OPHTHALMIC DRUG DELIVERY SYSTEM: AN OVERVIEW

Dr. B.K. Dubey¹, Mithun Bhoomick¹, Vimal Kumar Shahwal¹*, Abhay Upadhyay²

¹TIT College of pharmacy, Bhopal (M.P.). India
²College of pharmacy IPS Academy, Indore M.P.

Corresponding author*: vimalpharmacist1987@gmail.com

This article is available online at www.ssjournals.com

ABSTRACT

Ideal ophthalmic drug delivery must be able to sustain the drug release and to remain in the vicinity of front of the eye for prolong period of time. Ocular drug delivery is one of the interesting and challenging endeavors facing the pharmaceutical scientist. As an isolated organ the eye is very difficult to study from a drug delivery point of view. Eye drops and eye ointments are conventional ocular dosage forms. They have certain disadvantages like frequent administration, poor availability, massive and unpredictable doses, and drainage of medication by tear and nasolacrimal fluid. Most of ophthalmic drugs are administered topically in the form of eye drops, a dosage form consisting of buffered, isotonic, aqueous solution or suspensions of the drug. Ophthalmic CDDS (controlled drug delivery system) have been mainly prepared as gels, ointments, liposomes, micro and Nanoparticles, micro spheres and ocular minitablets (MT) or films or inserts.

KEY WORDS: Ocular drug delivery, ocular inserts, eye inserts, eye drug delivery.

1. INTRODUCTION

The eye as a portal for drug delivery is generally used foe local therapy against systemic therapy in order to avoid the risk of eye damage from high blood concentration of drug, which is not intended. The anatomy, physiology and biochemistry of the eye render this organ highly impervious to foreign substances. A significant challenge to the formulator is to circumvent the protective barriers of the eye without causing permanent tissue damage. Most ocular treatments like eye drops and suspensions call for the topical administration of ophthalmically active drugs to the tissues around the ocular cavity. These dosage forms are easy to instill but suffer from the inherent drawback that the majority of the medication they contain is immediately diluted in the tear film as soon as the eye drop solution is instilled into the cul-de-sac and is rapidly drained away from the pre-corneal cavity by constant tear flow and lacrimo-nasal drainage. Therefore, the target tissue absorbs a very small fraction of the instilled dose. For this reason, concentrated solutions and frequent dosing are required for the instillation to achieve an adequate level of therapeutic effect.¹ One of the new classes of drug delivery systems, ophthalmic inserts, which offer many advantages over conventional dosage forms, like increased ocular residence, possibility of releasing drugs at a slow and constant rate, accurate dosing, exclusion of preservatives and increased shelf life.²-⁴
The field of Ocular drug delivery is one of the interesting and challenging endeavors facing the pharmaceutical scientist. As an isolated organ the eye is very difficult to study from a drug delivery point of view. It is very difficult to obtain specimen of eye tissues containing drugs from humans, consequently one is compelled to use animal models as guide. As a result, unfortunately the human ocular disposition characteristics of virtually every important drug are incomplete or unknown. Despite these severe limitations significant improvement in Ocular drug delivery have been made. The improvements have been with objective of maintaining the drug in the biophase for an extended period. The anatomy, physiology and biochemistry of the eye render this organ impervious to foreign substances. Physiological barriers to diffusion and productive absorption of topically applied drug exist in the precorneal and corneal spaces. The precorneal constrains responsible for poor ocular bioavailability of conventional ophthalmic dosage forms are solution drainage, lacrimation, tear dilution, tear turnover and conjunctival absorption [Fig.I]. Drug solution drainage away from the precorneal area has been shown to be the most significant factor in reducing the contact time of the drug with the cornea and consequently ocular bioavailability of topical dosage forms. The instilled dose leaves the precorneal area within 2 minutes of instillation in humans. In rabbits the process of drainage, generally takes 5-10 minutes. However, most of the drugs are rapidly lost through nasolacrimal drainage immediately following dosing. Both the conjunctival and nasal mucosa has been indicated as the main potential sites for systematic absorption of topically applied drugs. Tears dilute the drug remaining in the cul-de-sac, which reduces the transcorneal flux of the drug. The drug entity, pH, tonicity of the dosage forms as well as formulation adjuvants can stimulate tear production.

The physiological constraints imposed by the protective mechanisms of the eye lead to low absorption of drugs and a short duration of the therapeutic effect on ocular drug delivery. Upon instillation of the eye drops only 1. 10% of the drug is bioavailable while the rest is drained out of the eye through lacrimal secretions. To overcome this problem various approaches have been reported, such as ointments, inserts and aqueous gels, to increase the ocular residence time of topically applied medication. Controlled drug delivery to the eye offer several advantages over conventional therapies like drug solutions or suspensions as eye drops. Ophthalmic inserts offer many advantages over conventional dosage forms, like increased ocular residence, possibility of releasing drugs at a slow and constant rate, accurate dosing, and exclusion of preservatives, increased shelf life and reduced systemic absorption.

2. DEFINITION

Eye drops and eye ointments are conventional ocular dosage forms. They have certain disadvantages like frequent administration, poor availability, massive and unpredictable doses, drainage of medication by tear and nasolacrimal fluid.

The ophthalmic delivery of drugs continues to be challenged by the intrinsic physiology of the eye. The efficient removal mechanism that operate at the site of action (rapid tear turn over, blinking) and the low corneal permeability act cooperatively to suppress
the effectiveness of ophthalmic formulations and to limit drug bioavailability to less than 5%. Moreover, systemic absorption of the drug and additives drained through nasolacrimal duct may result in undesirable effects. An effective way to achieve slow and prolonged absorption in ophthalmic practice is to incorporate a drug into a polymeric film, which when placed in the cul-de-sac of the eye exhibits a prolonged local release for drug action on tissue in the immediate vicinity.8

