Chapter – I

General Introduction
1. GENERAL INTRODUCTION

1.1 OCULAR DRUG DELIVERY

Ophthalmic drug delivery is one of the most interesting and challenging endeavors faced by Pharmaceutical scientists. The anatomy, physiology and biochemistry of the eye render this organ exquisitely impervious to foreign substances.\(^1\) The challenge to the formulation is to circumvent the protective barriers of the eye without causing any permanent tissue damage. The primitive ophthalmic solution, suspension and ointment dosage forms are clearly no longer sufficient to combat some present virulent diseases.

In spite of active and continued research and frequent introduction of novel ophthalmic drugs, ocular drug delivery does not seem to progress at the lively pace typical of oral, transdermal, or transmucosal delivery. The vast majority of existing ocular drug delivery systems are still fairly primitive and inefficient. Successful delivery of drugs into the eye is extremely complicated because the eye is protected by a series of complex defense mechanisms, which make it difficult to achieve an effective concentration of the drug within the target area of the eye.\(^2\)

Poor bioavailability of drugs from ocular dosage forms is mainly due to the tear production, non-productive absorption, transient residence time and impermeability of corneal epithelium as shown in Fig.1.1.
The drainage of the topically administered dose via the nasolachrymal system into the naso pharynx and the gastrointestinal tract take place when the volume of fluid exceeds lachrymal fluid (7 to 10µl). Thus, the contact time of the drug with ocular tissue is relatively short (1 to 2 minutes) mainly due to the spillage of the instilled eye drops from the pre corneal area.³

As a consequence of these mechanisms and factors, the rate of loss of drug from the eye can be 500 to 700 times greater than the rate of absorption into the anterior chamber and 1 to 5 % or less of the drug applied topically as a solution reaches the inner part of the eye as indicated in Fig.1.2
Thus it may be concluded that both trans conjunctival and transnasal absorption after drainage via the nasolachrymal duct are generally undesirable, not only because of the loss of active ingredient into the systemic circulation but also because of possible side effects. Therefore to optimize topical ocular drug delivery systems, prolonged contact time with the corneal surface and better penetration through cornea is necessary.

1.2 ANATOMY AND PHYSIOLOGY OF HUMAN EYE

Eye is the most important and sensitive organ, in fact it is the window of our soul. Delivering drugs to the front of the eye is an exceedingly complicated issue because of the numerous protective mechanisms that are present in the eye to shield the visual pathway from foreign chemicals. The extent of absorption of an ophthalmic drug is severely limited by physiological constraints. Among the factors that limit ocular absorption is the relatively impermeable corneal barrier. Design of modern ocular drug delivery systems is based on an understanding of the drug disposition pathways in the eye and the overall ocular pharmacokinetic/ pharmacodynamic profile.
Here is a brief discussion of the structures of the eye, which comes in contact with drug delivery systems administered topically, is given as follows.

1.2.1 **Structure of the ocular globe**

The eyeball has a wall consisting of three layers as given in Fig 1.3

- The outer coat or the sclera and cornea
- A middle layer or uveal coat
- The inner coat or retina

The sclera is made of fibrous tissues shaped as segments of two spheres, the sclera and cornea. The external part of the eye is covered by the mobile tarsal part of the eyelids. The thin skin of the lids folds easily over the eyeball and permits rapid opening and closing of the palpebral fissure. The eyelids are under involuntary (spontaneous or periodic blinking and reflex blinking) and voluntary control. They distribute the tear fluid over the eye, providing an optically smooth surface over the cornea. The shear rate during blinking is estimated to be about 20,000 S⁻¹ and the rheological properties of viscous ocular dosage forms instilled and consequently the bioavailability of the drug applied.

1.2.2 **Cornea**

Cornea is an optically transparent tissue that acts as the principal refractive element of the eye. The corneal diameter is about 11.7 mm with a radius of curvature of the anterior surface of about 7.8 mm. The corneal thickness is 0.5–0.7 mm and it is thicker in the center than in the limbus. The cornea is composed of epithelium,
Bowman's membrane, Stroma, Descement's membrane and endothelium. Usually, the corneal epithelium is the main barrier of drug absorption into the eye as seen in Fig. 1.3. The epithelium consists of 5 to 6 layers of cells. The cells of the basal layer are columnar. As they are squeezed forward by the new cells, they differentiate and exfoliate from the epithelial surface as flattened polygonal cells. Replacement of the epithelial cells occurs by mitotic division of the basal layer. The average life of a polygonal cell is about 4 to 8 days.

**Fig. 1.3  Schematic representation of the structure of the human eye**

### 1.2.3  Conjunctiva

The conjunctiva is a thin transparent membrane, which lines the inner surface of the eyelids and is reflected on to the globe. At the corneal margin, it is structurally continuous with the corneal epithelium. The membrane is vascular and moistened by the tear film. The conjunctiva is composed of an epithelium, a highly vascularised substantia propria and submucosa or episclera. The bulbar epithelium consists of 5 to
7 cell layers. The structure resembles a palisade and not a pavement when compared to the corneal epithelium. At the surface, epithelial cells are connected by tight junctions, which render the conjunctiva relatively impermeable. The conjunctival tissue is permeable to molecules up to 20,000 Da, whereas the cornea is impermeable to molecules larger than 5000 Da.\(^{15}\)

### 1.2.4 Sclera

The sclera constitutes the posterior five-sixth of the globe and provides the structural integrity that defines the shape and length of the eye. Sclera has three layers (anterior to posterior): episclera, scleral stroma and lamina fusca.\(^{16}\) It consists of primarily mucopolysaccharides and bundles of collagen fibrils. Compared to cornea, sclera is more permeable. For example, scleral permeabilities were higher than those in the cornea for some β-blockers, sucrose and inulin.

