CHAPTER I

INTRODUCTION

Most ocular diseases are treated with topical application of solutions administered as eye drops. These conventional dosage forms account for nearly 90% of the currently accessible marketed formulations. They are somewhat primitive and apart from solutions include suspensions, emulsions, ointments and gels. The practical reasons for selecting solutions are the generally favorable cost advantage, the greater simplicity of formulation development and production and acceptance by patients, despite a little blurring of vision (Fitzgerald and Wilson, 1994).

The conventional dosage forms are no longer sufficient to fulfill the present day requirements of providing a constant rate delivery for a prolonged time. The time course of drug released in the eye from a conventional dosage form allows a pulsed entry, resulting in a series of peaks and valleys in drug concentrations. These are most likely to represent periods of over and under dosing of varying lengths of time. The other problem encountered with the topical delivery of ophthalmic drugs is the rapid pre-corneal loss caused by drainage and tear turnover. After instillation of an eye drop, typically less than 5% of the applied drug penetrated the cornea and reaches the intraocular tissues, while a major fraction of the dose is often absorbed systemically via the conjunctiva and the nasolacrimal duct (Lang, 1995).

The advantages and disadvantages of conventional dosage forms are summarized below:

<table>
<thead>
<tr>
<th>Dosage Form</th>
<th>Advantages</th>
<th>Disadvantages</th>
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</thead>
<tbody>
<tr>
<td>Solutions</td>
<td>Convenient</td>
<td>Rapid pre-corneal elimination, loss of drug by drainage, no sustained action</td>
</tr>
<tr>
<td>Suspensions</td>
<td>Patient compliance, best for drugs with slow dissolution</td>
<td>Drug property decides performance. Rapid pre-corneal elimination</td>
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</table>
### Emulsions

- Prolonged release of drug from vehicle
- Patient non compliance, blurred vision, and possible oil entrapment

### Ointment

- Flexibility in drug choice, improved drug stability, increased tissue contact time, inhibition of dilution by tears, resistance to nasolacrimal drainage
- Sticking of eyelids, poor patient compliance, blurred vision, no true sustained effect, drug choice limited by partition coefficient

### Gels

- Comfortable. Less blurred vision than ointment
- No rate control on diffusion, matted eye-lids after use

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**1.1 CONTROLLED OCULAR DELIVERY SYSTEMS**

Frequent local instillations of ophthalmic drugs provide an unusually high drug and preservative concentration at epithelial surface. Consequently, ocular conditions are aggravated by over treatment. Repeated applications can cause biochemical and mechanical injuries as well as sensitivity reactions resulting in blephroconjunctivitis.

The need to reduce the local and systemic side effects and improvements in ocular bioavailability necessarily requires the use of controlled ocular delivery.

**1.1.1. Requisites of Controlled Ocular Delivery Systems**

- To provide sustained and controlled delivery.
- To increase the ocular bioavailability of drugs by increasing corneal contact time.
- To provide targeting within the ocular globe.
- To circumvent the protective barriers, drainage, lacrimation and diversion of exogenous chemicals into systemic circulation by conjunctiva.
• To provide comfort and compliance to the patient and yet improve the therapeutic performance of the drug over conventional systems.
• To overcome the side effects of pulsed dosing produced by the conventional systems.

The major approaches being undertaken to improve topical delivery of drugs (Lee, 1990) are:

1. Approaches to prolong the contact time of drug with corneal surface vehicle approach.
2. Approaches to enhance corneal permeability either by mild or transient structural alteration of corneal epithelium- enhancer approach.
3. Approaches to modify the chemical structure of the drug molecules to enhance their permeation characteristics pro-drug approach.

Some of the ophthalmic formulation trends that are being explored include

1. Polymeric solutions
   i. Non mucoadhesive viscosity enhancing polymers
   ii. Bioadhesive /mucoadhesive polymers
   iii. Phase transitions (or) in-situ gelling systems
   iv. Pseudolatices

2. Colloidal systems
   i. Liposomes
   ii. Nanoparticles
   iii. Niosomes
   iv. Pharmacosomes

3. Ocular inserts (Soluble and Insoluble)
4. Scleral/vitreal implants
5. Ocular penetration enhancers
6. Miscellaneous
The phase transition (or) *in-situ* gelling systems, ocular inserts and scleral/vitreal implants are dealt elsewhere under appropriate chapters.

