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Ocular Drug Delivery

S.A. Menqi & S.G. Deshpande
C.U. Shah College of Pharmacy, SNDT Women's University,
Santacruz (W) Juhu, Bombay-400049, India

I. INTRODUCTION

The field of ocular drug delivery is one of the most interesting and challenging endeavors facing the pharmaceutical scientist. This field has significantly improved over the past 10-20 years. As an isolated organ the eye is very difficult to study from a drug delivery point of view. It is very difficult to obtain specimens of eye tissue containing drugs from humans, consequently one is compelled to use animal models as guide. As a result, unfortunately the human ocular disposition characteristics of virtually every important drug are incomplete or unknown (Robinson, 1993).

Despite these severe limitations significant improvements in ocular drug delivery have been made. The improvements have been with objective of maintaining the drug in the biophase for an extended period. The anatomy, physiology and biochemistry of the eye render this organ impervious to foreign substances. It is a challenge to the formulator to circumvent the protective barriers of the eye so that the drug reaches the biophase in sufficient concentration (Lee & Robinson, 1986).

Physiological barriers to diffusion and productive absorption of topically applied drug exist in the precorneal and corneal spaces. The precorneal constraints responsible for poor ocular bioavailability of conventional ophthalmic dosage forms are solution drainage, lacrimation, tear dilution, tear turnover and conjunctival absorption (Robinson, 1989) (Fig. 4.1). Drug solution drainage away from the precorneal area has been shown to be the most significant factor in reducing the contact time of the drug with the cornea and consequently ocular bioavailability of topical dosage forms. The instilled dose leaves the precorneal area within 2 minutes of instillation in humans. In rabbits the process of drainage, generally, takes 5-10 minutes (Chrai et al., 1973). The ophthalmic dropper delivers 50-75 µL of the eyedrops. If the patient does not blink, the eye can hold about 30 µL without spilling on to the cheek. The natural tendency of the cul-de-sac is to reduce its volume to 7-10 µL. (Charai et al., 1974). However, most of the drug is rapidly lost through nasolacrimal drainage immediately following dosing. The drainage allows the drug to be absorbed across the nasal mucosa into the systemic circulation (Chang & Lee, 1987). The conjunctiva also possesses a relatively large surface area, 5 times the surface of cornea making the loss significant. Both the conjunctival and nasal mucosa have been indicated as the main potential sites for systemic absorption of topically applied drugs. Animal studies have demonstrated that the plasma levels after topical ocular administration are often comparable to those resulting from parenteral administration (Salminen, 1990). Tears dilute the drug remaining in the cul-de-sac which reduces the transcorneal flux of the drug. The drug entity, pH, tonicity of the dosage forms as well as formulation adjuvants can stimulate tear production (Conrad et al., 1978).

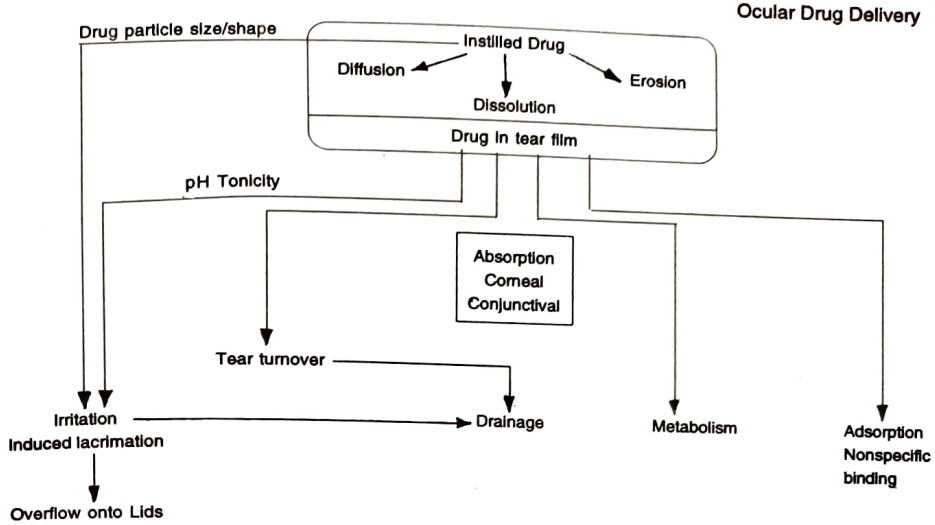
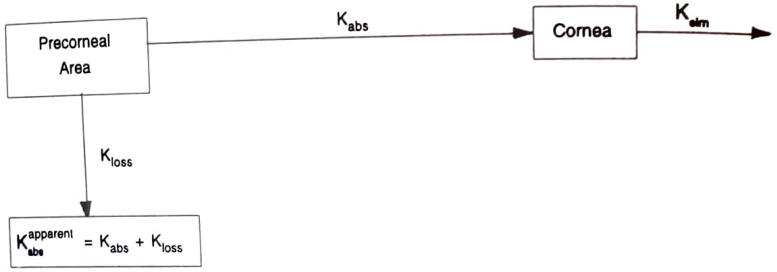


