OCCULAR DRUG DELIVERY SYSTEM

CONTENTS:

1. Introduction

2. Topical ocular drug delivery and the constraints to ocular therapy

3. Classification

4. Liquids
   4.1 Solutions and Suspensions
   4.2 Development Of Phase Transition System
   4.3 Graft copolymers
   4.4 Sprays
   4.5 Emulsions

5. Ocular drug delivery devices
   5.1 Soft Contact Lenses
   5.2 Soluble Ophthalmic Drug Inserts (SODI)
   5.3 Bioadhesive Ophthalmic Drug Inserts (BODI)
   5.4 Implantable Systems
   5.5 PROSERT®
   5.6 OCUSERT®
   5.7 Collagen Shields
   5.8 MYDRIASERT®

6. Colloidal systems for eye
   6.1 pharmacosomes
   6.2 neosomes
   6.3 discosomes
   6.4 pharmacosomes
   6.5 nanoparticles

7. Various chemical approaches for ocular drug delivery
   7.1 chemical drug delivery system:-
   7.2 enhancement of permeability by ion pair effect
   7.3 soft drug approach

8. Use of cyclodextrin

9. Evaluation:-

10. Research work done in ocular drug delivery
INTRODUCTION:

Except for skin, the eye is the most easily accessible site for topical administration of a medication.

Drugs are commonly applied to the eye for a localized action, on the surface, or in the interior of the eye.

A major problem in ocular therapeutics is the attainment of an optimal drug concentration at the site of action.

Poor bioavailability of drugs from ocular dosage forms is mainly due to the pre corneal loss factors which include tear dynamics, non-productive absorption, transient residence time in the cul-de-sac, and the relative impermeability of the corneal epithelial membrane.

Due to these physiological and anatomical constraints only a small fraction of the drug, effectively 1% or even less of the instilled dose, is ocularly absorbed.

The effective dose of medication administered ophthalmically may be altered by varying either the strength, volume, or frequency of administration of the medication or the retention time of medication in contact with the surface of the eye.

So far, attempts have been made to improve ocular drug bioavailability by extending drug residence time in the conjunctival sac and improving drug penetration across the cornea, the major pathway of drug entry into the internal eye.

The focus of this SEMINAR is on the recent developments in topical ocular drug delivery systems, the rationale for their use, their drug release mechanism, and the characteristic advantages and limitations of each system.

In addition, IT attempts to give various analytical procedures including the animal models and other models required for bioavailability and pharmacokinetic studies. The latter can aid in the design and predictive evaluation of newer delivery systems.
TOPICAL OCULAR DRUG DELIVERY AND THE CONSTRAINTS TO OCULAR THERAPY:

It is common knowledge that the ocular bioavailability of drugs applied topically as eye-drops is very poor. The absorption of drugs in the eye is severely limited by some protective mechanisms that ensure the proper functioning of the eye, and by other concomitant factors.

For example:

- drainage of the instilled solutions;
- lacrimation and tear turnover;
- metabolism;
- tear evaporation;
- non-productive absorption/adsorption;
- limited corneal area and poor corneal permeability; and
- binding by the lacrimal proteins.

The drainage of the administered dose via the nasolacrimal system into the nasopharynx and the gastrointestinal tract takes place when the volume of fluid in the eye exceeds the normal lacrimal volume of 7–10 microlitres. Thus, the portion of the instilled dose (one to two drops, corresponding to 50–100 microlitres) that is not eliminated by spillage from the palpebral fissure is quickly drained and the contact time of the dose with the absorbing surfaces (cornea and sclera) is reduced to a maximum of two minutes.

The lacrimation and the physiological tear turnover (16% per minute in humans in normal conditions) can be stimulated and increased by the instillation even of mildly irritating solutions. The net result is a dilution of the applied medication and an acceleration of drug
loss. It is now definitively established that the rate at which instilled solutions are removed from the eye varies linearly with instilled volume. In other words, the larger the instilled volume, the more rapidly the instilled solution is drained from the precorneal area. In sort, we can divide various factors into two classes:
1. which increases the bioavailability.
2. which decreases the bioavailability.

So looking to the constraints for ocular drug delivery, we should concentrate on two things:
1) To prolong the contact time of drug with corneal surface.
2) To enhance corneal permeability, either by mild or transient structural alteration of corneal epithelium or by modification of chemical structure of the drug molecules.

**CLASSIFICATION:**

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:

1. **LIQUIDS:** Solutions, Suspensions, Sol to gel systems, Sprays

2. **SOLIDS:** Ocular inserts, Contact lenses, Corneal shield, Artificial tear inserts, Filter paper strips

3. **SEMI-SOLIDS:** Ointments, Gels

4. **MISCELLANEOUS:** Ocular iontophoresis, Vesicular systems, Mucoadhesive dosage forms, Particulates, Ocular penetration enhancers: Use of Hyaluronic acid, Use of Hydroxy Beta Cyclodextrin.
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.