### 3. HISTORY

Many regions of the eye are relatively inaccessible to systematically administered drugs and as a result, topical drug delivery remains the preferred route in most cases. Drug may be delivered to treat the precorneal region for such infections as conjunctivitis and blepharitis, or to provide intraocular treatment via the cornea for diseases such as glaucoma and uveitis.17 Various approaches that have been attempted to increase the bioavailability and the duration of therapeutic action of ocular drugs can be divided into two categories. The first is based on the use of the drug delivery systems, which provide the controlled and continuous delivery of ophthalmic drugs. The second involves, maximizing corneal drug absorption and minimizing precorneal drug loss. The bioavailability of ophthalmic drug is however, very poor due to efficient protective mechanisms of the eye, blinking, baseline and reflex lachrymation and drainage remove rapidly foreign substances, including drug, from the surface of the eye as shown in Fig.1. Moreover, the anatomy, physiology and the barrier function of the cornea compromise the rapid absorption of drug.18 Frequent instillation of the eye drop is necessary to maintain a therapeutic drug level in the tear film or at the site of action but the frequent use of highly concentrated solution may induce toxic side effects(Fig. 1).19 Moreover, nasolachrymal drainage is also a major route to enter the circulatory system for drugs that applied through topical administration. For potent drugs, the systemic exposure through nasolachrymal drainage after topical administration can be sufficiently high to cause systemic toxicity.20 To enhance the amount of the active substances reaching the target tissue or exerting a local effect in the cul de sac, the residence time of drug in the tear should be lengthened. Moreover, once a day formulation should improve patient compliance. Recently, controlled and sustained drug delivery has become the standard in modern pharmaceutical design and an intensive research has been undertaken in achieving reliable, safety and effective product.1 Numerous strategies were developed to increase the bioavailability of ophthalmic drugs by prolonging the contact time between the drug and cornea/ conjunctival epithelium. The use of a water soluble polymer to enhance the contact time and possibly also the penetration of the drug was first proposed by Swan.21 Viscous semisolid preparations such as gels and ointments, proved a sustained contact with the eyes but they cause a sticky sensation, blurred vision and induce reflex blinking due to discomfort or even irritation.22 Films, erodible and nonerodible inserts, rods and shields are the most versatile drug delivery systems aimed at remaining for a long period of time in the front of the eye. These systems sustained and control drug
release and thus avoid pulsed entry. Another approach has been the application of in situ gelling system or phase transition system.23-25 A further approach to optimize the ocular dosage forms was the implementation of the mucoadhesive concept which was successful in buccal and oral application.

Eye is most interesting organ due to its drug disposition characteristics. For ailments of the eye, topical administration is usually preferred over systemic administration, 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. The medication, upon instillation, stimulates the protective physiological mechanisms, i.e., tear production, which exert a formidable defense against ophthalmic drug delivery. 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.26 Normal dropper used with conventional ophthalmic solution delivers about 50-75µl per drop and portion of these drops quickly drain until the eye is back to normal resident volume of 7µl. Because of this drug loss in front of the eye, very little drug is available to enter the cornea and inner tissue of the eye. Actual corneal permeability of the drug is quite low and very small corneal contact time of the about 1-2 min in humans for instilled solution commonly lens than 10%.27 Consequently only small amount actually penetrates the cornea and reaches intraocular tissue.28 Controlled drug delivery to the eye is restricted due to these limitation imposed by the efficient protective mechanism.29 Most of ophthalmic drugs are administered topically in the form of eye drops, a dosage form consisting of buffered, isotonic, aqueous solution or suspensions of the drug. Ophthalmic CDDS have been mainly prepared as gels, ointments, liposomes, micro and nanoparticles, microspheres and ocular minitablets (MT) or films or inserts.30 Ideal ophthalmic drug delivery must be able to sustain the drug release and to remain in the vicinity of front of the eye for prolong period of time. Consequently it is imperative to optimize ophthalmic drug delivery, one of the way to do so is by addition of polymers of various grades, development of viscous gel, development of colloidal suspension or using erodible or non erodible insert to prolong the precorneal drug retention.31 Bioadhesive systems utilized can be either microparticle suspension or polymeric solution. For small and medium sized peptides major resistance is not size but charge, it is found that cornea offers more resistance to negatively charged compounds as compared to positively charged compounds.

4. RECENT DEVELOPMENTS IN OPHTHALMIC DRUG DELIVERY

Most conventional ophthalmic dosage forms are simplistic. It is usual that water-soluble drugs are delivered through topical administration in an aqueous solution, and water-insoluble drugs are administered topically as an ointment or aqueous suspension. The major deficiencies of these conventional dosage forms include poor ocular drug bioavailability, pulse-drug entry after topical administration, systemic exposure
because of nasolacrimal duct drainage, and a lack of effective systems for drug delivery to the posterior segment of ocular tissue. Poor ocular drug bioavailability is the result of ocular anatomical and physiological constraints, which include the relative impermeability of the corneal epithelial membrane, tear dynamics, nasolacrimal drainage, and the high efficiency of the blood–ocular barrier. It is standard for only 1% or less of a topically applied dose to be absorbed across the cornea and thus reach the anterior segment of the eye. Pulse entry is a common, yet highly undesirable, pharmacokinetic characteristic associated with eye drops. The initial high drug concentration found in tears, followed by a rapid decline, poses a potential risk of toxicity, and suggests a requirement for frequent dosing. Attempts to overcome the toxicity associated with the high initial concentration without a requirement for frequent dosing form a challenging task, particularly in the case of potent drugs. Nasolacrimal drainage is the major factor for precorneal drug loss that leads to poor ocular bioavailability. It is also the major route of entry into the circulatory system for drugs that are applied through topical administration. For potent drugs, the systemic exposure through nasolacrimal drainage after topical administration can be sufficiently high to cause systemic toxicity. A recognized example is timolol; systemic toxicity has been reported for the ophthalmic solution of timolol following topical administration. Ocular drug delivery is one of the most fascinating and challenging tasks facing the Pharmaceutical researchers. One of the major barriers of ocular medication is to obtain and maintain a therapeutic level at the site of action for prolonged period of time. The anatomy, physiology and biochemistry of the eye render this organ exquisitely impervious to foreign substances. The challenging to the formulator is to circumvent the protective barriers of the eye without causing permanent tissue damage. The development of newer, more sensitive diagnostic techniques and therapeutics agents renders urgency to the development of maximum successful and advanced ocular drug delivery systems. The eye drop dosage form is easy to install but suffers from the inherent drawback that most of the instilled volume is eliminated from the pre-corneal area, resulting in a bioavailability ranging from 1-10% of total administrated dose. The poor bioavailability and rapid pre-corneal elimination of drugs given in eye drops is mainly due to conjunctival absorption, rapid solution drainage by gravity, induced lachrymation, blinking reflex, low corneal permeability and normal tear turnover. Because of poor ocular bioavailability, many ocular drugs are applied in high concentrations. This cause both ocular and systemic side-effects, which is often related to high peak drug concentrations in the eye and in systemic circulation. The frequent periodic instillations of eye drops are necessary to maintain a continuous sustained therapeutic drug level. This gives the eye a massive and unpredictable dose of medication. Suspension types of pharmaceutical dosage forms are formulated with relatively water insoluble drugs to avoid the intolerably high toxicity created by saturated solutions of water-soluble drugs. However, the rate of drug release from the suspension is dependent upon the rate of dissolution of the drug particles in the medium, which varies, constantly in its composition with the constant inflow and outflow of lachrymal fluid.
The conventional ocular dosage forms for the delivery of drugs are-
1. Eye drops (solution, suspension)
2. Ophthalmic Ointments

In order to overcome the constraints placed by these conventional ocular therapies viz. 39
a. Short residence time
b. Pulsed dosing of drug.
c. Frequent instillation
d. Large drainage factor.

