
Topical Ocular Drug Delivery – A Review

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The available ocular drug delivery systems are fairly primitive and inefficient, but the stage is set for the rational design of newer and significantly improved systems. This review will discuss the progress of various types of ocular drug delivery systems and their characteristic advantages and limitations of each system, thus improvements can be made to overcome the constraints imposed by the eye. Two main approaches, i.e. improvement in bioavailability and controlled drug delivery systems are discussed. Combination of drug delivery systems could open a new directive for improving the therapeutic response of a non-efficacious system.

Most commonly available ophthalmic preparations are eye drops and ointments. But these preparations when instilled into the cul-de-sac are rapidly drained away from the ocular cavity due to tear flow and lacrimal nasal drainage. Only a small amount is available for its therapeutic effect resulting in frequent dosing¹. Thus inefficient drug delivery into the eye occurs due to rapid tear turn over, lacrimal drainage and drug dilution by tears².

Topical administration for ocular therapeutics is ideal because of smaller doses required compared to the systemic use, its rapid onset of action and freedom from systemic toxicity. Topically applied ocular drugs have to reach the inner parts of the eye and transcorneal penetration is believed to be the major route for drug absorption. Corneal absorption is much slower process than elimination. For many drugs K_{loss} (First order elimination rate) is approximately 0.5-0.7/min and $K_{absorption}$ (First order absorption rate) is about 0.001/min. The sum of these two rate constants control the fraction of the applied dose absorbed into the eye³. So the ocular bioavailability can be increased by decreasing K_{loss} or by increasing $K_{absorption}$. The former can be achieved by modifying the ocular dosage forms and the latter by formulating ocular dosage forms containing lipophilic prodrugs or by adding penetration

enhancers. Therefore to optimize topical ocular drug delivery system prolonged contact time with the corneal surface and better penetration through cornea is necessary⁴.

A considerable amount of effort has been made in ophthalmic drug delivery since 1970's. The two main approaches attempted are improvement in bioavailability and controlled release drug delivery.

IMPROVEMENT IN BIOAVAILABILITY

Topical bioavailability can be improved by maximizing precorneal drug absorption and minimizing precorneal drug loss.

Viscosity enhancer:

In order to prolong precorneal residence time and to improve bioavailability attempts were made to increase the viscosity of the formulation. The viscosity enhancers used were hydrophilic polymers such as cellulose, polyalcohol and polyacrylic acid. sodium carboxy methyl cellulose is one of the most important mucoadhesion polymers having more adhesive strength⁵. The effects of polyacrylic acid and polyacrylamide based hydrogels are tested on miotic response of pilocarpine. Carbomer were used in liquid and semisolid formulations as suspending or viscosity increasing agents. Formulations including creams, gels and ointments were used as ophthalmic products⁶. Polycarbophil is

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water insoluble cross linked polyacrylic acid helps in the retention of the drug delivery system in the eye⁷ due to the formation of hydrogel bonds and mucoadhesive strength. Hyaluronic acid offers a biocompatible and biodegradable matrix for fabrication of ocular sustained release dosage form. Dosage forms based on the benzyl esters of hyaluronic acid were used for ophthalmic sustained release of methyl prednisolone. Films and microspheres were also prepared from hyaluronic acid. Polysaccharide such as xanthan gum was found to increase the viscosity⁸. Today, hydrophilic polymers continue to be used in formulation of ophthalmic products. But these functions are more for patient comfort and for bioadhesion rather than viscosity enhancement. Viscosity vehicles increases the contact time and no marked sustaining effect is seen.

Gels:

Gel formation is an extreme case of viscosity enhancement through the use of viscosity enhancers. So the dosing frequency can be decreased to once a day⁹. Cellulose acetate phthalate dispersion constituted a micro-reservoir system of high viscosity. Poloxamer 407 is used as an ophthalmic vehicle for pilocarpine delivery and found that the gel formation enhances the activity of pilocarpine¹⁰. Timolol maleate form thermogelling drug delivery system composed of cellulose ether ethylhydroxyethylcellulose¹¹. The effect of flurbiprofen a non steroidal anti inflammatory, formulated in carbopol 940 and pluronic F 127 hydrogels were compared in ocular hypertension. Gelrite is a polysaccharide (gellan gum), which forms a clear gel in the presence of mono or divalent cation. The high viscosity of the gel, however, results in blurring of vision and malting eyelids which substantially reduce patient acceptability. Sterilization is another drawback for large-scale production.