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.

These forms also have disadvantages:

1) The very short time the solution stays at the eye surface,
2) Its poor bioavailability (a major portion i.e. 75% is lost via nasolacrimal drainage),
3) 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.

There are two approaches to enhance the residence time of solution dosage form.

1) Addition of viscosity imparting agents.
2) Development of phase transition system (sol – to – gel system).

1) Viscosity Imparting Agents:-

An increased vehicle viscosity should correspond to a slower elimination from the pre ocular area and hence a greater trans corneal penetration of the drug into the anterior chamber. Examples:- PVA, polyvinylpyrrolidone (PVP), methylcellulose, Hydroxy ethyl cellulose, HPMC, and Hydroxy propyl cellulose (HPC).

It was suggested by Green and Downs that a minimum viscosity of 20 cps is needed for optimum corneal absorption.
2) Development Of Phase Transition System (Sol – To – Gel System):

The new concept of producing a gel in situ (e.g. in the cul-de-sac of the eye) was suggested for the first time in the early 1980s.

These systems, when instilled into the cul-de-sac, shift from the liquid form to the gel or solid phase.

The authors suggest that such systems can be formulated as drug-containing liquids suitable for administration by instillation into the eye, which upon exposure to physiological conditions will shift to the gel (semi-solid) phase, thus increasing the precorneal residence time and enhancing the ocular bioavailability of the drug.

Possible mechanisms for phase – transition system:-

A) Temperature Dependent System:
In situ gelling by a temperature change is produced when the temperature of polymeric dispersion is raised from 25 to 37°C. It can be prepared by using poloxamer 407 and Lutrol FC 127.

B) pH dependent system:
At formulation pH (4 – 6); it forms clear free flowing system but at physiological pH (7.4) of the eye, it forms firm gel which has capacity to release the drug for long time. The polymers used for this purpose are Carbopol, Cellulose acetate phthalate and chitosan. Generally, this system is used along with the viscosity imparting agents like MC, HPMC etc.

C) Ion Induced System:
This system is converted into gel when introduced in the ion concentration at the physiological condition of eye.

Examples:
1. Gelrite: which is the low acetylated gellan gum.

Gelrite has been granted regulatory approval as a pharmaceutical excipient and is marketed by Merck in a controlled-release glaucoma formulation called Blocadren® Depot (Timoptic-XE®).

Formulations with the in situ gel Gelrite can be administered to nasal or ocular mucosa as a low-viscosity solution. On contact with cations in tear fluid or nasal secretion the formulation will form a clear gel. This is caused by cross-linking of the negatively charged polysaccharide helices by monovalent and divalent cations (Na+, K+, Ca2+).

In an ion-free aqueous medium, Gelrite forms double helices at room temperature (sol in Fig. 1). This solution has a viscosity close to that of water and the helices are only weakly associated with each other (by van der Waals attraction). When gel-promoting cations are present some of the helices associate into cation-mediated aggregates, which cross-link the polymer (gel1). On heating the polysaccharide in an ion-free environment, the
polysaccharide becomes a disordered coil. However, on heating a sample with cations present, the nonaggregated helices melt out first, and the aggregated helices (gel2) melt out at a higher temperature in a second transition.

When calcium ions are predominant in the media, the gel formed due to interaction between $-\text{COOH}$ of Gelrite and $\text{Ca}^{++}$ has more gel strength as compared to the gel strength of gel formed due to interaction between $-\text{COOH}$ and $\text{K}^+$.  

2. **Sodium alginate:-**
Alginate is the block copolymer of the $\beta - D$ – mannuronic acid and alpha- $d$ – glucoronic acid. But only the glucuronic acid content is responsible for the gelling capacity. It forms 3 - dimensional gel in presence of calcium ions.
Calcium linked alginate gels have good mechanical properties even if prepared from very less concentration (i.e. 0.5% concentration) and they can physically entrap whole molecules and sustained release.

D) Enzyme dependent system:

Xanthan gum has capacity to form gel with the enzyme LYSOZYME which is present in the tear fluid.

No. of patented autoclavable in-situ gelling eye preparations are made by using vehicle containing the xanthan gum.

**Recent trends in sol-gel transition (graft copolymers):**

Graft copolymers are the polymers which are made up by grafting one polymer of desired charac. On the another one.

For example, poloxamer is thermo gelling polymer which is 1st converted in to monoamine terminated poloxamer and then its amine terminated part is grafted with the hyaluronic acid and the generated polymer is called poloxamer-g-hyaluronic acid which has dual properties means it has thermo gelling properties as well as penetration enhancing properties.

Another example is poloxamer-g-c6s (c6s = chondroitin -6 – sulphate).

