IJPSR (2010), Vol. 1, Issue 10 **(Review Article)**

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 27 May, 2010; received in revised form 19 August, 2010; accepted 15 September, 2010

AN OVERVIEW AND ADVANCEMENT IN OCULAR DRUG DELIVERY SYSTEMS

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Keywords:

Ocular Films,
Novel Ocular Drug Delivery System,
In-Situ Gel,
Ocular inserts,
Nanoparticles,
Niosomes

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ABSTRACT

Eye is most unique organ of the body. Various drug delivery systems are used to deliver drug into eyes are used but there are various limitations of conventional systems so researchers are finding new ways by which contact time, bioavailability and residence time can be enhanced as well as patient discomfort and frequency of dose can be reduced. The conventional dosage forms are account for 90% of currently accessible ophthalmic formulations. The major problem encountered is rapid precorneal drug loss. To improve ocular drug bioavailability, there are significant efforts directed towards newer drug delivery systems for ophthalmic administration. Newer research in ophthalmic drug delivery systems is directed towards a combination of several drug delivery technologies, that includes to develop systems which is not only prolong the contact time of the vehicle at the ocular surface, but which at the same time slow down the elimination of the drug. In this review various new drug delivery systems applied in eye like inserts, *in-situ* gel, liposomes, niosomes, nanoparticles, iontophorosis, corneal shields, drug embedded contact lenses, ocular wafers and films etc, are discussed.

INTRODUCTION: The dosage form or a drug delivery system containing any active pharmaceutical ingredient is administered to a patient through any route of administration to a patient. Dosage forms are administered directly to the eye for localized ophthalmic therapy. Most ocular treatments call for the topical administration of ophthalmic active drugs to the tissues around the ocular cavity[1]. Several types of dosage forms can be used as the delivery systems for the ocular delivery of drugs.

Physiology of Eye: A cross section of the eye shown in **Figure 1** .The internal structures of the eye and blood supply is illustrated in the same. The cornea, lens, and vitreous body are all transparent media with no blood vessels; oxygen and nutrients are transported to these nonvascular tissues by the aqueous humor. The aqueous humor has a high oxygen tension and about the same osmotic pressure as blood.

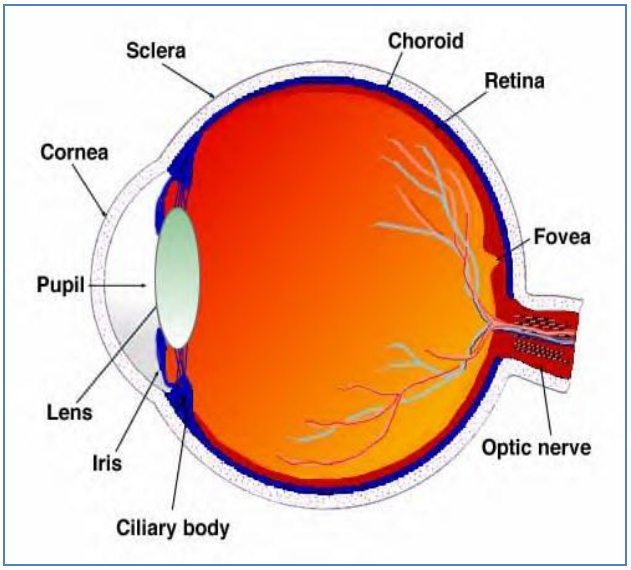

FIG. 1: CROSS SECTION OF THE EYE

The cornea also derives part of its oxygen need from the atmosphere, and if oxygen is excluded, the anaerobic metabolism results in increase in the intra corneal lactic acid concentration. This can produce edema sufficient to lead to the loss of corneal transparency and a temporary interference with vision. This may occur if a contact lens applied to the cornea does not permit the exchange of atmospheric oxygen or interferes with the capillary blood supply at the limbus [2].

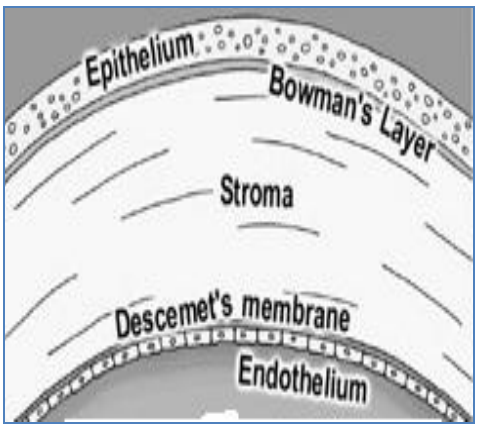

FIG. 2: SECTION THROUGH THE THROUGH THE CORNEA.

The cornea is covered by a thin epithelial layer, continuous with the conjunctiva at the cornea-sclerotic junction; the main bulk of the cornea is formed of criss-crossing layers of collagen and is bounded by elastic laminae on both front and back. A layer of endothelium covers its posterior surface. The cornea is richly supplied with free nerve endings. The transparent cornea is continued posterior into opaque white sclera, which consists of tough fibrous tissue. Both cornea and sclera withstand the intra-ocular tension constantly maintained in the eye [3].