Penetration enhancers:

They act by increasing corneal uptake by modifying the integrity of corneal epithelium. Chelating agents, preservatives, surfactants and bile salts were studied as possible penetration enhancers. But the effort was diminished due to the local toxicity associated with enhancers¹². Penetration enhancers have also been reported to reduce the drop size of conventional ophthalmic solutions especially if they do not elicit local irritation.

Prodrugs:

Prodrugs enhance corneal drug permeability through modification of the hydrophilic or lipophilicity of the drug¹³.

The method includes modification of chemical structure of the drug molecule, thus making it selective, site specific and a safe ocular drug delivery system. Drugs with increased penetrability through prodrug formulations are epinephrine¹³, phenylephrine, timolol, pilocarpine¹⁴ and albuterol.

Use of cyclodextrins:

Cyclodextrins act as carriers by keeping the hydrophobic drug molecules in solution and delivering them to the surface of the biological membrane, where the relatively lipophilic membrane has a much lower affinity for the hydrophilic cyclodextrin molecules and therefore they remain in the aqueous vehicle system. Optimum bioavailability can be achieved when just enough cyclodextrin (< 15%) is added to the aqueous eye drops solution to solubilise the lipophilic water insoluble drug¹⁵. But increased concentration will result in decrease in bioavailability.

Use of bioadhesive polymers:

The bioadhesive polymers¹⁶ adhere to the mucin coat covering the conjunctiva and the corneal surfaces of the eye, thus prolonging the residence time of a drug in the conjunctival sac. These polymers can be neutral, synthetic or semi synthetic. Polyacrylic acid, polycarbophil and hyaluronic acid are synthetic polymers commonly used. Chitosan is a bioadhesive vehicle suitable for ophthalmic formulation since it exhibits general biological properties such as biodegradability, nontoxicity and biocompatibility. Due its positive charge at neutral pH and ionic interaction with the negative charges of sialic acid occurs. Xanthan and carrageenan are also described as bioadhesive polysaccharides¹⁷.

IMPROVEMENT IN CONTROLLED DRUG DELIVERY

It is realized that the preferred system of ophthalmic delivery would provide improved bioavailability, site-specific delivery and with continuous drug release. So achievements have been made in the following areas:

***In situ* forming gels:**

The progress has been made in gel technology in the development of droppable gel. They are liquid upon instillation and undergo phase transition in the ocular cul-de-sac to form visco-elastic gel and this provides a response to environmental changes¹⁸. Three methods have been employed to cause phase transition in the eye surface. These are change in pH, change in temperature and ion activation.

pH:

In this method gelling of the solution is triggered by a change in the pH. CAP latex cross linked polyacrylic acid and derivatives such as carbomers are used. They are low viscosity polymeric dispersion in water which undergoes spontaneous coagulation and gelation after instillation in the conjunctival cul-de-sac¹⁹.

Temperature:

In this method gelling of the solution is triggered by change in the temperature. Sustained drug delivery can be achieved by the use of a polymer that changes from solution to gel at the temperature of the eye. But disadvantage of this is characterized by high polymer concentration (25% Poloxamers)²⁰. Methyl cellulose and smart hydrogels are other examples.

Ionic strength:

In this method gelling of the solution instilled is triggered by change in the ionic strength. Example is Gelrite. Gelrite is a polysaccharide, low acetyl gellan gum, which forms a clear gel in the presence of mono or divalent cations. The concentration of sodium in human tears is 2.6 g/l is particularly suitable to cause gelation of the material when topically installed into the conjunctival sac.

