

Review Article

An Insight into Ophthalmic Drug Delivery System

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ABSTRACT

Promising management of eye ailments take off effective concentration of drug at the eye for sufficient period of time. Dosage forms are administered directly to eye for localized ophthalmic therapy. Most of the treatments call for the topical administration of ophthalmic active drugs to the tissues around the ocular cavity. Conventional ophthalmic drug delivery systems including eye drops, ophthalmic ointments, are no longer sufficient to encounter eye diseases. This article reviews the constraints with conventional ocular therapy and explores various novel approaches like in-situ gel, ocular films or ocuserts, nanosuspension, collagen shields, latex systems, nanoparticles, liposomes, niosomes, iontophoresis, eye implants, etc to improve the ophthalmic bioavailability of drugs to the anterior chamber of the eye.

Keywords: Ophthalmic drug delivery, ocular drug delivery, newer drug delivery systems for eye.

INTRODUCTION

Eye is the window of our soul. The eye is unique organ from anatomical and physiological point of view. Without eye we can not enjoy the beauty of the nature. The eye has special attributes that allows local drug delivery and non-invasive clinical assessment of disease but also makes understanding disease pathogenesis and ophthalmic drug delivery challenges. Eye ailment can cause distress and angst in patients, with the ultimate fear of loss of vision or even facial disfigurement. Many parts of the eye are relatively inaccessible to systemically administered drugs and, as a result, topical drug delivery remains the preferred route in most cases. Drugs may be delivered to treat the precorneal region for such infections as conjunctivitis and blepharitis, or to provide intraocular treatment via the cornea for diseases such as glaucoma and uveitis.^[1]

Topical drug delivery is complicated by effective removal mechanisms (which operate to keep the ocular surface free from foreign substances) and the barriers of the precorneal area. These include the blinking reflex, tear turnover and low corneal permeability. Conventional eye drops require frequent instillation, it has been estimated that only 1-2 % of an instilled dose of pilocarpine hydrochloride, a drug used in the treatment of glaucoma, reaches its target tissue in the eye. In addition, eye drops are often difficult for patients to administer, particularly the elderly. Thus in recent years there has been significant effort directed toward the development of new systems for ophthalmic drug delivery. In this review the anatomy and physiology of the eye will be described, and the barriers to drug absorption highlighted. Furthermore the drugs and delivery systems used in their treatment will be discussed.

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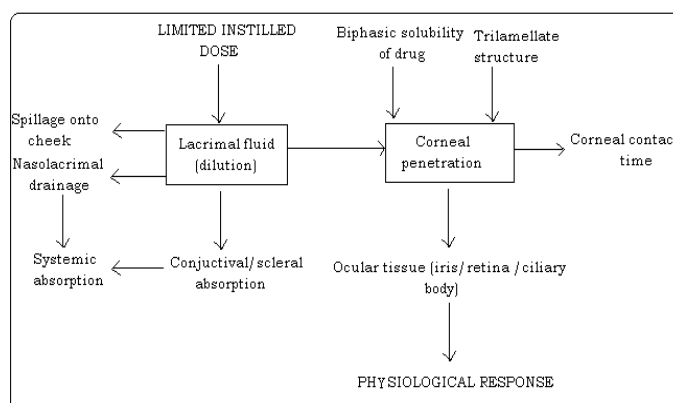


Fig. 1: Fate of ophthalmic drug delivery systems

Anatomy and Physiology of the Eye

The eye is a spherical structure with a wall consisting of three layers: the outer sclera, the middle choroid layer and the inner retina. The sclera is a tough fibrous coating that protects the inner layers. It is white except for the transparent area at the front, the cornea, which allows light to enter the eye (Fig. 2).

The choroid layer, situated inside the sclera, contains many blood vessels and is modified at the front of the eye as the pigmented iris. The biconvex lens is situated just behind the pupil. The chamber behind the lens is filled with vitreous humor, a gelatinous substance occupying 80 % of the eyeball. The anterior and posterior chambers are situated between the cornea and iris, and iris and lens, respectively and filled with aqueous humor. At the back of the eye is the light-detecting retina.