### 1.2.5 Tear Film

The exposed part of the eye is covered by a thin fluid layer, the so-called precorneal tear film. The film thickness is reported to be about 3–10 \(\mu\)m. The resident volume amounts to about 10 \(\mu\)l.\(^{17}\) According to the “Three layers theory” the precorneal tear film consists of a superficial lipid layer, a central aqueous layer and an inner mucus layer as represented in the Fig 1.4.\(^{18}\)

### 1.2.6 Superficial lipid layer

The superficial lipid layer (a 100-nm-thick multi molecular film) is secreted during blinking by the meibomian glands embedded in the tarsal plate of the eyelids
and the accessory sebaceous glands of Zeiss. The lipid layer spreads over the aqueous layer during eye opening. It consists mainly of sterol esters, triacylglycerols and phospholipids, free sterols and free fatty acids. The lipids play an important role in reducing the evaporation rate in a way that normal tear osmolality can be maintained, even when the tear flow is quite low. Patients with meibomian gland dysfunction show a high evaporation rate and a high tear osmolality.\textsuperscript{19} The lachrymal gland and the accessory gland contribute to the formation of the aqueous layer, containing inorganic salts, glucose and urea as well as retinol, ascorbic acid, various proteins, lipocalins (previously known as tear specific pre albumins) immunoglobulins, lysozyme, lactoferrin and glycoproteins.\textsuperscript{20}

Fig 1.4 Schematic representation of the precorneal tear film

Vitamin A and its derivatives are required for the normal growth and differentiation of the corneal/conjunctival epithelium. Vitamin A deficiency is associated with keratinization, reduction of goblet cell population, increase in conjunctival epithelial cell mitosis and disturbance of mucosal differentiation, mucin production and mucin gene expression.\textsuperscript{21} The osmolality of the tear film equals 310–
350 mOsm/kg in normal eyes and is adjusted by the principal inorganic ions Na+, K+, Cl⁻, HCO₃⁻, and proteins. The mean pH value of normal tears is about 7.4. Depending on age and diseases, values between 5.2 and 9.3 have been measured. Diurnal patterns of pH changes exist, with a general shift from acid to alkaline during the day. The buffer capacity of the tears is determined by bicarbonate ions, proteins, and mucins. Tears exhibit a non-newtonian rheological behaviour. The viscosity is about 3 mPas. The surface tension depends on the presence of soluble mucins, lipocalins and lipids. The mean surface tension value is about 44 mN/m. ²⁰

1.2.7 Mucus layer

The mucus layer, which is secreted on to the eye surface by the goblet cells, is intimately associated with the glycocalyx of the corneal/conjunctival epithelial cells.²² The mucus layer is very sensitive to hydration and forms a gel-layer with visco elastic rheological properties. It protects the epithelia from damage and facilitates the movements of the eyelids²³. Mucins improve the spreading of the tear film and enhance its stability and cohesion. Mucus is wiped over the surface of the eye by the upper eyelid during blinking. The mucus gel entraps bacteria, cell debris, and foreign bodies, forming “mucous threads” consisting of thick fibers arranged in bundles. These “threads” are transported during blinking to the inner canthus and expelled on to the skin. The mucus layer can form a diffusion barrier to macromolecules depending on the degree of network entanglement.²⁴ On the other hand, mucus can bind cationic substances because of the negative charges of mucins.

Mucus consists of glycoproteins, proteins, lipids, electrolytes, enzymes, mucopolysacchrides and water. The primary component of mucus is mucin, a high-
molecular-mass glycoprotein with sub units containing a protein core, approximately 800 amino acids long, of which about 200 are bearing polysaccharide side-chains.\textsuperscript{25,26}

Due to the composition, physicochemical properties and structure of the tear film, various factors will influence the mucoadhesion of ocular delivery systems.\textsuperscript{27} Various theories (electronic, adsorption, wetting, diffusion or interpenetration) were proposed to explain bioadhesion or mucoadhesion. In order to be a good mucoadhesive adjuvant, the polymer of the drug delivery system must make intimate contact with the mucus layer.\textsuperscript{28} The polymer chains must be mobile and flexible enough to inter diffuse into the mucus and penetrate to a sufficient depth in order to create a (strong entangled) network. They should interact with mucins by hydrogen bonding, electrostatic and hydrophobic interactions.\textsuperscript{29}

The tear film is only temporarily stable. The eyes cannot be kept open indefinitely.\textsuperscript{30} After 20–40 seconds, an unpleasant sensation compels humans to blink. In the short time interval between two blinks, rupture of the tear film occurs due to concentration gradients and dispersions forces on the mucus layer. The rupture causes de wetting of the cornea (dry spots formation), which irritate corneal nerve endings and induce blinking. During eyelid opening, a new tear film spreads over the external eye surface.\textsuperscript{31} The time of rupture of the mucus layer and the breakup time of the tear film depend on dispersion forces, the interfacial tension and viscous resistance of the mucus layer.\textsuperscript{32} During development of mucoadhesive dosage forms and selection of soluble or insoluble polymers and additives, these factors should be taken into consideration. Some topically applied drugs and vehicles influence the tear stability negatively or positively. Adverse effects of surfactants, benzalkonium chloride and
topical anaesthetics on the tear film stability are related to the decrease of the mucus–aqueous interfacial tension.  