5. CLASSIFICATIONS OF OPHTHALMIC DRUG DELIVERY SYSTEMS 42

A multitude of ocular dosage forms are available for delivery of drugs to the eye. These can be classified on the basis of their physical forms as follows:

A. Liquids: Solutions, Suspensions, Sol to gel systems, Sprays.
B. Solids: Ocular inserts, Contact lenses, corneal shield, Artificial tear inserts, Filter paper strips.
C. Semi-solids: Ointments, Gels.
D. Miscellaneous: Ocular iontophoresis, Vesicular systems, Mucoadhesive dosage forms, Particulates, Ocular penetration.

A. Liquids
Liquids are the most popular and desirable state of dosage forms for the eye. This is because the drug absorption is fastest from this state. The slow release of the drug from the suspended solids provides a sustained effect for a short duration of time.

1. Solutions and Suspensions
Solutions are the pharmaceutical forms most widely used to administer drugs that must be active on the eye surface or in the eye after passage through the cornea or the conjunctiva. The drug in the solution is in the solved state and may be immediately active. This form also have disadvantages; the very short time the solution stays at the eye surface, its poor bioavailability (a major portion i.e. 75% is lost via nasolacrimal drainage), the instability of the dissolved drug, and the necessity of using preservatives. A considerable disadvantage of using eye drops is the rapid elimination of the solution and their poor bioavailability. This rapid elimination is due to solution state of the preparation and may be influenced by the composition of the solution. The retention of a solution in the eye is influenced by viscosity, hydrogen ion concentration, the osmolality and the instilled volume. Extensive work has been done to prolong ocular retention of drugs in the solution state by enhancing the viscosity or altering the pH of the solution 41.

2. Sol to gel Systems
The new concept of producing a gel in situ (eg. in the cul-de-sac of the eye) was suggested for the first time in the early 1980s. It is widely accepted that increasing the viscosity of a drug formulation in the precorneal region will leads to an increased bioavailability, due to slower drainage from the cornea. Several concepts for the in situ gelling systems have been investigated. These systems can be triggered by pH, temperature or by ion activation. An anionic polymeric dispersion shows a low viscosity upto pH 5. 0, and will coacervate in contact with tear fluid due to presence of a carbonic buffer system which regulates the pH of tears. In situ gelling by a temperature change is produced when the temperature of polymeric dispersion is raised from 25 to
37°C. Ion activation of polymeric dispersion occurred due to the presence of cations in the tear fluid.

3. Sprays
Although not commonly used, some practitioners use mydriatics or cycloplegics alone or in combination in the form of eye spray. These sprays are used in the eye for dilating the pupil or for cycloplegic examination.

B. Solids
The concept of using solids for the eye is based on providing sustained release characteristics.

1. Ocular inserts
Ocular inserts are solid dosage form and can overcome the disadvantage reported with traditional ophthalmic systems like aqueous solutions, suspensions and ointments. The typical pulse entry type drug release behavior observed with ocular aqueous solutions (eye drops), suspensions and ointments is replaced by more controlled, sustained and continuous drug delivery using a controlled release ocular drug delivery system. The eye drops provided pulse entry pattern of drug administration in the eye which is characterized by transient overdose, relatively short period of acceptable dosing, followed by prolonged periods of under dosing. The ocular inserts maintain an effective drug concentration in the target tissues and yet minimize the number of applications consonant with the function of controlled release systems. Limited popularity of ocular inserts has been attributed to psychological factors, such as reluctance of patients to abandon the traditional liquid and semisolid medications, and to occasional therapeutic failures (e.g. unnoticed expulsion from the eye, membrane ruptures etc.). A number of ocular inserts were prepared utilizing different techniques to make soluble, erodible, nonerodible, and hydrogel inserts.

2. Contact lenses
Contact lenses can absorb water soluble drugs when soaked in drug solutions. These drug saturated contact lenses are placed in the eye for releasing the drug for long period of time. The hydrophilic contact lenses can be used to prolong the ocular residence time of the drugs.

3. Corneal shield
A non cross-linked homogenized, porcine scleral collagen slice is developed by a company (Biocor (Bausch and Lomb pharmaceuticals). Topically applied antibiotics have been used in conjunction with the shield to promote healing of corneal ulcers. Collagen shields are fabricated with foetal calf skin tissue and originally developed as a corneal bandage. These devices, once softened by the tear fluid, form a thin pliable film that confirms exactly to the corneal surface, and undergoes dissolution up to 10, 24 or 72 hours. Collagen film proved as a promising carrier for ophthalmic drug delivery system because of its biological inertness, structural stability and good biocompatibility. It was found that highest drug concentrations were found in the eyes treated with shields as compared to eye drops.

4. Artificial tear inserts
A rod shaped pellet of hydroxypropyl cellulose without preservative is commercially available (Lacrisset). This device is designed as a sustained release artificial tear for the treatment of dry eye disorders.

5. Filter paper strips
Sodium fluorescein and rose Bengal dyes are commercially available as drug impregnated filter paper strips. These dyes are used diagnostically to disclose corneal injuries and infections such as herpes simplex, and dry eye disorders.

C. Semi-solids
A wide variety of semisolids vehicles are used for topical ocular delivery which falls into two general categories: simple and compound bases. Simple bases refer to a single continuous phase. These include white petrolatum, lanolin and viscous gels prepared from polymers such as PVA, carbopol etc. Compound bases are usually of a biphasic type forming either water in oil or oil in water emulsions. A drug in either a simple or compound base provide an increase in the duration of action due to reduction in dilution by tears, reduction in drainage by way of a sustained release effect, and prolonged corneal contact time. The most commonly used semisolid preparation is ointments consisting of dispersion of a solid drug in an appropriate vehicle base. Semi-solids dosage forms are applied once or twice daily and provide sustained effects. The primary purpose of the ophthalmic ointment vehicle is to prolong drug contact time with the external ocular surface. But they present a disadvantage of causing blurring of vision and matting of eyelids. Ophthalmic gels are similar in viscosity and clinical usage to ophthalmic ointments. Pilopine HS is one of the ophthalmic preparations available in gel form and is intended to provide sustained action of pilocarpine over a period of 24 hours. Semi-solids vehicles were found to prolong the ocular contact time of many drugs, which ultimately leads to an enhanced bioavailability.