The cornea and its layers

The cornea is an optically transparent tissue that conveys images to the back of the eye and covers about one-sixth of the total surface area of the eyeball. It is an avascular tissue to

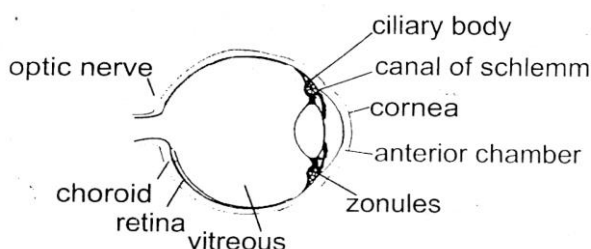


Fig. 2: Schematic cross section through a human eye which nutrients and oxygen are supplied via bathing with lachrymal fluid and aqueous humour as well as from blood vessels that line the junction between the cornea and sclera. The cornea is considered to be the main pathway for the permeation of drugs into the eye.^[2] It is approximately 0.5 mm thick in the central region, increasing to approximately 0.7 mm at the periphery and composed of five layers (Fig. 3).

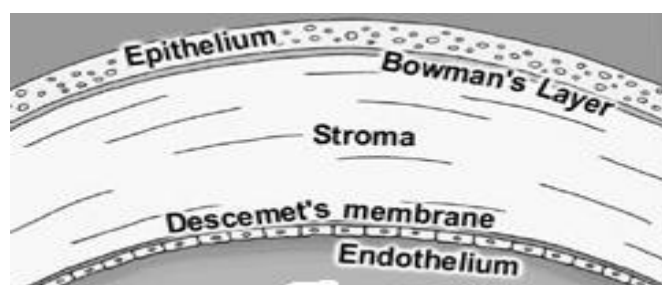


Fig. 3: Section through the cornea.

- The epithelium is squamous stratified, consisting of 56 layers of cells (increasing to 8-10 layers at the periphery), has a total thickness of around 50-100 μm and a turnover of about one cell layer per day. The tight junctions and hydrophobic domains in this layer make it the most important barrier to drug delivery.
- The Bowman's membrane is an acellular homogenous sheet, about 8-14 μm thick. This is positioned between the basement membrane of the epithelium and the stroma.
- The stroma, or *substantia propria*, accounts for around 90 % of the corneal thickness. It contains approximately 85 % water, and about 200-250 collagenous lamellae that are superimposed onto one another and run parallel to the surface. The lamellae provide physical strength while permitting optical transparency. The stroma has a relatively open structure and will normally allow the diffusion of hydrophilic solutes.
- The Descemet's membrane, which is secreted by the endothelium, lies between the stroma and the endothelium.
- The corneal endothelium is responsible for maintaining normal corneal hydration and consists of a single layer of flattened hexagonal cells 5 μm high and 20 μm wide. The endothelium is in direct contact with the anterior chamber and is subject to a passive influx of water from the aqueous humor towards the stroma. For a drug to cross the cornea effectively, it has to have both hydrophilic and lipophilic properties, and be sufficiently small to pass through tight junctions.

The conjunctiva

The conjunctiva is involved in the formation and maintenance of the precorneal tear film and in the protection of the eye. It is a thin, vascularised mucous membrane that lines the posterior surface of the eyelids and outer regions of

the cornea (Fig. 4). The conjunctival epithelium differs somewhat from that of the cornea, in that it is thicker and possesses mucus-secreting goblet cells. The human conjunctiva is between 2 and 30 times more permeable to drugs than the cornea and it has been proposed that loss by this route is a major path for drug clearance.^[3]