Oil in water emulsions:

Phospholipids and pluronics were used as the emulsifiers. Antioxidants were added to improve their shelf-life. The intra-ocular pressure reducing effect of a single, topically administered dose of a pilocarpine emulsion lasted for 29 h in rabbits compared to generic pilocarpine solution which lasted only for 5 h²¹. Oil in water emulsion is useful for delivery of water insoluble drugs, which is solubilised in the internal oil phase.

Colloidal particles:

The potential use of polymeric colloidal particles as ophthalmic drug delivery systems started in late 1970's. The first two systems studied in this area were pilocarpine cellulose acetate hydrogen phthalate latex systems and piloplex. But both the system could not enter commercial development because of various issues, like local toxicity, non-biodegradable polymer and large scale sterilization.

Liposomes:

The use of liposomes as a topically administered ocular drug delivery system began in the early stage of research into ophthalmic drug delivery. But the results were

favorable for lipophilic drugs and not for hydrophilic drugs. It was concluded that liposomes must be suitable for ocular drug delivery, provided, they had an affinity for, and were able to bind to, ocular surfaces, and release contents at optimal rates²². Positively charged liposomes have a greater affinity, to increase both precorneal drug retention and drug bioavailability. The addition of stearylamine to a liposomal preparation enhanced the corneal absorption of dexamethyl valerate. The corneal epithelium is thinly coated with negatively charged mucin to which the positive surface charge of the liposome may absorb more strongly. Coating with bioadhesive polymers to liposomes, prolong the precornea retention of liposomes. Carbopol 1342-coated pilocarpine²³ containing liposomes were shown to produce a longer duration of action.

Liposomal preparation of acetazolamide²⁴, hydrocortisone²⁵ and tropicamide²⁶ has been reported. Coating the liposome with bioadhesive polymer like carbopol increased the corneal retention followed by sustained action. Cyclosporin applied topically to the eye in the olive oil drops in a liposome encapsulated form and in a cellophane shield showed slow releasing property.

Nanoparticles:

Nanoparticles provide sustained release and prolonged therapeutic activity when retained in the cul-de-sac after topical administration and the entrapped drug must be released from the particles at an appropriate rate. To enhance particle retention, it is desirable to fabricate the particles with bioadhesive materials. Biodegradation is also a highly desirable property for the fabrication of nanoparticles. Most commonly used polymers are various poly (alkyl cyanoacrylates), poly Σ -caprolactone and polylactic-co-glycolic acid, which undergo hydrolysis in tears. Coating of nanoparticles with bioadhesive polymers improves the bioavailability. Chitosan coated nanocapsules improve the bioavailability²⁷. Nanoparticles as an ophthalmic drug delivery have been demonstrated for both hydrophilic and hydrophobic drugs^{28,29}.

Microparticulates:

They are drug containing, micron sized polymeric particles suspended in a liquid medium. Drugs can be physically dispersed in the polymer backbone³⁰. The drug is released in cul-de-sac through diffusion, chemical reaction, and polymer degradation and micro particles are larger than nanoparticles. Acyclovir loaded chitosan microspheres³¹ and Pilocarpine-loaded albumin or gelatin microspheres³² are available. Microparticulate technology

has the advantage of better patient acceptability, since they can be topically administered as an eye drop³³. But the manufacture and control of large scale manufacturing of sterile micro particulates is very challenging and expensive.

Inserts:

Solid inserts were introduced into the market 50 years ago. The first solid insert was described in 1948 in British Pharmacopoeia. It was an atropine containing gelatin wafer and in 1980's numerous systems were developed using various polymers and different drug release principles for controlled drug release.

Insoluble inserts are polymeric systems into which the drug is incorporated as a solution or dispersion³⁴. Ophthalmic inserts (ocuserts) have been reported using alginate salts, PVP, modified collagen and HPC, Ocufit is a silicone elastomer based matrix that allows for the controlled release of an active ingredient over a period of at least 2 weeks³⁵. Osmotically controlled inserts have also been described, where release is by diffusion and osmotically controlled³⁶.