**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.

**Emulsions**

w/o Micro emulsions offer a promising alternative. They are thermodynamically stable and optically isotropic colloidal systems with excellent wetting and spreading properties. Moreover, they are comprised of aqueous and oily components and therefore can accommodate both hydrophilic as well as lipophilic drugs.

w/o micro emulsions where administered in the eye; converted into the LC state which releases the drug slowly and produce a sustained release preparation for eye.

Cationic emulsions:

They are developed by the Novagali pharmaceuticals for ophthalmic applications.
The topical administration of a cationic emulsion onto the eye has shown to increase the residence time of the drug on the cornea, with a lower contact angle and an increased spreading coefficient in comparison with conventional eye drops and anionic emulsions. (as shown in the figures).
Novagali has screened most cationic lipids and has identified Oleylamine, which was developed as a proprietary excipient with a drug master file for Europe and USA.

In the case of the Back Of The Eye (BOTE) diseases, Novagali has designed specific cationic emulsions for non-invasive topical administration which allow the drug to migrate to the retina via the trans-scleral route from the cornea and conjunctiva which act as a reservoir. (as shown in the figure).

**Aqueous Suspensions**

A newer concept in suspensions is the use of microspheres or microparticulates. These are drug containing small polymeric particles (erodible, nonerodible, or ion-exchange resins) that are suspended in a liquid carrier medium.

Upon administration into the eye, the particles reside at the delivery site and the drug is released from the particle through diffusion, chemical reaction, polymer degradation, or ion-exchange mechanism.

Newer approaches, such as the use of mucoadhesive particulates, pH responsive particulates, nanoparticles etc., have also been used to formulate microparticulate dosage forms.

These dosage forms show significantly higher and sustained delivery in the eye.
Certain technological problems faced with these formulations include the production of stable suspensions, uniform dose per unit volume, efficient drug entrapment, reproducible and large-scale manufacture, and uniform particle size.

**SOLIDS:-**

All ocular drug delivery devices are kept under solids.

Advantages:-

Provide controlled, sustained and continuous drug delivery.

Avoid the side effects of pulsed drug delivery.

Maintain an effective drug concentration in the target tissues & minimize the number of applications.

But they are having limited popularity due to unnoticed expulsion from the eye, membrane rupture etc.

Examples:-

1. Soft Contact Lenses  
2. Implantable Systems  
3. Collagen Shields  
4. PROSERT™  
5. Soluble Ophthalmic Drug Inserts (SODI)  
6. Bioadhesive Ophthalmic Drug Inserts (BODI)  
7. OCUSERT™  
8. MYDRIASERT™

1. **Soft Contact Lenses** :-

Currently, approximately 100 million people are estimated to be wearing contact lenses, and the number is increasing exponentially. Although the main use of contact lenses is for correcting ametropia problems.

Ocular drug administration is particularly challenging and recent research has been directed towards the design of novel drug delivery systems capable of prolonging the permanence of the drug in the precorneal area and, thus, potentially increasing bioavailability and minimizing adverse effects.
Conventional hydrogel soft contact lenses have the ability to absorb some drugs and release them into the post-lens lacrimal fluid, minimizing clearance and sorption through the conjunctiva.

Their ability to be a drug reservoir strongly depends on the water content and thickness of the lens, the molecular weight of the drug, the concentration of the drug loading solution and the time the lens remains in it.

However, the ability of contact lenses to load drugs and to control their release is in general inadequate and the following approaches,

(i) covalent binding of the drug to the lens network via labile bonds;
(ii) inclusion of the drug in colloidal structures that are dispersed in the lens and are responsible for controlling drug release;
(iii) functionalization of the network with chemical groups that work as ion-exchange resins; and
(iv) creation in the lens structure of imprinted pockets that memorize the spatial features and bonding preferences of the drug and provide the lens with a high affinity and selectivity for a given drug. In this review, the possibilities and the advantages/drawbacks of these new types of contact lenses as drug delivery systems are critically analyzed.

EXAMPLE: Bionite lens (which was made from hydrophilic polymer: 2-hydroxy ethyl methacrylate).

2. Implantable Systems:

EXAMPLE 1: LACRISERT:

A rod shaped pellet of Hydroxypropyl Cellulose without preservative is commercially available (Lacrisert). This device is designed as a sustained release artificial tear insert for the treatment of dry eye disorders. It was developed by Merck, Sharp and Dohme in 1981.

EXAMPLE 2: VITRASERT:

An ocular implant (Vitrasert) for delivering ganciclovir for the treatment of cytomegalovirus (CMV) has also been developed.

This implant delivers the drug directly to the retina for over 5 months.

It is useful for patients with AIDS-associated cytomegalovirus retinitis.

The device was prepared by coating a ganciclovir pellet with PVA.

The pellet was then coated with ethylene vinyl acetate except on its top surface, and again coated with PVA.
The device lasted 4–5 months and all the treated eyes showed resolution of the CMV retinitis.

3. **Collagen Shields:**

Material: - porcine scleral tissue which bears a collagen composition similar to that of the human cornea.