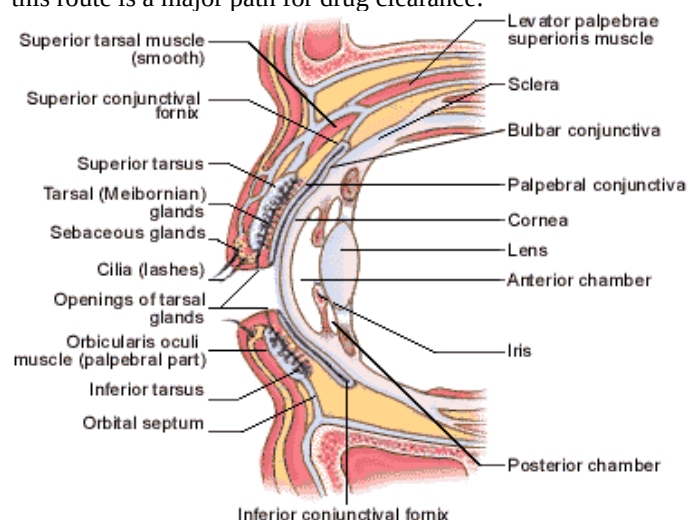


Fig. 4: The conjunctiva.

The nasolachrymal drainage system

The nasolachrymal drainage system (Fig. 5) consists of three parts: the secretory system, the distributive system and the excretory system. The secretory system consists of basic secretors that are stimulated by blinking and temperature change due to tear evaporation and reflex secretors that have an efferent parasympathetic nerve supply and secrete in response to physical or emotional stimulation.

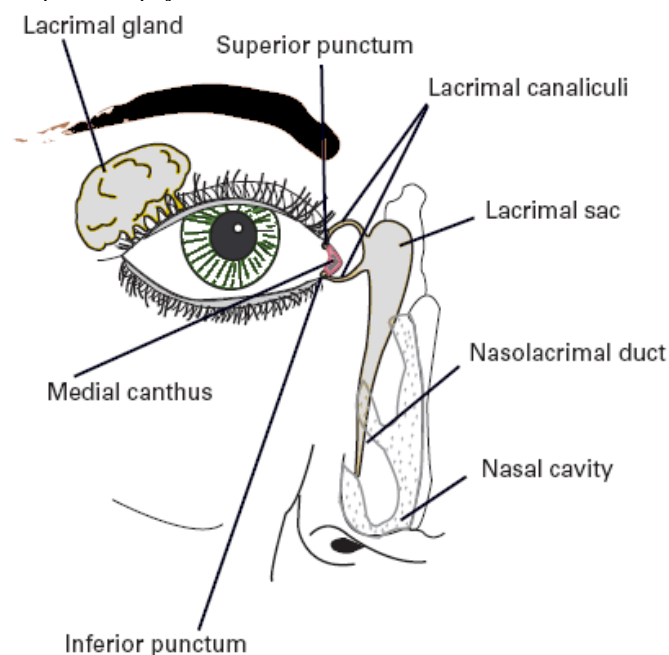


Fig. 5: The nasolachrymal drainage system.

The distributive system consists of the eyelids and the tear meniscus around the lid edges of the open eye, which spread tears over the ocular surface by blinking, thus preventing dry areas from developing.

The excretory part of the nasolachrymal drainage system consists of: the lacrimal puncta, the superior, inferior and common canaliculi; the lacrimal sac; and the nasolachrymal

duct. In humans, the two puncta are the openings of the lachrymal canaliculi and are situated on an elevated area known as the lachrymal papilla. It is thought that tears are largely absorbed by the mucous membrane that lines the ducts and the lachrymal sac, only a small amount reaches the nasal passages.

The cul-de-sac of the eye (the corners) normally holds around 7-9 μl of tears but can retain up to 20-30 μl if care is taken not to blink. The normal tear flow rate is 1 $\mu\text{l min}^{-1}$ and the pH is maintained at 6.5-7.6.

The precorneal tear film

The precorneal tear film is a highly specialized fluid layer that covers the corneal epithelium, conjunctiva and the walls of the conjunctival cul-de-sac. Tears are necessary for the nutrition of the cornea, the removal of unwanted materials including cells and bacteria, and for providing lubrication that allows the eyelids to move freely over the globe. Abnormalities of the tear film can lead to dysfunction of the conjunctiva and eyelids as well as to loss of corneal transparency.