6. CLASSIFICATION OCULAR INSERTS

(Based upon their solubility behavior)

1) Insoluble inserts
   a) Diffusion based
   b) Osmotic based
   c) Soft contact lenses

2) Soluble inserts

3) Bioerodible inserts

1. Insoluble ophthalmic inserts
The insoluble inserts have been classified into three groups:-
   a) Diffusion systems
   b) Osmotic systems
   c) Hydrophilic contact lenses.
The first two classes include a reservoir in contact with the inner surface of the rate controller and supplying drug thereto. The reservoir contains a liquid, a gel, a colloid, a semisolid, a solid matrix or a carrier-containing drug homogeneously or heterogeneously dispersed or dissolved therein. Carriers can be made of hydrophobic, hydrophilic, organic, inorganic, naturally occurring or synthetic material. The third class including the contact lenses. The insoluble of these devices is their main disadvantages, since they have to be removed after use.

a) Diffusion inserts
The diffusion systems are compared of a central reservoir of drug enclosed in specially designed semi permeable or micro porous membranes, which allow the drug to diffuse the reservoir at a precisely determined rate. The drug release from such a system is controlled by the lachrymal fluid permeating through the membrane until a sufficient internal pressure is reached to drive the drug out of the reservoir. The drug delivery rate is controlled by diffusion through the membrane, which one can be controlled (Table 1).
b) Osmotic inserts
The osmotic inserts are generally compared of a central part surrounded by a peripheral part. The first central part can be composed of a single reservoir or of two distinct compartments. In first case, it is composed of a drug with or without an additional osmotic solute dispersed through a polymeric matrix, so that the drug is surrounded by the polymer as discrete small deposits. In the second case, the drug and the osmotic solutes are placed in two separate compartments, the drug reservoir being surrounded by an elastic impermeable membrane and the osmotic solute reservoir by a semi permeable membrane. The second peripheral part of these osmotic inserts comprises in all cases a covering film made of an insoluble semi permeable polymer.

c) Soft contact lenses
These are shaped structure made up of a covalently crosslinked hydrophilic or hydrophobic polymer that forms a three-dimensional network or matrix capable of retaining water, aqueous solution or solid components. When a hydrophilic contact lens is soaked in a drug solution, it absorbs the drug, but does not give a delivery as precise as that provided by other non-soluble ophthalmic systems. The drug release from such a system is generally very rapid at the beginning and then declines exponentially with time. The release rate can be decreased by incorporating the drug homogeneously during the manufacture or by adding a hydrophobic component. Contact lenses have certainly good prospects as ophthalmic drug delivery systems.

2. Soluble Ophthalmic inserts
Soluble inserts correspond to the oldest class of ophthalmic inserts. They offer the great advantage of being entirely soluble so that they do not need to be removed from their site of application thus, limiting the interventions to insertion only. Types
a) Based on natural polymers e.g. collagen.
b) Based on synthetic or semi synthetic polymers.
The therapeutic agents is preferably absorbed by soaking the insert in a solution containing the drug, drying and rehydrating in before use on the eye. The amount of drug loaded will depend upon the amount of binding agent, upon the concentration of the drug solution into which the composite is soaked, as well as the duration of the soaking.

3. Biodegradable ophthalmic inserts
The biodegradable inserts are composed of material homogeneous dispersion of a drug included or not into a hydrophobic coating which is substantially impermeable to the drug. They are made of the so-called biodegradable polymers. Successful biodegradable materials for ophthalmic use are the poly (orthoesters) and poly (orthocarbonates). The release of the drug from such a system is the consequence of the contact of the device with the tear fluid inducing a superficial diversion of the matrix.

7. CONVENTIONAL OCULAR DRUG DELIVERY SYSTEM
The conventional ocular delivery systems are used ubiquitously in today’s ocular disease management are solutions, suspensions, these are sterile, contain a preservatives, is isotonic, has a pH of cirla 7.4 for patient comfort and has limited shelf life after opening.

Eye drops provide a pulse entry of the drug, followed by a rapid decline in drug concentration, the kinetics, of which approximately to the first order. To overcome these problems, it is the consensus of most clinicians that a solution or suspension form of a drug delivery system is preferred by the patient provided that extended duration can be accomplished with these forms.

8. ROLE OF POLYMER(S) IN DRUG DELIVERY

The first approach made towards research in the field of improving the ocular contact time of solutions utilizes the incorporation of polymers into an aqueous medium such as polyvinyl alcohol (PVA), polyvinyl pyrolidine (PVP), methylcellulose (MC), carboxymethyl cellulose (CMC), and hydroxypropyl cellulose (HPC). The increased solution viscosity reduced the solution drainage. Increasing the solution viscosity of pilocarpine solution from 1 to 100 cps through the incorporation of methylcellulose reduced the solution drainage rate constant 10 times while only a 2-fold increase in pilocarpine concentration in the aqueous humor was obtained. An optimal viscosity of 12-15 cps has been suggested for ocular drug absorption by Paton and Robinson. Natural polymers namely sodium haluronate and chondroitin sulfate are being investigated as viscosity inducing agents. Prolonged residence time with an extended duration of action for 1% pilocarpine has been observed with 0.2-0.3% sodium hyaluronate solutions. In considering approach of increasing solution viscosity to enhance ocular drug absorption the lipophilicity of the drug should be taken into account. The results to date suggest that increasing solution viscosity has limited utility in causing marked improvement in the amount of drug absorbed.