Drug loading: - by soaking in drug solution.

Structure: - 0.1 mm thickness
   - 6-9 mm diameter.

Advantages: -
   1) Biological inertness
   2) Structural stability
   3) Good biocompatibility
   4) Low cost of production

Disadvantages: -
   1) Insertion technique is difficult
   2) Expulsion of the shield may occur
   3) Not fully transparent and thus reduce visual acuity

Marketed products: -
   1) Medi lens® (Chiron, irvine, ca)
   2) Pro shield® (alcon, forworth, tx)

4. **PROSERT®:**

**PROSERT®** is an ophthalmic placebo insert which is insoluble, sterile and biocompatible. This system can contain one or several active components and allow its releasing in a programmed or controlled way.

**PROSERT®** is constituted of a matrix able to contain one or several active components, surrounded by a **dyalisant membrane** of a changeable thickness which allows the releasing controlled by the tears.

The entirety has the shape of a **small oblong cylinder (reservoir) with rounded forms.**
When PROSERT® is inserted in the conjunctival cul de sac, the tears enter into the device and saturate the mesh net intended to contain the active component. When the osmotic equilibrium is achieved, the active component is released through the dialysantic membrane and then is spread in the conjunctival bag. The releasing curve has an ascending phase up to achieve the equilibrium and then it’s stable; the releasing of the active component is done at constant speed.

5. MYDRIASERT:-

The first application of PROSERT® technology, is a mydriatic called MYDRIASERT® that received its Marketing Authorisation Application.

Mydriasert is an insoluble ophthalmic insert, gradually releasing two well-known active ingredients: phenylephrine and tropicamide. It is indicated in presurgical mydriasis. Mydriasert®, a new insoluble ocular insert, ensures a regular and slow in vivo release of the drug. This release allows the mydriasis to be obtained quickly and to be maintained during surgery.

6. OCUSERT:-

A truly continuous controlled release and Zero order kinetic fashion was achieved using ocusert. For hydrophilic Drugs.

Pilocarpine ocuserts (by Alza corporation of California.)

The system consists of a Pilocarpine – alginate core (drug) in gel form sandwiched between two transparent, rate controlling ethylene-vinyl-acetate copolymer membranes. Titanium dioxide encloses the drug reservoir circumferentially.

The microporous membrane permit the tear fluid to penetrate into the drug reservoir compartment to dissolve drug from the complex.
When this is placed under the upper or lower eyelid, the pilocarpine molecules dissolved in the lacrimal fluid are released through the rate-controlling membranes at predefined rates for a week.

Two types of Ocuserts® are available:
1. Ocusert® pilo-20
2. Ocusert® pilo-40

This device is more popular among younger patients as compared to elder population who have difficulties in insertion, do not retain device well and often do not notice if it falls out.

Clinical studies with the pilocarpine Ocusert® demonstrated that slow release of the drug can effectively control the increased intraocular pressure in glaucoma, with a minor incidence of side-effects, such as miosis, myopia, browache, etc.

The major drawback for using this therapy is high cost of the device and as this system is not biodegradable, required to be removed and replaced with a fresh one adds to the cost of already expensive therapy.

7. Soluble Ophthalmic Drug Inserts (SODI):-

A SODI is a soluble copolymer of acrylamide, N-vinyl pyrrolidone, and ethyl acrylate.

It is in the form of sterile thin films or wafers of oval shape, weighing 15 to 16 mg.

After introduction into the upper conjunctival sac, the SODI softens in 10 to 15 sec, conforming to the shape of the eyeball; in the next 10 to 15 min the film turns into a polymeric clot, which gradually dissolves within 1 hr, while releasing the drug.

The major advantage of these dosage forms is the reduced role of the clinician, since the form is dissolved by total or partial solubilization and there is no need to surgically remove the insert once the drug has been released.

But they have the drawback that they blur vision while the polymer is dissolving.

Release of the drug from the SODI is proposed to occur in two stages: 1) Hydration of the matrix by penetration of dissolution medium; and 2) Diffusion of the medium deep into the matrix and back-diffusion of the dissolved active principle.

8. Bioadhesive Ophthalmic Drug Inserts (BODI):-

The main problem encountered with conventional ophthalmic inserts is their site of application and the risk of expulsion from the site.

To overcome this drawback, a new type of ophthalmic insert incorporating a water-soluble bioadhesive component in its formulation has been developed to decrease the risk of
expulsion and ensure prolonged residence in the eye, combined with controlled drug release.

These inserts, named BODI, are totally eliminated so that they do not need to be removed, thus limiting manipulations to insertion only.

Tolerance studies confirmed the validity of the concept.

**OCULAR IONTOPHORESIS**

Basic concepts and transport mechanism:-

The basic electrical principle that oppositely charged ions attract and same charged ions repel is the central tenet of iontophoresis.