The eye is constantly cleansed and lubricated by the lachrymal apparatus, which consists of four structures; lachrymal glands, lachrymal canals, lachrymal sac, naso-lachrymal duct. The lachrymal fluid secreted by the lachrymal glands is emptied on the surface of the conjunctiva of the upper eyelid at a turnover rate of 16% per min. It washes over the eyeball and is swept up by the blinking action of the eyelids. Muscles associated with the blinking reflex compress the lachrymal sac. When these muscles relax, the sac expands, pulling the lachrymal fluid from the edges of the lids, along the lachrymal canals, into the lachrymal sacs. Gravitational force, in turn, moves the fluid down the naso- lachrymal duct into the inferior meatus of the nose. Thus the eyeball is continually irrigated by a gentle stream of

lachrymal fluid that prevents it from becoming dry and inflamed. The amount of lachrymal fluid renewed by the frequent involuntary blinking movements normally is just sufficient to keep pace with its disappearance from conjunctiva. However, an excessive formation and secretion of lachrymal fluid, or lacrimation, can occur when foreign bodies or other irritants get into the eye, when a bright light is shone into the eye, or in emotional stress [4].

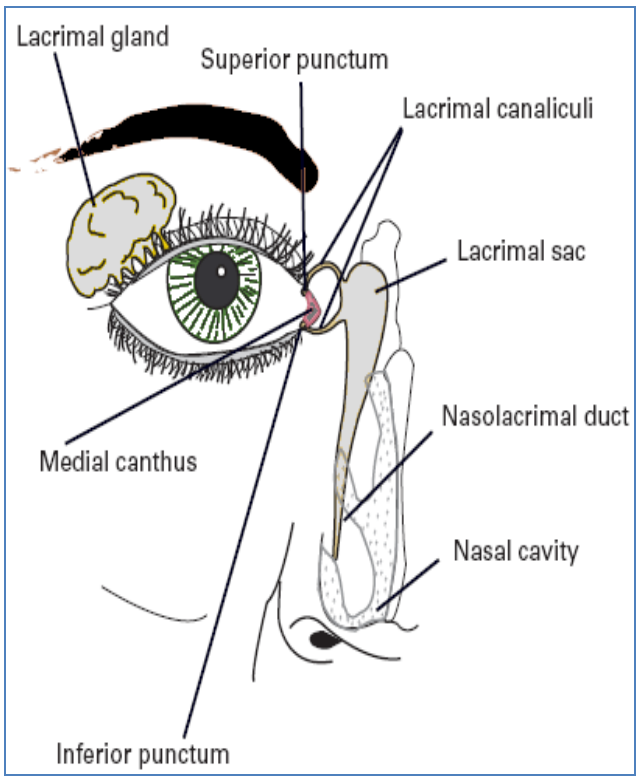

FIG. 3: THE NASOLACHRYMAL DRAINAGE SYSTEM.

The lachrymal fluid in humans has a normal volume of 7µl and is an isotonic aqueous solution of bicarbonate and sodium chloride (pH 7.4) that serves to dilute irritants or to wash the foreign bodies out of the conjunctival sac. It contains lysozyme, whose bactericidal activity reduces the bacterial count in the conjunctival sac. The rate of blinking varies widely from one person to another, with an average of approximately 20 blinking movements per min. During each blink movement the eyelids are closed for a short period of about 0.3 sec.

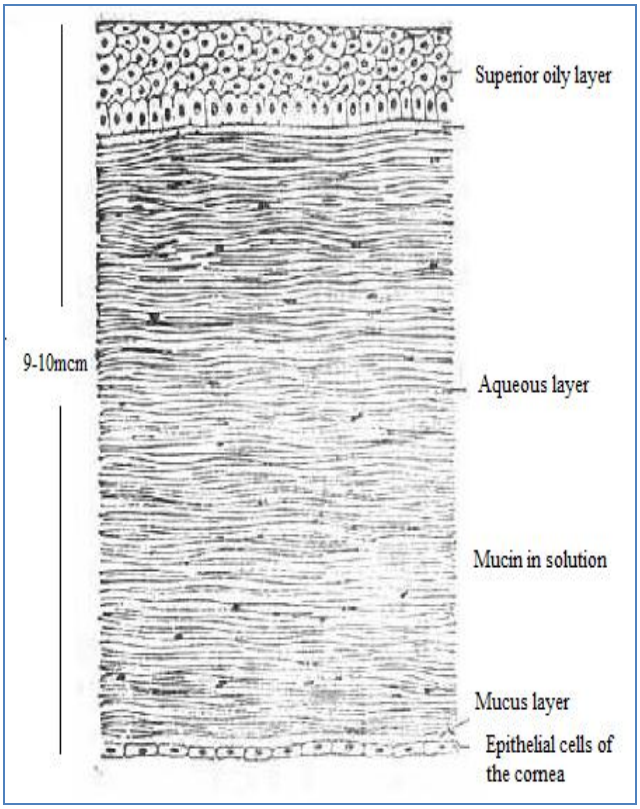

FIG. 4: STRUCTURE OF THE TEAR FILM IN THE HUMAN EYE

The aqueous humor in humans has a volume of approximately 300µl that fills the anterior chamber of the eye. Aqueous humor is secreted by the ciliary's processes and flows out of the anterior chamber at a turnover rate of approximately 1% / min .The drainage system has recently been defined at the sinus venous sclera, of low blood pressure. This drainage is an unspecific mechanical process different from the production of aqueous humor. The rate of drainage is comparable to the rate of production, thus maintaining a constant intra-ocular tension of 25-30 mm/Hg in humans [5].