OPHTHALMIC DISORDERS

Conditions treated by the topical application of drugs include:

- **Conjunctivitis** - an inflammation of the conjunctiva that may be caused by bacterial and viral infection, pollen and other allergens, smoke and pollutants.
- **Dry eye syndrome** - the inadequate wetting of the ocular surface.
- **Glaucoma** - the build up of pressure in the anterior and posterior chambers of the choroid layer that occurs when the aqueous humour fails to drain properly.
- **Iritis (anterior uveitis)** - commonly has an acute onset with the patient suffering pain and inflammation of the eye.
- **Keratitis** - an inflammation of the cornea, caused by bacterial, viral or fungal infection.
- Other conditions include the ophthalmic complications of Rosacea, blepharitis (inflammation of the lid margins) and chalazia (Meibomian cysts of the eyelid).

Drugs administered topically to the eye

Most ophthalmic drugs contain functional groups such as alcohol, carboxylic acid and phenol, which lend themselves to simple derivatisation. Prodrugs (pharmacologically inactive derivatives of drugs that are chemically or enzymatically converted to their active parent compound after administration) of pilocarpine and β -blocker have been used to enhance bioavailability.

DRUG DELIVERY SYSTEMS FOR THE EYE

The most common method of ocular drug delivery is the instillation of drops into the lower cul-de-sac. Such drops are usually drained quickly, aided by the blinking reflex, and the precorneal region returns to the normal resident volume of around 7 μl . The concentration of drug in the precorneal area provides the driving force for its transport across the cornea via passive diffusion. Thus, efficient ocular drug absorption requires good corneal penetration as well as prolonged contact time with the corneal tissue. Iontophoresis, prodrugs, ion pair formation and cyclodextrins have all been used as means of enhancing ocular drug absorption. An ideal topical ophthalmic formulation would enhance bioavailability by

sustaining drug release, while remaining in contact with the front of the eye for prolonged periods of time; modern formulations attempt to achieve this.^[4]

There are a wide variety of ophthalmic drug delivery systems on the market.^[5] Nevertheless, about 70 % of prescriptions for eye medication are for conventional eye drops. This is due to factors including expense, difficulty in bulk manufacture, patient compliance, efficacy and stability. The various types of ocular drug delivery vehicle in existence are discussed in the following sections. In all cases, one key requirement is that the formulation must be capable of being sterilized or produced in a sterile environment.

1. Liquids - eye drops/lotions

Eye drops may be solutions or suspensions and are comparatively convenient, safe, immediately active and acceptable to patients. An eye drop is sterile, contains a preservative (if not single use only), is isotonic, has a pH of about 7.4 for patient comfort and (if to be used more than once) has a limited shelf life after opening. Eye lotions are isotonic, sterile solutions for the irrigation of the eye, usually as a single use first aid treatment.^[5]

Eye drops provide a pulse entry of the drug, followed by a rapid decline in drug concentration, the kinetics of which approximate to first order. Many patients, particularly the very young and elderly find eye drops difficult to apply and may not receive the correct dose. Inter- and intra-subject variation in the therapeutic response is an inevitable consequence.^[6]

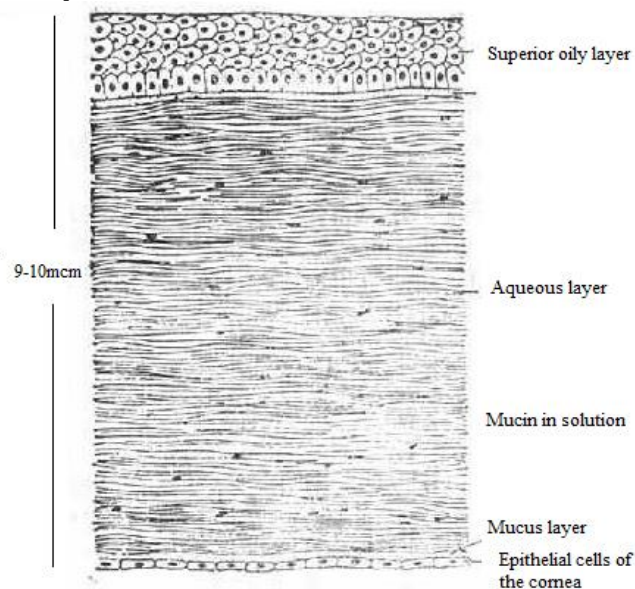


Fig. 6: Structure of the tear film in the human eye.