The ionized substances are driven into the tissue by electrorepulsion at either the anode (for positive drug) or the cathode (for negatively charged drug).

This ionic-electric field interaction, called also the Nernst-Planck effect, is the largest contributor to flux enhancement for small ions, but not the only one.

Gangarosa and Burnatte demonstrated enhanced delivery of neutral species by application of an electric field. This brought the modification of the classical Nersnt-Planck flux equation to include motion of the solvent, called the F: electroosmotic flow.

Electroosmotic flow is the bulk fluid flow which occurs when a voltage difference is imposed across a charge membrane. Since the human membranes are negatively charged above pH 4, the electroosmotic flow occurs from anode to cathode, as the flow of the cationic counterions.

For large monovalent ions the electroosmotic flow is the dominant flow mechanism.

The third mechanism, which enhances drug penetration, is the reversible damage effect of the electric current that increases tissue permeability.
The iontophoretic device:

The basic design of the iontophoretic devices is a direct current power source and two electrodes. The ionized drug is placed in the electrode compartment bearing the same charge, and the ground electrode is placed at a distal site on the body.

The more common approach is to fill an eye cup with the drug solution, while a metal electrode extended from the current supply submerges into the solution.

The eye cup with an internal diameter of 5–10 mm is placed over the eye and the drug solution is continuously infused into the cup during the iontophoretic treatment.

The eye cup has two ports: one delivers the drug solution and the other holds the metal electrode and aspirates air bubbles that can disrupt the current supply, thus creates a slightly negative pressure that maintains the applicator in place.

The ground electrode is attached usually to the ear of the animal, as close as possible to the former electrode, to obtain minimal resistance.

Different eye-cup shapes exist, including an annular shape silicone probe for transscleral iontophoresis (called FEyegate®, Optis, France) with a 13 mm opening to avoid contact with the cornea, used by Behar-Cohen, Hayden and Voigt. The different iontophoretic devices are presented in Figure below:
2nd generation iontophoresis for eye:-

At the last few years several publications on drug-loaded hydrogels for ocular iontophoresis revealed novel iontophoretic applicators using the drug-saturated gel approach.

Fisher, Vollmer and Parkinson et al. used a custom manufactured OcuPhori hydrogel (Iomed Inc., Salt Lake City, USA) composed of polyacetal sponge, for transscleral iontophoresis.

The drug applicator is a small silicone shell that contains a patented silver-silver chloride ink conductive element; a hydrogel pad to absorb the drug formulation; and a small, flexible wire to connect the conductive element to the dose controller (as shown in figure below).

At the time of administration, the dry hydrogel matrix is hydrated with the drug solution and placed against the sclera in the lower cul-de-sac of the rabbit eye. The return electrode can be positioned anywhere on the body to complete the electrical circuit.
Visulex is Aciont’s noninvasive, iontophoretic system for BOTE diseases. It works toward optimizing drug dosing control, therapeutic efficacy, and patient/physician compliance through consideration of relevant human factors. Visulex incorporates the following proprietary innovations in iontophoresis that will enable the practical delivery of therapeutics for key BOTE diseases:

- Dosing Controller with Key Safety Features for Ocular Iontophoresis;
- Simple, Comfortable, and Easy to Prepare Drug Applicator;
- Visulex ST: Optimized Selective Drug Transport and Flux Enhancement; and

The Visulex system consists of a user-friendly applicator, a dosing controller, and connecting wires. The device is designed specifically for ophthalmic applications and contains software and algorithm controls and a proprietary multi-electrode monitoring system that together optimize safety. The applicator slips comfortably into the lower cul-de-sac, while conforming to the curvature of the eye. A fine, pliable wire connects the applicator to the current...
controller. The return electrode can be positioned anywhere on the body to complete the electrical circuit (Figures 1 & 2).

Visulex ST has been formulated with a unique membrane system to increase drug transport efficiency over conventional iontophoretic systems. This selective process works by excluding the transport of extraneous non-drug ions, thus making drug ions the primary carrier of electrical current through scleral tissue. Aciont also is working on an innovative, iontophoretically delivered sustained-release system, Visulex SR.

Aciont intends to revolutionize BOTE drug delivery. By expanding noninvasive pharmacological treatment options, there will be a decreased need for ocular injections and surgically related procedures. Furthermore, Visulex SR increases interval times between treatments. Medical assistant administrations or self-administrations may be possible for certain applications.

**COLLOIDAL SYSTEMS FOR EYE:-**

**A) LIPOSOMES:-**

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

According to their size, liposomes are known as either small unilamellar vesicles (SUV) (10–100 nm) or large unilamellar vesicles (LUV) (100–3000nm). If more bilayers are present they are referred to as multilamellar vesicles (MLV).

Depending on the composition, liposomes can have a positive, negative, or neutral surface charge.