9. ADVANCEMENT

Films, erodible and non erodible inserts, rods and shields are the most logical delivery systems aimed at remaining for a long period of time in front of the eye. From a therapeutical point of view, inserts have been a success in the improvement of accurate dosing, drug bioavailability and by the reduction of systemic absorption, and consequently side effects. Inserts dissolve and/or erode on contact with the ocular surface and therefore need to be used in addition with other artificial tears to initiate the dissolving process. Considering the various mucoadhesion mechanisms, hydration or degree of swelling of the polymers plays an important role. In the case of dry or partially hydrated dosage forms, water movement from the mucus layer to the formulation can be a significant factor in mucoadhesion, being more important than molecular interpenetration. Hydrophilic polymers with poor mucoadhesive properties may be added to a mucoadhesive polymer with poor swelling characteristics to ensure fast swelling. Some additional polymers can hinder the formation of bonds between the mucoadhesive polymer and mucus by preferentially binding to the hydrated mucoadhesive polymer. There is also a reduction in the strength of the bond.
between the mucoadhesive polymer and mucin. The following recent trends are in existence:-

a) Membrane-bound ocular inserts (biodegradable and non-biodegradable) e.g. Ocusert®, Alza Corp.

b) Mucoadhesive dosage forms (ocular films or sheath, ophthaCoil, polymer rods, HEMA hydrogel, Dispersion, polysulfone capillary fiber)

c) Collagen shields, cyclodextrine based system, ophthalmic rods (artificial tear inserts e.g. Lacrisert®)

d) Filter paper strips (drug-impregnated filter paper strips for staining agent-sodium fluorescent, lissamine green and rose Bengal)

e) Soft contact lenses, implants, flexible coils and cotton pledgets (Drug presoaked hydrogel type, polymeric gels)

f) Phase Transition systems (in-situ gel formation system: ion-activated based, pH changed based, temperature change based)

g) Nanoparticles (Microspheres, nanosuspension, Amphiphilogels, Niosomes, Liposomes, Dendrimers and Quantum dots)

h) Ocular Iontophoresis and pumps

i) Chemical delivery systems vesicular systems.

10. PREPARATION OF OCULAR INSERTS

A flat square shaped glass molds having surface area 25 cm² were fabricated for casting the patches. The formulation of insert involves three steps viz. (i) Preparation of drug reservoir (ii) Preparation of rate controlling membrane (iii) Sealing of drug reservoir.

11. EVALUATION

Prepared inserts were evaluated for surface pH, thickness, weight variations, folding endurance and drug content uniformity.

a. Surface pH:

Surface pH was determined by allowing them to swell in a closed petridish at room temperature for 30 minutes in 0.1 ml of distilled water. pH paper was kept on surface and after one minute the colour developed was compared with the standard colour scale.

b. Thickness:

Thickness was evaluated using a micrometer of sensitivity of 0.001 mm, the average of ten readings was taken.

c. Folding endurance:

Folding endurance was determined by repeatedly folding a small strip of ocular film at the same place till it broke.

d. Drug Content uniformity:

Drug content was estimated by triturating ocular inserts in 20 ml of phosphate buffer pH 6.8 with the help of mortar and pestle. The solution was filtered and one ml solution was withdrawn, diluted and measured by UV-Visible Spectrophotometer at 290 nm.

e. In Vitro drug release studies

The in vitro release studies were carried out using a fabricated flow through apparatus, simulating the conditions of ocular cavity. The ocular insert was placed between ring shaped plastic mesh. The arrangement of the mesh was clamped with two baby nipples. The arrangement was fixed to the stand. From one end of the nipple was connected to the reservoir containing phosphate buffer (pH 7.4). A small orifice is made on the other
side of the nipple which acts as an outlet for collecting the sample. The arrangement is done in such a way that the dissolution medium will continuously flow on the ocular insert at a rate of 0.4 ml / minute. The temperature of the medium for the entire process was maintained at 37 ± 0.5°C. Samples were withdrawn at different time intervals and subjected to spectrophotometric analysis at 275 nm to find out the amount of drug released.

f. **Drug content**

Five ocular inserts were taken from each batch and dissolved or crushed in 10 ml of isotonic phosphate buffer pH 7.4 in a beaker and were filtered into 25 ml volumetric flask and the volume was made up to the mark with buffer. One ml of the above solution was withdrawn and the absorbance was measured by UV-VIS spectrophotometer at 285.6 nm after suitable dilutions.[76]

g. **In – vivo evaluation methods**

The controlled ocular drug delivery systems can be evaluated for its pharmacokinetic and pharmacodynamic profiles. The main objective of the pharmacokinetic studies is to determine the drug release from the dosage form to the eye. Rabbit is used as an experimental animal because of a number of anatomical and physiological ocular similarities and also due to larger size of the eye. Pharmacokinetic studies are performed by measuring drug concentration in various eye tissues eg. Lens, cornea, iris, ciliary body, retina sclera, aqueous and vitreous humor in rabbits. The intraocular pressure of the eye is measured with a tonometer. Ocular pharmacokinetic studies can also be carried out by tear fluid sampling, which is a non-invasive technique. Usually, disposable glass capillaries of 1ml capacity are used for sampling. The samples are collected from the marginal tear strip of the rabbits. The capillary force fills the tube rapidly and the small volume collected does not interfere with the ocular pharmacokinetics. Extreme care must be taken to avoid any corneal contact and possible induced lacrimation. To withdraw aqueous humour, rabbits are anaesthetized with ketamine and aqueous humour about 200ml is withdrawn from the anterior chamber using 1ml syringe with 26 guage needle. Vitreous samples are also obtained with 20 gauge needle. The entire cornea, lens, and iris-ciliary body are also removed and analyzed for the drug content.[68]

h. **% Moisture absorption**

The percentage moisture absorption test was carried out to check physical stability or integrity of the film at humid condition. The films were weighed and placed in desiccator containing saturated solution of aluminium chloride and 84% humidity was maintained.[69] After three days, the films were taken out and reweighed.[70] The % moisture absorption was calculated using the formulae

\[
\% \text{ Moisture absorption} = \frac{\text{Final weight} - \text{Initial weight}}{\text{Initial weight}} \times 100
\]

i. **% Moisture loss**

The percentage moisture loss was carried out to check the integrity of the film at dry condition. The films were weighted and kept in dessicator containing anhydrous calcium chloride. After three days, the films were taken out and reweighed.[71] The percentage moisture loss was calculated using the formulae

\[
\% \text{ Moisture loss} = \frac{\text{Initial weight} - \text{Final weight}}{\text{Initial weight}} \times 100
\]
12. ADVANTAGES OF OPHTHALMIC DRUG DELIVERY SYSTEMS

a) Increased accurate dosing. To overcome the side effects of pulsed dosing produced by conventional systems.
b) To provide sustained and controlled drug delivery.
c) To increase the ocular bioavailability of drug by increasing the corneal contact time. This can be achieved by effective adherence to corneal surface.
d) To provide targeting within the ocular globe so as to prevent the loss to other ocular tissues.
e) To circumvent the protective barriers like drainage, lacrimation and conjunctival absorption.
f) To provide comfort, better compliance to the patient and to improve therapeutic performance of drug.
g) To provide better housing of delivery system.
h) Ease of handling and insertion.
i) Lack of expulsion during wear.
j) Reproducibility of release kinetics (Zero-order drug delivery).
k) Applicability to variety of drugs.
l) Non-interference with vision and oxygen permeability.
m) Sterility, Stability.
n) Ease of manufacture

