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REVIEW

Ocular Preparations: The Formulation Approach

Indu Pal Kaur and Meenakshi Kanwar

University Institute of Pharmaceutical Sciences,
Panjab University, Chandigarh 160 014, India

ABSTRACT

The main aim of pharmacotherapeutics is the attainment of an effective drug concentration at the intended site of action for a sufficient period of time to elicit the response. A major problem being faced in ocular therapeutics is the attainment of an optimal concentration at the site of action. Poor bioavailability of drugs from ocular dosage forms is mainly due to the tear production, non-productive absorption, transient residence time, and impermeability of corneal epithelium. This article reviews: (1) the barriers that decrease the bioavailability of an ophthalmic drug; (2) the objectives to be considered in producing optimal formulations; and (3) the approaches being used to improve the corneal penetration of a drug molecule and delay its elimination from the eye. The focus of this review is on the recent developments in topical ocular drug delivery systems, the rationale for their use, their drug release mechanism, and the characteristic advantages and limitations of each system. In addition, the review attempts to give various analytical procedures including the animal models and other models required for bioavailability and pharmacokinetic studies. The latter can aid in the design and predictive evaluation of newer delivery systems.

The dosage forms are divided into the ones which affect the precorneal parameters, and those that provide a controlled and continuous delivery to the pre- and intraocular tissues. The systems discussed include: (a) the commonly used dosage forms such as gels, viscosity imparting agents, ointments, and aqueous suspensions; (b) the newer concept of penetration enhancers, phase transition systems, use of cyclodextrins to increase solubility of various drugs, vesicular systems, and chemical delivery systems such as the prodrugs; (c) the developed and under-development controlled/continuous drug delivery systems including ocular

inserts, collagen shields, ocular films, disposable contact lenses, and other new ophthalmic drug delivery systems; and (d) the newer trends directed towards a combination of drug delivery technologies for improving the therapeutic response of a non-efficacious drug. The fruitful resolution of the above-mentioned technological suggestions can result in a superior dosage form for both topical and intraocular ophthalmic application.

Key Words: *Analysis; Corneal permeability; Delivery systems; NODS; Ocular formulations; Polymers*

INTRODUCTION

Except for skin, the eye is the most easily accessible site for topical administration of a medication. Drugs are commonly applied to the eye for a localized action, on the surface, or in the interior of the eye. A major problem in ocular therapeutics is the attainment of an optimal drug concentration at the site of action. Poor bioavailability of drugs from ocular dosage forms is mainly due to the precorneal loss factors which include tear dynamics, non-productive absorption, transient residence time in the cul-de-sac, and the relative impermeability of the corneal epithelial membrane. Due to these physiological and anatomical constraints only a small fraction of the drug, effectively 1% or even less of the instilled dose, is ocularly absorbed. The effective dose of medication administered ophthalmically may be altered by varying either the strength, volume, or frequency of administration of the medication or the retention time of medication in contact with the surface of the eye. So far, attempts have been made to improve ocular drug bioavailability by extending drug residence time in the conjunctival sac and improving drug penetration across the cornea, the major pathway of drug entry into the internal eye.

The focus of this review is on the recent developments in topical ocular drug delivery systems, the rationale for their use, their drug release mechanism, and the characteristic advantages and limitations of each system. In addition, the review attempts to give various analytical procedures including the animal models and other models required for bioavailability and pharmacokinetic studies. The latter can aid in the design and predictive evaluation of newer delivery systems.

TOPICAL OCULAR DRUG DELIVERY AND THE CONSTRAINTS TO OCULAR THERAPY

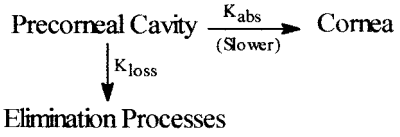
For ailments of the eye, topical administration is usually preferred over systemic administration for obvious reasons:

- the systemic toxicity of many ophthalmic drugs,
- the rapid onset of action, and
- the smaller dose required compared to the systemic route.

The topically applied ocular drugs have to reach inner parts of the eye to elicit responses. The transcorneal penetration is believed to be the major route for drug absorption. Most ocular drugs seem to penetrate the cornea by diffusion. The paracellular (i.e., through intercellular space) and the transcellular pathways (i.e., through intracellular space) are the two mechanisms for drug transport across the cornea. The cornea is divided into five layers (the epithelium, Bowman's membrane, the substantia propria or the stroma, Descemet's membrane, and the endothelium), but for all practical purposes it contains three primary layers, stacked sequentially from the outer to the inner surface: epithelium, stroma, and endothelium. The epithelium and the endothelium are rich in lipids; on the other hand, the stroma has a high water content. The epithelium is reported to be the rate-limiting barrier to transcorneal transport. Its barrier function depends favorably on the lipophilicity of molecules and excludes the macromolecules ($r > 10$ Å). The corneal epithelium is a layered structure of 50–100 μm thickness. The surface layer consists of desquamatory cells. These cells have skirting intercellular junctions, termed "tight junctions," forming a strong barrier. This explains

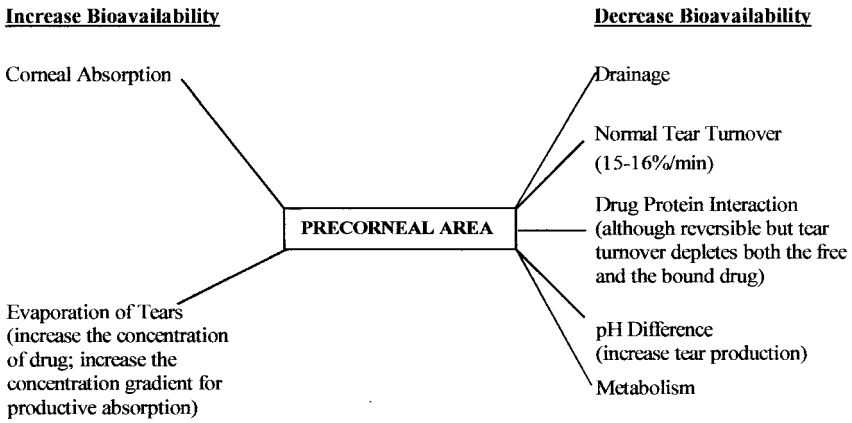
the poor permeability of the epithelium to non-lipophilic substances and the differential penetration of non-ionized forms. For smaller, lipophilic molecules, the stroma and the endothelium play a significant role, with the endothelium being more important. The corneal stroma is composed of collagen, and it is organized in parallel lamellae. It is highly hydrophilic, porous, and open-knit, so allows the hydrophilic molecules to pass easily. For macromolecules, the stroma provides a greater barrier than the endothelium (1). The corneal endothelium is a single-cell layer, lining the posterior surface of the cornea, in direct contact with the aqueous humor. High metabolic activity is associated with the cytoplasm of these cells. This layer regulates the passage of substances from the aqueous humor to the stroma. The endothelium is rich in phospholipids and thus is permeable to lipid-soluble materials and almost impermeable to ions.

Corneal absorption is a much slower process than elimination. A simplified ocular pharmacokinetic model describing the movement of a topically applied drug to the eye is shown in Sch. 1. For many drugs K_{loss} is approximately 0.5–0.7/min and K_{abs} is about 0.001/min. The sum of these two rate constants controls the fraction of the applied dose absorbed into the eye (2). The ocular bioavailability can thus be increased significantly by decreasing K_{loss} or by increasing K_{abs} (Sch. 2). 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.



Scheme 1.

Before reaching the anatomical barrier of the cornea, any drug molecule administered by the ocular route has to cross the precorneal barriers. These are the first barriers that slow the penetration of an active ingredient into the eye, and consist of the tear film and the conjunctiva. Tears form a notable and weighty barrier to penetration of the drug molecule. The anterior corneal surface of the eye is kept moist by tears, secreted as a lachrymal fluid from the lachrymal glands. They cover the cornea in the form of a film. The tear film consists of three distinct layers: the posterior layer rich in glycoproteins elaborated by the goblet cells of the conjunctival epithelium; the middle watery layer containing lysozyme with an antibacterial activity; and the outer oily layer which minimizes the evaporation of the tears. The medication, upon instillation, stimulates the protective physiological mechanisms, i.e., tear production, which exert a formidable defense against ophthalmic drug delivery. The drug moiety is subjected to the negative influences of tears, such as: (1) an increased tear turnover leading to an increased spillage and dilution of the drug; (2) reflex blinking causing an accelerated clearance via tears; (3) binding of the drug molecule to the tear proteins thus reducing the effective concentration of drug in contact with the cornea; and (4) buffering action of the



Scheme 2. Precorneal factors that influence bioavailability of topically applied ophthalmic drugs.

carbonic acid and weak organic acids present in tears affecting the extent of ionized/unionized forms of the drug and hence its bioavailability. A drop of an aqueous solution, irrespective of the instilled volume, is eliminated completely from the eye and the eye returns to the normal lachrymal lake volume within 5–6 min of its application. This results in a very short period during which the drug has access to the ocular tissues (3).

Even though the major route by which most ophthalmic drugs enter the eye is the cornea, recently a minor alternative route involving the conjunctiva and the sclera has been proposed for drugs that are poorly absorbed across the cornea due to their physicochemical properties (4,5). The conjunctiva is a mucus tissue, lining the inner surfaces of the eyelids and covering the eyeball, which it protects. It is well supplied with blood, which is why it is regarded as a non-productive route, based on the assumption that drug entering the conjunctiva is picked up by the general circulation and does not contribute to intraocular drug levels. However, it has been observed that drugs picked up by the non-corneal route may enter certain intraocular tissues. This mechanism bypasses the anterior chamber and thus may spare the internal layers of the cornea from the possible ill effects of the drugs and hence attain a direct access to the uveal tract. A relatively high scleral permeability, compared to the cornea, has motivated various researchers to investigate transcorneal drug delivery locally to the back of the eye (e.g., the retina) (6,7).

It is suggested that ocular penetration via the sclero-conjunctival route is more rapid (for a hydrophilic drug) than via the transcorneal route (8). Even though there is little information regarding the factors related to the drug, its vehicle, and the physiology of the eye which may collectively control the contribution of corneal and non-corneal routes, Ahmed et al. (4) have described the various physicochemical determinants of drug diffusion across these tissues. They have proposed three possible pathways for the diffusion of drug molecules across the sclera: (a) through perivascular spaces; (b) through the aqueous media of gel-like mucopolysaccharides; or (c) across the scleral substance composed of a matrix of collagen fibrils. Thus, it may be stated that the optimization of the non-corneal route may help in the design and evaluation of newer ocular delivery systems.

Another serious concomitant of the elimination of topically applied drugs from the precorneal area is the nasal cavity, with its greater surface area and higher permeability of the nasal mucosal membrane compared to that of the cornea. The ocular drugs are thus prone to absorption into the systemic circulation through the nasal mucosal lining, which is contiguous with the conjunctival sac (9). Thus, it may be concluded that the transconjunctival absorption (into the blood) and the transnasal absorption after drainage via the nasolacrimal duct are both undesirable. This is so not only because of the loss of active ingredient into the systemic circulation, but also because of possible side-effects. For instance, the effects of beta-blockers on the heart upon topical administration into the eye for the treatment of wide-angle glaucoma (10).

These precorneal factors considerably restrict the penetration of eye drops, and only about 10% or even less of the active ingredients in them reach the aqueous humor and the eye tissues. The anatomical and physiological barriers impede the free access of drug, and even less than 1% of the total drug administered is available for eliciting the biological response.