In vitro liposome–corneal interaction studies showed that liposomes were taken up by the corneain the order

\[
\text{MLV}^+ > \text{SUV}^+ >> \text{MLV}^- > \text{SUV}^- > \text{MLV}=\text{SUV}
\]

The reason for this apparent difference is not clear, but it is known that the corneal epithelium is thinly coated with negatively-charged mucin to which the positive surface charge of the liposomes may absorb more strongly.

Liposomes are a potentially useful ocular drugdelivery system due to the simplicity of preparation and versatility in physical characteristics, but suffer from the disadvantage of instability (due to the hydrolysis of phospholipids normally used in their preparation), limited drug-loading capacity, and technical difficulties in obtaining a sterile liposomal preparation.

**B) NIOSOMES:-**

In order to circumvent the limitations of liposomes such as chemical instability, oxidative degradation of phospholipids, cost, and variable purity of natural phospholipids, niosomes were developed.

They are the vesicles formed by some members of the dialkyl polyoxyethylene ether non-ionic surfactant series has been suggested.

It is reported that a vesicular system is formed when a mixture of cholesterol and a single-alkyl chain, non-ionic surfactant is hydrated.

The resultant vesicles, termed “niosomes”, can entrap solutes, are osmotically active, and relatively stable.

Niosomes have also been reported as successful ophthalmic carriers.
C) DISCOSOMES:-

Disc shaped neosomes are known as discosomes.

Discomes, in addition to their many advantages, seem to have a special advantage towards the ocular route, wherein their large size may prevent their drainage into the systemic pool.

Furthermore, their “disc” shape provides for a better fit in the cul-de-sac of the eye.

Non-ionic surfactant-based discoidal niosomes (discomes) of timolol maleate have been reported to be promising systems for the controlled ocular administration of water-soluble drugs, releasing the drug in a biphasic profile.

D) 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 a lipid molecule, thus generating an amphiphilic prodrug.

The amphiphilic prodrug is converted to pharmacosomes on dilution with water.

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

E) NANOPARTICLES:-

Nanoparticles are among the most widely studied colloidal systems over the past two decades.

These are polymeric colloidal particles, ranging from 10nm to 1 mm, in which the drug is dissolved, entrapped, encapsulated, or adsorbed.

They represent promising drug carriers for ophthalmic application.

They are further classified into nanospheres (small capsules with a central cavity surrounded by a polymeric membrane) or nanocapsules (solid matricial spheres).

Marchal-Heussler et al. found that the nanocapsules show a better effect than the nanospheres, probably because the drug (betaxolol, carteolol) is in an unionized form in the oily core and can diffuse at a greater rate into the cornea. Diffusion of the drug from the oily phase to the corneal epithelium seems to be more effective than diffusion from the internal matrix of the nanospheres.
Several authors suggest that the better efficiency of nanocapsules is due to their bioadhesive properties, resulting in an increase in the residence time and biological response.

However, it was observed that nanoparticles consisting of poly(alkylcyanoacrylate) damaged the corneal epithelium by disrupting the cell membranes.

**VARIOUS CHEMICAL APPROACHES FOR OCULAR DRUG DELIVERY**

**A) CHEMICAL DRUG DELIVERY SYSTEM:-**

A chemical delivery system (CDS), is an inactive species obtained by chemical modifications of the active agent based on metabolic considerations.

Conceptually, a CDS upon its administration will undergo several predictable enzymatic transformations via inactive intermediates and finally deliver the active species to the target site.

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.

Other drugs with increased penetrability through prodrug formation are phenylephrine 1, timolol, tilisolol, pilocarpine, albuterol, idoxuridine, etc.

Site specific and stereo specific beta blockers (Alprenolol and Betaxolol are also the examples of cdds.

Prostaglandin F2a ester prodrugs have been reported to have better aqueous stability than prostaglandins.

**B) ENHANCEMENT OF PERMEABILITY BY ION PAIR EFFECT**

Most of the beta blockers like Timolol and Carteolol are highly hydrophilic in nature. Therefore they suffer permeability problems.
Addition of sorbitol into the preparation produces ion-pair complex with hydrophilic drug and this ion pair complex has properties similar to the lipophilic drug so it can penetrate easily through the corneal epithelium and problem of permeability can be solved.

C) SOFT DRUG APPROACH:-

It produces the desired pharmacological activity at the site of application but at other sites do not show any action even though the same receptor is present.

Example:- Adaprolol – A ß-BLOCKER
A NEW TOPICAL ANTIGLAUCOMA AGENT

Advantages:-
1. Good corneal permeability
2. Better stability
3. Less side effects (bronco-constriction) because site specific activity.

USE OF CYCLODEXTRIN:-

The effects of cyclodextrins on drug solubility, permeability, chemical stability and delivery through biological membranes have been investigated by a number of research groups (Rajewski & Stella 1996; Uekama et al. 1998; Loftsson & Järvinen 1999; Masson et al. 1999; Stella et al. 1999; Uekama 1999; Loftsson & Masson 2001).