Polymers are frequently added to ophthalmic solutions and suspensions in order to increase the viscosity of the vehicle; this prolongs contact with the cornea, often enhancing bioavailability.^[7] The types of polymers used are typically high molecular weight hydrophilic molecules that are unlikely to cross biological membranes. They include synthetic polymers such as polyvinyl alcohol, and poloxamers; and polysaccharides such as hyaluronic acid, the cellulose derivatives (methylcellulose, hydroxymethylcellulose and carboxymethylcellulose), dextran, xanthan and gellan. If these polymers are mucoadhesive, i.e. polymers such as polyacrylic acids or chitosan that can adsorb onto the conjunctival or corneal surfaces, this may confer an additional advantage.^[8-9]

It has been reported that an increase in the corneal penetration of a drug is at a maximum if the viscosity of the eye drop solution is about 15 to 150 mPaS. Any further increase in viscosity would have less effect on the drainage rate and tear film thickness and has been implicated with interference of vision and resisting movement of the eyelids.^[10]

Colloidal systems, encompassing liposomes and micro- and nanoparticles, have been studied as drug carriers in ophthalmic drug delivery over many years.

Colloidal particles are subjected to the same clearance mechanisms as other foreign bodies that may come into contact with the ocular surface, and tend to be washed away by reflex tearing. Larger particles are more likely to be entrapped under the eyelids or in the inner canthus and so remain in contact with the corneal and conjunctival epithelia for extended periods. For patient comfort, it is considered that solid particles intended for ophthalmic use should not exceed 5-10 μm diameter. The use of a bioadhesive polymer (e.g. a polyacrylic acid, chitosan, hyaluronic acid) that prolongs the residence time in the precorneal region may confer an advantage.^[11-12] One interesting approach involves the use of lectins to selectively bind particulates to the required area of the precorneal region for extended periods.^[13]

Liposomes are membrane-like vesicles, consisting of phospholipid bi-layers surrounding an aqueous compartment. They are classified as either small unilamellar vesicles (SUV) (10-100 nm), large unilamellar vesicles (LUV) (100-3000 nm) or, if a number of bi-layers are present, multilamellar vesicles (MLV). The potential of liposomes as a topical ophthalmic drug delivery system is restricted by their stability and limited drug-loading capability.^[14] In addition, large-scale manufacture of liposome is expensive and technically challenging.

Microparticles have an average particle size greater than 1 μm and may be microcapsules or microspheres. Microspheres are monolithic particles, perhaps of insoluble drug or drug dispersed in a polymer matrix, whereas microcapsules consist of a polymeric membrane surrounding a solid or liquid drug reservoir. Upon topical instillation, the particles reside in the ocular cul-de-sac, and the drug is released from the particles through diffusion or polymer degradation.^[15] Techniques for the manufacture of particles include: denaturation or cross-linking of macromolecules in emulsion, interfacial polymerization; formation of emulsions and solvent removal, solution enhanced dispersion by supercritical fluids and spray drying.

Nanoparticles are solid colloidal drug carriers ranging from 10 to 1000 nm. These may also be made from the insoluble drug, or the drug may be entrapped within the particle or adsorbed onto its surface. The payload (the dose of drug delivered) is comparatively small and represents a limiting factor for the use of nanoparticles in drug delivery. A wide range of polymers has been used in the manufacture of micro- and nanoparticles for ophthalmic drug delivery including poly (alkyl) cyanoacrylate, polylactic acid and albumin.