Fig. 4.1

Topical application of ophthalmic drugs is further made inefficient by tear turnover which is about 16% in humans. Due to these factors typically less than 1% of the drug reaches the aqueous humor (Mishima et al., 1966). Metabolism in the precorneal area has been shown to account for the further loss of the drug. The low fraction of the applied dose further undergoes rapid elimination from the intraocular tissues and loss through the canal of Schlemn or via absorption through the ciliary body or suprachoroid into episcleral space (Lee et al., 1982). Binding of drug to protein also contributes to the loss of drugs through the precorneal parallel elimination loss pathway. The tears contain both free and bound drug which is rapidly drained from the front of the eye.

Due to potential drug loss from the front of the eye the apparent absorption rate constant is due to both corneal absorption and precorneal loss. Drug absorption rate constants are in the range of K_{abs} 0.01-0.001 min^{-1} in contrast to the precorneal loss constant which is usually 1-2 orders higher K_{loss} 0.2-0.5 min^{-1}. Yet the aqueous humor drug concentration vs time profiles from a topical dose show that the time to reach a maximum level in the aqueous humor is generally short of the order of 20-30 minutes suggesting that corneal drug permeability is high. Actually corneal permeability to drugs is quite low and thus the reason for the early maximum level of the drug has to do with the enormous loss of drug from the front of the eye. This kinetic phenomenon is known as elimination loss pathway as shown in Fig. 4.2. Contributing to the poor ocular bioavailability is the hydrophobic structure of the corneal epithelium. Anatomically cornea consists of five distinct layers which anteriorly to posteriorly are the epithelium, Bowman's membrane, stroma, Descmet's membrane and endothelium (Fig. 4.3). The epithelium and endothelium are cellular and lipophilic. The epithelium is composed of five to six layers where as the endothelium is one cell thick. The stroma represents about 90% of thickness of the cornea. It contains 76-80% of water while the remainder consists of collagen fibrils (Schoenwald, 1987). Drugs gain access into the eye by simple passive diffusion. Huang et al (1983), measured permeability coefficient of a group of β-blocking agents across various layers of the cornea to determine the contribution of each layer to the total diffusional resistance. Each of the three barriers were found to contribute significantly to diffusional resistance of drugs of intermediate lipophilicity. However, the epithelium is the predominant

rate limiting barrier for hydrophilic drugs whereas the stroma is rate limiting for most of the lipophilic drugs. Recent studies suggest that the noncorneal route of absorption involving penetration across the sclera and conjuctiva may be significant for drug molecules with poor corneal permeability. Studies with inulin (Paton & Ahmed, 1985), timolol maleate (Ahmed et al., 1987b) gentamicin (Bloomfield et al., 1978) and PGF_2 (Bito & Baroody, 1982) suggest that these drugs gain access through the non-corneal route. However, the corneal absorption represents the major mechanism of absorption for the most therapeutic entities.



K_{loss} - 0.2-0.5 min^{-1}
K_{abs} - 0.01-0.001 min^{-1}
K_{loss}^{app} = 0.2-0.5 min^{-1}

Fig. 4.2.

The physiological barriers to topical corneal absorption force the clinician to recommend frequent doses of drug at extremely high concentrations. This pulsed type of dosing (Fig. 4.4) is represented with many side effects. It has been noted that the administration of topical timolol in the treatment of open angle glaucoma has resulted in therapeutic concentration of timolol in systemic circulation (Kaila et al., 1985). Frequent local instillations of antiglaucoma agents, antibiotics, antivirals, and sulfonamides provide an unusually high drug and preservative concentrations at the epithelial surface resulting in ocular cytopathologies.