FORMULATION APPROACHES TO IMPROVE OCULAR BIOAVAILABILITY

Currently, ocular drugs and delivery systems are undergoing a process of design optimization, as the inherent constraints of the eye lead to a slow absorption of topically applied drugs. The challenge faced by scientists involved in ophthalmic pharmaceutical research is to improve ocular drug bioavailability from less than 1–3% to at least 15–20%. Investigations (11) aimed at improving topical bio-availability are being pursued along the following lines.

1. Based on (a) maximizing precorneal drug absorption and (b) minimizing precorneal drug loss.
2. Based on the use of drug delivery systems, which provide the controlled and continuous delivery of ophthalmic drugs to the pre- and intraocular tissues.

Dosage Forms Affecting Precorneal Parameters

Aqueous Gels/Hydrogels

In order to increase the contact time between the drug and the ocular surface, and thus improve the bioavailability of the applied drug, a number of

water-soluble or insoluble natural, synthetic, and semi-synthetic viscous vehicles have been developed during the last 50 years. The aqueous gels typically utilize such polymers as polyvinyl alcohol (PVA), polyacrylamide, poloxamer, hydroxypropyl methylcellulose (HPMC), carbomer, polymethylvinylether maleic anhydride, and hydroxypropyl ethylcellulose. Swellable water-insoluble polymers, called hydrogels, or polymers having peculiar characteristics of swelling in aqueous medium give controlled drug delivery systems. The release of a drug from these systems occurs via the transport of the solvent into the polymer matrix, leading to its swelling. The final step involves the diffusion of the solute through the swollen polymer, leading to erosion/dissolution. Poly(acrylic acid) hydrogel has been reported to augment significantly the ocular bioavailability of tropicamide in humans, with respect to both a viscous solution and a paraffin ointment (12). Saettone et al. (13) also evaluated the relative capacity of different synthetic hydrogels, e.g., poly(acrylic acids), poly(acrylamide), and ethylene maleic anhydride, to be retained in the eye and found that one of the poly(acrylic acids) and poly(acrylamide) produced an almost threefold increase in bioavailability with respect to the aqueous solution of the drug pilocarpine. Such preliminary studies indicate and confirm the positive properties of these hydrogels. Crosslinked poly(acrylamide) has been used as a transparent microgel (present in Orcolon®) for experimental surgery-induced glaucoma (14). Orcolon (Optical Radiation Corporation, Azusa, CA) has however been withdrawn from the market because of the complications associated with its use (15,16). Chemically or thermally-treated gelatin swells in water to form a hydrogel (Gelfoam®, Upjohn Company) and has been proposed as a carrier in controlled ophthalmic delivery (17). These preparations are found to be more comfortable, and an increased bioavailability has been found in the case of aqueous gels over aqueous suspensions, but they have the disadvantage of producing blurred vision (although less than that produced by ointments) (18). There is no rate control on the diffusion of the drug from the gels. The drawbacks of difficulty in sterilization and easy bacterial contamination have thus far limited their large-scale production and clinical use. However, these vehicles present explicit characteristics such as high viscosity, ensuring prolonged retention and a better miscibility with the lachrymal fluid, which helps in the release of water-soluble drugs (19). Moreover, these agents are usually biocompatible.

Viscosity-Imparting Agents

Viscosity-increasing polymers are usually added to ophthalmic drug solutions on the premise that an increased vehicle viscosity should correspond to a slower elimination from the preocular area and hence a greater transcorneal penetration of the drug into the anterior chamber (13). The polymers used include PVA, polyvinylpyrrolidine (PVP), methylcellulose, hydroxyethyl cellulose, HPMC, and hydroxypropyl cellulose (HPC). An increase in viscosity of a formulation by addition of xanthan gum, which is a polysaccharide, was found to delay the clearance of the instilled solution by the tear flow. The corneal contact time of these formulations was evaluated over a period of more than 20 min by gamma scintigraphy (20). Zaki et al. (21) studied the precorneal drainage of radio-labeled solutions containing varying concentrations of PVA or HPMC to produce a viscosity range between 10.2 and 102 mPa sec. The drainage was measured in both rabbits and man by gamma scintigraphy. Their results indicated that the solution drainage was faster in man than in rabbits, with a more pronounced effect on viscosity. Significant retardation of drainage in man was noted at the higher polymer concentrations (0.9% HPMC or 5.85% PVA). It was suggested by Green and Downs (22) that a minimum viscosity of 20 cst is needed for optimum corneal absorption. Saettone et al. (23) found that amongst PVA, HPMC, and PVP, used for solutions of tropicamide at concentrations yielding the same viscosity of 20 cst, PVA was more effective. This is because of its adhesive properties and its capability to increase the thickness of the precorneal tear film (24). Saettone et al. (13) indicated that the retention of drug in the precorneal tear film is not strictly related to the viscosity of the vehicle, but rather to the surface spreading characteristics of the vehicle and to the ability of a polymer to drag water as the vehicle spreads over the ocular surface with each blink. Viscous vehicles increase the contact time of the preparations to varying degrees, but so far no marked sustaining effect has been attained (25).

In vitro diffusion tests are being used to evaluate the release pattern of the drug from these preparations (gels and viscous solutions). Some workers (26) have used diffusion cells similar to those

described by Bottari et al. (27) to study the release pattern of ophthalmic gels and other viscous solutions. Cells of known specifications covered with a suitably treated cellophane membrane are immersed in the diffusion medium (simulated tear fluid). Formulations may also be tested by using a 30-mesh stainless steel screen cover instead of the membrane. A USP rotating paddle apparatus II (speed 50 rpm) is also used for the purpose. Aliquots of medium are withdrawn at selected times and analyzed spectrophotometrically. Hui and Robinson (28) have also used the USP rotating basket method, wherein they placed a known amount of the polymer containing progesterone in a basket assembly, connected to a stirrer motor (120 rpm), using pH 7.4 isotonic Sorensen buffer as the medium. Stevens et al. (29) have described an in vitro model representative of in vivo conditions to measure the time–release profiles from slow-releasing gels and suspensions. They have reproduced in vitro the small volume and the slow exchange rate of the human precorneal tear reservoir. The concentration of drug is analyzed continuously from the sample reservoir. Cohen et al. (30) have studied the release rate of pilocarpine under static conditions by adding 1 mL of eye drops to 5 mL of releasing medium in a 10-mL glass tube and under mixing conditions by placing 8 mL of eye drops solution into a dialysis tubing of cellulose ester membrane (MW CO 8000), immersed in 40 mL of releasing medium (simulated tear fluid).

Use of Cyclodextrins to Increase the Solubility of Drugs in Aqueous Eye Drop Solutions

The solubilizing abilities of cyclodextrins depend largely on their abilities to form water-soluble drug–cyclodextrin complexes. Cyclodextrins act as true 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 or aqueous tear fluid. The ocular availability of drugs in the aqueous cyclodextrin-containing eye drop solutions depends on several factors, such as the release of the drug from the cyclodextrin complex and the partition of the drug molecules into and then through the cornea or the conjunctival epithelium. Optimum penetration enhancement is obtained when just enough cyclodextrin is used to solubilize all drug in the vehicle (31,32). Conflicting results have been reported about the use of cyclodextrin, e.g., in some studies addition of cyclodextrin resulted in enhanced drug bioavailability while in other studies addition of cyclodextrin resulted in decreased bioavailability (33,34). This inconsistency in results could be due to improper usage of cyclodextrins. An optimum bioavailability would be expected when just enough cyclodextrin (<15%) is added to the aqueous eye drop solution to solubilize the lipophilic water-insoluble drug. Addition of too much cyclodextrin will decrease the bioavailability by retaining the drug molecules in the aqueous tear fluid. In general, the hydrophilic cyclodextrins are non-toxic upon topical application, as shown by various animal species and humans (35). Jansen et al. (36) found that dimethyl-β-cyclodextrin is toxic to the corneal epithelium and thus should not be used for corneal ophthalmic formulations. Reer et al. (37) have shown that 2-hydroxypropyl-β-cyclodextrin possesses the most favorable toxicological properties.

Aqueous Suspensions

Suspensions are dispersions of finely divided relatively insoluble drug substances in an aqueous vehicle containing suitable suspending and dispersing agents. Because of a tendency for the particles to be retained in the cul-de-sac, the contact time and duration of action of a suspension exceed those of a solution (38). While the retention increases with an increase in the particle size, as does the irritation of the eye, the rate of dissolution of the suspended drugs increases with decreasing particle size. Thus an optimum particle size has to be selected for each type of drug, and it is recommended that the particles in an ophthalmic suspension should be $\not>10\,\mu m$ in size. Certain kinetic models have been proposed to predict the effect of particle size, concentration, and changes in drainage rate on the bioavailability of suspensions (39). Furthermore, it may be added here that the mean dose and the uniformity of amounts administered in a single drop depend upon the redispersibility of drug particles by shaking. It must be kept in mind that in any suspension system changes in storage temperature and prolonged storage can cause the smallest particle to dissolve and the largest particle to become

larger, thus giving a more extended effect. The spillover and drainage of a suspension leading to the loss of both solution and suspended solid can also affect the drug availability and absorption. Moreover, a change in crystal structure, i.e., polymorphism, may occur during storage, resulting in an alteration in the suspension characteristics causing solubility changes reflected in an increased or decreased bioavailability.

A newer concept in suspensions is the use of microspheres or microparticulates. These are drug-containing small polymeric particles (erodible, nonerodible, or ion-exchange resins) that are suspended in a liquid carrier medium. Upon administration into the eye, the particles reside at the delivery site and the drug is released from the particle through diffusion, chemical reaction, polymer degradation, or ion-exchange mechanism. Newer approaches, such as the use of mucoadhesive particulates (40), pH-responsive particulates, nanoparticles (41,42), etc., have also been used to formulate microparticulate dosage forms. These dosage forms show significantly higher and sustained delivery in the eye (43,44). Certain technological problems faced with these formulations include the production of stable suspensions, uniform dose per unit volume, efficient drug entrapment, reproducible and large-scale manufacture, and uniform particle size.

Ophthalmic Sprays

An alternative delivery of pilocarpine (4% solution) via a spray (single application) to closed eyelids was found to be an effective delivery method for intraocular miosis (45).

Ointments

Ointments are useful as drug carriers for improving bioavailability and sustaining drug release. An attractive feature of ointments is their entrapment in the fornices, which thereby serve as a reservoir of the drug (46). There is more flexibility in the choice of drug to be incorporated into an ointment base, as even drugs with low water solubility can be suitably delivered to the eye. Moreover, the stability of drugs is sometimes improved in ointments. The ointments are reported to be sustained on the surface of the eye for up to 2–4 or even 8 hr after application (47). Ophthalmic ointments containing different sorption promoters have also been formulated and reported to show significantly higher release rates, relative to ointments without these promoters (48). However, dosage variability with ointments is greater than with solutions and the ointments interfere with vision unless their use is limited to bedtime instillation. Sticking together of the eyelids results in poor patient compliance. Drug molecules may be entrapped within the ointment base or may not be released at the site of action due to a favorable partitioning towards the base. Thus, a true "sustaining effect" is not achieved. Tang-Liu et al. (49) have reported higher drug concentrations in conjunctiva and aqueous humor with ofloxacin 0.3% ophthalmic solution in comparison to an ointment with the same concentration.