2. Eye ointments

Ointments are semisolid preparations intended for external application. They are usually formulated using mixtures of semisolid and solid hydrocarbons (paraffin's),

which have a melting or softening point close to body temperature and are non-irritating to the eye.

Ointments may be either simple bases, where the ointment forms one continuous phase, or compound bases where a two-phased system (e.g. an emulsion) is employed. The medicinal agent is added to the base either as a solution or as a finely micronized powder. Upon instillation in the eye, ointments break up into small droplets and remain as a depot of drug in the cul-de-sac for extended periods. Ointments are therefore useful in improving drug bioavailability and in sustaining drug release. Although safe and well tolerated by the eye, ointments suffer with relatively poor patient compliance due to blurring of vision and occasional irritation.^[16] For this reason they are often used as a means of nighttime medication.

3. Aqueous gels

Aqueous gels (hydrogels) consist of high molecular weight, hydrophilic, cross-linked polymers or co-polymers that form a three-dimensional network in water. These gels have been shown to combine significantly longer residence times in the cul-de-sac with increased drug bioavailability. Typical gelling agents include cellulose derivatives, polyvinyl alcohol, hyaluronic acid and carbomer.

The *in situ* forming gels are viscous liquids that shift to a gel phase upon exposure to physiological conditions. These systems are more acceptable for patients since they are administered into the eye as a solution, after which they undergo transition into a gel. Studies have shown that the precorneal residence times of some *in situ* gelling systems can be several hours.^[17-18] The polymers used for these gelling systems exhibit reversible phase transitions. The change in viscosity can be due to a change in pH, temperature or ionic strength.^[15] *In situ* gel forming materials include gellan gum, poloxamer and cellulose acetate phthalate latex.

4. Solid matrices and devices

A number of solid polymeric inserts and discs have been developed as ophthalmic drug delivery systems. Inserts allow for accurate dosing, reduced systemic absorption and in some cases, better patient compliance resulting from a reduced frequency of administration and a lower incidence of visual and systemic side effects. Inserts are affected to a lesser extent by nasolachrymal drainage and tear flow than the more conventional dosage forms, and are associated with reliable drug release and longer residence times in the conjunctival cul-de-sac.^[16] However, patient resistance to placing a solid object in the precorneal region is an issue of some significance.

A number of inserts are currently available on the market or in the latter stages of development. These inserts have been classified as degradable or non-degradable (i.e. those that have to be removed on completion of therapy). Various materials have been utilized in the development of degradable inserts, including polyvinyl alcohol, hydroxypropylcellulose, polyvinylpyrrolidone and hyaluronic acid. Non-degradable inserts have been shown to provide more predictable release rates than soluble inserts^[10] and are prepared from insoluble materials such as ethylene vinyl acetate copolymers and styrene-isoprene-styrene block copolymers. Some examples of the various types of inserts available or in development are presented in Table 1 and also in Figs. 7 and 8.

Table 1. Ocular insert devices.	
Name	Description
Bioadhesive ophthalmic drug inserts (BODO) ^[19]	Adhesive rods based on mixtures of hydroxypropyl cellulose, ethylcellulose, poly acrylic acid cellulose acetate phthalate
Collagen shields ^[20-21]	Erodable discs composed of cross-linked porcine sclera) collagen
'Dry Drops' ^[22]	A preservative-free drop of hydrophilic polymer solution (hydroxypropyl methylcellulose) that is freeze-dried on the tip of a soft hydrophobic carrier strip, immediately hydrates in the tear film
Gelfoam ^[23]	Slabs of Gelfoam impregnating with a mixture of drug and Cetyl ester wax in chloroform
Lacrisert ^[24]	Rod-shaped device made from hydroxypropyl cellulose used in the treatment of dry eye syndrome as an alternative to artificial tears
Minidisc or ocular therapeutic system (OTS) ^[24]	4-5 mm diameter contoured either hydrophilic or hydrophobic disc
NODS (New or novel ophthalmic delivery system) ^[25]	Medicated solid polyvinyl alcohol flag that is attached to a paper-covered handle. On application, the flag detaches and gradually dissolves, releasing the drug
Ocuserts ^[26]	Flat, flexible elliptical insoluble device consisting of two layers enclosing a reservoir, used commercially to deliver pilocarpine for 7 days
Ophthalmic inserts ^[27]	A cylindrical device containing mixtures of silicone elastomer and sodium chloride as a release modifier with a stable polyacrylic acid (PAA) or polymethylacrylic acid (PMA) interpenetrating polymer network grafted onto the surface
SODI (Soluble Ocular Drug Insert) ^[24]	Small oval wafer, composed of a soluble copolymer consisting of acrylamide, N-vinylpyrrolidone and ethyl acrylate, softens on insertion