This intra-ocular pressure remains fairly constant even when the arterial pressure widely fluctuates. It rises slightly when the external ocular muscles contract and on winking .It is known that the focusing mechanism of the eye depends upon the existence of a fairly constant intra-ocular tension. If the tension is too high, as in glaucoma the ciliary's muscles may not be able to bring about accommodation. The high intra-ocular pressure may also cause the

restriction of the retinal circulation with resultant damage to the retina. On the other hand, an excessive reduction in the intra-ocular tension may slacken the suspensory ligaments of the lens and allows the latter to bulge [1]. One of the major problems encountered with the topical delivery of ophthalmic drugs is the rapid and extensive precorneal loss caused by the drainage and high tear fluid turnover. Lacrimation and blinking are actually efficient protective mechanisms, which keep the eye free of foreign substances, but they prevent efficient ocular residence time of conventional eye drops is limited to a few minutes and the ocular absorption of a topically applied drug is reduced to approximately1-10%. Furthermore, drug uptake occurs as a massive pulse entry, followed by a rapid decline. The drug is mainly absorbed systemically via conjunctiva and nasal mucosa, which may result in some undesirable side effects [6].

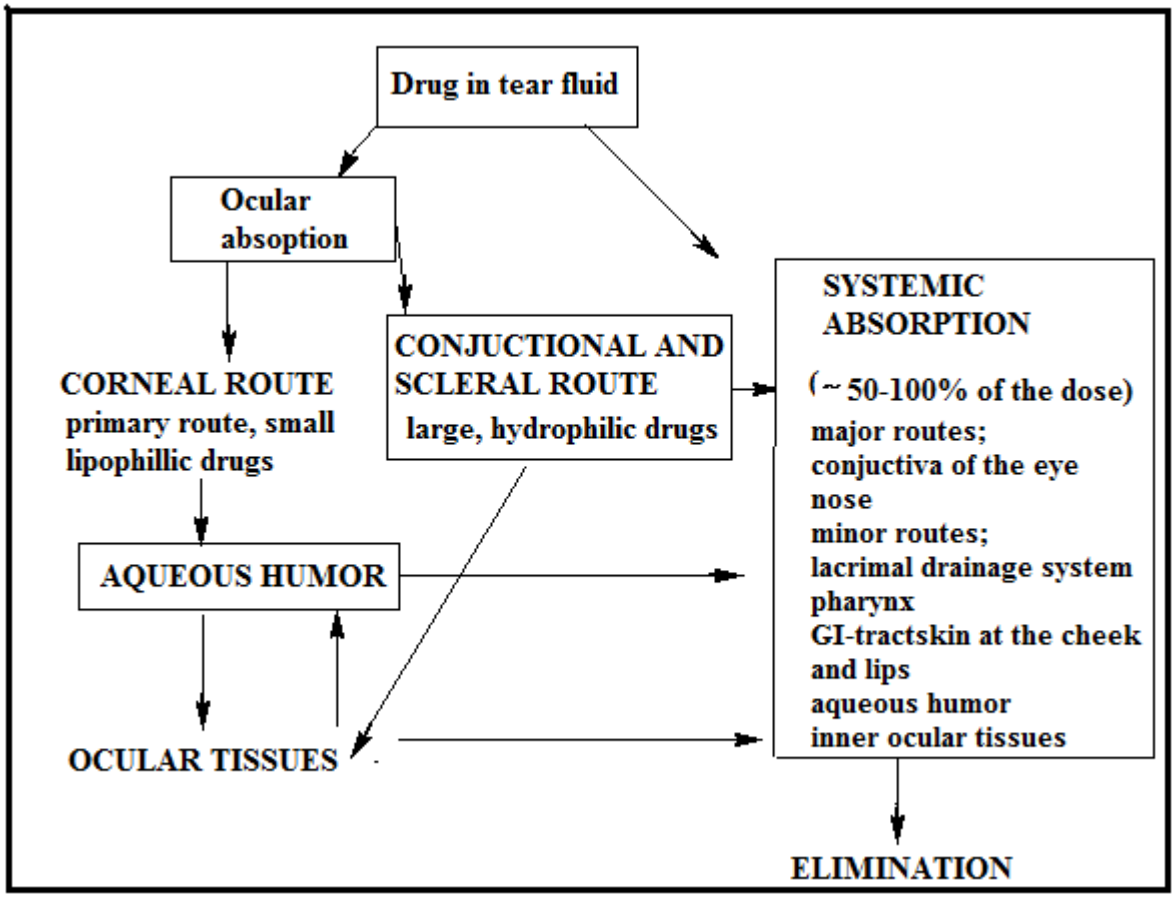

FIG.5. FATE OF OPHTHALMIC DRUG DELIVERY SYSTEMS

The eye drop dosage form is easy to instill but suffers from the inherent drawback that the majority of the medication. Its contents are immediately diluted in the tear film as soon as the solution is instilled into the cul-de-sac and is rapidly drained away from the precorneal cavity by constant tear flow, a process that proceeds more intensively in inflamed than in the normal eyes, and lachrymal- nasal drainage. Therefore only a small fraction of the instilled dose is absorbed into the target tissues (e.g. 1 to 2% only is available to the aqueous humor), and relatively concentrated solution is required for instillation to achieve an adequate level of therapeutic effect. The frequent periodic instillation eye drops becomes necessary to maintain a continuous sustained level of medication. This gives the eye a massive and predictable dose of medication, and unfortunately, the higher the drug concentration in the eye drop solution, the greater the amount of drug lost through naso-