1.1.2 Polymeric Solutions

1.1.2.1. Non mucoadhesive viscosity enhancing polymers

A popular approach is to incorporate soluble polymers into and aqueous solution to increase vehicle viscosity, thereby prolonging drug contact with the cornea (Chrai and Robinson, 1974; Lee, 1985; Ludwig Van Ooteghem, 1988 and Pergande, 1985). Typically, these polymers are high molecular weight molecules (5000-10000 Daltons) which cannot cross biological membranes and include various cellulosic polymers, polyvinyl alcohol, polyacrylic acid hydrogels, and hyaluronic acid, poloxamer and polysaccharide components. Drugs of various solubilities such as pilocarpine, tropicamide, betaxolol, timolol, prednisolone, fluorometholone, progesterone, indomethacin etc, have been incorporated into these gels.

Patton and Robinson (1975) reported that an increase in the corneal penetration of an ophthalmic drug would be maximum at a viscosity of about 15 to 150 CP, and further viscosity increase produce less effect on drainage rate and tear film thickness and are often associated with interference with vision and resistance to eyelid movements.

1.1.2.2 Non Mucoadhesive polymers

A. Cellulosic Polymers

Cellulosic polymers are widely used as Newtonian viscolyzers into ophthalmic preparations.

Mainly used polymers are;

- Methyl Cellulose (MC)
- Hydroxy Ethyl Cellulose (HEC)
- Hypromellose (HPMC)
- Hydroxy Propyl Cellulose (HPC)
These Derivatives have common properties:

They present a wide range of viscosity (400 to 15,000 cP).

They are compatible with many topically applied drugs.

They can be easily sterilized by heat (120°C).

They increase the stability of the lacrimal film.

They are topically well tolerated.

B. Poly Vinyl Alcohol (PVA)

PVA was introduced into ophthalmic preparations in the early 1960s and was reported to have a superior corneal contact time as a Newtonian polymer solution based on animal studies. PVA can lower the surface tension of water, reduce interfacial tension at an oil/water interface and enhance tear film stability. This film forming property together with the properties cited for cellulosic polymers has led to the widespread use of PVA as a drug delivery vehicle and artificial tear preparation (Benedetto et al., 1975).

C. Poly Vinyl Pyrrolidone (PVP)

Podder et al. (1992) demonstrated that isoviscous 0.75% HPC, 3.75% PVA, 6% PVP and 2.5% Hyaluronic Acid (HA) all reduced the systemic absorptions of timolol, but not to the same extent, PVP, which was most effective in enhancing ocular timolol absorption, was also most effective in reducing systemic absorption. There was an approximately two-fold difference between PVP and the other three polymers. Conceivable, spreading of the drained dose may also be influenced by the chemical nature of the polymer independently of viscosity, thus explaining the difference in effectiveness in reducing systemic timolol absorption among the polymers. Newtonian polymers studied for over 20 years led to contradictory reports. For the same viscosity, results seemed to depend finally on the nature of the polymer. The comparison between the polymers does not reveal always the same rank order.
1.1.2.3. Bioadhesive/Mucoadhesive Polymers

Any polymer solution/suspension placed in the eye first encounters mucin at the cornea and conjunctiva surface. If the polymer adheres to mucin, the interaction is referred to as mucoadhesion.

Bioadhesive/mucoadhesive systems can generally be either polymeric solution or microparticulate suspensions (Gurney et al., 1985). They are retained in the cul-de-sac through adhesive bonds established with the mucin or the epithelium, thus increasing the corneal contact time.

Based on the results of numerous studies Robinson concluded that poly anions were better than poly cations, for both bioadhesiveness and toxicity reasons.

A. Hyaluronic Acid

The sodium salt of hyaluronic acid (SAH) is a high molecular weight biological polymer present in the extracellular matrix.

In the eye SHA is present in the vitreous body and in lower concentrations, in the aqueous humor. It is non-immunogenic and is composed of repeating disaccharide units of glucuronic acid and N-acetyl glucosamine.