13. CORNEAL BARRIER LIMITATION FOR TOPICALLY ADMINISTERED DRUG.

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

1. Improving ocular contact time
2. Enhancing corneal permeability
3. Enhancing site specificity

14. THE OTHER FACTORS AFFECTING DRUG RELEASE

- Penetration of the inclusion.
- Swelling of the matrix.
- Dissolution of the drug and the polymers.
- Relaxation of the polymeric chain

15. CHARACTERISTICS OF OPHTHALMIC DRUG DELIVERY

a. Good corneal penetration.
b. Prolong contact time with corneal tissue.
c. Simplicity of instillation for the patient.
d. Non irritative and comfortable form (viscous solution should not provoke lachrymal secretion and reflex blinking)
e. Appropriate rheological properties and concentrations of the viscous system.

16. PHYSIOLOGICAL BARRIERS OF OPHTHALMIC DRUG DELIVERY SYSTEM

1. Physiological barriers to diffusion and productive absorption of topically applied drug exist in the precorneal and cornealspaces. The precorneal constraints responsible for poor ocular bioavailability of conventional
ophthalmic dosage forms are solution drainage, lacrimation, tear dilution, tear turnover and conjunctival absorption.74

2. Drug solution drainage away from the precorneal area has been shown to be the most significant factor in reducing the contact time of the drug with the cornea and consequently ocular bioavailability of topical dosage forms.

3. The instilled dose leaves the precorneal area within 2 minutes of installation in humans. The ophthalmic dropper delivers 50-75 µl of the eye drops. If the patient does not blink, the eye can hold about 30 µl without spilling on to the cheek. The natural tendency of the cul-de-sac is to reduce its volume to 7-10 µl. However, most of the drug is rapidly lost through nasolacrimal drainage immediately following dosing. The drainage allows the drug to be absorbed across the nasal mucosa into the systemic circulation. The conjunctiva also possesses a relatively large surface area, 5 times the surface of cornea making the loss significant. Both conjunctival and nasal mucosa has been indicated as the main potential sites for systemic absorption of topically applied drugs.75

17. MECHANISM OF CONTROLLED SUSTAINED DRUG RELEASE INTO THE EYE74,75

1. The corneal absorption represents the major mechanism of absorption for the most conventional ocular therapeutic entities.

2. Passive Diffusion is the major mechanism of absorption for nor erodible ocular insert with dispersed drug.

3. Controlled release can further regulated by gradual dissolution of solid dispersed drug within this matrix as a result of inward diffusion of aqueous solution.

Ocular irritation study
Six albino rabbits were used in the study and were examined thoroughly for any preexisting ocular damage. The selected formulation was then placed in one eye of each animal by gently pulling the lower eyelid away from the eye ball (conjunctival cul-de-sac). The lids were then being gently held together for one second and the animal is released. The other eye, remaining untreated was served as the control. The eyes of each rabbits were examined 24, 48 and 72 hrs after treatment for irritation, inflammation etc by naked eye or by means of a pen torch. At the time of examination period each rabbit was scored for ocular reaction. The test may considered positive if three or more animal exhibit positive reactions at any observation period.

18. CONCLUSION

Solutions and aqueous suspensions are the pharmaceutical forms most widely used to administer drugs that must be active on the eye surface or in the eye after passage through the cornea or conjunctiva. A considerable disadvantage of using eye drops is the rapid elimination of the solution and their poor bioavailability. The ophthalmic drug delivery discusses, minimize the precorneal factors and prolong drug activity at its site of action. This can be achieved by adopting the novel in situ gel approach. These gels are easy to instill at the same time improved ocular bioavailability by increasing the
duration of contact with corneal tissue, thereby reducing the frequency of administration required increase of conventional ophthalmic solutions, thus optimizing ocular therapy.