lachrymal drainage system. Subsequent absorption of this drained drug, if it is high enough, may result in undesirable systemic side effects [2]. Furthermore, the intra-ocular concentration of medication surges to a peak every time eye drops are instilled; the drug level then declines rapidly at an exponential pattern as time passes. A plot of intra-ocular drug concentration verses time yields a series of peaks of drug level, which may surpass the toxic threshold of the drug, separated by extended valleys of drug level below the critical level required to achieve the desired therapeutic efficacy [1, 7].

Sustained and controlled delivery of drugs to the ocular tissues continue to remain a major objective for formulation scientists and engineers in light of the emergence of more potent drugs and biological response modifications with limited biological half-lives. Another physiological constraint is the limited permeability of cornea resulting in low absorption of ophthalmic drugs. A major portion of the administered dose drains into the naso-lachrymal duct and thus can cause unwanted systemic side effects. Additionally, the rapid elimination of the drug through the punctum results in a short duration of the therapeutic effect resulting in a frequent dosing regimen. A significant challenge for the formulation is to circumvent these protective barriers of the eye without causing permanent damage to the tissue [3].

To overcome these problems, various ophthalmic vehicles, such as ointments. suspensions, micro- and nanocarrier system inserts and liposome's have been investigated. Another option is to increase the viscosity of the instilled solution .The incorporation of soluble polymers into aqueous solutions increases solution's viscosity and therefore drug retention. These kinds of topically applied formulations find their application as drug delivery systems or as tear substitutes in the treatment of keratitoconjunctivitissicca [8].

Suspension-type pharmaceutical dosage forms have also been widely used for ocular medication. Suspension formulations also have some inherent drawbacks. For example, they are generally formulated with relatively water-insoluble drugs to avoid the intolerable high toxicity created by saturated solutions of water-soluble drugs. However, the rate of drugs release from the suspension is dependent upon the rate of dissolution of drug particles in the medium, which varies constantly in its composition with the constant inflow of lachrymal fluid and out flow of lachrymal fluid. A basic concept shared by most scientists in ophthalmic research and development is that the therapeutic efficacy of an ophthalmic drug can be greatly improved by prolonging its contact with the corneal surface [1, 8].

The sites of action for most ophthalmic drugs are located in the inner eye. Although external eye structures are readily accessible, the biological barriers, mainly the corneal epithelium limit ocular drug absorption. Consequently, after instillation of an eye drop, typically less than 5% of an applied dose reaches the intra-ocular tissues. This is due to tightness of the corneal barrier and rapid loss of the instilled solution from the precorneal area. The goal of ophthalmic drug delivery systems has traditionally been to maximize ocular drug absorption rather than to minimize systemic absorption [4].

Drug delivery can make a big difference in ocular drug treatment. Ocular bioavailability after topical eye drop administration, the most common form of ocular medication, is less than 5% and often less than 1%. Unfortunately only the diseases of the anterior segment of the eye can be treated with eye drops. From the drug delivery point of view the eye is very interesting, as small multi compartmental system with various tissues, their boundaries, and fluid flow factors. Unless highly selective drug targeting systems are developed, the local administration remains as the mainstay in ocular drug

treatment. On the other hand, local administration avoids some of the problems that are associated with systemic administration [9]. Although the conventional dosage forms dominate the field of ocular drug delivery, the history has shown that many new pharmaceutical concepts were introduced to the clinical practice for the first time in ophthalmology. Ocusert® (Launched in 1975 by Alza Corp.) was the first really advanced drug delivery system. Currently ocular drug delivery technology is facing great challenges and opportunities [5].

Viscosity and Ocular Residence: The physiological requirement to preserve acuity pose significant problems in achieving sustained drug concentrations particular associated with the need to provide a transparent formulation, reducing irritancy and avoid rapid clearance. Tonicity or solubility considerations limit the concentration of the active to about 2% w /v which equates to a maximum dose of around 500-600 µg in a single drop [10]. Particulates and ointments can be used and may increase exposure of the pericorneal area but the advantages produced by emulsion formulations can be varied. In a micro emulsion for example, if drug has high affinity for oil phase, there is a like hood of clearance before sufficient time has been allowed for partition from the vehicle to the tissue. For this reason the depot release is low, although persistence from the oil-based formulation may be significant.[6]

Drug Elimination from Lacrimal Fluid: Several mechanisms such as a relatively impermeable corneal barrier and rapid drainage of the instilled solution protect the eye. Mechanistic studies have shown that drugs are mainly eliminated from the pre-corneal lachrymal fluid by solution drainage, lacrimation and nonproductive absorption to the conjunctiva of the eye as shown in **Fig. 6**.