Ludwig and Van Ooteghem (1992) found that a 0.25% SHA solution increased the pre-corneal residence time of fluorescein in humans. Snibson et al. (1990) demonstrated through γ scintigraphic studies that the residence times of 0.2 % and 0.3% of SHA solutions on the cornea were significantly longer for patients having dry eye syndrome than in healthy subjects. This was due to alteration of tear mucin in dry eyes, which might have modified the interaction of SHA with the ocular surface.

SHA has been proposed as vehicle of choice in tear substitutes because it offers protection against damages caused by benzalkonium chloride, which is frequently used as a preservative in ocular formulations (Wysenbeek et al., 1988). The ability of SHA to prolong drug release by increasing pre-corneal drug residence time has been studied in animals for several ophthalmic drugs such as pilocarpine, timolol etc. (Camber et al., 1987). Residence time of gentamicin in humans was found to be 2.23 fold more when a
0.25% w/v solution of SHA formulation was instilled, than in an isotonic phosphate buffer solution (Bernatcherz et al. 1993).

Other uses of SHA in ophthalmic therapy include a) protecting corneal endothelial cells during intraocular surgery b) replacing vitreous humor c) during cataract surgery to maintain the shape of the anterior chamber.

B. Polyacrylic Acid Hydrogels

Polyacrylic acids or Carbopol resins are acrylic acids based on polymers which are available in a range of molecular weights and may either be linear, branched or cross-linked. Polyacrylic acids are one of the most pseudoelastic polymers with important bioadhesive properties.

Davies et al (1991) evaluated the pre-corneal clearance of pilocarpine (1%) in Carbopol 934P solution compared to that of an equi-viscous non-mucoadhesive PVA solution and buffer (phosphate buffered saline-PBS) in the rabbit. They observed that the pre-corneal retention of the Carbopol solution was significantly greater than that of the PVA solution, which in turn was significantly greater than that of PBS. Comparable experiments have been carried out by Saettone et al. (1982, 1989) with pilocarpine in the rabbit eye. The polyacrylic acid gel (5% w/v Carbopol 941) formed a stable pre-corneal film for up to 2 hours post instillation. A repeat of the study using the less soluble drug tropicamide increased the duration of the effect more significantly compared to a pilocarpine solution.

Weinreb and Jani (1992) evaluated the ocular bioavailability of 0.25% betaxolol suspension based on polyacrylic acid (viscosity 100 to 150 cP s) in comparison with a 0.5% betaxolol solution in rabbits. The results suggested that the suspension provided a more constant release of betaxolol than the solution.

Thermes et al. (1992) evaluated the ocular bioavailability of 0.5% timolol (Timoptol®) in rabbits compared to 0.5% timolol in isoviscous solutions of PVA, polyacrylic acid and timolol-polyacrylic acid salt (PAA salt). The results indicated that the bioadhesive PAA polymers produced lower ocular concentrations than those of PVA and the concentration versus time profile was flatter. This could be consistent with the slower
release of timolol from PAA and the longer retention of the vehicle in the conjunctival sac by mucoadhesion.

Further the efficacy of carbopol in enhancing pre-corneal residence time has been extensively studied by incorporating tracers such as sodium fluorescein (Ludwig et al., 1990), or active compounds such as pilocarpine (Deshpande and Satish, 1989), or prednisolone (Allen, 1984).

In ocular formulations, carbopol presents the following advantages (Liu et al., 1989):

- Generally more comfortable than soluble and insoluble inserts.
- Instilled like ointments
- Less blurred vision as compared to ointments

And some disadvantages like;

- No rate control on drug instability, e.g. pilocarpine
- Matted lids in the morning
- No true sustaining effect unless dissolution control

Carbopol is also used to stabilize the tear film, and to protect the corneal epithelium with a prolonged action allowing a stable artificial pre-corneal film.

**B.1 Polycarbophil**

Polycarbophil is a water insoluble cross-linked polyacrylic acid polymer which swells and incorporates large quantities of water. Gurny et al. (1985) has described polycarbophil as very sensitive to pH and electrolyte and hence a number of possible approaches wherein a low viscosity polycarbophil solution, when placed in the eye rapidly thickened to trap drug particles.

Middleton and Robinson (1991) used a slightly different approach to deliver the steroid fluorometholone to the eye using combination of *in-situ* viscosity increase and mucoadhesion. They found that a hypnotic, slightly acidic polycarbophil vehicle could be administered as drop but would gel in the pre-corneal pocket. The formulation allowed the
normal does of 0.1 % fluorometholone steroid suspension to be decreased by half while maintaining aqueous humor drug levels above the therapeutic minimum for 8 hours in rabbits.