1.3 CONVENTIONAL OPHTHALMIC DOSAGE FORMS

The majority of the ophthalmic drugs are administered topically in the form of conventional formulations. Conventional ophthalmic dosage forms include solutions, suspensions and ointments.

1.3.1 Solutions

It is most widely used and it is easy to administer drugs that are active on the eye surface or in the eye after passage through the cornea or conjunctiva. In spite of their limitations (i.e., quick elimination from the pre corneal area resulting in poor bioavailability) are still given top priority by formulators because they are relatively simple to prepare, filter, sterilize and are cost effective.

1.3.2 Suspensions

Suspensions are widely used for formulations involving poorly soluble drugs such as anti-inflammatory steroids. Ocular suspensions, however, have several disadvantages. Proper shaking is required, which if not done can lead to inconsistency in the administered dose. A fine sediment may form that can be difficult to disperse with gentle shaking. Polymorphic change in the suspended drug to form a less soluble or insoluble form of the drug.
1.3.3 Ointments

An important feature of the ointment is that it remains in the conjunctival cul-de-sac forming a reservoir of the drug. Moreover, the disappearance from the pre corneal areas of a drug administered in an ointment vehicles is very slow (0.5% per min) when compared with the elimination by the normal lachrymal turnover (about 16 per min). These preparations possess several disadvantages include greasiness, vision blurring effects etc., and are generally used as night medications.\textsuperscript{37}

The conventional ophthalmic drug delivery systems like suspensions, solutions and ointment show drawbacks such as increased pre corneal elimination, high variability in efficiency and blurred vision respectively. To overcome these drawbacks there are various formulation approaches to increase ocular bioavailability.

Various approaches that have been attempted to increase the bioavailability and duration of therapeutic action of ocular drugs can be divided into two categories.

- Maximizing corneal drug absorption and minimizing pre corneal drug loss.
- Drug delivery system to provide controlled and continuous delivery of ophthalmic drug to the pre and intra ocular tissue.\textsuperscript{38}

However, failures of the initial attempts lead to the advent of novel approaches in the field of ocular drug delivery.
1.4 NOVEL OPHTHALMIC DOSAGE FORMS

Ocular targeted therapy has enormously been advanced by implementation of new methods of drug delivery and targeting using novel ophthalmic delivery system. Some of the novel ocular dosage forms are discussed below:

1.4.1 Polymeric solutions

The addition of polymer like methyl cellulose, polyvinyl alcohol, hydroxyl propyl cellulose and poly vinyl pyrrolidone to the eye drop solution increases the corneal penetration of the drug. This is presumably due to an increased tear viscosity which decreases or otherwise rapid initial drainage rate, increases the corneal contact time and thus sustains to some extent the initial tear concentration of the drug.\textsuperscript{39}

1.4.2 \textit{In-situ} activated gel forming system

A more desirable dosage form would be one that can be delivered in a drop form, create little to no refractive index problem for vision and dosed no more frequently than once or twice daily. This can be achieved by using \textit{in-situ} gel forming ophthalmic drug delivery system. This system prepared from polymers that exhibit reversible phase transition (sol-gel-sol) and pseudoplastic behavior to minimize interference with blinking, increase in pre-corneal residence time and enhanced ocular bioavailability.
Depending on the method employed to cause sol-to-gel phase transition on the ocular surface, the following three types of system have been recognized.

1. Change in temperature
2. Change in pH
3. Change in ionic concentration or Electrolyte composition.

1.4.3 Mucoadhesive dosage forms

These systems can be either polymeric solution or micro particle suspensions. They are retained in the cul-de-sac through adhesive bonds established with the mucus or the epithelium thus increasing the corneal contact time.\(^{40}\)

1.4.4 Ocular inserts

Ocular inserts are solid dosage form and maintain the 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 factor, such as reluctance of patients to abandon the traditional liquid and semisolid medications and to occasional therapeutic failures\(^{41}\) (eg: unnoticed expulsion from the eye, membrane rupture etc.,)

1.4.5 Nanoparticles

Nanoparticles are defined as particles with a diameter of less than 1 \(\mu\)m, consisting of various bio degradable materials, such as natural or synthetic polymers, lipids, phospholipids and even metals. Drugs can be either integrated in the matrix or attached to the surface. Nanoparticles made up of various biodegradable polymers like
polylactides (PLAs), polycyanoacrylate, poly (D,L-lactides), natural polymers like chitosan, gelatine, sodium alginate and albumin can be used effectively for efficient drug delivery to the ocular tissues. Nanoparticulate drug delivery has demonstrated promising results in ophthalmic drug delivery over the last 10 years.\textsuperscript{42} The development of various nanoparticulate-based drug delivery systems, like nanoparticles, nanoemulsions, nanosuspensions, liposomes, dendrimers, niosomes, cyclodextrins and so on, can enhance the rate of ophthalmic drug delivery to a significant degree.