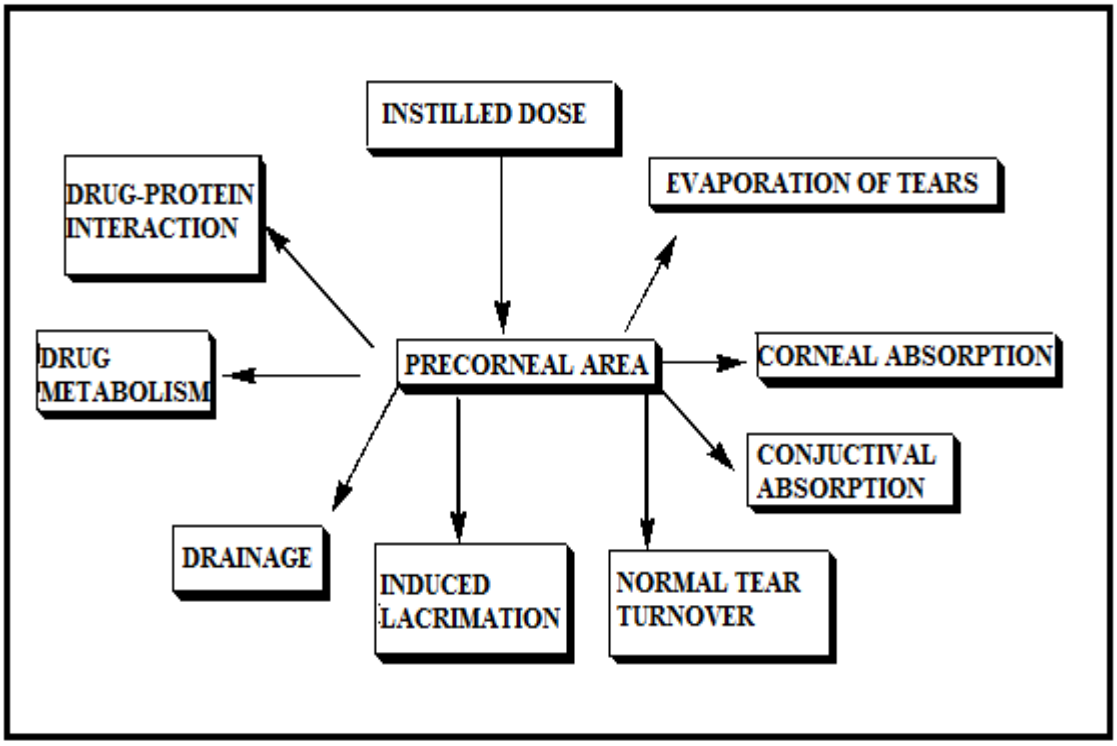

FIG. 6: ELIMINATION OF DRUGS FROM DIFFERENT ROUTES

These factors and the corneal barrier limit the penetration of the topically administered drug into the eye. Only a few percent of the applied dose is delivered into intra-ocular tissues and

the major part (50-100%) of the dose is absorbed systemically as shown in **Fig. 7**.

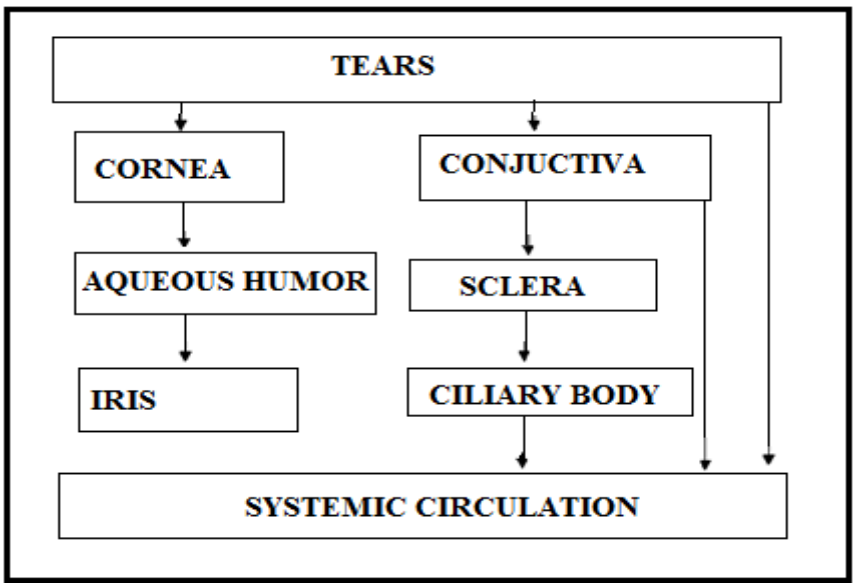

FIG.7. FACTORS AND CORNEAL BARRIER LIMITATIONS FOR PENETRATION OF TOPICALLY ADMINISTERED DRUG

The normal commercial eyedropper delivers a drop volume of 25-56µl (average 39µl). When an eye drop is instilled, the human *cul-de-sac* may momentarily contain a 30µl volume, but the instilled solution is rapidly removed by spillage from the conjunctiva sac or loss through the Punta to the lachrymal drainage system until the tears return to their normal volume (7µl). The initial first order drainage rate of eye drops from ocular surface is typically 0.5-0.7ml/min in rabbits and 1.5ml/min in humans. This rate decreases with larger eye drop volumes .If the volume of an eye drop is decreased to 5-10µl and the concentration, the ocular bioavailability can be substantially increased and systemic absorption decreased. It has been shown, using a mass transport theorem, that maximally a four-fold improvement in ocular bioavailability may be achieved for topically applied drugs with a low corneal permeability, if the applied volume is decreased sufficiently [4, 10].