C. Chitosan and other polysaccharides

Chitosan is a polycationic biopolymer obtained by the alkaline deacetylation of chitin. It is a bioadhesive vehicle suitable for ophthalmic formulations due to its favorable biodegradability, non-toxicity and biocompatibility. In fact, due to its positive charge 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 (Lehr et al., 1992; Henriksen et al., 1996; He et al., 1998). A suspension of bioadhesive microspheres made of chitosan seems a promising means of topical administration of acyclovir to the eye (Genata et al., 1997).

Recently xanthan and carrageen have been described as bioadhesive polysaccharides showing sustained release properties and adequate ocular compatibility (Thermes et al., 1992; Verschwen et al., 1996).

1.1.2.4 Pseudolatices

There are a new class of polymeric colloidal dispersion and film forming agent used for topical applications in animals and human beings used for sustaining the drug activity in-vivo (Vyas et al. 1992). Organic solution of polymers is dispersed in as aqueous phase to form an o/w type emulsion. Water is removed partially to an extent and the residual water is sufficient enough to keep the polymeric phase dispersed. Such dispersions are called pseudolatices, which on application leave an intact non-invasive continuous polymer film which releases drug(s). The drug from such systems is released slowly over a period of time ensuring better ocular bioavailability and patient compliance by avoiding frequent instillation of preparations.

1.1.3 Colloidal Systems

The various colloidal systems used for ocular delivery are liposomes, nanoparticles, niosomes, pharmacosomes and discomes. These systems clearly have some distinct advantages, which could be enumerated as
• These colloidal carriers are biocompatible and have minimum side effects.
• Degradation products formed after the release of drugs are biocompatible.
• Provide patient compliance, as there is no difficulty of administration as observed in the case of inserts.
• Prevent metabolism of drugs from the enzymes present at tear/corneal epithelium interface.
• No tissue irritation and damage as caused by penetration enhancers.
• Provide a prolonged and sustained release of drug.

1.1.3.1. Liposomes

Liposomes are vesicles made of phospholipid layers limiting concentric aqueous cavities. Depending on the phospholipids’ nature and the method of preparation used, liposomes are classified as MLV (Multilamellar Vesicles), LUV (Large Unilamellar Vesicles) and SUV (Small Unilamellar Vesicles) (Puisieux and Delattre, 1985; Puisieux and Truepel, 1989). The size of the vesicles range from 10 nm for SUV to 10µm for MLV. The external surface can be positively charged, negatively charged or neutral.

The structural diversity of liposomes in terms of size, composition, surface charge, bilayer fluidity and ability to incorporate almost any drug regardless of solubility or to carry on their surface, cell specific ligands have been used for the production of formulation that are optimal for clinical use.

Liposomes can enhance or reduce the ocular absorption of encapsulated agents applied to the eye. The nature and extent of altered ocular uptake of liposome associated agents appear to depend on a number of factors like physico-chemical properties of the entrapped agent, chemical composition and physical characteristic of liposomes used and method of ocular administration of the liposomal formulations.

Liposomes have gained considerable attention for ocular drug delivery. They have been primarily investigated as a modality to enhance corneal drug absorption. This is achieved through their ability to come in intimate contact with the corneal and conjunctival surfaces, thereby increasing the probability of drug absorption.

Smolin et al. (1981) first showed that liposome-associated idoxuridine is superior to the solution form of the drug in the treatment of herpes simplex dermatitis in rabbits.
Idoxuridine liposomes were shown to promote the corneal permeation of drug (Dharma et al., 1986). Different liposomal formulations of atropine and atropine sulfate were studied. It was found that atropine entrapped in multilamellar lipid vesicles with positive surface charge displayed the most prolonged effect; whereas, preparations containing atropine sulfate were shorter acting than atropine (Meisner et al., 1989). The influence of mucoadhesive polymers on the in-vitro release and in-vivo ocular bioavailability of pilocarpine nitrate entrapped in liposomes was studied (Durrani et al., 1992). 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 choridities (Al-Muhammed et al., 1996).