Penetration Enhancers

The transport characteristics across the cornea can be maximized by increasing the permeability of the corneal epithelial membrane (50–56). The stratified corneal epithelial cell layer is a "tight" ion-transporting tissue because of the high resistance of 12–16 $k\Omega\,cm^2$ being exhibited by the paracellular pathway (57). So, one of the approaches used to improve ophthalmic drug bioavailability lies in increasing transiently the permeability characteristics of the cornea with appropriate substances known as penetration enhancers or absorption promoters. The transport process from the cornea to the receptor site is a rate-limiting step, and permeation enhancers increase corneal uptake by modifying the integrity of the corneal epithelium (58). Inclusion of these agents such as cetylpyridinium chloride (59,60), ionophore such as lasalocid (61), benzalkonium chloride (BAC) (62–64), Tween 20 (65), parabens (56,66), saponins (65,66), Brij® 35, Brij® 78, Brij® 98, ethylenediaminetetraacetic acid (EDTA) (11), bile salts (67), and bile acids (such as sodium cholate, sodium taurocholate, sodium glycodeoxycholate, sodium taurodeoxycholate, taurocholic acid, chenodeoxycholic acid, and ursodeoxycholic acid), capric acid (56), azone, fucidic acid, hexamethylene lauramide, saponins (56), hexamethylene octanamide, and decylmethyl sulfoxide (68) in different formulations have shown a significant enhancement in corneal drug absorption. Penetration enhancers have also been reported to reduce the drop size of conventional ophthalmic solutions, especially if they do not elicit local irritation (69). The aforementioned agents belong to the general class of surfactants. Because of their hydrophilic/lipophilic character the surfactants

are absorbed from the epithelium, where they may change the physical properties of the cell membrane by the removal of phospholipids and also by membrane solubilization. At low concentration these surfactants are incorporated into the lipid bilayer, which changes the physical properties of the cell membrane. When the lipid bilayer is saturated, mixed micelles begin to form, resulting in the removal of phospholipids from the cell membrane and also membrane solubilization. Bile acids and salts act by changing the rheological properties of biological membranes. Owing to their mucolytic properties they can increase diffusion through the membrane by inducing a transient change in its structure and permeability. Further, it has been indicated that these agents promote the transport of hydrophilic and macromolecular compounds, mainly through a porelike route such as intercellular channels rather than through partitioning into the cell membrane (67).

Many researchers have demonstrated that some preservatives significantly increase the corneal permeability of ophthalmic drugs (2,70). Amongst the currently used preservatives, BAC shows the highest promoting effect on corneal drug penetration. The use of BAC (0.01%) causes cells of the corneal epithelium to peel at their borders (71), and also enlarges intercellular spaces in superficial cells of the cornea. The addition of BAC (0.005%) enhances the transport per cent (2.5-fold) and P_{app} of S1033, a novel prostaglandin derivative used as an antiglaucoma agent (62).

Another class of permeation promoters is calcium chelators like EDTA, which act by loosening tight junctions between superficial epithelial cells, thus facilitating paracellular transport (11,72). The Ca^{2+} depletion does not act directly on the tight junctions, rather it induces global changes in the cells including disruption of actin filaments and adherent junctions, leading to diminished cell adhesion and activation of protein kinases (73). Grass and Robinson (74) were among the first to emphasize the positive effect of chelating agents on corneal drug absorption. They found that 0.5% EDTA doubled the ocular absorption of topically applied glycerol and cromolyn sodium. Newton et al. (75) reported that azone, a transdermal absorption promoter, increased the ocular delivery of instilled cyclosporin and enhanced its immunosuppression activity. Various penetration enhancers, azone (laurocapam), hexamethylene lauramide, hexa-methylene octanamide, and decylmethyl sulfoxide, were studied for their effect on cimetidine and all of them were found to enhance the corneal permeability of cimetidine. The effect of azone on a series of structurally unrelated drugs, ranging from hydrophilic to lipophilic character, was also studied. Azone enhanced the transcorneal penetration of hydrophilic drugs but retarded the apparent drug permeation across the cornea for lipophilic drugs (68).

However, the unique characteristics and great sensitivity of the corneal/conjunctival tissues impose great caution in the selection of enhancers with regard to consideration of their capacity to affect the integrity of epithelial surfaces. There is evidence that penetration enhancers themselves can penetrate the eye and may therefore lead to unknown toxicological complications, e.g., BAC was found to accumulate in the cornea for days (76). Similarly, EDTA was found to reach the iris–ciliary body in concentrations high enough to alter the permeability of the blood vessels in the uveal tract, indirectly accelerating drug removal from the aqueous humor (77). Repeated application of 0.5% EDTA was observed to significantly alter the corneal epithelial architecture, even though a single application was well tolerated (2). Azone at 0.2% concentration or higher is irritating, discomforting, and/or toxic to the eyes (78). Saponins cause eye irritation when used at the 0.5% level (65). Bile salts and surfactants cause irritation of the eye and nasal mucosa (70,79). Rojanasakul et al. (80) used laser scanning confocal microscopy and electrophysiological techniques to confirm that, although all enhancers (in particular, EDTA, digitonin, and sodium deoxycholate) significantly increase corneal permeability, they may also cause severe cellular membrane damage.

Various in vitro corneal penetration studies have been proposed to calculate the apparent permeability coefficients, lag times, and corneal clearances of ophthalmic formulations. Three different models have been developed for these studies.

The first model takes physiological and formulation variables into account, it:

- allows for pulse introduction of drugs,
- allows the contact time to be varied, and
- is useful for the detection of drugs/formulations that can damage the cornea (81).

In the second model freshly excised rabbit cornea is mounted in a perfusion apparatus. Samples are

withdrawn from the receptor side over a period of 3–5 hr. At the end of the experiment the solution from both the donor (epithelial) and the receptor (endothelial) side and the cornea are analyzed for the remaining drug (11).

The third model has been developed for ionizable drugs. It consists of five compartments, in series, to simulate the tear film, epithelium, stroma, endothelium, and aqueous humor, represented by plane sheet barriers of physiological thickness. The tear film is assumed to be perfectly mixed and the stroma completely stagnant. Four routes of drug loss, including lachrymal drainage, conjunctival absorption, aqueous drainage, and iris–ciliary body absorption, are also included in the model (82).

Ocular penetration enhancers cause increased corneal hydration. This hydration level (HL) is evaluated and taken as an index of cellular and tissue damage. Method: the scleral ring is carefully removed and the wet corneal weight, W_w, obtained. Then each corneal sample is desiccated at 100°C for 6 hr to give the corresponding dry corneal weight, W_d. The percentage HL, defined as $[1-(W_d/W_w)]\times 100$, is determined both on the untreated corneas (removed no later than 30 min after death of the animal) and on corneas recovered from penetration tests performed in the presence of enhancers (11).

Bioadhesive Polymers

Conventional aqueous solutions topically applied to the eye have the disadvantage that most of the instilled drug is lost within the first 15–30 sec after instillation, due to reflex tearing and drainage via the nasolacrimal duct. One of the goals in ophthalmic research has been directed toward an increase of drug absorption and duration of contact time. The most frequent approach to achieve improved drug efficacy is exemplified by the use of viscosified solutions. Nevertheless, viscosity alone cannot significantly prolong the residence time. This can be considered, in part, as the premise of using bioadhesive polymers to enhance drug absorption. The capacity of some polymers to adhere to the mucin coat covering the conjunctiva and the corneal surfaces of the eye forms the basis for ocular mucoadhesion. These systems markedly prolong the residence time of a drug in the conjunctival sac, since clearance is now controlled by the much slower rate of mucus turnover than the tear turnover rate. Bioadhesive polymers are usually macromolecular hydrocolloids with numerous hydrophilic functional groups and possess the correct charge density (83). These bioadhesive polymers can be natural, synthetic, or semi-synthetic in nature. The synthetic polymers, such as polyacrylic acid (84,85), polycarbophil (25), and biopolymers, notably hyaluronic acid, a ubiquitous component of animal extracellular tissue, have shown a prolonged retention in ocular tissues. These synthetic mucoadhesives, including water-soluble polymers that are linear chains and water-insoluble polymers that are swellable networks joined by crosslinking agents, are the most commonly used bioadhesives in ophthalmic drug delivery systems. Typically, these polymers have high molecular weight (5000–10,000 Da), cannot cross biological membranes, and include cellulosic components like sodium carboxy methylcellulose (CMC), or are polyanionic in nature, like polyacrylic acid (PAA). The ocular concentration of timolol improved three- to ninefold in the presence of sodium CMC compared with nonviscous eyedrops (86). Acetazolamide formulated in CMC, compared with the saline solution of the drug in patients with unilateral open-angle glaucoma, was found to have a longer duration of action. However, the results were not spectacular and were significant only when using high drug concentrations (87).

Crosslinked polyacrylic acid has been shown to have excellent mucoadhesive properties, causing significant enhancement in ocular bioavailability (28). According to Robinson (88), the best bioadhesive polymers are polyanions such as polyacrylic acids, i.e., Carbopol® 934P, polycarbophil, and CMC. Fucidic acid, an antibiotic, formulated in PAA (fucithalmic) gives a long-lasting antibiotic efficiency (89). LeBourlais et al. (90) have tested PAA polymeric gels in aqueous/non-aqueous solvents incorporating the immunosuppressive agent cyclosporin and have reported a significantly improved drug corneal penetration with these agents. Hyaluronic acid is a high-molecular weight biological polymer consisting of linear polysaccharides present in the extracellular matrix. In addition to its mucoadhesive properties, sodium hyaluronate is an attractive ophthalmic drug delivery vehicle because of its high water-binding capacity, nonirritancy, increased viscosity, and pseudoplastic behavior (25).

Chitosan, a polycationic biopolymer obtained by alkaline deacetylation of chitin, is a bioadhesive

vehicle suitable for ophthalmic formulations since it exhibits several favorable biological properties such as biodegradability, non-toxicity, and biocompatibility. In fact, due to its positive charges at neutral pH, an ionic interaction with the negative charges of sialic acid residues of the mucus has been proposed as its mechanism of mucoadhesion (91–93). A suspension of bioadhesive microspheres made of chitosan seems a promising means of topical administration of acyclovir to the eye (40). Recently, xanthan and carrageenan have been described as bioadhesive polysaccharides showing sustained release properties and adequate ocular compatibility (94,95). Copolymerization of the bioadhesive polymer PAA with Pluronic®, a thermally-induced, phase-separating graft polymer, has been reported to yield a bioadhesive vehicle with a prolonged residence time plus a prolonged drug release period in contact with mucosal surfaces such as the eye (83). Hoffman et al. (96) have reported newer polymeric gels with a biphasic activity for accomplishing both ocular drug retention and prolonged release of drug from the vehicle.

In vitro evaluation of polymer bioadhesion, expressed as the force required to separate a polymer specimen from a freshly excised rabbit conjunctival membrane, can be measured by using a precision balance (97).

Phase Transition Systems

These systems, when instilled into the cul-de-sac, shift from the liquid form to the gel or solid phase. In case of poloxamer 407, the viscosity of the solution increases when its temperature is raised to the eye temperature (98), and the cellulose acetate phthalate latex (99) coagulates when its native pH of 4.5 is raised by the tear fluid to pH 7.4. Gelrite®—an ion-activated, in situ-gelling polymer, forms a clear gel in the presence of cations, e.g., calcium or sodium ions present in the tears, and increases the corneal residence time and in turn the bioavailability of the drug (26,100). Edsman et al. (101) have reported that the ocular residence time of gels is dependent on their rheological properties. Furthermore, Edsman et al. (102) have reported a concentration dependence of the contact time of the poloxamer preparations such that high initial concentration would be required to make the preparation gel at room temperature, even before instillation. They indicated that it is not a promising system, giving a maximum contact time of around 1 hr. On the other hand, a hypotonic solution of Gelrite which gelled on contact with the tear fluid (containing electrolytes) was found to remain in the human eye for up to 20 hr (103). A novel in situ-forming ophthalmic drug delivery system using an aqueous solution of sodium alginate, which can gel in the eye without the addition of external calcium ions or other bivalent/polyvalent cations, has been proposed for prolonged delivery of pilocarpine (30). An increase in pH from 4.0 to 7.4, or temperature from 25°C to 37°C, of a system prepared by a combination of carbopol and methyl cellulose resulted in an increase in viscosity, tau, and yield point (104). The authors suggest that such systems can be formulated as drug-containing liquids suitable for administration by instillation into the eye, which upon exposure to physiological conditions will shift to the gel (semi-solid) phase, thus increasing the precorneal residence time and enhancing the ocular bioavailability of the drug.