Compared to the initial drainage rate, the normal rate of tear turnover is much slower, approximately 0.16µl /min to 1.2µl/min in humans and 0.07µl /min to 0.5µl /min in rabbits. Ocular administration of irritating drugs or vehicles increases the drug loss from the pre-corneal area to a further extent due to induced lacrimation. An important route of drug loss from the lachrymal fluid is systemic absorption through the conjunctiva of the eye. The conjunctiva is a thin, vascular membrane that lines the inner surface of the eyelids and covers the anterior part of sclera [7].

Conventional Ocular Formulations for Ocular Drug Delivery: The conventional drug delivery systems like solutions, suspensions and ointments are no longer sufficient to fulfill the present day requirements of providing a constant rate delivery and prolonged time. The advantages and disadvantages of using conventional dosage form of delivery are shown in **Table 1**. Comparison for ophthalmic dosage form the criteria for their selection on the basis of duration of action of drug, bio-availability, its cost effectiveness, safety and patient complacencies are summarized in **Table 2**: Conventional dosage forms are solutions, suspensions, ointments, gels, erodible inserts, ocular films and non-erodible inserts [11].

TABLE 1: COMPARISON FOR OPHTHALMIC DOSAGE FORM

DOSAGE FORMS	ADVANTAGES	DISADVANTAGES
Solutions	• Convenience	• Rapid pre-corneal elimination, • Loss of drug by drainage, • No sustained action.
Suspensions	• Patient compliance • Best for drugs with slow dissolution.	• Drug properties decide performance • Loss of both solution and suspended solid.
Emulsions	• Prolonged release of drug from vehicle • Enhanced pulsed entry	• Patient non compliance • Blurred vision • Possible oil entrapment.
Gels	• Comfortable • Less blurred vision than ointment	• No rate control on diffusion • Matted eyelids after use.
Ointment	• Flexibility in drug choice • Improved drug stability • Increased tissue contact time • Inhibition of dilution by tears • Resistance to naso- lachrymal drainage	• Sticking of eyelids • Poor patient compliance • Blurred vision • No true sustained effect • Drug choice limited by partition co-efficient
Erodible inserts	• Sophisticated and effective delivery system • Flexibility in drug type and dissolution rate • Need only be introduced into eye and not removed	• Patient discomfort • Requires patient insertion • Movement of system around eye can cause abrasion
Non-erodible inserts	• Controlled rate of release • Prolonged delivery • Flexibility for type of drug selected • Sustained release	• Patient discomfort • Irritation to eye • Patient placement and removal

TABLE 2: CRITERIA FOR SELECTION OF OCULAR DOSAGE FORMS

GELS	INJECTIONS	INSERTS	OINTMENTS	ORALS	SOLUTIONS	SUSPENSIONS
Drug; Long duration required	Drug; Target site Accessibility Onset of response	Drug; Long Duration required	Drug; Long Duration required	Drug; Impermeable Topically Few systemic side effects	Drug; Soluble Less potent	Drug; Insoluble Drug potent
Low bioavailability	--	Low bioavailability	Low bioavailability	--	Required high concentration	--
Intermediate cost	Requires physician	High cost per dose	Low cost	Low to moderate cost	Low cost	Low cost
Some blurring	--	No blurring	Severe blurring	--	Little blurring	Little blurring
Selection; Simple administrational reduced frequent administration	Selection; Last alternative surgical application	Selection; Good control of rate of drug administration younger patient	Selection; Slight threatening	Selection; Drug designed not optimized	Selection; Convenient accepted	Selection; Convenient Accepted some extend duration
Safety	Safety	Safety; Unnoticed expulsion	Safety	Safety	Safety; Solution clear	Safety; Solutions cloudy

Requisites of Controlled Ocular Delivery [12]:

- It provides the better housing to the delivery system.
- To circumvent the protective barriers like drainage, lacrimation and diversion of exogenous chemicals into the systemic circulation by the conjunctiva
- To increase the ocular bioavailability of drug by increasing corneal contact time. This can be achieved by effective coating or adherence to corneal surface so that the released drug effectively reaches the anterior chamber.
- To overcome the side effects of pulsed dosing produced by conventional systems.
- To provide comfort and compliance to the patient and yet improve the therapeutic performance of the drug over conventional systems.
- To provide sustained and controlled drug delivery.
- To provide targeting within the ocular globe, so as to prevent the loss to other ocular diseases.

Ocular drug and delivery system are currently undergoing a process of design optimization due to inherent physiological and anatomical constraint of the eye leading to limited absorption of topically applied drug. Two major approaches are being undertaken to improve topical delivery drugs, which are [13];

- Approaches to prolong the contact time of drug with corneal surface.

- Approaches to enhance corneal permeability either by mild or transient structural alteration of corneal epithelium or by modification of chemical structure of the drug molecules.