Their studies show that hydrophilic cyclodextrin act as true carriers by keeping the lipophilic water-insoluble drug molecules in solution and delivering them to the membrane surface where they partition from the cyclodextrin cavity into the lipophilic membrane.

The relatively lipophilic membrane has low affinity for the large hydrophilic cyclodextrin molecules or the hydrophilic drug/cyclodextrin complexes, which thus remain in the aqueous skin exterior, e.g. the aqueous tear fluid.

cyclodextrins enhance drug penetration into the eye by carrying the lipophilic water-insoluble drug molecules through the aqueous mucin layer and thereby increasing drug availability at the lipophilic eye surface (as shown in Fig.)
EVALUATION:-

SOLUTIONS:–
1) pH
2) sterility
3) osmolarity

SUSPENSIONS:–
1) particle size
2) adsorption on the inner wall of container

PHASE – TRANSITION SYSTEMS:–
1) gelling efficiency
2) transparency of formed gel
3) release pattern

SEMISOLIDS:–
1) ease of application
2) particle size if drug is suspended.

OCULAR INSERTS:–

(i) Uniformity of Thickness
Insert thickness should be measured at three different points using Micrometer screw gauge and mean film thickness should be noted.

(ii) Uniformity of Weight

(iii) Drug Content Uniformity

(iv) Percentage Moisture Absorption
Individual inserts were weighed and placed in a desiccator maintained at high relative humidity using an excess amount of salt in solution. After three days the
inserts were taken out and reweighed. The percentage moisture absorption was calculated using the formula,

\[
\text{% Moisture Absorption} = \frac{\text{Final Wt.} - \text{Initial Wt}}{\text{Initial Wt}} \times 100
\]

(v) **Percentage Moisture Loss**

Percentage moisture loss is carried out to check the integrity of the film at dry conditions. Inserts are weighed individually and kept in a desiccator containing anhydrous calcium chloride. After three days, inserts are taken out and reweighed. Percentage moisture loss is calculated using the formula,

\[
\text{% Moisture Loss} = \frac{\text{Initial Wt} - \text{Final Wt.}}{\text{Initial Wt}} \times 100
\]

(vi) **In vitro Drug Release Study**

(vii) **Draize Eye Irritancy Test**

The Draize eye irritancy test is currently the most valuable and reliable method for evaluating hazard or safety of a substance introduced into or around the eye.

Eye irritancy potential of a substance is determined on the basis of its ability to cause injury to the cornea, iris, and conjunctiva when a substance is applied to the eye. Testing is carried out on adult albino rabbits of either sex.

All rabbits are maintained under 12 h light and dark cycles and are fed with green vegetables throughout the course of study. Food and water is allowed *ad libitum*.