1.4.6 Microemulsion

Microemulsions are an interesting alternative to topical ocular drug delivery, because of their intrinsic properties and specific structures they can be easily prepared through emulsification, can be easily sterilized, are stable and have a high capacity for dissolving drugs. In this case, these systems act as penetration enhancers to facilitate corneal drug delivery. There are many formulations of microemulsions intended for ophthalmic use.\textsuperscript{43}

1.4.7 Dendrimers

Dendrimers are macromolecular compounds made up of a series of branches around an inner core. They are attractive systems for drug delivery because of their nanometer size range, ease of preparation and functionalization and their ability to display multiple copies of surface groups for biological recognition processes. Because of these properties, they can be used as an effective vehicle for ophthalmic
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drug delivery moieties\textsuperscript{44}. So, greater possibilities can be explored by using dendrimers as ophthalmic drug delivery vehicles.

1.4.8 Cyclodextrins

Cyclodextrins (CDs) are a group of cyclic oligosaccharides capable of forming inclusion complexes with many drugs. Through CD complexation, the aqueous solubility of some hydrophobic drugs can be enhanced without changing their molecular structure and their intrinsic abilities to permeate biological membranes. In ophthalmic preparations, co-administration of CDs has been reported to increase corneal penetration, ocular absorption and the efficacy of poorly water-soluble drugs such as dexamethasone, cyclosporin, acetazolamide, and so on. It is seen that CDs act as true carriers by keeping hydrophobic drug molecules in solution and delivering them to the surface of the corneal epithelium where they partition. CDs increase aqueous stability and bioavailability of ophthalmic drugs\textsuperscript{45}.

1.4.9 Vesicular system for ocular drug delivery

The various vesicular system used for ocular delivery are liposomes, niosomes, pharmacosomes and discomes\textsuperscript{46}. Of which liposomes and niosomes find application. These systems have advantage over other systems which can be enumerated as,

- No difficulty of insertion as in the case of ocular inserts.
- No tissue irritations and damage as caused by penetration enhancer.
Provide patients compliance as there is no difficulty of insertion as observed in the case of inserts.

The vesicular carriers are biocompatible and have minimum side effects.

Degradation products formed after the release of drugs are biocompatible.

They prevent the metabolism of drugs from the enzymes present at tear / corneal epithelium interface.

Provide a prolonged and sustained release of drug.

Drug enclosed in the vesicles allows for an improved partitioning and transport through the cornea.

Moreover they offer a promising avenue to fulfill the need for an ophthalmic drug delivery system that has a convenience of a drop but will localize and maintain drug activity at its site of action.  

1.4.10 Liposomes

Liposomes are small artificial vesicles that can be produced from natural non-toxic phospholipids and cholesterol. Because of their size, amphiphilic properties and biocompatibility, liposomes are promising systems for ocular drug delivery.

1.4.11 Niosomes

Niosomes (Non ionic surfactant vesicles) are microscopic lamellar structure of size range between 10 to 1000 nm and are formed on admixture of non ionic surfactant of the alkyl or dialkyl poly glycerol ether class and cholesterol with subsequent hydration in aqueous media. The non ionic surfactants should be bio-
degradable, biocompatible and non-immunogenic. It acts as a depot releasing the drug in controlled manner and also provides better drug concentration at the site of action administered by oral, parenteral, ocular, nasal and topical routes.\textsuperscript{50}

### 1.5 NIOSOMES - VESICULAR DRUG DELIVERY SYSTEM

Paul Ehrlich, in 1909, initiated the era of development for targeted delivery when he envisaged a drug delivery mechanism that would target directly to diseased cell. Since then, numbers of carriers were utilized to carry drug at the target organ/tissue, which include immunoglobulins, serum proteins, synthetic polymers, liposomes, microspheres, erythrocytes, niosomes etc.\textsuperscript{51}

Drug targeting can be defined as the ability to direct a therapeutic agent specifically to desired site of action with little or no interaction with non target tissue. The concept of targeted drug delivery is designed for attempting to concentrate the drug in the tissues of interest while reducing the relative concentration of the medication in the remaining tissues. As a result, drug is localised on the targeted site. Hence, surrounding tissues are not affected by the drug. In addition, loss of drug does not happen due to localisation of drug, leading to get maximum efficacy of the medication.\textsuperscript{52} Different carriers have been used for targeting of drug, such as immunoglobulin, serum proteins, synthetic polymers, liposome, microspheres, erythrocytes and niosomes.

Niosomes are one of the best among these carriers. Structurally, niosomes are similar to liposomes and also are equiactive in drug delivery potential but high chemical stability and economy makes niosomes superior than liposomes. Both
consist of bilayer, which is made up of non-ionic surfactant in the case of niosomes and phospholipids in case of liposomes.\textsuperscript{53,54} The structure of niosomes is shown in the Fig 1.5.