Vesicular/Colloidal Systems

These are represented as liquid-retentive drug delivery systems containing the drug in a carrier. They give a sustained and prolonged release of the medicament, thus eliminating frequent dosing, and the reduction in dose leads to a decreased incidence of side effects. They can be used to target the drug molecule to a specific tissue. The carriers used should be biocompatible, non-irritant, and biodegradable. The various vesicular systems being used in ocular drug delivery include the following.

Liposomes

A liposome is defined as a structure consisting of one or more concentric spheres of lipid bilayers separated by water or aqueous buffer compartments with a diameter ranging from 80 nm to 100 μm. Drug molecules depending upon their solubility are encapsulated in either the aqueous phase or the lipid bilayer (105). Thus, liposomes can accommodate both hydrophilic and lipophilic compounds, and it is possible to apply water-insoluble drugs in a liquid dosage form (106). Liposomes can enhance corneal drug absorption, achieved through their ability to come into intimate contact with the corneal and conjunctival surfaces. The earlier studies showed that liposome-associated idoxuridine is superior to the solution form of the drug in the

treatment of herpes simplex keratitis in rabbits (107,108).

According to their size, liposomes are known as either small unilamellar vesicles (SUV) (10–100 nm) or large unilamellar vesicles (LUV) (100–3000 nm). If more bilayers are present they are referred to as multilamellar vesicles (MLV). Depending on the composition, liposomes can have a positive, negative, or neutral surface charge. Schaeffer and Krohn (109) investigated the lecithin-mediated attachment of liposomes to freshly excised cornea and its influence on transcorneal drug flux. They tested SUV and MLV with neutral, positive, or negative surface charge. In vitro liposome–corneal interaction studies showed that liposomes were taken up by the cornea in the order $MLV^+ > SUV^+ \gg MLV^- > SUV^- > MLV = SUV$. The reason for this apparent difference is not clear, but it is known that the corneal epithelium is thinly coated with negatively-charged mucin to which the positive surface charge of the liposomes may absorb more strongly (110). The in vitro and in vivo efficacy of dexamethasone sodium phosphate liposomes as an ocular system was studied, and the delivery of the drug was evaluated in rabbit eyes. Positively-charged liposomal formulations of the drug provided the highest drug concentration at the anterior segments of the eye, thus proving useful for the therapy of eye inflammations such as iritis and choroiditis (111). Liposomal preparation of acetazolamide has recently been reported (112). Lipid microspheres of hydrocortisone have been reported to deliver the drug to the anterior ocular tissues more significantly than ophthalmic suspensions (44). Milani et al. (113) showed in a rat model that encapsulation of an immunosuppressive and a lipophilic drug, cyclosporin, into liposomes improved the survival rate of the corneal grafts in comparison with an oily vehicle. Liposomes are a potentially useful ocular drug delivery system due to the simplicity of preparation and versatility in physical characteristics, but suffer from the disadvantage of instability (due to the hydrolysis of phospholipids normally used in their preparation), limited drug-loading capacity, and technical difficulties in obtaining a sterile liposomal preparation (114). Taniguchi et al. (115) have reported that the stearylamine used to prepare positive liposomes was toxic to the cells and also appeared to be irritating to the eye.

The possibility of using liposomes in combination with other newer technologies has also been suggested and explored successfully by several workers, e.g.: (1) Durrani et al. (116) and Davies et al. (117) showed that coating the liposomes with bioadhesive polymer (carbopol) increased the corneal retention, and demonstrated a biphasic response with an initial low intensity, followed by a sustained action; (2) Pleyer et al. (118) applied cyclosporin topically to the eye in olive oil drops (control), in a liposome-encapsulated form, and in a collagen shield soaked in the liposome preparation. Both the test formulations showed higher concentration (with respect to the control) in the cornea, indicating the possibility of combining liposomes with collagen shields to further improve its slow-releasing property.

Niosomes

In order to circumvent the limitations of liposomes such as chemical instability, oxidative degradation of phospholipids, cost, and variable purity of natural phospholipids, vesicle formation by some members of the dialkyl polyoxyethylene ether non-ionic surfactant series has been suggested. It is reported that a vesicular system is formed when a mixture of cholesterol and a single-alkyl chain, non-ionic surfactant is hydrated. The resultant vesicles, termed "niosomes", can entrap solutes, are osmotically active, and relatively stable. Niosomes have also been reported as successful ophthalmic carriers. Non-ionic surfactant-based discoidal niosomes (discomes) of timolol maleate have been reported to be promising systems for the controlled ocular administration of water-soluble drugs, releasing the drug in a biphasic profile (119). Discomes, in addition to their many advantages, seem to have a special advantage towards the ocular route, wherein their large size may prevent their drainage into the systemic pool. Furthermore, their "disc" shape provides for a better fit in the cul-de-sac of the eye.

Pharmacosomes

This is the term used for pure drug vesicles formed by the amphiphilic drugs. Any drug possessing a free carboxyl group or an active hydrogen atom (–OH, NH_2) can be esterified (with or without a spacer group) to the hydroxyl group of a lipid molecule, thus generating an amphiphilic prodrug. The amphiphilic prodrug is converted to pharmacosomes on dilution with water. The pharmacosomes

show greater shelf stability, facilitated transport across the cornea, and a controlled release profile.

Nanoparticles/Nanospheres

Nanoparticles are among the most widely studied colloidal systems over the past two decades. These are polymeric colloidal particles, ranging from 10 nm to 1 μm, in which the drug is dissolved, entrapped, encapsulated, or adsorbed (120). They represent promising drug carriers for ophthalmic application (42,121). They are further classified into nanospheres (small capsules with a central cavity surrounded by a polymeric membrane) or nanocapsules (solid matricial spheres). MarchalHeussler et al. (122) found that the nanocapsules show a better effect than the nanospheres, probably because the drug (betaxolol, carteolol) is in an unionized form in the oily core and can diffuse at a greater rate into the cornea. Diffusion of the drug from the oily phase to the corneal epithelium seems to be more effective than diffusion from the internal matrix of the nanospheres.

Several authors (123) suggest that the better efficiency of nanocapsules is due to their bioadhesive properties, resulting in an increase in the residence time and biological response. Das et al. (124) found a five times higher corneal concentration of cyclosporin when using nanocapsules in comparison to the oily solution of the drug. Alonso et al. (125) have also reported that the nanoparticles of poly-ε-caprolactone containing cyclosporin show a better corneal absorption with respect to the oily solution of the drug. However, some authors (122,126–128) observed that nanoparticles consisting of poly(alkylcyanoacrylate) damaged the corneal epithelium by disrupting the cell membranes.

Chemical Delivery Systems

A chemical delivery system (CDS), is an inactive species obtained by chemical modifications of the active agent based on metabolic considerations. Conceptually, a CDS upon its administration will undergo several predictable enzymatic transformations via inactive intermediates and finally deliver the active species to the target site (129). In order to enhance the partitioning and corneal bioavailability of topically applied drugs, intensive research is being done on the prodrug approach, which is also a type of CDS. This approach to enhance corneal drug absorption has met successful commercial realization as well. The method includes modification of the chemical structure of the drug molecule, thus making it selective, site-specific, and a safe ocular drug delivery system. Epinephrine penetration was improved 10-fold by formulating a prodrug, Dipivefrin® (130). Other drugs with increased penetrability through prodrug formation are phenylephrine (131), timolol (132), tilisolol (133), pilocarpine (134,135), albuterol (136), idoxuridine, etc. Prostaglandin $F_{2\alpha}$ ester prodrugs have been reported to have better aqueous stability than prostaglandins (137).

The lipophilicity and hence the corneal penetration of a drug can also be increased through ion-pair formation. Ion-pair association is a coulombic association between large organic ions of opposite charge. The ions are transferred better when associated rather than individually. In animals, the method has been used with success to transfer the anti-inflammatory agent sodium chromoglycate (the di-anion) across the cornea by coupling it with a quaternary ammonium chloride. The use of ion-pair formation to promote corneal drug absorption has also been reported (138–141). These investigations found that the extent of drug ionization (i.e., the pH of the medium and the pK_a of the drug) and the chain length of the ion-pairing agent are the two important factors determining the extent of ocular drug penetration through ion-pair formation. The enhancement of absorption is either due to an increase in the availability of the drug at the corneal surface or from the shielding of the charge on the drug by the ion-pairing agent, thus allowing it to diffuse across the lipid environment of the corneal epithelium.

Soft drugs and site-specific chemical delivery systems are the other two novel chemical approaches of drug design. A soft drug, by definition, is a biologically-active compound characterized by a predictable and controllable in vivo destruction (metabolism) to non-toxic metabolite(s) after producing a therapeutic effect. Among the various soft drug design approaches (142), the ''inactive metabolite'' approach has been found to be the most useful for designing ocular drugs.

Drug Delivery Systems Providing Controlled and Continuous Ocular Delivery

The typical ''pulse entry''-type drug release behavior observed with ocular aqueous solutions

(eye drops), suspensions, and ointments can be replaced by more controlled, sustained, and continuous drug delivery, using a controlled-release ocular drug delivery system. These systems can achieve therapeutic action with a smaller dose and fewer systemic and ocular side-effects.

Implantable Systems

These systems are as yet less popular as they require minor surgery by which the polymeric system (into which the drug has been incorporated) is implanted inside the eye. The benefits of this dosage form are: (a) increased selectivity of drug action achieved by the zero-order release rate of the system; and (b) decreased frequency of administration. Implantable pumps are the most widely researched systems. The Alzet osmotic pump is a 2-mm long device with a 6.5-mm diameter. It is effective for 1–2 weeks. Polylacticacid (PLA) and its copolymers with glycolic acid (PLGA) have been used extensively as implants (143). Hashizoe et al. (144) have reported a scleral plug using PLGA for the controlled release of doxirubicin in the vitreous. Kimura et al. (145) have also reported a vitreal drug delivery system using an implantable, biodegradable, PLA device for the controlled release of adriamycin. An ocular implant (Vitrasert) for delivering ganciclovir for the treatment of cytomegalovirus (CMV) has also been developed (146). This implant delivers the drug directly to the retina for over 5 months. Similar studies have also been reported earlier, where Sanborn et al. (147) implanted intraocular non-biodegradable drug delivery devices into patients with AIDS-associated cytomegalovirus retinitis. The device was prepared by coating a ganciclovir pellet with PVA. The pellet was then coated with ethylene vinyl acetate except on its top surface, and again coated with PVA. The device lasted 4–5 months and all the treated eyes showed resolution of the CMV retinitis.

Insoluble Inserts

These are solid or semi-solid sterile preparations, of appropriate size and shape, designed to be inserted behind the eyelid or held on the eye and to deliver drugs for topical or systemic effect. These are polymeric systems into which the drug is incorporated as a solution or dispersion. Inserts are further subdivided into the following.

Membrane-Controlled Reservoir Inserts

Solid-state ocular inserts (ocuserts) represent a category of dosage form which is better than the traditional ophthalmic systems (148,149). The Alza Corporation (USA) first marketed ocular inserts and described them as systems that release the drug at a programmed rate for a specified period of time. They produced a membrane–reservoir-type device, containing pilocarpine and alginic acid in the core reservoir, placed between a transparent, lipophilic ethylenevinyl acetate rate-controlling membrane. Ophthalmic inserts have also been reported using alginate salts, PVP (150), modified collagen (151), and HPC (152,153). Ocufit® SR is a silicone elastomer-based matrix that allows for the controlled release of an active ingredient over a period of at least 2 weeks (154). It was designed to fit the shape and size of the human conjunctival fornix. The placebo devices have been retained for ≥ 7 days with only minor adverse reactions (155). Timolol inserts of silicone tubing have also been reported to result in a higher systemically-absorbed fraction of the timolol dose than the eye drop, but the peak timolol concentration and the daily absorbed amount of timolol were decreased (156).