A series of six rabbits are used for testing the eye irritation potential of the polymer. One placebo insert is made up of gelatin sandwiched using films of ethyl cellulose devoid of the drug placed into the cul-de-sac of the rabbit while other eye serve as a control.
<table>
<thead>
<tr>
<th>S.No</th>
<th>Drug</th>
<th>Formulation</th>
<th>Category</th>
<th>Polymers / Bases</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Pilocarpine</td>
<td>Ointment</td>
<td>Miotic agent</td>
<td>Petrolatum bases</td>
</tr>
<tr>
<td>2</td>
<td>Pilocarpine</td>
<td>Emulsion</td>
<td>Miotic agent</td>
<td>----</td>
</tr>
<tr>
<td>3</td>
<td>Pilocarpine</td>
<td>Sol to gel</td>
<td>Miotic agent</td>
<td>C.A.P.</td>
</tr>
<tr>
<td>4</td>
<td>Pilocarpine</td>
<td>Matrices</td>
<td>Miotic agent</td>
<td>HPC &amp; PVP</td>
</tr>
<tr>
<td>5</td>
<td>Pilocarpine</td>
<td>Hydrogel</td>
<td>Miotic agent</td>
<td>Polyacrylic acid and Polyacrylamide</td>
</tr>
<tr>
<td>6</td>
<td>Dexamethasone</td>
<td>Suspension</td>
<td>Anti-inflammatory</td>
<td>----</td>
</tr>
<tr>
<td>7</td>
<td>Dexamethasone</td>
<td>Ocularinsert</td>
<td>Anti-inflammatory</td>
<td>C.A.P., Eudragit RS. 100 and RL 100</td>
</tr>
<tr>
<td>8</td>
<td>Pilocarpine nitrate</td>
<td>Ocularinsert</td>
<td>Miotic agent</td>
<td>Collagen</td>
</tr>
<tr>
<td>9</td>
<td>Pilocarpine nitrate</td>
<td>Ocularinsert</td>
<td>Miotic agent</td>
<td>Na hyaluronate</td>
</tr>
<tr>
<td>10</td>
<td>Tropicamide</td>
<td>Ocularinsert</td>
<td>Mydriatic agent</td>
<td>Na hyaluronate</td>
</tr>
<tr>
<td>11</td>
<td>Pilocarpine nitrate</td>
<td>Gel</td>
<td>Miotic agent</td>
<td>Polyacrylic acid</td>
</tr>
<tr>
<td>12</td>
<td>Timolol</td>
<td>Sol to gel</td>
<td>Anti-glaucoma agent</td>
<td>GelriteÔ</td>
</tr>
<tr>
<td>13</td>
<td>Timolol Maleate</td>
<td>Ocular insert</td>
<td>Anti-glaucoma agent</td>
<td>(PVME - MA)</td>
</tr>
<tr>
<td>14</td>
<td>Methyl Prednisolone</td>
<td>Microspheres</td>
<td>Anti-inflammatory</td>
<td>Na hyaluronate</td>
</tr>
<tr>
<td>15</td>
<td>Flurbiprofen</td>
<td>Gels</td>
<td>Anti-inflammatory</td>
<td>Pluronic F 127</td>
</tr>
<tr>
<td>16</td>
<td>Timolol maleate</td>
<td>Solutions</td>
<td>Anti-glaucoma agent</td>
<td>Polyacrylic acid</td>
</tr>
<tr>
<td>17</td>
<td>Penicillin G</td>
<td>Liposomes</td>
<td>Antibiotic</td>
<td>Phospholipids</td>
</tr>
<tr>
<td>18</td>
<td>Pilocarpine</td>
<td>Solution</td>
<td>Miotic agent</td>
<td>Na hyaluronate</td>
</tr>
<tr>
<td>19</td>
<td>Timolol maleate</td>
<td>In-situ forming gel</td>
<td>Anti-glaucoma agent</td>
<td>HPMC and Polyacrylic acid</td>
</tr>
<tr>
<td>20</td>
<td>Gentamicin, Tobramycin and Ciprofloxacin</td>
<td>Iontophoresis</td>
<td>Anti-infective agents</td>
<td>---</td>
</tr>
<tr>
<td>21</td>
<td>Gentamicin, Tobramycin and Ciprofloxacin</td>
<td>Corneal collagen shield</td>
<td>Anti-infective agents</td>
<td>Collagen</td>
</tr>
<tr>
<td>22</td>
<td>Sulphacetamide sodium and</td>
<td>Solution</td>
<td>Anti-infective agents</td>
<td>---</td>
</tr>
<tr>
<td></td>
<td>Product Name</td>
<td>Formulation</td>
<td>Function</td>
<td>Adjuvants</td>
</tr>
<tr>
<td>---</td>
<td>------------------------------</td>
<td>-------------------</td>
<td>---------------------</td>
<td>----------------------------------</td>
</tr>
<tr>
<td>23</td>
<td>Pilocarpine</td>
<td>Solution</td>
<td>Miotic agent</td>
<td>----</td>
</tr>
<tr>
<td>24</td>
<td>Piroxicam</td>
<td>Microemulsion</td>
<td>Anti-inflammatory</td>
<td>Poloxamer and Stearylamine</td>
</tr>
<tr>
<td>25</td>
<td>Indomethacin</td>
<td>Nanocapsules</td>
<td>Anti-inflammatory</td>
<td>Poloxamer</td>
</tr>
<tr>
<td>26</td>
<td>Hydrocortisone</td>
<td>Solution</td>
<td>Anti-inflammatory</td>
<td>HP-ß-CD</td>
</tr>
<tr>
<td>27</td>
<td>Indomethacin</td>
<td>Nanocapsules</td>
<td>Anti-inflammatory</td>
<td>Chitosan and Poly-L-Lysine</td>
</tr>
<tr>
<td>28</td>
<td>Pilocarpine Hydrochloride</td>
<td>Gels</td>
<td>Miotic agent</td>
<td>Pluronic F127,MC,HPMC</td>
</tr>
<tr>
<td>29</td>
<td>Ciprofloxacin</td>
<td>Ocular insert</td>
<td>Anti-infective</td>
<td>HPMC,MC,PVP</td>
</tr>
<tr>
<td>30</td>
<td>Insulin</td>
<td>Ocular devices</td>
<td>Anti diabetic</td>
<td>Gelatin sponge</td>
</tr>
<tr>
<td>31</td>
<td>Tropicamide</td>
<td>Liposomes in gel.</td>
<td>Mydriatic agent</td>
<td>Polycarbophil</td>
</tr>
<tr>
<td>32</td>
<td>Indomethacin</td>
<td>Solution</td>
<td>Anti-inflammatory</td>
<td>Pluronic F68&amp; F127</td>
</tr>
<tr>
<td>33</td>
<td>Ketorolac Tromethamine</td>
<td>Ocular Inserts</td>
<td>Anti-inflammatory</td>
<td>HPMC,PVP,MC</td>
</tr>
</tbody>
</table>