![Fig 1.5 Structure of niosomes](image)

1.5.1 Types of niosomes

Generally, the niosomes have been classified as a function of the number of bilayer (eg:MLVs, SUVs) or as a function of size (eg:LUV’s SUVs) or as a function of the method of preparation (e.g: REV-Reverse phase evaporation, DRV – Dried Reconstituted vesicles)

1. Multilamellar vesicles (MLVs) – 0.5µm to 10µm in diameter
2. Large unilamellar vesicles (LUVs) – 0.1µm to 1µm in diameter
3. Small unilamellar vesicles (SUVs) – 25-500 nm in diameter.\textsuperscript{55}
1.5.2 Merits and demerits of niosomes

Merits

- Niosomes are novel drug dosage form for drug molecules having a wide range of solubility as their infrastructure consists of hydrophilic and hydrophobic part.

- Vesicles have flexible characteristic properties by altering vesicle’s characteristics like vesicle composition, size, lamellarity, tapped volume, surface charge and concentration of niosomes.

- As vesicle suspension is water based vehicle hence it provides better patient compliancy than oil based dosage forms

- They improve the oral bioavailability of poorly absorbed drugs, by delaying clearance from the circulation and by protecting the drug from biological environment thereby improve the therapeutic performance of the drug molecules

- They are osmotically active, stable and also increases the stability of entrapped drug.

- Oral, parenteral as well as topical routes can be adopted as administration routes.

- The surfactants are biodegradable, biocompatible and non immunogenic.

- They improve the therapeutic performance of the drug by protecting it from the biological environment and restricting effects to target cells, thereby reducing the clearance of the drug.

- Handling and storage of surfactants requires no special conditions
Demerits

- The aqueous suspensions of niosomes may have limited shelf life due to fusion aggregation, leaking of entrapped drugs and hydrolysis of encapsulated drugs.

- The method of preparation of multilamellar vesicles such as extrusion, sonication, are time consuming and may require specialized equipments for processing.\(^{56}\)

1.5.3 Structural components of niosomes

Non Ionic Surfactants

The non ionic surfactants orient themselves in bilayer lattices where the polar or hydrophilic heads align facing aqueous bulk (media) while the hydrophobic head or hydrocarbon segments align in such a way that the interaction with the aqueous media would be minimized. To attain thermodynamic stability, every bilayer folds over itself as continuous membrane i.e forms vesicles so that hydrocarbon/ water interface remains no more expose.

Mainly following types of non ionic surfactants are linked for the preparation of niosomes.

**Alkyl ethers**: L’Oreal described some surfactants for the preparation of niosomes are as follows:

1) Surfactant- I (Mol Wt 473) is \(C_{16}\) monoalkyl glycerol ether with average of three glycerol units.
2) Surfactant- II (Mol Wt 972) is diglycerol ether with average of the seven glycerol units.

3) Surfactant III (Mol Wt 393) is ester linked surfactant. Other than alkyl glycerol, alkyl glycosides and alkyl ethers bearing polyhydroxyl head groups are also used in formulation of niosomes.

**Ester linked surfactants**

These surfactants have ester linkage between hydrophilic and hydrophobic groups and have been studied for its use in the preparation and delivery of sodium stibogluconate to the experimental marine visceral leishmaniasis.

**Sorbitan Esters**

They are most preferred surfactant used for the preparation of niosomes amongst this category of surfactants. These are most widely used ester linked surfactants especially in food industry. The commercial sorbitan esters are mixtures of the partial esters of sorbitol and its mono and di-anhydrides with oleic acid. These have been used to entrap wide range of drugs.

**Alkyl Amides**

These are alkyl galactosides and glucosides which have incorporated amino acid spacers. The alkyl groups are fully or partially saturated C\textsubscript{12} to C\textsubscript{22} hydrocarbons and some novel amide compounds have fluorocarbon chains.
Fatty Acids and Amino Acid Compounds

These are amino acids which are made amphiphilic by addition of hydrophobic alkyl side chains and long chain fatty acids which form “Ufasomes” vesicles formed from fatty acid bilayers.

Cholesterol

Sterols are important components of the cell membrane and their presence in membrane affect the bilayer fluidity and permeability. Cholesterol a waxy steroid metabolite is usually added to the non-ionic surfactants to provide rigidity and orientational order. It does not form the bilayer itself and can be incorporated in large molar ratios. Cholesterol is an amphiphilic molecule, it orients its OH group towards aqueous phase and aliphatic chain towards surfactant’s hydrocarbon chain. Rigidization is provided by alternative positioning of rigid steroidal skeleton with surfactant molecules in the bilayer by restricting the movement of carbons of hydrocarbon. Cholesterol is also known to prevent leakage by abolishing gel to liquid phase transition. It prevents the vesicle aggregation by the inclusion of molecules that stabilize the system against the formation of aggregates by repulsive steric or electrostatic forces that leads to the transition from the gel to the liquid phase in niosome systems. As a result of this, the niosome become less leaky in nature.