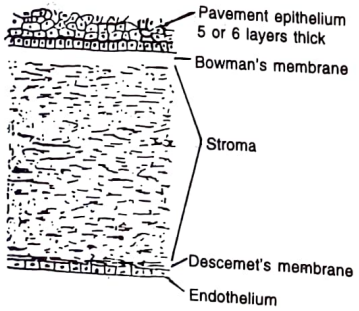


Fig. 4.3

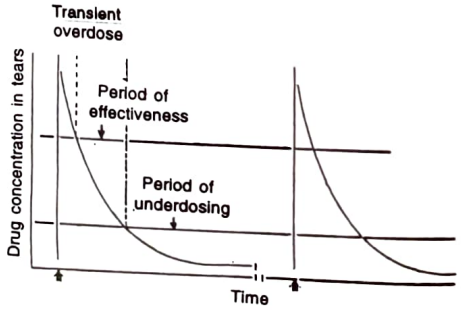


Fig. 4.4

The existing ocular drug delivery systems are thus fairly primitive and inefficient. However, the design of ocular systems is undergoing gradual transition from an empirical to rational basis. Interest in the broad areas of ocular drug delivery has increased in recent years due to an increased understanding of a number of ocular physiological process and pathological conditions. The focus of this review is the approaches made towards optimization of ocular delivery systems. Attempts have been made towards :

(i) improving ocular contact time
(ii) enhancing corneal permeability
(iii) enhancing site specificity.

II. CONVENTIONAL OCULAR DELIVERY SYSTEMS

The conventional ocular drug delivery systems used ubiquitously in today's ocular disease management are solutions, suspensions. The origin of solutions and suspensions has been the *collyrium* attributed to Romans and Greeks. The preparation was a cake made of gum resembling a small bar of soap within which the drug was incorporated. A small piece of cake was dissolved in water, milk or egg white for use as eyedrops.

Drugs used in the eye till today fall into one of the several categories including miotics, mydriatics, cycloplegics antibacterials, antiglaucoma drugs, surgical adjuncts, diagnostics and a category of drugs for miscellaneous uses.

Besides the active ingredients, therapeutically inactive ingredients in ophthalmic solution or suspension are necessary to perform one of more of the following functions: adjustment of tonicity, buffering and adjustment of pH, stabilizing the active ingredients against decomposition, increasing solubility, imparting viscosity and acting as a solvent.

Aqueous solutions, as already stated, suffer from the disadvantages of being quietly removed from the front of the eye resulting in poor ocular bioavailability (Shell, 1984). It is the consensus of most clinicians that a solution or suspension form of a drug delivery system is preferred by the patient provided that extended duration can be accomplished with these forms.

III. ROLE OF POLYMER(S) IN DRUG DELIVERY

The first approach made towards research in the field of improving the ocular contact time of solutions utilizes the incorporation of polymers into an aqueous medium such as polyvinyl alcohol (PVA), polyvinyl pyrrolidine (PVP), methylcellulose (MC), carboxymethyl cellulose (CMC), and hydroxypropyl cellulose (HPC). The increased solution viscosity reduces the solution drainage. Increasing the solution viscosity of pilocarpine solution from 1 to 100 cps through the incorporation of methyl cellulose reduced the solution drainage rate constant 10 times while only a 2-fold increase in pilocarpine concentration in the aqueous humor was obtained (Chrai & Robinson, 1974). An optimal viscosity of 12-15 cps has been suggested for for ocular drug absorption by Paton & Robinson (1976). Saettone et al., (1984) compared five polymers PVA, PVP, MC, CMC, low molecular weight HPC all at 73 $\pm$ 2.5 cps on the basis of changes in pupillary diameter brought about by 0.2% tropicamide in humans. The largest increase in ocular bioavailability with an increase of 3.7 times was seen with polyvinyl alcohol. Natural polymers namely sodium hyaluronate and chondroition sulfate are being investigated as viscosity inducing agents. These glycosamines when incorporated into topical formulations have offered increase in product efficiency through their unique physiochemical and polyelectrolyte behavior (Limberg, 1987). Prolonged residence time with an extended duration of action for 1% pilocarpine has been observed with 0.2 - 0.3% sodium hyaluronate solutions (Camber et al., 1987). In considering approach of increasing solution viscosity to enhance ocular drug absorption the lipophilicity of the drug should be taken into account. No statistically significant increase in aqueous humor concentrations of drug whose octanol/buffer partition coefficient exceeded 10 was observed on increasing the solution viscosity from 1- 90 cps by Grass & Robinson (1984). The results to date suggest that increasing solution viscosity has limited utility in causing marked improvement in the amount of drug absorbed.