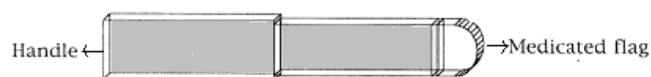


Fig. 7. The NODS device.

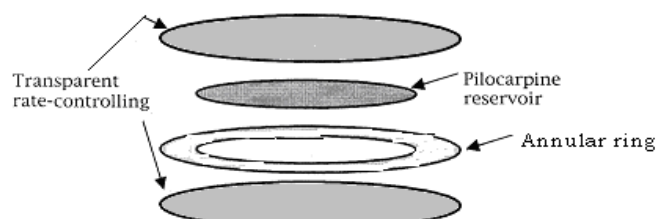


Fig. 8. The 'Ocusert'.

CONCLUSION

Given the problems associated with their use, it may be considered surprising after so many years that eye drops are still the drug delivery system of choice in ophthalmic drug delivery. The formulation of a delivery system that is readily sterilized, economic and patient friendly, while allowing controlled drug delivery and optimum bioavailability, remains a challenge to pharmaceutical scientists.

REFERENCES

1. Le Boulrais C, Acar L, Zia H, Sado PA, Needham T, Leverage R. Ophthalmic drug delivery systems-Recent Advances. *Progress in Retinal and Eye Research* 1998; 17:33-58.
2. Robinson JC. Ocular anatomy and physiology relevant to ocular drug delivery. In: Mitra AK (ed), *Ophthalmic Drug Delivery Systems*, Marcel Dekker: New York, US, 1993, 29-57.
3. Davies NM. Biopharmaceutical considerations in topical ocular drug delivery. *Clinical and Experimental Pharmacology and Physiology* 2000; 27: 558-562.
4. Le Boulrais CA, Treupel-Acar L, Rhodes CT, Sado PA, Leverage R. New ophthalmic drug delivery systems. *Drug Development and Industrial Pharmacy* 1995; 21: 19-59.
5. Lang JC. Ocular drug delivery conventional ocular formulations. *Advanced Drug Delivery Reviews* 1995; 16: 39-43.
6. Maurice DM. The dynamics and drainage of tears. *International Ophthalmology. Clin.* 1973; 13: 103-115.
7. Mishima S, Maurice DM. Oily layer of tear film and evaporation from corneal surface. *Experimental Eye Research* 1961; 1: 39-45.
8. Ludwig A, Van Ootenhgm M. Influence of viscolyzers on the residence of ophthalmic solutions evaluated by slit lamp fluorophotometry. *S.T.P. Pharmaceutical Sciences* 1992; 2: 81-87.
9. Davies NM, Farr SJ, Hadgraft J, Kellaway IW. Evaluation of mucoadhesive polymers in ocular drug delivery. I. Viscous solutions. *Pharmaceutical Research*, 1991; 8: 1039-1043.
10. Patton TF, Robinson JR. Ocular evaluation of polyvinyl alcohol vehicle in rabbits. *Journal of Pharmaceutical Sciences* 1975; 64:1312-1315.
11. Robinson JR. Mucoadhesive ocular drug delivery systems. In: Gurny R and Junginger HE (eds), *Bioadhesion Possibilities and Future Trends*. Wissenschaftliche Verlagsgesellschaft mbH:Stuttgart, Germany, 1990, 109-123.
12. Zimmer AK, Chetoni P, Saettone MF, Zerbe H, Kreuter J. Evaluation of pilocarpine-loaded albumin particles as controlled drug delivery systems for the eye. II. Co-administration with bioadhesive and viscous polymers. *Journal of Controlled Release*, 1995; 33: 31-46.
13. Nicholls TJ, Cook DJ, Rogers DJ, Green KL, Smart JD. Lectins in ocular drug delivery - An in vivo study of lectin retention on ocular surfaces. *Pharmaceutical Sciences* 1997; 3: 1-5.