Osmotically-controlled inserts have also been described (149). These consist of a central or multiple compartments containing the drug in an inert permeable membrane and the osmotic fluid (agents: mannitol, sorbitol, glucose, calcium lactate, etc.) in a semi-permeable membrane. Drug release starts as soon as the system comes into contact with the dissolving medium, which penetrates into the osmotic compartment causing a rise in pressure, thus squeezing the compartment containing the active ingredient. The release is diffusion and osmotically-controlled.

Kushnick et al. (157) have reported a systemic pilocarpine toxicity due to the leakage of the ocusert system. So an in-depth evaluation of such systems is suggested. Furthermore, these systems are less popular among the elderly who have difficulty with insertion, do not retain the device well, and often do not even notice if it falls out. Many patients feel a foreign body sensation in the eye. Besides the high cost involved in its fabrication, ocusert is a non-biodegradable system and because of the insolubility of the Ocusert® device, it must be removed after use (158). The inserts, although well tolerated, tend to swell and partially fragment after prolonged

wear. Hence, it is recommended that they are not worn for more than 12 hr, despite the potential for prolonged release over several days (159).

Ocular Therapeutic System (OTS) or Minidisc

These are controlled-release monolithic matrix-type devices consisting of a contoured disc with a convex front and a concave back surface, designed so as to fit the eyeball (133,160–162). The principle component is α,ω-bis(4-methacryloxybutyl)-polydimethyl siloxane. The OTS can be made hydrophilic or hydrophobic to permit extended release of both water-soluble and water-insoluble drugs. They were reported to be very comfortable when placed behind the top or bottom of the eyelid.

Soft Contact Lenses

These form a special class of insoluble ophthalmic inserts. The most widely used material for these is poly-2-hydroxyethyl methacrylate. Its copolymers with PVP are used both to correct eyesight and to hold and deliver drugs. The latter is possible because of the tendency of its constituent polymers to absorb up to 80% water (163). The active ingredient is incorporated either by prior soaking or instillation after fitting the lens, or both. Since the drug is not bound to the matrix, it dissolves rapidly in the tears and its release cannot be accurately controlled. However, a controlled release could be obtained by binding the active ingredient via biodegradable covalent linkages (164).

Soluble Inserts

These consist of all monolytic polymeric devices that at the end of their release are no longer present in the eye either because of dissolution or erosion. These devices are further classified into the following.

Soluble Ophthalmic Drug Inserts (SODI)

A SODI is a soluble copolymer of acrylamide, *N*-vinyl pyrrolidone, and ethyl acrylate. It is in the form of sterile thin films or wafers of oval shape, weighing 15 to 16 mg. After introduction into the upper conjunctival sac, the SODI softens in 10 to 15 sec, conforming to the shape of the eyeball; in the next 10 to 15 min the film turns into a polymeric clot, which gradually dissolves within 1 hr, while releasing the drug. A single SODI application containing 2.7 mg of pilocarpine has been reported to replace 4 to 12-drop instillations or three to six applications of ointment, and to constitute a valid once-a-day therapy even for long-term treatment of glaucoma (165). A soluble insert containing gentamicin sulfate and dexamethasone phosphate has been developed by Baeyens et al. (166) for the treatment of infections. The addition of corticosteroids along with an antibiotic is indicated in certain clinical situations, so as to limit the precorneal damage caused by the infection. The new system ensures a concomitant release of the two drugs for the first 10 hr, followed by a sustained release of gentamicin over a period of 50 hr due to its combination with cellulose acetate phthalate. The major advantage of these dosage forms is the reduced role of the clinician, since the form is dissolved by total or partial solubilization and there is no need to surgically remove the insert once the drug has been released. But they have the drawback that they blur vision while the polymer is dissolving. Release of the drug from the SODI is proposed to occur in two stages: (1) hydration of the matrix by penetration of dissolution medium; and (2) diffusion of the medium deep into the matrix and back-diffusion of the dissolved active principle (167). Roopa et al. (168) have designed an ocular film containing ciprofloxacin hydrochloride. The film is reported to dissolve completely in the conjunctival sac, providing the daily dose of the drug in a single application. A packed film retained its activity and sterility for 13–14 months. Problems associated with these films include individual tolerance and trained personnel for its application.

Bioadhesive Ophthalmic Drug Inserts (BODI)

The main problem encountered with conventional ophthalmic inserts is their site of application and the risk of expulsion from the site. To overcome this drawback, a new type of ophthalmic insert incorporating a 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. These inserts, named BODI, are totally eliminated so that they do not need to be removed, thus limiting manipulations to insertion only (149,158,169). A BODI based on gentamicin, obtained by extrusion of a mixture of polymers, 5 mm long by 2 mm in diameter, showing a release

time of about 72 hr has been reported (170). The BODI drastically diminished the risk of expulsion. Tolerance studies confirmed the validity of the concept (158).

Collagen Shields

Succinylated collagen was used to fabricate erodible inserts for placement in the fornix for long-term delivery of gentamicin into the eye (171). However, the physical properties of these inserts were inappropriate and the system failed when inserted into the conjunctival sac of cattle (172). So studies on inserts were superseded by research work on collagen shields. Collagen shields are manufactured from porcine scleral tissue, which bears a collagen composition similar to that of the human cornea. The shields are hydrated before being placed on the eye, having been stored in a dehydrated state. The drug is loaded into the collagen shield simply by soaking it in the drug solution. It forms a clear, pliable, thin film, approximately 0.1 mm in thickness, with a base curve of 9 mm that conforms to the corneal surface. Designed to slowly dissolve within 12, 24, or 72 hr, the shield has stimulated much interest as a potential sustained ocular delivery system (58). As the shields dissolve, they provide a layer of collagen solution that seems to lubricate the surface of the eye, minimize rubbing of the lids on the cornea, and foster epithelial healing (173). The collagen matrix: (a) acts as a reservoir, increasing the contact time between drug and cornea; (b) reversibly binds drug molecules which are subsequently released in a delayed mode; and (c) reduces the likelihood of systemic toxicity, especially if dose reduction is possible (174). Commercially available products on the market, e.g., MediLens® (Chiron, Irvine, CA) and ProShield® (Alcon, Fort Worth, TX) are prepared from bovine corium tissue and last between 24 and 48 hr on the cornea (175). Collagen shields presoaked in tobramycin were used to treat a *Pseudomonas aeruginosa*-infected cornea excoriation (176). Lee et al. (177) tested various combinations of drugs in the same collagen shield. This system was not recommended for a multidrug delivery system. Moreover, shields are not individually fit for each patient (as are soft contact lenses), the insertion technique is difficult, and expulsion of the shield may occur (16). Also, the shields are not fully transparent and thus reduce visual acuity. However, collagen shields are appropriate delivery systems for both hydrophilic and hydrophobic drugs with poor penetration properties. Because of their biological inertness, structural stability, good biocompatibility, and low cost of production, they have proven to be a promising carrier for ophthalmic drug delivery systems.

New Ophthalmic Delivery Systems (NODS)

Several NODS have been reported by various workers which are different from the above-mentioned controlled release systems. One of the NODS consists of 50 mm by 6 mm strips containing a small separable water-soluble tag, coated with a film of PVA in which the active ingredient is incorporated. Its total weight is approximately 500 μg including 40% active ingredient. When in contact with the tear film, in the conjunctival fold, the tag separates from the strip and gradually releases the drug (178). The anhydrous composition of this form is an advantage for drugs that are sparingly soluble in water or unstable at physiological pH (179). Another NODS produced an eightfold increase in bioavailability of pilocarpine with respect to standard eye drop formulations, and a high percentage of patients declared that they preferred NODS to drops or found them to be equally acceptable (180). A NODS designed to deliver a precise amount of an ocular medication for an extended period of time has been reported by Bentley (181). The device is made of water-soluble PVA with a median molecular weight of 98,000. Kelly et al. (182) also developed a NODS of pilocarpine (based on PVA films) with an eightfold increase in ocular bioavailability. Greaves et al. (180) observed that pilocarpine delivered in a NODS decreased the intraocular pressure and increased the bioavailability. The higher tolerability of NODS vs. Isopto-Naturale R eye drops in a two-period crossover study is reported (183). The ophthalmic rod (OR) is another NODS, made of non-toxic plastic (184). The active substance is deposited as a thin film on the end of the rod and the rod is rubbed against the conjunctiva of the lower lid to deliver the drugs. Alani and Hammerstein (184) have reported the use of clonidine ORs for patients with glaucoma and suggest them as an alternative to eye drops. With the use of ORs the problems of preservation, sterility, and cross-infection are overcome. Moreover, administration of the product in dry form increases its residence time and bioavailability compared to the

eyedrops (180). Gwon et al. (185) have reported ORs coated with fluorescein to be soft, safe, comfortable, and easy to use.

Drug disposition studies in ocular fluids and tissues have to be carried out to study the constant rate of infusion of these formulations, and different methods have been proposed for the same. A plastic well has been designed by Eller et al. (186) for topical administration into rabbit eyes. The base of the device, tightly closed with silicone grease, fits over the eye, except the central portion, which forms a well and permits the drug solution to remain in direct contact with the cornea but excludes the sclera. The rabbits are anesthetized 10 min prior to the start of the experiment. The drug solution is added to the well at time zero and the rabbits are sacrificed periodically. The aqueous humor and iris–ciliary body are removed and extracted at each time period, and are analyzed for the drug and its metabolites (187). This method is helpful in studying intraocular penetration rate and ocular bioavailability of ophthalmic formulations. The degree of drug penetration is expressed as the maximum ocular tissue concentration measured in micrograms per milliliter or micrograms per gram. Drug distribution in ocular fluids and tissues can be determined by anesthetizing the rabbits at preselected times after topical administration of the drug. The posterior and anterior aqueous humor samples are withdrawn and analyzed for drug concentration. Similarly, the cornea and ciliary body may be removed from the sacrificed rabbit, weighed, put into a measured volume of water or other suitable solvent, boiled, mixed, and analyzed for drug concentration (188).

Gamma scintigraphy is another elegant way to gain an insight into the actual in vivo distribution pattern of dosage forms, and is being used for the measurement of ophthalmic bioavailability. By measuring the precorneal clearance of a drug including a radioactive tracer, the ocular bioavailability can be measured (10,21,189). Slit lamp fluorophotometry is also being used to evaluate the precorneal kinetics of eye formulations containing a fluorescent tracer in humans. It is a non-invasive method, causing minimal disturbance to normal physiological functions. The fluorescence decay of sodium fluorescein in the precorneal film in humans has been measured with a slit lamp fluorophotometer (190,191). The clearance of fluorescein at each time interval gives the aqueous humor flow from the formula: clearance $= \Delta M/(c \times \Delta t)$, where ΔM is the loss of fluorescein in the combined cornea and anterior chamber during the time Δt and c is the average concentration in the anterior chamber during the interval, estimated from the initial and final fluorescence and assuming a single exponential decay (192). Brubaker (193) determined aqueous humor flow from the rate of clearance of fluorescein after subtracting the presumed rate of diffusional clearance (0.25 μL/min).

CONCLUSION

The development of ophthalmic drug delivery systems is easy and complicated at the same time: easy because all the diseases are concentrated in the same organ and can thus be easily targeted, and complicated because the eye has specific characteristics which make the development of ocular drug delivery systems extremely difficult. However, the stage is set for improved systems.