III. MUCOADHESIVES:

Polymeric mucoadhesive vehicles i.e. vehicles which are retained in the eye by virtue of non-covalent bonds established with the corneal conjuctival mucin have recently attracted the attention of several investigators for their capacity of extending the preocular residence times (Robinson, 1990). Coating the external surfaces of the globe of the eye is a thin film of glycoprotein referred to as mucin. Goblet cells in the conjuctiva secrete this material and it forms a thin layer over the conjunctiva and cornea. The mucin molecule is capable of picking up about 40-80 times its weight of water due to substantial number of sugar groups that line the polypeptide backbone (Holly, 1973). The mucin layer forms a part of the precorneal tear film a very thin fluid layer that continuously bathes the corneal epithelium, conjuctiva and the conjuctival cul-de-sac. The tear film consists of three main classes of components, the lipid portion secreted by the mebimain glands, the mucin, a family of glycoproteins produced by the conjuctival goblet cells and the aqueous portion a salt solution secreted by the main and accessory lachrymal glands. These layers are shown in Fig. 4.5 (Wolff, 1954). Macromolecules with the exception of some substituted glycols cannot readily enter the body. A molecular weight of 5000-10000 is generally considered high enough to prevent to any appreciable absorption through the skin or mucosal tissue. Consequently adducts when applied topically can function as depot agents (Ranade, 1990). Natural and synthetic polymers (Table 4.1) that bind to mucin or epithelial surfaces have been used for drug delivery via the nose, buccal cavity and intestine. These bioadhesive polymers help in prolonging the release of drug from a dosage from by localizing it at a specific site where mucus is present. They remain in contact with the precorneal tissues until mucin turnover causes elimination of the polymer (Park & Robinson, 1984). Good mucoadhesion in the eye is achieved with polymers possessing the correct charge density , number of polar groups for hydrogen bonding, and balance of lipophilic to hydrophilic sections in the polymer chain. The molecular interaction between mucin and mucoadhesives can be conceptualized as establishment of intimate contact by diffusion and network expansion of polymer chains with subsequent interpenetration (Mikas & Peppas, 1986). The physical model is as depicted in Fig. 4.5. Hydrogen bonding has been stated to play an important role in bioadhesion since it is the protonated form of the anionic mucoadhesive that is held responsible for bioadhesion (Pritchard, 1971). However, the interaction between a cationic polymer and mucin is largely viewed as an electrostatic attraction.

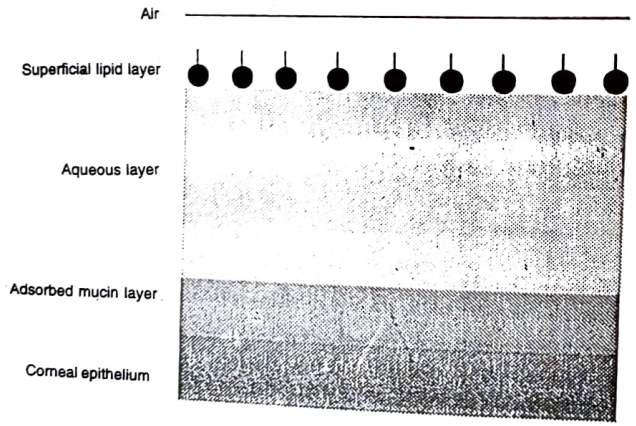


Fig. 4.5

Table 4.1. Some Representative Mucoadhesives with their Mucoadhesive Performance

Substance	Adhesive performance
Carboxymethylcellulose	Excellent
Carbopol	Excellent
Carbopol and hydroxypropyl cellulose	Good
Carbopol base with white petrolatum/hydrophilic petrolatum	Fair
Carbopol 934 and EX 55	Good
Poly (methyl methacrylate)	Excellent
Poly acrylamide	Good
Poly (acrylic acid)	Excellent
Polycarbophil	Excellent
Homopolymers and copolymers of acrylic acid and butyl acrylate	Good
Gelatin	Fair
Sodium alginate	Excellent
Dextran	Good
Pectin	Poor
Acacia	Poor
Povidone	Poor
Poly (acrylic acid) crosslinked with sucrose	Fair

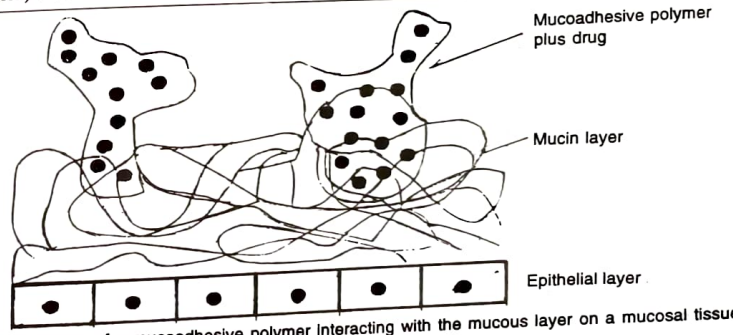


Fig. 4.6. Depiction of a mucoadhesive polymer interacting with the mucous layer on a mucosal tissue.