The recent formulation trends that are currently being explored include polymeric solution, phase transition, collagen shields, pseudolactices ocular penetration enhancers, ocular sonophoresis and various ocular drug delivery devices [7].

Ocular Dosage Forms [13]:

- Polymeric solutions
- Phase transitions systems
- Muco-adhesive/bio-adhesive systems
- Pseudolattices
- Collagen shields
- Ocular penetration enhancers
- Ocular drug delivery devices
- Particulate systems for ocular drug delivery
- Vesicular systems for ocular drug delivery

1. **Polymeric solutions:** The additions of polymers like methylcellulose, polyvinyl alcohol, hydroxypropyl methylcellulose and polyvinyl pyrrolidone to the eye drop solution increases the corneal penetrations of drug.

2. **Phase transition systems:** These are liquid dosage forms which shift to the gel or solid phase when instilled in the *cul-de- sac*. Polymers that are normally used are luterol c-127 and polxamer- 407 whose viscosity increases, when its temperature raised to 37°C .Cellouse acetate phthalate too coagulates, when its native pH of 4.5 is raised by tear fluid to pH 7.4.

3. **Muco-adhesive dosage forms:** Any polymer solution /suspension placed in the eye, first encounters mucin at the cornea and conjunctival surface. If the polymer adheres to the mucin, the interaction is referred to as muco-adhesion, mucus on the corneal surface is provided by the goblet containing conjunctiva that is not tightly bound so that a corneal adhesive would attach to cornea itself and to be a true bio-adhesion.

4. **Collagen shields:** Collagen shields promote wound healing and perhaps more important to delivery to deliver a variety of medications to the cornea and other ocular tissues. Collagen is structural protein of bones, tendons ligaments and skin. Collagen comprises more than 25% of the total body

portion in mammals. It is main constituent of food grade gelatin.

5. **Pseudolattices:** Pseudolattices are a new class of polymeric colloidal dispersion and films forming agents used for typical application into the animals and human being used for sustaining the drug activity *in-vivo*. Organic solution of polymer is dispersed in an aqueous phase to form an o/w type emulsion.

6. **Ocular penetration enhancers:** Like acting filament inhibitors, surfactants, bile salts, chelators and organic compounds have been used to increase the bioavailability of topically applied peptides and protein which are otherwise poorly absorbed due to unfavorable molecular size, charge, hydrophilic as well as their susceptibility to degradation by peptidases in the eye.

7. **Ocular drug delivery devices [14-15]:** There are three types;

    1. Matrix type drug delivery systems
    2. Capsule type delivery systems
    3. Implantable drug delivery systems

    1. **Matrix type drug delivery systems:** These are the devices that have the therapeutic agent, which is incorporated or impregnated with in the polymer, for controlled release of drug. E.g.; Hydrophilic soft contact lenses, soluble ocular inserts (**fig. 9**).

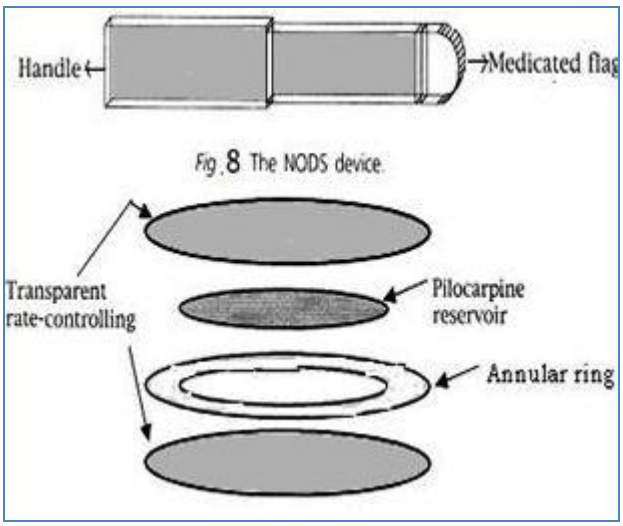

FIG. 8: OCCUSERTS

- **Hydrophilic soft contact lenses**: Several kinds of polymers have been used for the preparation of these lenses. They are made up of hydro gels that absorb certain amounts of aqueous solution, because of this property they have been found useful for drug delivery to anterior of the eye.
- **Soluble ocular inserts**: Soluble ocular inserts, such as polyvinyl alcohol insert, the soluble ophthalmic drug inserts and polypeptides devices are matrix type polymeric devices used for drug delivery to eye.

TABLE 3: OCULAR INSERT DEVICES

NAME	DESCRIPTION
Bioadhesive ophthalmic drug inserts (BODI) [16]	Adhesive rods based on mixtures of hydroxypropyl cellulose, ethyl cellulose, poly acrylic acid cellulose acetate phthalate.
Collagen shields [17, 18]	Erodible discs composed of cross-linked porcine sclera) collagen.
'Dry Drops' [19]	A preservative-free drop of hydrophilic polymer solution (hydroxypropyl methylcellulose) that is freeze-dried on the tip of a soft hydrophobic carrier strip, immediately hydrates in the tear film.
Gelfoam[20]	Slabs of Gelfoam impregnating with a mixture of drug and Cetyl ester wax in chloroform.