Soluble inserts consists of all monolytic polymeric devices that at the end of their release, the device dissolve or erode. Soluble ophthalmic drug inserts is a soluble copolymer of acrylamide, N-vinyl pyrrolidone and ethyl acrylate. It is a sterile thin film or wafer of oval shape. The system soften in 10-15 sec after introduction in to the upper conjunctival sac, gradually dissolves within 1 h, while releasing the drug. A soluble insert containing gentamycin sulphate and dexamethasone phosphate has been developed Pilocarpine insert for glaucoma is also reported. But these systems have the draw back that they blur vision while the polymer is dissolving. Water soluble bioadhesive component in its formulation has been developed to decrease the risk of expulsion and ensure prolonged residence in the eye, combined with controlled drug release. They are bioadhesive ophthalmic drug inserts. A system based on gentamycin obtained by extrusion of a mixture of polymers, showing a release timer of about 72 h has been reported. Due to difficulty with self-insertion, foreign body sensation, only few insert products are listed and pharmaceutical manufacturers are not actively developing inserts for commercialization.

Implantable systems:

The poly lactic acid and its copolymers with glycolic acid have been used extensively as implants. An ocular

implant for delivering ganciclovir for the treatment of cytomegalovirus has also been developed³⁷. This delivers drug directly to the retina for over 5 months. These systems are less popular as they require minor surgery.

Minidisc:

Minidisc is a controlled release monolithic matrix type device consisting of a contoured disc with a convex front and a concave back surface³⁶. The principle component is a (1) bis (4-methacryloxybutyl)-polydimethyl siloxane. They can be made hydrophilic and hydrophobic to permit extended release of both water soluble and water insoluble drugs.

Soft contact lenses:

The most widely used material is poly-2-hydroxyethylmethacrylate. Its copolymers with PVP are used both to correct eyesight and hold and deliver drugs. Controlled release can be obtained by binding the active ingredient via biodegradable covalent linkages³⁹.

Niosomes:

Niosomes are reported as successful ophthalmic carriers. Discoidal niosomes (discomes) of timolol maleate have been reported to be promising systems for the controlled ocular administration of water soluble drugs⁴⁰. The disc shape provides for a better fit in the cul-de-sac of the eye and then large size may prevent their drainage into the systemic pool.

Pharmacosomes:

They are the vesicles formed by the amphiphilic drugs. Any drug possessing a free carboxyl group or an active hydrogen atom (-OH, -NH₂) can be esterified to the hydroxyl group of a lipid molecule, thus generating an amphiphilic prodrug. These are converted to pharmacosomes on dilution with water. They show greater stability, facilitated transport across the cornea and a controlled release profile¹⁶.

Collagen shields:

They are manufactured from porcine scleral tissue, which bears a collagen composition similar to that of human cornea. They are hydrated before being placed on the eye and the drug is loaded with the collagen shield simply by soaking it in the drug solution. They provide a layer of collagen solution that lubricates the eye. Collagen shields presoaked in tobramycin were used to treat *Pseudomonas aeruginosa* infected cornea excoriation³⁸. But shields are

not fully transparent and thus reduce visual activity. But they are appropriate delivery systems for both hydrophilic and hydrophobic drugs with poor penetration properties.

RECENT DEVELOPMENTS

New ophthalmic delivery system includes ocular inserts, collagen shields, ocular films, disposable contact lens and other Novel drug delivery systems like niosomes⁴⁰ and nanoparticles²⁹. Newer trend is a combination of drug delivery technologies for improving the therapeutic response of a non efficacious drug. This can give a superior dosage forms for topical ophthalmic application.

CONCLUSIONS

Among these drug delivery systems, only few products have been commercialized. An ideal system should have effective drug concentration at the target tissue for an extended period of time with minimum systemic effect. Patient acceptance is very important for the design of any comfortable ophthalmic drug delivery system. Major improvements are required in each system like improvement in sustained drug release, large scale manufacturing and stability. Combination of drug delivery systems could open a new directive for improving the therapeutic response of a non-efficacious system. They can overcome the limitations and combine the advantages of different systems.

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