The poor patient acceptance of ointments has prompted several workers (Bottari et al., 1973; Goldberg, 1979; Schoenwald & Boltralik, 1979; March et al., 1982; Miller & Donoran, 1982) to investigate aqueous gels as vehicles to improve ocular bioavailability of both water soluble and oil soluble drugs. Ointments are semi solid preparations consisting of dispersion of the solid drug in the appropriate vehicle base. The vehicle base is either a single continuous phase or a compound base. A single phase is an oleaginous base consisting of white petroleum and lanolin. Compound bases usually involve oil-aqueous systems forming either oil-in-water or water-in-oil systems. Ointments have served as useful vehicles to improve drug bioavailability and sustain drug release. The ointment gets entrapped in the fornices there by serving as a drug reservoir (Norn, 1972). Unfortunately the ointments are not well accepted by patients due to interference with vision and precorneal disappearance of drugs administrated in an ointment has been reported to be as low as 0.5% per min. However, this does not seem to hold true for water soluble drugs. Seig & Robinson (1979) have demonstrated that pilocarpine, a water soluble drug, was released rapidly from an oleaginous ointment providing only a modest improvement in the extent of corneal absorption with no sustaining effect. In contrast both an enhanced and sustained corneal

absorption was seen with fluorometholone, an oil soluble drug. Gels although instilled like ointments are more comfortable and have the advantage of less blurred vision than ointments. However, the patients often complain of matted eyelids after use. Among the mucoadhesives mentioned Carbopols have been used in the preparation of gels. Pilocarpine in gel dosage forms utilizing an acrylic polymer has recently become available and delivers 24 h pilocarpine dose from single night time replacement in the cul-de-sac (Fig. 4.7).

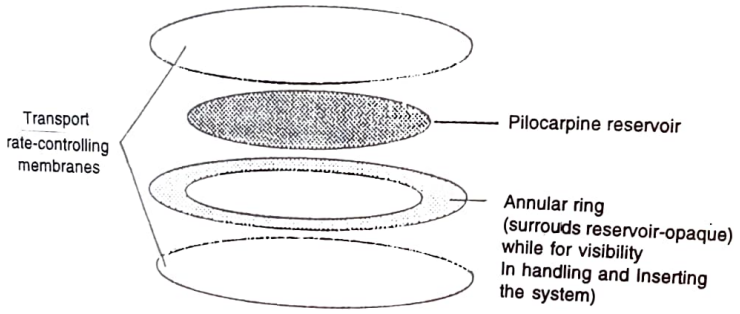


Fig. 4.7

The pioneering work of Hui & Robinson (1985) illustrated the utilization of bioadhesive polymers in the enhancement of ocular bioavailability of progesterone. Subsequently, Saettone et al., (1989) undertook a study of evaluating the efficiency of a series of bioadhesive dosage forms for ocular delivery of pilocarpine and tropicamide. Hyaluronic acid has emerged as one of the promising mucoadhesive agent. The data collected so far reveals that the physiochemical property of the drug has an impact on the efficiency of the delivery system. Drugs incorporated so far into these gels are pilocarpine, lidocaine, benzocaine, prednisolone acetate, prednisolone sodium phosphate, fluoromethalone, tropicamide, ethoxzolamide and hydroxyethoxzolamide (Bottari et al., 1979; Miller et al., 1982; Saettone et al., 1980; Kupferman et al., 1981; Kupferman et al., 1982; Lewis et al., 1984). Overall, a 3-5 fold improvement in corneal drug absorption has been reported.

IV. OPHTHALMIC INSERTS

In the recent years, there has been explosion of interest in the polymer based delivery devices. Adding further dimension to topicals thereby is the use of polymers such as collagen and fibrin fabricated into erodible inserts for placement in cul-de-sac. Utilization of the principles of controlled release as embodied by ocular inserts offers an attractive approach to the problem of prolonging precorneal drug residence times. Ocular inserts also offer the potential advantage of improving patient compliance by reducing the dosing frequency. The desired criteria for a controlled release ocular insert are :

(i) comfort,
(ii) lack of explosion,
(iii) ease of handling and insertion,
(iv) non interference with vision and oxygen permeability,
(v) reproductibility of release kinetics,
(vi) sterility,
(vii) stability, and finally
(viii) ease of manufacture.