REFERENCES

1. Chien YW. Ocular drug delivery and delivery systems. In: Novel drug delivery systems. Edn 2, Marcel Dekker, New York, 1992, 269.
2. Kawakami S, Nishida K, Mukai T, Yamamura K, Nakamura J, Sakeda T, and Sasaki H. Controlled release and ocular absorption of tilisolol utilizing ophthalmic insert-incorporated lipophilic prodrugs J. Control. Release 2001; 76(3): 255.
3. Sasaki H, Tie C, Nishida K, and Nakamura J. Drug release from an ophthalmic insert of a beta-blocker as an ocular drug delivery system J. Control. Release 1993; 27(2): 127.
4. Baleens V, Catalos V, Boisrame B, Varesio E and Gurney R. Optimized release of dexamethasone and gentamicin from a soluble ocular insert for the treatment of external ocphthalamic infections. J. Control. Release 1998; 52: 215
5. SS Chrai; SS Paton; A Mehta; JR Robinson, J.Pharm. Sci., 1973, 62, 1112.
6. JM Conard; WA Reay; RE Polcyin; JR Robinson, J. Parent Drug Assoc., 1978, 32,149
7. Barbu E, Sarvaiya I, Green KL, Nevel TG and Tsibouk J. Vinlypyrrolidone-co- (meth) acrylic acid insert for ocular drug delivery: synthesis and evaluation. J Biomed Mater Res A 2005; 74: 343-9.
8. Chari SS, Makoid MC, Erikson SP and Robinson JR. Drop size and initial dosing frequency problems of topically applied ophthalmic drugs. J. Pharm. Sci.1974; 64: 333.
9. Desai SD and Blanchard J. Ocular drug formulation and delivery. In J. Swarbrick, and J. Boylar (eds.), Encyclopedia of Pharmaceutical Technology, Vol. 3, Marcel Dekker, New York, 1994, pp. 43.76.
10. Schoenwald RD. Ocular drug delivery, pharmacokinetic considerations. Clin. Pharmacokinnet.1998;18:255.269.
11. Lee VHL. Precorneal, corneal and postcorneal factors. Drugs Pharm. Sci.1993; 58:59.81
12. Attis MA, Kassem MA and Safewat S. In vivo performance of [3H] dexamethasone ophthalmic film delivery systems in the rabbit eye. Int. J. Pharm. 1998;47:21.30.
13. Barath S, and Hiremath SR. Ocular delivery system of perfloxacin mesylate. Pharmazie1999; 54:33.38 (1999).
14. Lee, V. H. L. and Robinson, I. R. (1979). Ocuserts for improved drug delivery and better patient compliance. J. Pharm. Sci. 68 (1): 673.
15. Udupa, N. (1993). In vitro evaluation of flurbiprofen ophthalmic inserts. Pharma Times 31 (361): 26.
16. Rastogi, S. K., Vayas, N. and Mishra, B. (1996). In vitro and in vivo evaluation of pilocarpine hydrochloride ocuserts. The Eastern Pharmacist. 99: (458): 41.
17. C.A.Le-Bourlais, A.L.Treupel, C.T. Rhodes, P.A.Sado, R.Leverge, New-ophthalmic drug delivery system, Drug Devel. Ind. Pharm. 21 (1998) 19-59.
18. V.H.L. Lee, J.R. Robinson, Review: topical ocular drug delivery: recent
development and future challenges, J.Ocul. Pharmacol. 2 (1986) 67-108
19. A. Topalkara, C. Guler, D.S. Arici, M.K. Arici, Adverse effects of topical antiglaucoma drugs on the ocular surface, Clin. Exp. Ophthalmol. 28 (2000) 113-117.
20. A. Urtti, L. Salminen, Minimizing systemic absorption of topically administered ophthalmic drugs, Surv. Ophthalmol. 37 (1993) 435-456.
21. K.C. Swan, The use of methylcellulose in ophthalmology, Arch. Ophthalmol. 33 (1945) 378–380.
22. O. Dudinski, B.C. Finnin, B.L. Reed, Acceptability of thickened eye drops to human subjects, Curr. Ther. Res. 33 (1983) 322-337.
23. H. Ibrahim, C. Bindschaedler, E. Doelker, P. Buri, R. Gurny, Concept and development of ophthalmic pseudo-lattices triggered by pH, Int. J. Pharm. (1991) 211-219.
24. S.C. Miller, M.D. Donovan, Effects of poloxamer 407 gel on the miotic activity of pilocarpine nitrate in rabbits, Int. J. Pharm. 12 (1982) 147-152.
25. A. Rozier, C. Mazuel, J. Grove, B. Plazonnet, Gelrite®: a novel, ion activated in situ gelling polymer for ophthalmic vehicles: Effect on bioavailability of timolol, Int. J. Pharm. 57 (1989) 163-168.
26. Shell JW, Drug Dev. Res., 1985, 6, 245-261.
27. Shell JW, J. Toxicol. Cut. & Ocular Toxicol, 1982, 1(1), 49-63.
28. Patton TF, and Robinson JR, J. Pharm. Sci., 1976, 65, 1295-1301.
29. Wood RW, Lee VHE, Kreutzer J and Robinson JR, Int. J. Pharm, 1985, 23, 175-183.
30. Prajapati PA, Poddar SS, Patel MM, Der Pharmacia Lettre, 2010, 2 (1) 467-474.
31. Patton TF, Robinson JR, J. Pharm. Sci., 1975, 65, 1312-1315.
32. Hui HW and Robinson JR, Int. J. Pharm., 1985, 26, 203-213.
33. Peyman, GA and Ganiban, GJ Adv. Drug Deliv. Rev., 1995, 16, 107–123
34. Lee VHL and Robinson, JR J. Ocul. Pharmacol. Ther., 1986, 2, 67–108
35. Urtti, A. and Salminen, L. Surv. Ophthalmol. 1993, 37, 435–456
36. Katz, I. M., Shaped ophthalmic inserts for treating dry eyes syndrome. U.S. Patent. 1982; 4,343,787.
37. Chrai, S.S., and Robinson, J.R., “Ocular evaluation of methyl cellulose vehicle in albino rabbits”. J. Pharm. Sci., 1974; 63: 1218.
38. Zaki, I., Fitzgerald, P., Hardy, J.G., and Wilson, C.G., “Comparison of effect of viscosity on the precorneal residence of solution in rabbit and man”. J. Pharm. Pharmacol, 1986; 38: 463.
39. Lee, V.H.L., and Robinson, J.F., “Review: Topical ocular drug delivery; recent developments and future challenges”. J. Ocul. Pharmacol., 1976; 2: 67.
40. Saettone, M.F., and Salminen, L., “Ocular inserts for topical delivery”. Advanced drug delivery reviews, 1995; 16(1): 95.
41. Schoenwald, R.D., “Ocular Pharmacokinetics/Pharmacodynamics chapter-4, In: Ophthalmic Drug Delivery Systems, Vol – 58, Marcel Dekker, Inc., New York. 1993; 83-103.
42. Krishna N, Brown F. Am. J. Ophthalmol, 1964, 57, 99.
43. Lerman S, Davis P, Jackson W B. Can. J. Ophthalmol. 1973, 8, 114 - 118.
44. Vasantha R, Sehgal P K, Rao P. Int. J. Pharm. 1988, 47, 95 - 102.
45. Kyyronen K, Hume L, Benedetti L, Urtti A., Topp E, Stella V. Int. J. Pharm. 1992, 80, 161- 169.
46. Di Colo, G., Burgalassi S., Chetoni,P. “Gel forming ocular inserts for ocular controlled delivery”, Int.J.Pharm.,2001Mar 14;215(1-2):101-11.
47. Shell, J.W., and Gale, R.M., “Topical composition containing steroidal in two forms released independently from polymeric carrier”, U.S. Patent. 1984; 4, 432,964.
48. Gurtler, F., and Gurny, R., ‘Patent literature review ofophthalmic inserts”. Drug Dev. Ind. Pharm., 1995;21(1):1
49. Bloomfield, S.E., Miyata, T., Dunn, M.W., et al., “Soluble gentamacin ophthalmic inserts as a delivery system “. Arch Ophthalmol. 1978; 96:885.
50. Ahmed, I., Gokhale, R.D., et al., “Physicochemical determinants of drug diffusion across the conjunctiva, sclera and cornea”. J. Pharm. Sci., 1987; 76: 583.
51. Elter, M.G., Schoenwald, R.D., et al., “Optimization models for corneal penetration of ethoxyzolamide analogues”. J. Pharm. Sci., 1985; 74: 155.
52. Patton, T. F., and Robinson, J.R., “Quantitative precorneal disposition of topically applied pilocarpine nitrate in rabbit eye”. J. Pharm. Sci., 1976; 65: 1295.
53. Himmelstein, K.J., Guvenir, I., and Palton, T.P., “Preliminary Pharmacokinetics model of pilocarpine uptake and distribution in the eye”. J. Pharm. Sci., 1978; 67: 603.
54. Di Colo, G., Zambito,Y. A study of release mechanism of different ophthalmic drug from erodible ocular inserts based on poly (ethylene oxide), Eur J Pharm Biopharm.2002 Sep; 54(2):193-9.
55. Grass, G.M., and Robinson, J.R., “Mechanisms of corneal drug penetration II: Ultra structural analysis of potential pathways for drug movements”. J. Pharm. Sci., 1988; 77:15.
56. Alvarez-Lorenzo, C., Hiratani, H. Soft contact lenses capable of sustained delivery of timolol. J.Pharm. Sc. 2002Oct; 91(10):2182-92
57. SS Chrai; JR Robinson, J.Pharm. Sci., 1974, 63, 1218.
58. TF Paton; JR Robinson, J. Pharm. Sci., 1976, 65, 1295.
59. O Camber; P Edman; R Gury, Curr. Eye Res., 1987, 6,779.
60. RC Zeimer; B Khoobehi; MR Niesman; RL Magin, Invest. Ophthalmol Vis. Sci.,1988, 29, 1179
61. Davis, J. L., Gilger, B.C., Robinson, M.R. Novel approaches to ocular drug delivery. Curr Opin Mol ther.2004 Apr; 6(2):195-205.
62. Sklubalova, Z., “In-situ gelling polymer for ophthalmic drops” Ceska Slov Farm.2005 Jan;54(1):4- 10.
63. Jibry, N., Heenan R.K., Murdan, S. Amphiphilogels for drug delivery. Pharm Res.2004 Oct; 21(10):1852-61.
64. Mainardes, R. M., Urban, M.C., Cinto, P.O., Chaud, M.V. Colloidal carriers for ophthalmic drug delivery. Curr drug targets.2005 May; 6(3): 363-71.
65. Robinson J.C., Mitra A. K ,Marcel, Dekker,Ophthalmic Drug Delivery Systems,. (Ed.), New York, 1993, 29–57.
66. Balasubramaniam J, Srinatha A, Pandit JK, Gopalnath. In Vitro microbiological evaluation of polyvinyl alcohol based ocular inserts of ciprofloxacin hydrochloride. Indian J Pharma Sci 2006; 68 (5): 626-630.
67. Rao V, Shyale S. Preparation and Evaluation of ocular inserts containing norfloxacin. Turk J. Med Sci 2004; 34: 239 – 246.
68. Ali A, Sharma SN Ind. J.Hosp.Pharm. 1991, 28, 165-169.
69. Ubaidulla U, Reddy MV, Ruckmani K. Transdermal therapeutic system of carvedilol: Effect of hydrophilic and hydrophobic matric on in vitro and in vivo characteristics. AAPS PharmSciTech.2007; 8:E1-E8.
70. Dhanaraju MD, Sivakumar VR, Bhaskar K. Bioadhesive ocuserts matrix for ophthalmic administration of ciprofloxacin HCl. Indian Drugs.2002; 39: 222-224.
71. Mundada AS, Shrikhande BK. Design and evaluation of soluble ophthalmic insert for controlled release of ciprofloxacin hydrochloride. Drug. Dev. Ind. Pharm.2006; 32:443-448
72. Marco Fabrizio Saettone, Lotta Salminen, Ocular inserts for topical delivery, Turkey J Pharm Sci1995; 95-106
73. Jain N.K, Menqui S.A and Deshpande S.G. “Controlled and Novel Drug Delivery”, CBS publishers; New Delhi;1STEdition(2005); 82
74. Lee V.H; Robinson J.R, Ocular drug delivery system, Biopharm J of Ocular Pharmacol 1986 ;2(1);84-86
75. Robinson J.R, “Ocular drug delivery system”,1989;5(12); 839
76. Venugopal K, Saha RN. New, simple and validated UV spectrophotometric method for the estimation of Gatifloxacin in bulk and formulations. IL Farmaco.2005; 60:906-912.