Neutral positively charged and negatively charged liposomes of acetazolamide were evaluated for their entrapment efficiency, drug release and in-vivo activity (El-Gazayerly and Hikal, 1997). The percent entrapment efficiency and the proportion of drug released were higher for positively charged and neutral liposomes, respectively. A good correlation existed between the percent inhibition of carbonic anhydrase activity and the amount of drug released from the liposomes.

Acyclovir containing liposome systems were developed for ocular delivery (Law and Hung, 1998). It was found that the charge characteristics of liposomes greatly influenced the drug release rate and the loading efficiency. The positively charged liposomes showed a faster release rate at a higher molar ratio of charge-inducing agents, whereas the negatively charged liposomes demonstrated a slower release rate at a higher molar ratio of charge-inducing agents. The positively charged liposomes showed a lower release rate than the negatively charged liposomes. The in-vitro corneal penetration and in-vivo corneal absorption of acyclovir demonstrated that the positively charged liposomes resulted in a penetration rate lower than the negatively charged liposomes and free acyclovir in solution (Law et al., 2000). An in-vivo study indicated that the extent of acyclovir absorption from the positively charged liposomes was higher than that from the negatively charged liposomes and free acyclovir. The deposition of acyclovir in the cornea was higher from the positively charged liposomes and it was suggested that the positively
charged liposomes formed a completely coated layer on the corneal surface, resulting in an increase of acyclovir absorption.

A four-fold increase in the passage of penicillin G across rabbit cornea and ten-fold enhancement of indoxole passage across rat cornea was observed when liposomal formulations were compared with solutions of the respective compounds (Shaffer and Krohn, 1982). Several other reports (Tanaguchi, et al., 1985; Nagersenkar et al., 1999) suggested that incorporation of positive charge on the surface of liposome can prolong the pre-corneal retention time and enhance ocular bioavailability.

The effectiveness of liposomes in ocular drug delivery has been shown to depend on numerous factors but mainly on the liposomal surface charge, a property that has been reported as a major determinant on the pre-corneal vesicle retention (Fitzgerald et al., 1987; Guo et al., 1989). A common conclusion from the various studies is that positively charged liposomes increase the corneal penetration of drugs when compared to neutral or negatively charged liposomes. This behavior was attributed to the mucoadhesion mediated electrostatic interaction between the positive liposomes and negatively charged mucin.

1.1.3.2. Nanoparticles

Despite the potential value of the liposomes, there are some limitations to their use as ocular drug carriers, the most important being their instability and their limited loading capacity. Hence, as an alternative, the biodegradable polymeric nanoparticles and nanocapsules have been proposed as ocular delivery systems.

Nanocapsules are polymeric colloidal systems ranging in size from 10 to 1000 nm. They are classified into two groups: nanospheres and nanocapsules.

Nanospheres are small solid matrical spheres constituted of a dense solid polymeric network, developing a large specific area (Rollot et al., 1986). The drug can be either incorporated or be adsorbed on to the surface.

Nanocapsules are small capsules formed of a central cavity (oil droplet) surround by a polymeric membrane (Le Bouralaie et al., 1995).

The first studies concerned systems constituted of pilocarpine loaded nanospheres of poly (methyl methacrylate –acrylic acid) co-polymer (Piloplex®). In clinical trials, Piloplex® lowered the intraocular pressure.
It has been shown that polyalkyl cyanoacrylate (PACA) and poly-ε-Caprolactone (PECL) nanoparticles have the ability to improve the corneal penetration of hydrophilic, lipophilic drugs and as well as some macromolecules like metipranolol (Losa et al., 1993); indomethacin (Calvo et al., 1996a, b) and cyclosporine A (Calvo et al., 1996c).

Losa et al., (1991) evaluated amikacin sulfate suspensions associated to polybutyl cyanoacrylate and reported that all drug molecules, which are deabsorbed from the nanospheres diffuse quickly enough across the cornea more easily than free molecules, which remain in the lacrimal fluid. These results agreed with the conclusion of Marchal-Heussler et al. (1990) who had demonstrated that the superficial charged and the binding type of the drug onto nanospheres were the most important factors regarding the improvement of the therapeutic response of Betaxolol chloride. In another study Marchal-Heussler et al., (1992) used nanospheres or nanocapsules to increase the ocular absorption of betaxolol. Three polymers were tested namely polyisobutyl cyanoacrylate, a copolymer of lactic and glycolic acid and PECL. The decrease in intraocular pressure were much more pronounced with the colloidal carriers made of PECL than with the carriers prepared with the other polymers as well as the commercial eye drops.