Controlled release systems for ophthalmic use encompass both erodible and nonerodible systems. Appeal for erodible systems stems from the fact that these do not have to be removed from body tissues. It should be anticipated that an erodible ocular insert is more prone to demonstrate variability in release kinetics from patient to patient than a non-erodible insert. This is due to the fact that the rate of tear production as well as concentration of metabolic enzymes in the tear film of the eye also varies considerably from patient to patient. Although the erodible inserts offer the advantage of convenience in administration the greater reliability of the non-erodible inserts for each potential ocular application cannot be neglected.

Nonerodible inserts

The non erodible systems include :

(i) Ocusert, and
(ii) Contact lens.

(i) Ocusert

The Ocusert therapeutic system, developed by Alza Corporation has probably been first practical realization of the dreams and endeavors in the field of inserts. It is a flat, flexible, elliptical device consisting of three layers as shown in Fig. 4.8. Two outer layers of ethylene vinyl acetate (EVA) enclose the inner core of pilocarpine gelled with alginate. A retaining ring of EVA impregnated with titanium dioxide for visibility enclose the drug reservoir circumferentially (Friederich, 1974). It is preprogrammed to release pilocarpine at constant rate of 20 or 40 µg/hr around the clock for 7 days. The higher release rate of Ocusert Pilo 40 is achieved by making its rate controlling membrane thinner and by the use of flux enhancer di (2 ethyl-hexyl) phthalate (Urquhart, 1980). Both the systems are used in the treatment of chronic glaucomas. Since the introduction of Ocusert there has been a proliferation of erodible inserts prepared primarily for the delivery of pilocarpine (Bloomfield et al., 1978; Miyazaki, 1982; Katz et al., 1977; Grass et al., 1989; Saettone et al., 1984). However, none of them are comparable to Ocusert with respect to duration of action. Although the advantage of precise controlled rate of delivery has been achieved with ocusert it is coupled with a number of disadvantages such as patient comfort, placement, and removal of insert which may lead to inadvertent loss of system from the eye. It has been observed that retention of these inserts are a function of size and shape (Katz & Blackman, 1977). Smaller devices are better retained than larger ones and rod shaped are better retained than oval ones.

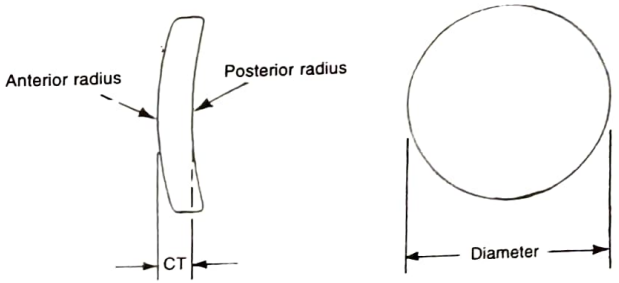


Fig. 4.8

(ii) Contact Lens

The use of presoaked hydrophilic contact lenses for ocular drug delivery has been examined for a number of drugs (Hillman, 1975; Ramer & Gasset 1974; Matoba & Mucculley, 1985; Allen & Raph, 1985;

Massimo & Spitznas, 1988; Jain, 1988). Therapeutic soft lenses are often used to aid corneal wound healing in patients with infection, corneal ulcers, characterized by marked thinning of the cornea (Matoba & Mucculley, 1985). Unfortunately the residence time of drugs using commonly available presoaked lenses is not significantly prolonged. It has been seen that most of the drug contact lens is released within the first 30 min. (Shell & Bakes, 1974). The use of the preservative benzalkonium chloride has come into question due to its toxic effect on the corneal epithelium (Hillman, 1975). Moreover the supply of oxygen to the eye and the build up of harmful metabolite such as CO_2 which has been implicated in complications arising from the improperly fitted contact lens should also be taken into account.

An alternative approach to presoaking soft contact lenses in drug solutions is to incorporate the drug either as a solution or suspension of solid particles in the monomer mix. The polymerization is then carried out to fabricate the contact lenses (Bawa, 1987; Bawa & Ruscio, 1990). This technique has demonstrated the promise of longer times of release upto 180 h as compared to presoaked contact lenses. Furthermore, the problem of concentration of preservative is eliminated, since the drug is added without any preservative. However, the greatest advantage associated with the use of contact lenses has been the problem of discomfort and difficulty in handling and insertion particularly in case of presoaked contact lenses.