Lacrisert [22]	Rod-shaped device made from hydroxypropyl cellulose used in the treatment of dry eye syndrome as an alternative to artificial tears.
Minidisc or ocular therapeutic system (OTS) [22]	4-5 mm diameter contoured either hydrophilic or hydrophobic disc.
NODS (New or novel ophthalmic delivery system) [23]	Medicated solid polyvinyl alcohol flag that is attached to a paper-covered handle. On application, the flag detaches and gradually dissolves, releasing the drug.
Occuserts [20]	Flat, flexible elliptical insoluble device consisting of two layers enclosing a reservoir, used commercially to deliver pilocarpine for 7 days.
Ophthalmic inserts [22]	A cylindrical device containing mixtures of silicone elastomer and sodium chloride as a release modifier with a stable polyacrylic acid (PAA) or polymethylacrylic acid (PMA) interpenetrating polymer network grafted onto the surface.
SODI (Soluble Ocular Drug Insert) [23]	Small oval wafer, composed of a soluble copolymer consisting of acrylamide, N-vinylpyrroiidone and ethyl acrylate, softens on insertion.

1. **Capsular type drug delivery systems:**
- These are the devices that have a therapeutic agent encapsulated with in closed compartment surrounded by a polymer membrane.
- Ex-Occuserts
- Occuserts
- A truly continuous controlled release and zero order kinetic fashion was achieved using occusert [8].

2. **Implantable drug delivery:** Implantable devices which have been developed and used include an osmotic mini-pump, a drug pellet coated with polyvinyl alcohol and ethylene acetate and poly sulfone capillary fiber. The generic osmotic mini pump (Alzet®) is a useful implantable drug delivery system with a constant drug delivery rate with a pumping duration of up to 2 weeks

TABLE 4: EXAMPLES OF THE DRUGS USED IN OPHTHALMIC DRUG DELIVERY SYSTEMS

CLASSIFICATION	EXAMPLES (AVAILABLE AS OPHTHALMIC SOLUTION, SUSPENSION OR OINTMENT)	INDICATION
Antibacterials	0.5-1% Chloramphenical, 0.3 & 0.5% gentamicin, o.3% ciprofloxacin, 1% fusidic acid, 0.3% levofloxacin, 0.3% ofloxacin, 0.3% lomefloxacin, 0.3% norfloxacin, moxifloxacin, 10% sulphacetamide sodium	Dacryocystitis, conjunctivitis, cataract, ophthalmia neonatum, keratitis, blephritis
Antivirals	Acyclovir, idoxuridine, vidarabin, trifluridine, ganciclovir	Viral infection eg dendritic corneal ulcers, keratitis, keratoconjuctivitis sicca
Corticosteroids	0.1% Betamethasone, dexamethasone, prednisolone acetate and phosphate, fluorometholone, hydrocortisone, loteprednole, rimexolone	keratoconjuctivitis sicca, uveitis, episleritis, scleritis
Mast cell stabilizers	Lodoxamide, sodium cromoglycate, nedocromil, pemirolast, ketotifen, olopatadine	keratoconjuctivitis sicca, conjunctivitis
Anti-inflammatory agents	Diclofenac sodium, flurbiprofen, ketorolac	Inflammation and allergic conjunctivitis
Antihistamines	Antazoline, emedastine, levocabastine	conjuctivitis

Miotics (parasympathomimetics)	Pilocarpine (1, 2 and 4%)	Glaucoma [21]
Adrenergic agonists (sympathomimetics)	Adrenaline, apraclonidine, brimonidine tartrate, dipivefrine	Glaucoma [21, 24]
Beta-blockers	Timolol maleate, betaxolol, carteolol, levobunolol, metipranolol,	Glaucoma [21,25,26]
Local anaesthetics	Amethocaine, lignocaine	Anaesthesia during surgery procedures
Antifungals	5% natamycin	Fungal infection,
Carbonic anhydrase inhibitors (CAI)	acetazolamide, diclofenamide, methazolamide, brinzolamide, dorzolamide,	Glaucoma [21]
Vasoconstrictors	Naphazoline, tetryzoline	keratoconjuctivitis sicca,
Antiseptic	5% povidone-iodine	cataract
Artificial tears	Carbomer, carboxy methyl cellulose, hypromellose, polyvinyl alcohol, sodium hyaluronate, polyvidone	Conjunctivitis, dry eyes, episcleritis
Cycloplegics (Mydriatics)	Atropine SO_4, cyclopentolate HCl, homatropine HBr, scopolamine (hyoscine HBr), tropicamide	Keratitis, uveitis
Immunosuppresants	Cyclosporin	Uveitis, corneal transplantation
Prostaglandin analogues	Bimatoprost, latanoprost, travoprost, unoprostone isopropyl	Primary open angle glaucoma[21]

CONCLUSION AND FUTURE SCOPE: Advanced technology in ocular drug delivery is burgeoning field and based on the use of nanocarriers (nanoparticles, liposomes, dendrimers) has been investigated recently with the aim of enhancing frontal ocular drug delivery. These systems are claimed to provide a prolonged residence time at the ocular surface, minimising the effect of natural eye clearance systems.

It has been argued that, when combined with controlled drug delivery, it should be possible to provide drug therapeutic levels for a prolonged time at the site of action. The use of nanoparticles and other forms of ocular drug delivery have been reviewed in several excellent texts; in future also the research in this field will definitely take a momentum.

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