14. Nagarsenker MS, Londhe VY, Nadkarni CID. Preparation and evaluation of liposomal formulations of tropicamide for ocular drug delivery. *International Journal of Pharmaceutics* 1999; 190: 63-71.
15. Ding S. Recent developments in ophthalmic drug delivery. *PSTT*, 1998; 1: 328-335.
16. Sasaki H, Yamamura K, Mukai T, Nishida K, Nakamura M. Enhancement of ocular drug penetration. *Critical Reviews in Therapeutic Drug Carrier Systems* 1999; 16: 85-146.
17. Hui HW, Robinson JR. Ocular drug delivery of progesterone using a bioadhesive polymer. *International Journal of Pharmaceutics* 1985; 26: 203-213.
18. Meseuger G, Gurny R, Buri P, Rozier A, Plazonnet B. 1993. Gamma scintigraphic study of precorneal drainage and assessment of miotic response in rabbits of various ophthalmic formulations containing pilocarpine. *International Journal of Pharmaceutics* 1993; 95: 229-234.
19. Gurtler F, Kaltsatos V, Boisrame B, Gurny R. Long-acting soluble Bioadhesive Ophthalmic Drug Insert (BODI) containing gentamicin for veterinary use: optimization and clinical investigation. *Journal of Controlled Release* 1995; 33: 231-236.
20. O'Brien TP, Sawusch MR, Dick JD, Hamburg TR, Gottsch JD. Use of collagen corneal shields versus soft contact lenses to enhance penetration of topical tobramycin. *Journal of Cataract and Refractive Surgery* 1988; 14: 505-507.
21. Unterman SR, Rootman DS, Hill JM, Parelman JJ, Thompson HW, Kaufman HE. Collagen shield drug delivery: therapeutic concentrations of tobramycin in the rabbit cornea and aqueous humour. *Journal of Cataract and Refractive Surgery* 1988; 15: 500-504.
22. Diestelhorst M, Grunthal S, Suverkrup R. Dry Drops: a new preservative-free drug delivery system. *Graefes Archives Clinical and Experimental Ophthalmology* 1999; 237: 394-398.
23. Simamora P, Nadkarni SR, Lee YC, Yalkowsky SH. Controlled delivery of pilocarpine. 2. In vivo evaluation of Gelfoam device. *International Journal of Pharmaceutics* 1998; 170: 209-214.
24. Bawa R. Ocular Inserts. In: Mitra AK (ed), *Ophthalmic Drug Delivery Systems*. Marcel Dekker Inc.: New York, US, 1993, 223-260.
25. Lawrenson JG, Edgar DF, Gudgeon AC, Burns JM, Geraint M, Nas BA. Comparison of the efficacy and duration of action of topically applied proxymetacaine using a novel ophthalmic delivery system versus eye drops in healthy young volunteers. *British Journal of Ophthalmology* 1993; 77: 713-715.
26. Quigley HA, Pollack IP, Harbin TS. Pilocarpine ocuserts. Long term clinical trials and selected pharmacodynamics. *Archives of Ophthalmology* 1975; 93: 771-775.
27. Chetoni P, Di Colo G, Grandi M, Morelli M, Saettone MF, Darougar S. Silicone rubber/hydrogel composite ophthalmic inserts: preparation and preliminary in vitro/in vivo evaluation. *European Journal of Pharmaceutics and Biopharmaceutics* 1998; 46: 125-132.