Erodible inserts

Several erodible drug inserts have been prepared and tested for ocular use: Pilocarpine containing carboxymethyl cellulose wafers (Hadded & Loucas, 1975; Maichuk, 1975), polyvinyl alcohol disc. (Grass et al., 1975; Grass et al., 1984) or rods (Bondi & Harwood, 1988). Wafers of collagen containing gentamicin sulfate have been prepared and extended ocular residence times has been achieved. In addition, erodible ocular inserts containing hydrophobic polycarboxylic acids have been described as well (Heller & Baker, 1974). Despite the efforts only three devices have been marketed to date :

(i) The Lacrlserts,
(ii) SODI, and
(iii) Minidisc.

(i) Lacrisert

The lacrisert is a sterile rod-shaped device made of hydroxypropyl cellulose without any preservative is used for the treatment of dry eye syndromes. This device was introduced by Merck, Sharp and Dohme in 1981 (Lamotte et al., 1985). It weighs 5 mg and measures 12.7 mm in diameter with a length of 3.5 mm. Lacrisert is useful in the treatment of patients with keratitis sicca whose symptoms are difficult to treat with artificial tear alone. It is inserted into the inferior fornix where it imbibes water from the conjunctiva and cornea, forms a hydrophilic film which stabilizes the tear film and hydrates and lubricates the cornea. Day long relief of dry eye syndrome has been reported from a single insert placed in the eye early in the morning (Lamberts et al., 1978). In a cross over study comparing slow release artificial tear inserts with liquid artificial tears, Katz et al., (1978) found that 78% of their 32 Keratoconjuncti-vitis sicca patients preferred inserts to drops. No change in slit lamp appearance of inferior fornix was seen. The visual acuity remained unaltered on average, during the study. Replacement of four times an hr regimen by once or twice daily regimen is the benefit achieved with this dosage form.

(ii) The SODI

Soluble ocular drug insert (SODI) is a small oval wafer which was developed by Soviet scientists for cosmonauts who could not use eyedrops in weightless conditions (Maichuk, 1976).The unit is made from acrylamide, N-vinylpyrrolidone and ethylacrylate designated as ABE (Maichuk, 1985). It is in the form of sterile thin films of oval shape weighing 15 to 16 mg. After introduction in the inferior cul-de-sac where wetted by the tear film it softens in 10-15 seconds and assumes the curved configuration of the globe. During the following 10-15 min., the film turns into a viscous polymer mass, thereafter in 30 - 60 min. it becomes a polymer solution. A single SODI application has been reported to replace 4-12 drops instillations or 3-6 applications of ointment and constitutes a valid once a day therapy for the treatment of glaucoma and trachoma (Maichuk & Erichev, 1981).

(iii) Ocular therapeutic system or minidisc

Bawa et al., (1988) have reported the development of a controlled release device for the eye known as the ocular therapeutic systems (OTS) or minidisc. The OTS consists of a contoured disc with a convex front and a concave back surface in the contact with the eyeball. It is like a miniature contact lens with a diameter of 4-5 mm. The symmetric circular design (Fig. 4.9) of the minidisc in contrast with the elliptical or rod shape eliminates the need to align a particular geometric axis of the device with the eyelid margin.

The major component of the OTS is a silicone based prepolymer-α-ω-bis(4-methacryloxy)- butyl polydimethyl siloxane (M_2Dx) where M represents methacryloxybutyl and D represents dimethylsiloxane functionalities. The OTS can be hydrophilic or hydrophobic to permit extended release of both water soluble and insoluble drugs. Studies have been conducted with sulfisoxazole, a poorly water soluble drug incorporated in a hydrophilic matrix (Bawa et al., 1988). The in-vivo dissolution studies demonstrated that the drug was released from OTS for 170 h. However the hydrophobic OTS released gentamicin sulfate for longer than 320 hr. Gamma irradiation and heat exposure of the system were found to slow down the drug release rates (Bawa & Nandu, 1990) The authors suggested that this may be due to additional cross linking of the polymer matrix by gamma irradiation.

The new ophthalmic delivery system

The new ophthalmic delivery system (NODS) is a method of presenting drugs to the eye within a water soluble drug loaded film. It provides for accurate, reproducible dosing in an easily administered preservative free form. The drug is incorporated into a water soluble polyvinyl alcohol film. Each NODS consists of a drug loaded film or (flag) attached to a handle film by means of thin membrane (Fig. 4.10). The NODS is approximately 50 mm in length, 6 mm in width, the flag is semicircular in shape and has an area of 22 mm^2 and a thickness of 20 μm and a total weight of 500 μg of which 40% can be drug. On contact with the tear film in the lower conjunctival sac the membrane quickly dissolves releasing the flag into the tear film. The flag hydrates and disperses allowing diffusion and absorption of the drug.

