 6 (8): 427 – 436
41. Cloninger MJ. Biological applications of dendrimers. Curr Opin Chem Biol 2002;6(6): 742 – 748 .
42. Lee VH. Improved ocular drug delivery by use of chemical modifications (prodrugs), in Edman. P Ed. Biopharmaceutics of Ocular Drug Delivery , CRC Press , Boca Raton, FL1993; 121 – 143
43. JarvinenT, Jarvinen K. Prodrugs for improved ocular drug delivery. Adv Drug Deliv Rev1999; 19 (2): 203 – 224
44. Kaur IP , Smitha R. Penetration enhancers and ocular bioadhesives: Two new avenuesfor ophthalmic drug delivery. Drug Dev Ind Pharm.2002; 28 (4) 353 – 369
45. Szejtli J. Medicinal applications of cyclodextrins . Med. Res. Rev.1994; 14 (3):353 –386
46. Jarho P, Jarvinen K, Urtti A, Stella VJ, Jarvinen T. Modified beta – cyclodextrin(SBE7 - beta- CyD) with viscous vehicle improves

the ocular delivery and tolerability of pilocarpine prodrug in rabbits. J Pharm Pharmacol1996; 48 (3): 263 – 269.

47. Sasaki H, TeiC , Nishida K . Drug release from an ophthalmic insert of a beta – blockeras an ocular drug delivery system. J Controlled Release 1993; 27 (2):127 – 137 .
48. Lee VH. New directions in the optimization of ocular drug delivery. J Ocul. Pharmacol1990; 6 (2): 157 – 164.
49. Vandervoort J, Ludwig A. Preparation and evaluation of drug loaded gelatin nanoparticles for topical ophthalmic use. Eur J Pharm Biopharm 2004; 57 (2): 251 -261.