| Table 1: Components of diffusional inserts |
|-----------------------------------------|
| Central reservoir | Glycerin, ethylene glycol, propylene glycol, water, methyl cellulose mixed with water, sodium alginate, poly (vinylpyrrolidone), polyoxyethylene stearate. |
| Micropores membrane | Polycarbonates, polyvinyl chloride, polysulfones, cellulose esters, crosslinked poly (ethyl oxide), cross-linked polyvinylpyrrolidone, and cross-linked polyvinyl alcohol. |
### Table 2: Types of Matrix

| Type of Matrix                        | Components                                                                 |
|--------------------------------------|-----------------------------------------------------------------------------|
| Water permeable matrix               | Ethylene - vinyl esters copolymers, Divers-plasticized polyvinyl chloride (PVC), polyethylene, cross-linked polyvinyl pyrrolidone (PVP) |
| Semi permeable membrane              | Cellulose acetate derivatives, Divers – Ethyl vinyl acetate (EVA), polyesters of acrylic and methacrylic acids (Eudragit®). |
| Osmotic agents                       | Inorganic – magnesium sulfate, sodium chloride, potassium phosphate dibasic sodium carbonate and sodium sulfate. Organic- calcium lactate, magnesium succinate and tartaric acid. Carbohydrates – Sorbitol, mannitol, glucose and sucrose |

### Table 3: Components Of Soluble Inserts Containing Synthetic Polymers:

| Type of Component                       | Components                                                                 |
|-----------------------------------------|-----------------------------------------------------------------------------|
| Soluble synthetic polymers              | Cellulose derivatives – Hydroxypropyl cellulose methylcellulose, hydroxyethyl cellulose and hydroxypropyl cellulose. Divers – Polyvinyl alcohol, ethylene vinyl acetate copolymer. |
| Additives                               | Plastisizer – Polyethylene glycol, glycerin, propylene glycol Enteric coated polymer – Cellulose acetate phthalate, hydroxypropyl methylcellulose phthalate. Complexing agent – Polyvinyl pyrrolidone. Bioadhesives – Polyacrylic acids. |
Fig. 1 Factors attributing to poor bioavailability of ophthalmic formulation.