(a) For example, drug delivery systems have been developed which are able to retain the drug at the site of action for a sufficient length of time. Newer research is directed at the development of novel biodegradable polymers such as third-generation poly(ortho esters) and polyanhydrides (194–197). Research has also been conducted in the use of these delivery systems for sites other than the precorneal area (154,198). These polymeric devices not only improve the drug bioavailability, but also decrease the side-effects. However, the polymers used must be biocompatible and most of these drug delivery systems have so far only been tested on animals. These systems should be introduced into the market for use by patients.

(b) The new tendency of research in ophthalmic drug delivery systems is also directed towards a combination of several drug delivery technologies. This combination of drug delivery systems could open a new directive for improving the therapeutic response of a non-efficacious system. These combinatorial drug delivery systems have a great potential for combining the advantages of different systems and overcoming their limitations. The various systems which have been suggested in the literature include the following.

- Use of polymer (Carbopol® 1342)-coated liposomes which increase both the residence time and the bioavailability of the entrapped drug (116,117).

- A combination of new drug dosage forms (prolonged residence time) with prodrugs (enhanced transcorneal penetration) as one of the best ways to improve bioavailability and tolerance (167).
- A suspension of bioadhesive microspheres made of chitosan as a promising means for topical administration of drug to the eye (40).
- Dispersion of liposomes into a thermosensitive gel made of a copolymer of ethylene oxide and propylene oxide (Poloxamer® 407). At high copolymer concentrations (20–30%) and from a temperature of approximately 20°C onwards, Poloxamer 407 passes from the sol to gel state. The system offers a new potential for the ocular delivery of drugs (199).
- Kaufman et al. (16) have developed a new drug delivery system, collasomes. They combine collagen pieces or particles and a viscous vehicle that can be instilled beneath the eyelid, thereby simplifying application and reducing the blurring of vision. Collasomes hydrated in a solution of sodium fluorescein and suspended in a methyl cellulose vehicle are used as a model for delivery of water-soluble drugs. The collasomes are well tolerated, and because the collagen particles are suspended in carrier vehicles, they can be instilled effectively by patients in much the same fashion as drops or ointments.
- Grammer et al. (200) investigated collagen corneal shields soaked with liposomal formulations. The liposomes remained intact in the course of uptake into and release from the shields. Since the release kinetics of liposome-encapsulated hydrophilic and lipophilic markers are similar to the release of a non-encapsulated drug, the combination may be useful with respect to encapsulation of drugs which do not penetrate the ocular surface, as well as to prolong the corneal contact time of the liposomes.
- Use of cyclodextrins as an alternative approach to increase the aqueous solubility of the drug without affecting the lipophilicity of the drug molecule. They act as true drug carriers by keeping the hydrophobic drug molecules in solution, and deliver them to the surface of the biological membrane.

A fruitful resolution of these technological suggestions can result in a superior dosage form for topical application. A primary consideration in the design and development of new and improved ocular drug formulation and delivery systems should be ease of use and comfort to the patient.

The future challenges faced by topical ocular drug delivery systems are as follows.

1. The ocular bioavailability must be increased from less than 1% to 15–20% of the administered dose.
2. Most of the currently marketed ocular drugs were initially developed for non-ocular applications, hence their low or non-specificity. So there is a need to develop new drug candidates primarily intended for ocular use.
3. Further studies to fully exploit the potential of non-corneal routes, especially for ionic/water-soluble moieties and also drug molecules with a preferential corneal absorption (and minimum absorption through nasal mucosa), should be explored.
4. Appropriate design and packaging of these delivery systems needs further research.

A careful study and implementation of the above-mentioned methods in the formulation of topical eye preparations can help in developing effective preparations. It is the need of the hour that the pharmacist delves into the problems faced by topical eye formulations and comes up with possible solutions to these problems.

REFERENCES

1. Prausnitz, M.R.; Noonan, J.S. J. Pharm. Sci. **1998**, *87*, 1479–1488.
2. Lee, V.H.L.; Robinson, J.R. J. Ocul. Pharmacol. **1986**, *2*, 67–108.
3. Chrai, S.S.; Makoid, M.C.; Eriksen, S.P.; Robinson, J.R. J. Pharm. Sci. **1974**, *63*, 333–338.
4. Ahmed, I.; Gokhlae, R.D.; Shali, M.V. J. Pharm. Sci. **1987**, *76*, 583–586.
5. Ashton, P.; Podder, S.K.; Lee, V.H.L. Pharm. Res. **1991**, *8*, 1166–1174.
6. Edwards, A.; Prausnitz, M.R. AIChE J. **1998**, *44*, 214–215.
7. Olsen, T.W.; Edelhauser, H.F.; Lim, J.I.; Geroski, D.H. Invest. Ophthalmol. Vis. Sci. **1995**, *36*, 1893–1903.
8. Romanelli, L.; Valeri, P.; Morrone, L.A.; Pimpinella, G.; Graziani, G.; Tita, B. Life Sci. **1994**, *54*, 877–885.
9. Desai, S.D.; Blanchard, J. In *Encyclopedia of Pharmaceutical Technology*; Swarbick, J., Boylan, J.C., Eds.; Marcel Dekker: New York, 1994; Vol. 11, 43–75.

10. Meseguer, G.; Gurny, R.; Buri, P. J. Drug Target. **1994**, *2*, 269–288.
11. Saettone, M.F.; Chetoni, P.; Cerbai, R.; Mazzanti, G.; Baghiroli, L. Int. J. Pharm. **1996**, *142*, 103–113.
12. Saettone, F.; Giannaccini, B.; Savigni, P.; Wirth, A. J. Pharm. Pharmacol. **1980**, *32*, 519–521.
13. Saettone, F.; Giannaccini, B.; Teneggi, A.; Savigni, P.; Tellini, N. J. Pharm. Pharmacol. **1982**, *34*, 464–466.
14. Kaufman, P.L.; LutjenDrecoll, E.; Hubbard, W.C.; Erickson, K.A. Ophthalmology **1994**, *101*, 1672.
15. Siegel, M.J.; Spiro, H.J.; Miller, J.A.; Siegel, L.I.; Southfield, M. Arch. Ophthalmol. **1991**, *109*, 1496.
16. Kaufman, H.E.; Steinemann, T.L.; Lehman, E.; Thompson, H.W.; Varnell, E.D.; Labarre, J. J. Ocul. Pharmacol. **1994**, *10*, 17–27.
17. Nadkarni, S.R.; Yalkowsky, S.H. Pharm. Res. **1993**, *10*, 109–112.
18. Johanson, S.; Pedersen, E.R.; Prause, J.U. Arch. Ophthalmol. Scand. **1996**, *74*, 253–258.
19. Patton, F.; Robinson, J.R. J. Pharm. Sci. **1998**, *64*, 1312–1316.
20. Meseguer, G. J. Ocul. Pharmacol. Ther. **1996**, *12*, 487–488.
21. Zaki, I.; Fitzgerald, P.; Hardy, J.G.; Wilson, C.G. J. Pharm. Pharmacol. **1986**, *38*, 463–466.
22. Green, K.; Downs, S. J. Pharm. Sci. **1975**, *68*, 1176–1178.
23. Saettone, M.F.; Giannaccini, B.; Ravecca, S.; LaMarca, F.; Tota, G. Int. J. Pharm. **1984**, *20*, 187–202.
24. Deshpande, A.A.; Heller, J.; Gurny, R. Crit. Rev. Ther. Drug Carrier Sys. **1998**, *15*, 381–420.
25. Saettone, M.F.; Chetoni, P.; Torracca, M.T.; Burgalassi, S.; Giannaccini, B. Int. J. Pharm. **1989**, *51*, 203–212.
26. Rozier, A.; Mazuel, C.; Grove, J.; Plazonnet, B. Int. J. Pharm. **1989**, *57*, 163–168.
27. Bottari, F.; DiColo, G.; Nannipieri, E.; Saettone, M.F.; Serafini, M.F. J. Pharm. Sci. **1974**, *63*, 1779–1783.
28. Hui, H.W.; Robinson, J.R. Int. J. Pharm. **1985**, *26*, 203–213.
29. Stevens, L.E.; Missel, P.J.; Lang, J.C. Anal. Chem. **1992**, *64*, 715–723.
30. Cohen, S.; Lobel, E.; Trevgoda, A.; Peled, Y. J. Contr. Rel. **1997**, *44*, 201–208.
31. Fridriksdottir, H.; Loftsson, T.; Stefansson, E. J. Contr. Rel. **1997**, *44*, 95–99.
32. Loftsson, V.; Fridriksdottir, H.; Thorisdottir, S.; Stefansson, E.; Siguroadottir, A.M.; Guomundsson, O.; Sigthorsson, T. Eur. J. Pharm. Sci. **1994**, *1*, 175–180.
33. Freedman, K.A.; Klein, J.W.; Crosson, C.E. Curr. Eye Res. **1993**, *12*, 641–647.
34. Suhonen, P.; Järvinen, T.; Lehmussaari, K.; Reunamaki, T.; Urtti, A. Pharm. Res. **1995**, *12*, 529.
35. Fromming, K.H.; Szejtli, J. In *Cyclodextrins in Pharmacy*; Kluwer Academic: Dordrecht, 1994.
36. Jansen, T.; Xhonneur, B.; Mesens, J.; Borgers, M. Lens Eye Tox. Res. **1990**, *7*, 459–468.
37. Reer, O.; Bock, T.K.; Muller, B.W. J. Pharm. Sci. **1994**, *83*, 1345–1349.
38. LeBourlais, C.; Acar, L.; Zia, H.; Sado, P.A.; Needham, T.; Leverge, R. Progr. Retin. Eye Res. **1998**, *17*, 33–58.
39. Sieg, J.W.; Robinson, J.R. J. Pharm. Sci. **1975**, *64*, 931–936.
40. Genta, I.; Conti, B.; Perugini, P.; Pavanetto, F.; Spadaro, A.; Puglisi, G. J. Pharm. Pharmacol. **1997**, *49*, 737–742.
41. Lenaerts, V.; Gurny, R. In *Bioadhesives Drug Delivery Systems*; CRC Press: Boca Raton, FL, 1990; 203–204.
42. Li, V.H.; Wood, R.W.; Kreuter, J.; Harmia, T.; Robinson, J.R. J. Microencaps. **1986**, *3*, 213–218.
43. Joshi, A. J. Ocul. Pharmacol. **1994**, *10*, 29–45.
44. Komatsu, A.; Ohashi, K.; Oba, H.; Kakehashi, T.; Mizushima, Y.; Shirasawa, E.; Horiuchi, M. Jpn. J. Ophthalmol. **1988**, *32*, 41–43.
45. Doe, E.A.; Campagna, J.A. J. Ocul. Pharmacol. Ther. **1998**, *14*, 1–4.
46. Norn, M.S. Acta Ophthalmol. **1972**, *50*, 206–209.
47. Gebhardt, B.M.; Kaufman, H.E. J. Ocul. Pharmacol. Ther. **1995**, *11*, 319–327.
48. Grzeskowiak, E.; Partyka, D. Farm. Pol. **1994**, *50*, 108–112.
49. Tang-Liu, D.D.S.; Lambert, J.; Blancaffor, S.; Gwon, A. J. Ocul. Pharmacol. Ther. **1995**, *11*, 57–63.
50. Lee, V.H.L. In *Ophthalmic Drug Delivery Systems*; Mitra, A.K., Ed.; Marcel Dekker: New York, 1993; 59–82.
51. Lee, V.H.L. In *Biopharmaceutics of Ocular Drug Delivery*; Edman, P., Ed.; CRC Press: Boca Raton, FL, 1993; 121–143.
52. Liaw, J.; Robinson, J.R. Int. J. Pharm. **1992**, *88*, 125–140.
53. Liaw, J.; Robinson, J.R. In *Ophthalmic Drug Delivery Systems*; Mitra, A.K., Ed.; Marcel Dekker: New York, 1993; 369–381.
54. Saettone, M.F.; Chetoni, P.; Cerbai, R.; Mazzanti, G. Proc. Int. Symp. Contr. Rel. Bioact. Mater. **1994**, *21*, 91–592.
55. Sasaki, H.; Igarashi, Y.; Nagano, T.; Yamamura, K.; Nishida, K.; Nakamura, J. J. Pharm. Pharmacol. **1995**, *47*, 17–21.
56. Sasaki, H.; Igarashi, Y.; Nagano, T.; Nishida, K.; Nakamura, J. Pharm. Res. **1995**, *12*, 1146–1150.
57. Marshall, W.S.; Klyce, S.D. J. Membr. Biol. **1983**, *73*, 275–282.
58. Lee, V.H.L. J. Contr. Rel. **1990**, *11*, 79–90.
59. Gadbey, R.E.; Green, K.; Hull, D.S. J. Pharm. Sci. **1979**, *68*, 1176–1178.
60. Mikkelson, T.J.; Chrai, S.S.; Robinson, J.R. J. Pharm. Sci. **1973**, *62*, 1942–1945.