PECL nanocapsules of indomethacin coated with chitosan (CS) and poly-L-Lysine (PLL) were designed based on a strategy that combines the features of PECL nanocapsules as ocular carriers with the advantage of a cationic mucoadhesive coating (Calvo et al., 1997). The CS and PLL coatings conferred a higher positive surface charged to the nanocapsules. Nevertheless, they did not modify the release profile of indomethacin from the colloidal system. The CS coating showed a two-fold increase in the ocular bioavailability, while the PLL coating failed to increase the ocular bioavailability of indomethacin when compared to the uncoated particles. It was concluded that the specific nature of CS, rather than the positive charge, was responsible for the enhanced uptake of the CS-coated nanocapsules.

Nanoparticle colloidal systems of flurbiprofen and diflunisal were investigated (Pignatello et al., 2001 and 2002) using acrylate polymers (Eudragits). Sodium ibuprofen loaded polymeric nanoparticle suspensions were made with Eudragit RS polymer with the aim of improving the availability of ibuprofen (Pignatello et al., 2002). The release studies indicated a controlled release profile of ibuprofen from the nanoparticles. The in-vivo efficacy was assessed on the rabbit eye after induction of an ocular trauma (paracentesis).
An inhibition of the miotic response to the surgical trauma was achieved, comparable to a control aqueous eye-drop formulation, even though a lower concentration of free drug in the conjunctival sac was reached from the nanoparticle system. The ocular bioavailability of piroxicam in rabbits was enhanced when the drug was delivered by means of albumin microspheres (Giunchedi et al., 2000). Lipid microspheres of hydrocortisone have been reported to deliver the drug to the anterior ocular tissues more significantly than ophthalmic suspensions (Komatsu et al., 1998).

1.1.3.3 Niosomes

In order to circumvent the limitations of liposomes, vesicle formation by some membrane 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 a promising system for the controlled ocular administration of water soluble drugs (Vyas et al., 1998). Discomes 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 may provide for a better fit in the cul-de-sac of the eye.

1.1.3.4 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, NH₂) can be esterified (with or without a spacer group) to the hydroxyl group of 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 (Kaur and Kanwar, 2000).

1.1.4 Penetration Enhancers

The transport characteristics across the cornea can be maximized by increasing the permeability of the corneal epithelial membrane (Lee, 1993a, 1993b; Liaw and Robinson,
The stratified corneal epithelial cell layer is “tight” ion transporting tissue because of the high resistance of 12-16 kΩ cm² being exhibited by the paracellular pathway (Marshall and Klyce, 1983). So one of the approaches used to improve ophthalmic drug bioavailability lies in increasing transiently the permeability characteristics of the cornea with permeation 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 (Lee, 1990). Inclusion of cetylpyridinium chloride (Gadbey et al., 1979; Mikkelson et al., 1973), lasalocid (Mitra, 1983), benzalkonium chloride (BAC) (Higaki et al., 1996); Marsch and Maurice, 1971; Sasaki et al., 1995c), Tween 20 (Chiou and Chuang, 1989), parabens (Sasaki et al. 1994 and 1995b), Brij® 35, Brij® 78, Brij® 98, ethylene diamine tetra acetic acid (EDTA) (Saettone et al., 1996), bile salts (Morimoto et al., 1987) and bile acids (sodium cholate, sodium taurocholate, sodium glycodeoxycholate, sodium taurodeoxycholate, taurocholic acid, chenodeoxycholic acid chenodeoxycholic acid and ursodeoxycholic acid), capric acid (Sasaki et al. 1995b), azone, fusidic acid, hexamethylene lauramide, saponis (Sasaki et al. 1995b), hemamethylene octanamide and decylmethyl sulfoxide (Tang- Liu et al., 1994) 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 (Van-Santvliet and Ludwig, 1998). The afore-mentioned agents belong to the general class of surfactants. Because of their hydrophilic/lipophilic character the surfactants are absorbed by 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 concentrations 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 acid and salts act by changing the rheological properties of biological membranes. Owing to their mucolytic properties they can increase diffusion through the membrane by inducting a transient change in its structure and permeability.