Charge Inducers

Charge inducers increase the stability of the vesicles by induction of charge on the surface of the prepared vesicles. It acts by preventing the fusion of vesicles due to repulsive forces of the same charge and provide higher values of zeta potential. The
commonly used negative charge inducers are dicetyl phosphate, dihexadecyl phosphate and lipoamine acid and positive charge inducers are sterylamine and cetyl pyridinium chloride. Only 2.5-5 mol percentage concentration of charged molecules is tolerable because high concentration can inhibit the niosome formation.\textsuperscript{58}

1.5.4 Factors affecting physico-chemical properties of niosomes\textsuperscript{59,60}

Various factors that affect the physico-chemical properties of niosomes are

- Nature of Surfactants
- Structure of Surfactants
- Amount and type of surfactant
- Membrane Composition
- Nature of Encapsulated Drug
- Temperature of Hydration
- Method of Preparation
- Resistance to Osmotic Stress

1.5.5 Method of Preparation of niosomes

![Method of preparation of niosomes](image)

Fig 1.6 Method of preparation of niosomes
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Preparation of small unilamellar vesicles

- Sonication
- Micro fluidization

Preparation of multilamellar vesicles

- Hand shaking method (Thin film hydration technique)
- Trans-membrane pH gradient (inside acidic) drug uptake process (remote loading)

Preparation of large unilamellar vesicles

- Reverse phase evaporation technique (REV)
- Ether injection method

Miscellaneous

- Multiple membrane extrusion method
- Emulsion method
- Lipid injection method
- The “bubble” method
- Formation of niosomes from proniosomes

Separation of unentrapped drug

The removal of unentrapped solute from the vesicles can be accomplished by various techniques, which include:
1.5.6 Applications

Niosomal drug delivery is potentially applicable to many pharmacological agents for their action against various diseases. Few of their therapeutic applications are as follows: 71-75

- Targeting of Bioactive agents
  - To Reticulo-Endothelial System (RES)
  - To organs other than reticulo-endothelial system (RES)

- Neoplasia

- Delivery of peptide drugs

- Immunological applications of Niosomes

- Niosome as a carrier for Hemoglobin

- Transdermal delivery of drugs by niosomes

- Diagnostic imaging with Niosomes

- Leishmaniasis therapy

- Niosome formulation as a brain targeted delivery system for the vasoactive intestinal peptide (VIP)

- Niosomes in Ophthalmic drug delivery
Other Applications

- Sustained Release
- Localized Drug Action

1.6 **IN-SITU GEL DRUG DELIVERY SYSTEM**

The conventional ocular drug delivery systems like solutions, suspensions and ointments show drawbacks such as increased precorneal elimination, high variability in efficiency and blurred vision respectively so there was a need for developing advanced drug delivery system.\(^{76}\) *In-situ* forming polymeric formulations were developed to overcome the drawbacks in conventional drug therapy. These systems are in solution form before administering in the body, but once administered these systems undergo gelation.\(^{77}\) The formation of gels depends on factors like change in a specific physico-chemical parameter (pH, temperature, ion-sensitive) by which the drug gets released in a sustained and controlled manner.\(^{78}\)

1.6.1 **Advantages of *in-situ* ocular drug delivery system**

- To provide sustained and controlled drug delivery
- To increase the ocular bioavailability of drug by increasing the corneal contact time
- Drug effect is prolonged hence frequent instillation of drug is not required
- Patient compliance and enhance therapeutic performance of drug
- Generally more comfortable than insoluble or soluble insertion
- System provides ease of administration.\(^{79,80}\)
1.6.2 Ideal characteristics of polymers for preparation of *in-situ* ophthalmic gels

- It should be biocompatible
- It is capable of adhering to the mucus membrane
- Preferred pseudo plastic behavior of polymer
- Good tolerance and optical clarity is more preferred
- It should influence the tear behavior
- The polymer should be capable of decreasing the viscosity with increasing shear rate.$^{81,82}$

1.6.3 Mechanisms of *in-situ* gelation

**pH triggered *in-situ* gelation**

Pseudolatexes and carbomers have been reported to function as *in-situ* gelling polymers upon modification of pH. Their aqueous dispersions or solutions become viscous gels after instillation in the cul-de-sac due to change in the pH. Solvent evaporation process and salting out process are commonly used methods for preparation of ophthalmic pseudo latexes.$^{83}$

First preliminary investigations of pH sensitive latex for ophthalmic administration began in early 1980s and have been extensively studied by Boye. He proposed the preparation of latexes containing pilocarpine with cellulose acetate phthalate (CAP) The choice of this polymer was determined by its compatibility with active compound , stability and its ability to be a free running solution at pH 4.2 and gel at pH 7.2. Carbomer a cross linked acrylic acid polymer also shows pH mediated
phase transitions as the pH is raised above its pKa of about 5.5. Polymers containing acidic or alkaline functional groups that respond to changes in pH are called pH sensitive polymers. The pH is an important signal, which can be addressed through pH responsive materials. Gelling of the solution is triggered by a change in pH at pH 4.4 the formulation is a free-running solution which undergoes coagulation when the pH is raised by the tear fluid to pH 7.4. The pH change of about 2.8 units after instillation of the formulation (pH 4.4) into the tear film leads to an almost instantaneous transformation of the highly fluid latex into a viscous gel. The polymers with a large number of ionizable groups are known as poly electrolyte. Swelling of hydrogel increases as the external pH increases in the case of weakly acidic (anionic) groups, but decreases if polymer contains weakly basic (cationic) groups. Mechansim of pH sensitive system is shown in the Fig 1.7.