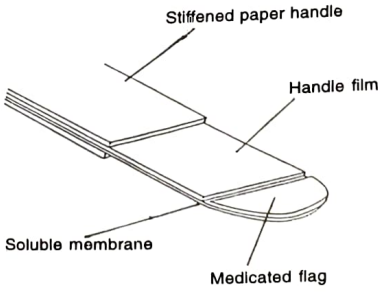


Fig. 4.9

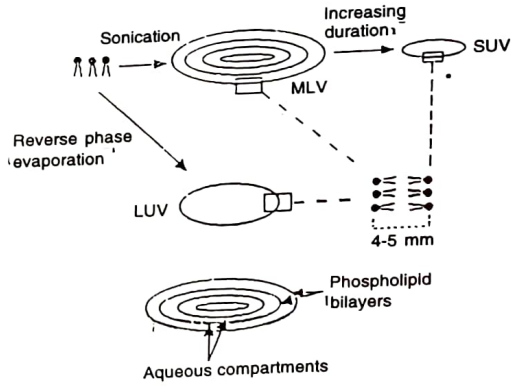


Fig. 4.10

The handle is provided with a paper backing for strength. Both soluble drugs such as pilocarpine and insoluble drugs such as tropicamide can be formulated into the NODS. Kelly et al., (1989) compared the magnitude of the miotic and light reflex responses to NODS containing 40, 80, 170 µg pilocarpine nitrate with a 2% commercially available eyedrops in healthy volunteer. An eight fold greater bioavailability was observed compared to the conventional eye drop. The delivery of an insoluble drug in NODS has also shown improved bioavailability compared with a standard solution (Richardson, 1990).

Corneal collagen shields

Collagen is a structural protein that can be safely applied to the body for a variety of medical and cosmetic purposes. The creation of collagen shield has provided a means to promote wound healing and perhaps more importantly to deliver a variety of modifications to the cornea and other ocular tissues. Bloomfield et al., (1978) were the first to suggest that collagen might provide a suitable ocular carrier for sustained ocular drug delivery. The study published in 1978 showed that wafer shaped collagen inserts impregnated with gentamicin produced the highest levels of drug in tear film, and tissue, in the rabbit eye compared to drops, ointments and conjuctival injection.

To prepare the collagen shields, collagen is extracted and moulded into a contact lens configuration. The shields are 14.5 mm in diameter with a 9 mm base curve and thickness of 0.15 - 0.19 mm. The shields are sterilized by gamma irradiation then dehydrated and individually packaged for storage and shipping (Artandi, 1964). Drugs can be incorporated in the collagen matrix during manufacture absorbed into the shields in the eye. As the shield dissolves the drug is released gradually in the tear film, maintaining high concentrations on the corneal surface and increasing drug permeation through the cornea and into the aqueous humor (Shofner et al., 1989).Over the years various drugs have been incorporated into the collagen matrix of the shields. Clinical studies have shown that collagen shields are easy to use in the ophthalmologist's office, prevent delay in begining therapy, and maintain concentration of the drug in the eye without the need for frequent instillation of drops. O'Brien et al., (1988) applied 3mg/ml tobramycin drops for treating infections due to *P. aeruginosa* for every 5 min for a total of six doses to three groups of rabbit eyes, those with collagen bandage lenses and controls receiving only the topical drops. The level of tobramycin concentration in the aqueous humor 15 min after the last dose was nine times higher in eyes with collagen shields compared with the eye with bandage lenses and ten times higher than in the eyes receiving only topical drops. A number of drugs have been incorporated into corneal shields for e.g. prednisolone (Sawusch et al., 1989), cyclosporine (Reidy et al., 1990,) Table 4.2 (Friedberg et al., 1991). The simplicity of use and the convenience afforded by shields make them an attractive delivery device. However the development of this modality for drug delivery is still in relative infancy. With continuation of research on broad front collagen shields could become a commonly employed technological improvement technology.

Table 4.2. Studies of Collagen Shield Drug Delivery

Drug	*Compared with collagen shield*	*Assay site*	*Overall result with collagen shield*
Gentamicin	Loading dose + frequent drops	Tears	Comparable at all sites
		Cornea	
Vancomycin	Loading dose + frequent drops	Aqueous	
		Tears	Comparable at all sites
Tobramycin	Soft contact lens	Cornea	
Tobramycin	Subconjunctival injection	Aqueous	Superior
		Cornea	Comparable at sites