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 formulations1. 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%: Various ocular delivery systems, such as 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 surface2.

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 μm thick and is the first structure encountered by topically applied drugs. The trilaminar structure of the tear film is shown in figure 2.

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.

The cul-de-sac normally holds 7 – 9 μL of tear fluid, with the normal tear flow rate being 1.2 – 1.5 μL/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.

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, two to three layers of polygonal wing cells, and a single layer of basal columnar cells, allowing for minimal paracellular transport.

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. 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. 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.

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.

Formulation Considerations

Irritation of the eye following the use of a 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. 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.

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. Among the range of hydrophilic polymers investigated in the area of ocular drug delivery are polyvinyl alcohol (PVA) and polyvinyl pyrrolidone (PVP), cellulose derivatives such as methylcellulose (MC), and polyacrylic acids (carbopol).

It has a great influence on the rheological properties of viscous ocular dosage forms and consequently the bioavailability of the incorporated drug. Newtonian systems do not show any real improvement in bioavailability below a certain viscosity and blinking becomes painful, followed by reflex tearing, if the viscosity is too high. 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.

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. 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 derivatives or PVA.

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.

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. 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 derivatives, 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 physiochemical 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 derivatives such as carbopol, methacrylates and polycarboxhils. 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. Carbopol 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.

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.

389
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 preparations23.

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 adsorbed24. 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 nanoparticles25. 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 acrylate, 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 carbachol. 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 μm. Owing to their amphiphilic nature, liposomes can accommodate both lipophilic (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 gel29.

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-immunogenic30. 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 bioavailability32, 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 derivatives32.

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 electrostatic 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 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 use of MEs in ocular delivery is very attractive due to all the factors previously mentioned, render MEs promising ocular delivery systems. 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.

Table 2: Colloidal ocular drug delivery system

<table>
<thead>
<tr>
<th>Drug</th>
<th>Formulation</th>
<th>Polymer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pilocarpine</td>
<td>Nanoparticles</td>
<td>Gelatin</td>
</tr>
<tr>
<td>Hydrocortisone</td>
<td>Nanoparticles</td>
<td>Albumin</td>
</tr>
<tr>
<td>Pilocarpine</td>
<td>Nanoparticles</td>
<td>Albumin methacrylate acrylic acid copolymer (Piloplex)</td>
</tr>
<tr>
<td>Betaxolol</td>
<td>Nanoparticles</td>
<td>Poly-ε-caprolactone (PECL), polyisobutyl cyanoacrylate (PLGA)</td>
</tr>
<tr>
<td>Carteolol</td>
<td>Nanoparticles</td>
<td>Poly-ε-caprolactone (PECL)</td>
</tr>
<tr>
<td>Ciclosporine</td>
<td>Nanoparticles</td>
<td>Chitosan</td>
</tr>
<tr>
<td>Indomethacin</td>
<td>Nanoparticles</td>
<td>Chitosan - and poly - L- lysine coated poly - ε - caprolactone</td>
</tr>
<tr>
<td>Acrillevir</td>
<td>Nanoparticles</td>
<td>PEG - coated PLA nanospheres</td>
</tr>
<tr>
<td>Ibuprofen</td>
<td>Nanoparticles</td>
<td>Eudragit RS100</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>Microspheres</td>
<td>Eudragit RS100 and RL100</td>
</tr>
<tr>
<td>Piroxicam</td>
<td>Microspheres</td>
<td>Pectin, Albumin</td>
</tr>
<tr>
<td>Pilocarpine</td>
<td>Liposomes</td>
<td>Carbopol - coated liposomes</td>
</tr>
<tr>
<td>Timolol</td>
<td>Niosomes</td>
<td>Chitosan - and carbopol - coated Niosomes</td>
</tr>
<tr>
<td>Retinol</td>
<td>Microemulsions</td>
<td>Tween 60 and 90, soy bean</td>
</tr>
<tr>
<td>cyclosporine</td>
<td>NLC</td>
<td>Polyethylene glycol</td>
</tr>
<tr>
<td>Diclofenac</td>
<td>Liposome</td>
<td>Monostearate</td>
</tr>
<tr>
<td>sodium</td>
<td></td>
<td>Phosphatidylerine Chitosan</td>
</tr>
<tr>
<td>acetzolamide</td>
<td>niosome</td>
<td>span 60 ketamine HCl injection, cholesterol</td>
</tr>
<tr>
<td>flurbiprofen</td>
<td>Nanostructured lipid carrier</td>
<td>Chitosan Oligosaccharides</td>
</tr>
</tbody>
</table>

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 drug27. 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 effects38,39. 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 derivatives 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, possess 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 needs42.

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 calcin solution at all time points.

Development, and Manufacturing that w/o MEs undergo phase transition into lamellar liquid crystals (LLCs) 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 solution36.

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.
Cyclodextrins complexation generally results in improved wettability, dissolution, solubility, and stability in solution as well as reduced side effects\(^45\).

**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 as 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\(^45\).

**Table 3: Other Approaches for Ocular Drug Delivery**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Formulation</th>
<th>Polymer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epinephrine</td>
<td>Prodrug</td>
<td>Dipivalyl epinephrine</td>
</tr>
<tr>
<td>Pilocarpine</td>
<td>Prodrug</td>
<td>0, 0' (Xylylene)bispilocarpic acid esters</td>
</tr>
<tr>
<td>Ganciclovir</td>
<td>Prodrug</td>
<td>Ganciclovir acylester</td>
</tr>
<tr>
<td>Cromoclycin</td>
<td>Penetration enhancers</td>
<td>EDTA</td>
</tr>
<tr>
<td>Atenolol</td>
<td>Penetration enhancers</td>
<td>Polyoxyethylene alkyl ethers (Brij), bile salts</td>
</tr>
<tr>
<td>Chloramphenicol, diclofenac, cyclosporin</td>
<td>Penetration enhancers</td>
<td>Cyclodextrins</td>
</tr>
<tr>
<td>Sulfonamide carbonic anhydrase inhibitors</td>
<td>Penetration enhancer</td>
<td>Hydroxy propyl beta cyclodextrin</td>
</tr>
<tr>
<td>Pilocarpine nitrate</td>
<td>Penetration enhancer</td>
<td>Hydroxy propyl beta cyclodextrin</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>Ocular insert</td>
<td>Hydroxypropyl - β - cyclodextrin Mixture of polyvinyl alcohol, glycerylbehenate, xanthan gum, iota carrageenan, Eudragit®RS, RL for coating.</td>
</tr>
<tr>
<td>Fluorescein,</td>
<td>Ocular inserts</td>
<td>Medical grade silicone elastomers and rubbers</td>
</tr>
<tr>
<td>Gentamycin</td>
<td>Ocular inserts</td>
<td>HPMC lyophilisate on carrier strip</td>
</tr>
<tr>
<td>Ofloxacin</td>
<td>Ocular inserts</td>
<td>CAP, carbomer, HPMC, HPC, EC, PEO 200, 400, 900, and 2000 [163]</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>Ocular inserts</td>
<td>Sodium alginate, Eudragit, polyvinylacetate</td>
</tr>
<tr>
<td>Pradofloxacin</td>
<td>Ocular inserts</td>
<td>Hydrogel coating on thin metallic wire (OphthaCoil)</td>
</tr>
</tbody>
</table>

**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 they will also increase the complexity of the system can be developed.

REFERENCES

42. Jarho P, Jarvinen K, Urtti A, Stela VJ, Jarvinen T. Modified beta – cyclodextrin(SBE7 - beta- CyD) with viscous vehicle improves