Fig 1.7 Mechanism of pH sensitive system
Temperature triggered in-situ gel

Temperature is the most widely used stimulus in environmentally responsive polymer systems. The change of temperature is not only relatively easy to control, but also easily applicable both in vitro and in vivo. In this system, gelling of the solution is triggered by change in temperature, thus sustaining the drug release. These hydrogels are liquid at room temperature (20–25 °C) and undergo gelation when in contact with body fluids (35–37 °C), due to an increase in temperature. The use of biomaterial whose transitions from sol-gel is triggered by increase in temperature is an attractive way to approach in-situ formation. Poloxamers, commercially available as pluronic are the most commonly used thermal setting polymers in ophthalmology. Depending on the ratio and the distribution along the chain of the hydrophobic and hydrophilic subunits, several molecular weights are available, leading to different gelation properties. Pluronic F – 127, which gives colorless and transparent gels, is the most commonly used polymer in pharmaceutical technology. Hydrogels based on pluronic are commonly prepared by solubilization of the polymer in cold water (5–10º C) followed by gelation upon warming to ambient temperature. Three principle mechanisms have been proposed to explain the liquid – gel phase transition after an increase in temperature, including the gradual desolvation of the polymer, increased micellar aggregation and increased entanglement of the polymeric network.

The polymers which show temperature induced gelation are poloxamer or pluronics, cellulose derivatives (methyl cellulose, HPMC,ethyl (hydroxyl ethyl) cellulose (EHEC) and xyloglucan etc. Mechanism of temperature sensitive is shown in the Fig 1.8.
Ion activated \textit{in-situ} gelation

In this method gelling of the solution instilled is triggered by change in the ionic strength. It is assumed that the rate of gelation depend on the osmotic gradient across the surface of the gel. The aqueous polymer solution forms a clear gel in the presence of the mono or divalent cations typically found in the tear fluids. The electrolyte of the tear fluid and especially Na+, Ca2+ and Mg2+ cations are particularly suited to initiate gelation of the polymer when instilled as a liquid solution in the conjunctival cul-de-sac. The polymer which shows osmotically induced gelation is Gelrite or Gellan gum, Hyaluronic acid and Alginates etc. Recently, some other natural polymers believed to be able to form \textit{in-situ} gels by interacting with the lachrymal fluid have been evaluated as potential adjuvants in ophthalmic formulation. These include carragenans, xyloglucans and some algimated that are rich in guluronic acid residues. Mechanism of Ion activated system is shown in the Fig 1.9.
1.7  GLAUCOMA: AN OVERVIEW

Glaucoma is a group of diseases of the eye characterized by damage to the ganglion cells and the optic nerve. Glaucoma is the leading cause of irreversible blindness in the world. It generally occurs in people over 40 years of age but may also occur in younger persons including children. Glaucoma is a disease characterized mainly by an increase in intraocular tension, if sufficiently high and persistent, leads to irreversible blindness. If left untreated, these effects may lead to various degrees of vision loss and blindness. Increased intraocular pressure (IOP) remains the most important risk factor for the development of glaucoma. Glaucoma is typically classified as either open angle or angle closure (closed angle), based upon causes of increased intraocular pressure as seen in Fig 1.10.
These are many sub types of glaucoma, but they can all be considered to be a type of optic neuropathy. Raised intraocular pressure (above 21mmHg or 2.8KPa) is the most important and only modifiable risk factors for glaucoma.\textsuperscript{92,93}

### 1.7.1 Epidemiology

It is estimated that there are more than 60 million cases of glaucoma worldwide and it will increase to 80 million by 2020.\textsuperscript{94} The estimated prevalence of glaucoma is 2.65% in people above 40 years of age. Globally, primary open-angle glaucoma (POAG) is more prevalent than primary angle closure glaucoma (PACG) and responsible for around three fourth of all glaucoma cases. Overall glaucoma is the second major cause of blindness after cataract and refractive errors. More importantly it is the most common cause of irreversible blindness globally. It is estimated that more than 3 million people are blind due to glaucoma.\textsuperscript{95}

In India, the estimated number of cases of glaucoma is 12 million, around one fifth of the global burden of glaucoma. Although in the Caucasian population, around
two third of cases are POAG, in the Indian population an equal proportion of open-angle and closed-angle glaucoma is seen.\(^9^6\) The prevalence of POAG in rural south India among 40+ populations was estimated as 1.7% in the ACES study. The prevalence was comparatively higher in the urban south India-Chennai Glaucoma Study (3.5%).\(^9^7\) More importantly it was observed that more than 90% cases of glaucoma were undiagnosed and identified only at the time of survey (98.6% in the Chennai Glaucoma Study and 93% in ACES). The National Blindness survey 2001 showed that glaucoma is the third major cause of blindness in India and responsible for 5.9% of blindness (VA <6/60).\(^9^8\) There has been a more than threefold increase in proportion of glaucoma blindness compared to that found in the previous National survey in 1986-1989.\(^9^9\) It is perceived that glaucoma blindness is underestimated in these surveys as the blindness is defined on visual acuity criteria instead of visual fields which are defining criteria for glaucoma.