61. Mitra, K. Passive and Facilitated Transport of Pilocarpine Across the Corneal Membrane of the Rabbit. Ph.D. Thesis, University of Kansas, Lawrence, KS, 1983.
62. Higaki, K.; Takeuchi, M.; Nakano, M. Int. J. Pharm. **1996**, *132*, 165–173.
63. Marsch, R.J.; Maurice, D.M. Exp. Eye Res. **1971**, *11*, 43–48.
64. Sasaki, H.; Nagano, T.; Yamamura, K.; Nishida, K.; Nakamura, J. J. Pharm. Pharmacol. **1995**, *47*, 703–707.
65. Chiou, G.C.Y.; Chuang, C. J. Pharm. Sci. **1989**, *78*, 815–818.
66. Sasaki, H.; Tei, C.; Yamamura, K.; Nishida, K.; Nakamura, J. J. Pharm. Pharmacol. **1994**, *46*, 871–875.
67. Morimoto, K.; Nakai, T.; Morisaka, K. J. Pharm. Pharmacol. **1987**, *39*, 124–126.
68. Tang-Liu, D.S.; Richman, J.B.; Weinkam, J.R.; Takruri, H. J. Pharm. Sci. **1994**, *83*, 85–90.
69. VanSantvliet, L.; Ludwig, A. Eur. J. Pharm. Biopharm. **1998**, *45*, 189–198.
70. Green, K. In *Biopharmaceutics of Ocular Drug Delivery*; Edman, P., Ed.; CRC Press: Boca Raton, FL, 1993; 43–49.
71. Pfister, R.R.; Burstein, N. Invest. Ophthalmol. **1976**, *15*, 246–259.
72. Hochman, J.; Artrusson, P. J. Contr. Rel. **1994**, *29*, 253–267.
73. Citi, S. J. Cell Biol. **1992**, *117*, 169–178.
74. Grass, G.M.; Robinson, J.R. J. Pharm. Sci. **1988**, *77*, 3–14.
75. Newton; Gebhardt, B.M.; Kaufman, H.E. Invest. Ophthalmol. Vis. Sci. **1988**, *29*, 208–215.
76. Green, K.; Chapman, J.M.; Cheeks, L. Jr.; Clayton, R.M.; Wilson, M.; Zehir, A. J. Toxicol.-Cut. Ocular Toxicol. **1987**, *2*, 89–107.
77. Grass, G.M.; Robinson, J.R. J. Pharm. Sci. **1984**, *73*, 1021–1027.
78. Ismail, M.; Chen, C.C.; Richman, J.B.; Andersen, J.S.; Tang-Liu, D.D.S. Pharm. Res. **1992**, *9*, 817–821.
79. Merkus, F.W.H.M.; Schipper, N.G.M.; Hermeus, W.A.J.J.; Remeiju, S.G.; Verhoef, J.C. J. Contr. Rel. **1993**, *24*, 201–208.
80. Rojanasakul, Y.; Liaw, J.; Robinson, J.R. Int. J. Pharm. **1990**, *66*, 131–142.
81. Richman, J.B.; Tang-Liu, D.D.S. J. Pharm. Sci. **1990**, *79*, 153–157.
82. Friedrich, S.W.; Cheng, Y.L.; Savelle, B.A. J. Ocul. Pharmacol. **1993**, *9*, 229–249.
83. Robinson, J.R.; Mlynek, G.M. Adv. Drug Del. Rev. **1995**, *16*, 45–50.
84. Park, K.; Robinson, J.R. Int. J. Pharm. **1984**, *19*, 107–127.
85. Smart, J.D.; Kellaway, I.W.; Worthington, H.E.C. J. Pharm. Pharmacol. **1984**, *36*, 295–299.
86. Kyyrönen, K.; Urtti, A. Invest. Ophthalmol. Vis. Sci. **1990**, *31*, 1827–1833.
87. Tous, S.S.; ElNasser, K.A. STP Pharma Sci. **1992**, *2*, 125–131.
88. Robinson, J.R. STP Pharma Sci. **1989**, *5*, 839–846.
89. Horven, I. Acta Ophthalmol. Copenh. **1993**, *71*, 165–168.
90. LeBourlais, C.; Chevanne, F.; Turlin, B.; Acar, L.; Zia, H.; Sado, P.A.; Needham, T.E.; Leverge, R.J. Microencaps. **1997**, *14*, 457–467.
91. Lehr, C.M.; Bouwstra, J.A.; Schach, E.H.; Junginger, H.E. Int. J. Pharm. **1992**, *78*, 43–48.
92. Henriksen, I.; Green, K.L.; Smart, J.D.; Smistad, G.; Karlsen, J. Int. J. Pharm. **1996**, *145*, 231–240.
93. He, P.; Davis, S.S.; Illum, L. Int. J. Pharm. **1998**, *166*, 75–88.
94. Thermes, F.; Grove, J.; Chastaing, G.; Rozier, A.; Soper, K.; Plazonnet, B. STP Pharma Sci. **1992**, *2*, 88–92.
95. Verschwen, E.; Van-Santvliet, L.; Ludwig, A. STP Pharma Sci. **1996**, *6*, 203–210.
96. Hoffman, A.; Chen, G.; Kaang, S.; Priebe, D.T. Proc. Int. Symp. Contr. Rel. Bioact. Mater. **1995**, *22*.
97. Ching, S.; Park, H.; Kelly, P.; Robinson, J.R. J. Pharm. Sci. **1985**, *74*, 399–405.
98. Miller, S.C.; Donovan, M.D. Int. J. Pharm. **1982**, *12*, 147–152.
99. Gurny, R.; Boye, T.H.; Ibrahim, H. J. Contr. Rel. **1985**, *2*, 353–361.
100. Deasy, P.B.; Quigley, K.J. Int. J. Pharm. **1991**, *73*, 117–123.
101. Edsman, K.; Carlfors, J.; Harju, K. Int. J. Pharm. **1996**, *137*, 233–241.
102. Edsman, K.; Carlfors, J.; Peterson, R. Eur. J. Pharm. Sci. **1997**, *6*, 105–112.
103. Carlfors, J.; Edsman, K.; Petersson, R.; Jornving, K. Eur. J. Pharm. Sci. **1998**, *6*, 113–119.
104. Kumar, S.; Haglund, B.O.; Himmelstein, K.J. J. Ocul. Pharmacol. **1994**, *10*, 47–56.
105. Oppenheim, R.C. In *Drug Delivery Systems Characteristics and Biomedical Applications*; Juliano, R.J., Ed.; Oxford University Press: New York, 1980; 177–188.
106. Meisner, D.; Mezei, M. Adv. Drug Del. Rev. **1995**, *16*, 75–93.
107. Smolin, G.; Okumoto, M.; Feiler, S.; Condon, D. Am. J. Ophthalmol. **1981**, *91*, 220–225.
108. Dharma, S.K.; Fishman, P.H.; Peyman, G.A. Acta Ophthalmol. **1986**, *64*, 298–301.
109. Schaeffer, E.; Krohn, D.L. Invest. Ophthalmol. Vis. Sci. **1982**, *22*, 220–227.
110. Shek, P.N.; Barber, R.F. Biochim. Biophys. Acta **1987**, *902*, 229–236.
111. AlMuhammed, J.; Ozer, A.Y.; Ercan, M.T.; Hincal, A.A. J. Microencaps. **1996**, *13*, 293–306.