Some preservatives significantly increase the corneal permeability of ophthalmic drugs (Lee and Robinson, 1986; Green, 1993). Amongst the currently used preservatives, BAC shows the highest promoting effect on corneal drug penetration. The use of BCA
(0.01%) causes cells of the corneal epithelium to peel at their borders (Pfister and Burstein, 1976), and also enlarges the intercellular spaces in superficial cells of the cornea.

Another class of permeation enhancers is calcium chelators like EDTA, which act by loosening the tight junctions between the superficial epithelial cells, thus facilitating paracellular transport (Hochman and Artrusson, 1994; Saettone et al 1996). Grass and Robinson (1998) were among the first to emphasize the positive effect of chelating agents on corneal drug absorption. Newton et al. (1988) reported that azone, a transdermal absorption promoter, increased the ocular delivery of instilled cyclosporine and enhanced its immune suppression activity. The effect of azone on a series of structurally unrelated drugs, ranging from hydrophilic to lipophilic character, was studied. Azone enhanced the transcorneal penetration of hydrophilic drugs, but retarded the apparent drug permeation across the cornea for lipophilic drugs (Tang-Liu at al, 1994).

The major risk associated with the use of permeation enhancers is that they themselves can penetrate the eye and may therefore lead to unknown toxicological complications. BAC was found to accumulate in the cornea for days (Green et al., 1987). 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 (Grass and Robinson, 1984). Repeated application of 0.5% EDTA was observed to significantly alter the corneal epithelial architecture, even though a single application was tolerated (Lee and Robinson, 1986). Azone at 0.3% concentration or higher is irritating, discomforting and toxic to the eyes (Ismail et al., 1992). Saponins cause eye irritation when used at 0.5% level (Chiou and Chuang, 1989). Bile salts and surfactant cause irritation of the eye and nasal mucosa (Green, 1993; Merkus et al., 1993), Rojanasakul et al. (1990) used laser scanning confocal microscopy and electro-physiological 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.

1.1.5. Miscellaneous

1.1.5.1 The Cyclodextrins

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 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 (Fridriksdottir et al., 1997; Loftsson et al., 1994). 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 cyclodextrin decreased bioavailability (Freedman et al., 1993; Suhonen, et al., 1995).

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 (Fromming and Szejtli, 1994). Jansen et al., (1990) found that dimethyl β-cyclodextrin is toxic to the corneal epithelium and thus should not be used for corneal ophthalmic formulations. (Reer et al.1994) have shown that 2 hydroxy propyl-β-cyclodextrin possesses the most favorable toxicological properties.

1.1.5.2. Ophthalmic Sprays

An alternative delivery of pilocarpine (4% solution) via a spray (single application) to closed eye lids was found to be an effective delivery method for intraocular miosis (Doe and Campagna, 1998).

1.1.5.3 Chemical Delivery Systems

A chemical delivery system (CDS) is an inactive species obtained by chemical modification of the active agent based on metabolic considerations. Conceptually, a CDS upon its administration will undergo several predictable enzymatic transformations via inactive intermediates and finely deliver the active species to the target site (Reddy and Bodor, 1993). 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® (Karback et al., 1976). Other drugs with increased penetrability through prodrug formation are phenylephrine (Chien and Scoenwald, 1986), timolol (Bundgaard, et al., 1988), Tilisolol (Sasaki et al., 1993), pilocarpine (Bundgaard et al., 1986; Jarvine et al., 1992), albuterol (Chetoni et al., 1994), idoxuridine etc. Prostaglandin F₂α ester prodrugs have been reported to have better aqueous stability than prostaglandin.

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 compound. The use of ion pair formation to promote corneal drug absorption has also been reported (Davis et al., 1978; Kato and Iwata, 1988a, b, c). These investigations found that extent of drug ionization 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 to drug design. A soft drug, by definition, is a biologically active compound characterized by predictable and controllable in-vivo destruction (metabolism) to non toxic metabolites (s) after producing a therapeutic effect. Among the various soft drug-design approaches (Bodor 1984) the inactive metabolite approach has been found to be the most useful for designing ocular drugs.