112. ElGazayerly, O.N.; Hikal, A.H. Int. J. Pharm. **1997**, *158*, 121–127.
113. Milani, J.K.; Pleyer, U.; Dukes, A.; Chou, J.; Lutz, S.; Ruckert, D.; Schmidt, K.B.; Mondino, J. Ophthalmology **1993**, *100*, 890–896.
114. Lee, V.H.L.; Urrea, P.T.; Smith, R.E.; Schanzlin, D. J. Surv. Ophthalmol. **1985**, *29*, 335–348.
115. Taniguchi, K.; Yamamoto, Y.; Itakura, K.; Miichi, H.; Hayashi, S. J. Pharmacobiodynam. **1988**, *11*, 607–611.
116. Durrani, M.; Davies, N.M.; Thomas, M.; Kellaway, I.W. Int. J. Pharm. **1992**, *88*, 409–415.
117. Davies, N.M.; Farr, S.J.; Hadgraft, J.; Kellaway, I.W. Pharm. Res. **1992**, *9*, 1137–1144.
118. Pleyer, U.; Elkins, B.; Ruckert, D.; Lutz, S.; Grammer, J.; Chou, J.; Schmidt, K.H.; Mondino, B. J. Curr. Eye Res. **1994**, *13*, 177–181.
119. Vyas, S.P.; Mysore, N.; Jaitlely, V.; Venkatesan, N. Pharmazie **1998**, *53*, 466–469.
120. Kreuter, J. In *Bioadhesive Drug Delivery Systems*; Lenaerts, V., Gurny, R., Eds.; CRC Press: Boca Raton, FL, 1990; 203–212.
121. Fitzgerald, P.; Hadgraft, J.; Kreuter, J.; Wilson, C.G. Int. J. Pharm. **1987**, *40*, 81–84.
122. MarchalHeussler, L.; Sirbat, D.; Hoffman, M.; Maincent, P. Pharm. Res. **1993**, *10*, 386–390.
123. Zimmer, K.; Kreuter, J. Adv. Drug Del. Rev. **1995**, *16*, 61–73.
124. Das, S.K.; Tucker, I.G.; Hill, D.J.; Ganguly, N. Pharm. Res. **1995**, *12*, 534–540.
125. Alonso, M.J.; Calvo, P.; VilaJato, J.L.; Lopez, M.I.; Llorente, J.; Pastor, J.C. 1995. Increased Ocular Corneal Uptake of Drugs Using Poly-ε-caprolactone Nanocapsules and Nanoemulsions. In 22nd International Symposium on Controlled Release Bioactive Materials, July 30th–August 4th, 1995, Seattle, WA.
126. Calvo, P.; Thomas, C.; Alonso, M.J.; VilaJato, J.; Robinson, J.R. Int. J. Pharm. **1994**, *103*, 283–291.
127. MarchalHeussler, L.; Fessi, H.; Devissaguet, J.P.; Hoffman, M.; Maincent, P. STP Pharma Sci. **1992**, *2*, 98–104.
128. Zimmer, K.; Kreuter, J.; Robinson, J.R. J. Microencaps. **1991**, *8*, 497–504.
129. Reddy, K.; Bodor, N. Indian J. Pharm. Sci. **1993**, *55*, 163–167.
130. Karback, M.B.; Podos, S.M.; Haibin, T.S.; Madell, A.; Becker, B. Am. J. Ophthalmol. **1976**, *81*, 768–772.
131. Chien, S.; Schoenwald, R.D. Biopharm. Drug Dispos. **1986**, *7*, 453–462.
132. Bundgaard, H.; Buur, A.; Chand, S.; Lee, V.H.L. Int. J. Pharm. **1988**, *46*, 77–88.
133. Sasaki, H.; Igarashi, Y.; Nishida, K.; Nakamura, J. Int. J. Pharm. **1993**, *93*, 49–60.
134. Bundgaard, H.; Falch, E.; Larsen, C.; Mikkelsen, T. J. Pharm. Sci. **1986**, *75*, 36–43.
135. Järvinen, T.; Suhonen, P.; Auriola, S.; Vepsalainen, A.; Urtti, A.; Peura, P. Int. J. Pharm. **1992**, *79*, 233–242.
136. Chetoni, P.; Crotti, P.; Saettone, M.F. Int. J. Pharm. **1994**, *105*, 147–155.
137. ChengBennett, A.; Chan, M.F.; Chen, G.; Gac, T.; Garst, M.E.; Gluchowski, C.; Kaplan, L.J.; Protzman, C.E.; Woodward, D.F. Br. J. Ophthalmol. **1994**, *78*, 560–567.
138. Davis, S.S.; Tomlinson, E.; Wilson, C.G. Br. J. Pharmacol. **1978**, *64*, 444–445.
139. Kato, A.; Iwata, S. J. Pharmacobiodynam. **1988**, *11*, 115–120.
140. Kato, A.; Iwata, S. J. Pharmacobiodynam. **1988**, *11*, 181–185.
141. Kato, A.; Iwata, S. J. Pharmacobiodynam. **1988**, *11*, 330–334.
142. Bodor, N. Med. Res. Rev. **1984**, *4*, 449–469.
143. Jalil, R.U. Drug Dev. Ind. Pharm. **1990**, *16*, 2353–2355.
144. Hashizoe, M.; Ogura, Y.; Kimura, H.; Moritera, T.; Honda, Y.; Kyo, M.; Hyon, S.; Ikada, Y. Arch. Ophthalmol. **1994**, *112*, 1380–1384.
145. Kimura, H.; Ogura, Y.; Hashizoe, M.; Nishiwaki, H.; Honda, Y.; Ikada, Y. Invest. Ophthalmol. Vis. Sci. **1994**, *35*, 2815–2819.
146. Kunou, N.; Ogura, Y.; Hashiozoe, M.; Honda, Y.; Hyon, S.H.; Ikada, Y. J. Contr. Rel. **1995**, *37*, 143–150.
147. Sanborn, G.E.; Anand, R.; Torti, R.E.; Nightingale, S.D.; Cal, S.X.; Yates, B.; Ashton, P.; Smith, T. Arch. Ophthalmol. **1992**, *110*, 188–195.
148. ElShanaway, S. STP Pharma Sci. **1992**, *2*, 337–341.
149. Gurtler, F.; Gurny, R. Drug Dev. Ind. Pharm. **1995**, *21*, 1–18.
150. Urtti, A.; Justin, M.; Miinalainen, O. Int. J. Pharm. **1985**, *25*, 165–178.
151. Vasantha, R.; Seghal, P.K.; Rao, K.P. Int. J. Pharm. **1988**, *47*, 95–102.
152. Attia, M.A.; Kassein, M.; Safwat, A. Int. J. Pharm. **1988**, *47*, 21–30.
153. Urtti, A.; Salminen, L.; Miinalainen, O. Int. J. Pharm. **1985**, *23*, 147–161.
154. Daragour, S. Ocular Insert for the Fornix. U.S. Patent 5,147,647, 1992.
155. Saettone, M.F.; Salimen, L. Adv. Drug Del. Rev. **1995**, *16*, 95–106.
156. Urtti, A.; Rouhiainen, H.; Kaila, T.; Saano, V. Pharm. Res. **1994**, *11*, 1278–1282.
157. Kushnick, H.; Liebmann, J.M.; Ritch, R. Arch. Ophthalmol. **1996**, *114*, 1432.
158. Gurtler, F.; Kalsatos, V.; Boisrame, B.; Gurny, R. J. Contr. Rel. **1995**, *33*, 231–236.

159. Dimitriu, S.; Popa, M.; Vancea, D.; Costin, D. J. Bioact. Compat. Polym. **1988**, *3*, 370–383.
160. Bawa, R.; Dais, M.; Nandu, M.; Robinson, J.R. New Extended Release Ocular Drug Delivery System: Design, Characterization and Performance Testing of Minidisc Inserts. In Proceedings of International Symposium on Controlled Release of Bioactive Materials, Lincolnshire, IL, 1988; 106a–107b.
161. Greaves, G.L.; Oljenic, O.; Wilson, C.G. STP Pharma Sci. **1992**, *2*, 13–33.
162. Sasaki, H.; Tei, C.; Knishida, K.; Jnakamura, J. J. Contr. Rel. **1993**, *27*, 127–137.
163. Casini, M. In *Ophthalmic Drug Delivery*: *Biopharmaceutical*, *Technological and Clinical Aspects*; Fidia Research Series, 1987; Vol. 11.
164. Vairon, J.P.; Yean, L.; Meslard, J.C.; Subira, F.; Bunel, C. Immobilisation Reversible sur Polymeres et Liberation Controlee. Application aux Lentilles Corneennes Reservoirs de Medicaments. L'Actualite Chimique, Sept–Oct, 1992.
165. Maichuk, Y.F.; Erichev, V.P. Glaucoma **1981**, *3*, 239–242.
166. Baeyens, V.; Kaltsatos, V.; Boisrame, B.; Varesio, E.; Veuthey, J.L.; Fathi, M.; Balant, L.P.; Gexfabry, M.; Gurny, R. J. Contr. Rel. **1998**, *52*, 215–220.
167. Aiache, J.M.; ElMeski, S.; Beyssac, E. J. Biomater. Appl. **1997**, *11*, 329–348.
168. Roopa, K.U.; Singh, U.V.; Udupa, N. Indian J. Pharm. Sci. **1993**, *55*, 148–150.
169. Gurtler, F.; Gurny, R. Invest. Ophthalmique Bioadhesif. Eur. Patent Appl. 561.695-Al, 1993.
170. Saettone, M.F.; Torracca, M.T.; Pagano, A.; Giannaccini, B.; Rodriguez, L.; Cini, M. Int. J. Pharm. **1992**, *86*, 159–166.
171. Bloomfield, S.E.; Miyata, T.; Dunn, M.W.; Bueser, N.; Stenzel, K.H.; Rubin, A.L. Arch. Ophthalmol. Vis. Sci. **1978**, *34*, 2581–2587.
172. Punch, P.I.; Costa, N.D.; Edwards, M.E.; Wilcox, G.E. J. Vet. Pharmacol. Ther. **1987**, *10*, 37–42.
173. Poland, D.E.; Kaufman, H.E. J. Cataract Refract. Surg. **1988**, *14*, 489–491.
174. Kaufman, H.E. J. Cataract Refract. Surg. **1988**, *14*, 487–488.
175. Sintzel, M.B.; Bernatchez, S.F.; Tatabay, C.; Gurny, R. Eur. J. Pharm. Biopharm. **1996**, *42*, 358–374.
176. Sawusch, M.R.; O'Brien, T.P.; Dick, J.D.; Gottsch, J.D. Am. J. Ophthalmol. **1988**, *106*, 279–281.
177. Lee, B.L.; Matoba, A.Y.; Osato, M.S.; Robinson, N.M. Am. J. Ophthalmol. **1992**, *114*, 212–215.
178. Lawrenson, J.G.; Edgar, D.F.; Gudegeo, N.; Burns, J.M.; Geraint, M.; Barnard, N.A. Br. J. Ophthalmol. **1993**, *77*, 713–715.
179. Greaves, G.L.; Wilson, C.G. Adv. Drug Del. Rev. **1993**, *11*, 349–383.
180. Greaves, G.L.; Wilson, C.G.; Brimingham, A.T.; Richardson, M.C.; Bently, P.H. Br. J. Clin. Pharmac. **1992**, *33*, 603–609.
181. Bentley, P.H. A New Ophthalmic Delivery System (NODS). In Proceedings of 9th Pharmaceutical Technology Conference, Vendhoven, Holland, 1990; Abstract Vol. 2, 7.
182. Kelly, J.A.; Molyneux, P.D.; Smith, S.A.; Smith, S.E. Br. J. Ophthalmol. **1989**, *73*, 360–362.
183. Diestelhorst, M.; Krieglstein, G.K. Int. Ophthalmol. **1994**, *18*, 1–4.
184. Alani, S.D.; Hammerstein, W. Graefes. Arch. Clin. Exp. Ophthalmol. **1990**, *228*, 302–304.
185. Gwon, A.; Borrmann, L.R.; Dyzman, E.; Robins, D.S.; Shen, D. Ophthalmology **1986**, *93*, 82–85.
186. Eller, M.G.; Schoenwald, R.D.; Dixson, J.A.; Segarra, T.; Barknecht, C.F. J. Pharm. Sci. **1985**, *74*, 525–549.
187. Putnam, M.L.; Schoenwald, R.D.; Duffel, M.W.; Barknecht, C.F.; Segarra, T.M.; Campbell, D.A. Invest. Ophthalmol. Vis. Sci. **1987**, *28*, 1373–1382.
188. Maren, T.H.; BarIlan, A.; Caster, K.C.; Katritzky, A.R. J. Pharm. Exp. Ther. **1987**, *241*, 56–63.
189. Wilson, C.G.; Olejnik, O.; Hardy, J.G. J. Pharm. Pharmacol. **1983**, *35*, 451–454.
190. Ludwing, A.; Ooteghem, M.V. Acta Helv. **1986**, *61*, 236–240.
191. Ludwing, A.; Ooteghem, M.V. Int. J. Pharm. **1989**, *54*, 95–102.
192. Maus, T.L.; Larsson, L.; McLaren, J.W.; Brubaker, R.F. Arch. Ophthalmol. **1997**, *115*, 45–49.
193. Brubaker, R.F. In *Duane's Clinical Ophthalmology*; Tasman, W., Jaeger, E.A., Eds.; Lippincott, Philadelphia 1990; Vol. 3, 1–11.
194. Bernatchez, S.F.; Merkli, A.; Minh, T.L.; Tabatabay, C.; Anderson, J.M.; Gurny, R. J. Biomed. Mater. Res. **1994**, *28*, 1037–1046.
195. Zignani, M.; Bernatchez, S.F.; Minh, T.L.; Tabatabay, C.; Gurny, R. Biomed. Mater. Res. **1997**, *31*, 641–648.
196. Jampel, H.D.; Thibault, D.; Leong, K.W.; Uppal, P.; Quigley, H.A. Invest. Ophthalmol. Vis. Sci. **1993**, *34*, 3076–3083.
197. Uppal, P.; Jampel, H.D.; Quigley, H.A.; Leong, K.W. J. Ocular Pharmacol. **1994**, *10*, 471–473.
198. Ness, R.A. Microporous Ocular Device. U.S. Patent 3,828,777, 1974.
199. Bochot, A.; Fattal, E.; Grossiord, J.L.; Puisieux, F.; Cauvreur, P. Int. J. Pharm. **1998**, *162*, 119–127.
200. Grammer, J.B.; Kortüm, F.A.; Wolburg, H.; Lüdtke, R.; Schmidt, K.H.; Thiel, H.J.; Pleyer, U. Curr. Eye Res. **1996**, *15*, 815–823.