Worldwide glaucoma “silent thief of sight” is the leading cause of irreversible blindness. Most of the type it causes no pain and produces no symptoms until it becomes fetal and caused blindness. About 37 million people across the globe are blind due to glaucoma and in India 1.2 lakh people blind patients add every year due to this menace as represented statistically in Fig 1.11\(^1^0^0\)
1.7.2 Etiology (Study of the causes of disease)

Optic nerve damage caused by the different types of glaucoma is a result of a variety of initiating factors. Genetic predisposition, physical changes, systemic diseases or medications may increase a person’s risk of developing damage that may be broadly classified as intraocular pressure dependent (most commonly) or intraocular pressure independent. Increased intraocular pressure remains the major etiologic risk factor for the development of glaucoma. Myopia may be an additional risk factor, especially in younger patients. Glaucoma can occur as a secondary manifestation of systemic disorders or trauma.

1.7.3 Aqueous humour

The aqueous humour is a transparent, watery fluid similar to plasma, but containing low protein concentrations. It is secreted from the ciliary epithelium, a structure supporting the lens. It fills both the anterior and the posterior chambers of
the eye and is not to be confused with the vitreous humour, which is located in the space between the lens and the retina, also known as the posterior cavity or vitreous chamber. 104

**Composition**

- Amino acids: transported by ciliary muscles
- 98% water
- Electrolytes

Sodium = 142.09 Potassium = 2.2 - 4.0 Calcium = 1.8 Magnesium = 1.1 Chloride = 131.6 HCO3- = 20.15 Phosphate = 0.62 pH = 7.4 Osm = 304.

- Ascorbic acid
- Glutathione
- Immunoglobulin’s

**Production**

Aqueous humour is secreted into the posterior chamber by the ciliary body, specifically the non-pigmented epithelium of the ciliary body (pars plicata). 5 alpha-dihydrocortisol, an enzyme inhibited by 5-alpha reductase inhibitors, may be involved in production of aqueous humour. 105

**Drainage**

Aqueous humour is continually produced by the ciliary processes and this rate of production must be balanced by an equal rate of aqueous humour drainage. Small
variations in the production or outflow of aqueous humor will have a large influence on the intraocular pressure.

The drainage route for aqueous humour flow is first through the posterior chamber, then the narrow space between the posterior iris and the anterior lens (contributes to small resistance), through the pupil to enter the anterior chamber. From there, the aqueous humour exits the eye through the trabecular meshwork into Schlemm's canal (a channel at the limbus, i.e., the joining point of the cornea and sclera, which encircles the cornea) It flows through 25–30 collector canals into the episcleral veins. The greatest resistance to aqueous flow is provided by the trabecular meshwork (esp. the juxtacanalicular part), and this is where most of the aqueous outflow occurs. The internal wall of the canal is very delicate and allows the fluid to filter due to high pressure of the fluid within the eye. 

1.7.4 Pathogenesis

There are five stages in the pathogenesis of glaucoma:

(1) A variety of initial events, causing

(2) Changes in aqueous outflow, resulting in

(3) Increased IOP, which leads to

(4) Optic nerve atrophy and finally,

(5) Progressive loss of vision.

1.7.5 Types of Glaucoma

Open-angle glaucoma

In open-angle glaucoma, a physical blockage occurs within the trabecular meshwork that retards elimination of aqueous humor. The obstruction is presumed to
be between the trabecular sheet and the episcleral veins, into which the aqueous humor ultimately flows. The impairment of aqueous drainage elevates the intraocular pressure to between 25 and 35 mm Hg (normal intraocular pressure is 10 to 20 mm Hg) indicating that the obstruction is usually partial. This increase in intraocular pressure is sufficient to cause progressive cupping of the optic disk and eventually visual field defects as shown in the Fig 1.12

![Fig 1.12 Schematic representation of mechanism of open angle and angle closure glaucoma](image)

**Angle-closure glaucoma**

In angle-closure glaucoma, increased intraocular pressure is caused by papillary blockage of aqueous humor outflow and is more severe. The basic requirements leading to an acute attack of angle closure are a papillary block, a narrowed anterior chamber angle and a convex iris. When a patient has a narrow anterior chamber or a pupil that dilates to a degree where the iris comes in greater contact with the lens, there is interference with the flow of aqueous humor from the posterior to the anterior chamber. Because aqueous humor is continually secreted, pressure from within the posterior chamber forces the iris to bulge forward. This may progress to complete blockage. The pathological complications of angle closure
and open angle glaucoma include the formation of cataracts, adhesion of the iris to the cornea, atrophy of the optic nerve and retina, complete blockage of aqueous outflow and ultimately blindness.\(^ {109}\)

**Congenital glaucoma**

Congenital glaucoma is a rare disorder in which intraocular pressure is increased as a result of developmental abnormalities of the ocular structures in the newborn or infant.\(^ {110}\) It may occur in association with other congenital abnormalities and anomalies such as homocystinuria and Marfan’s syndrome.

**Normal-tension glaucoma**

The etiology and pathogenesis of normal tension glaucoma remain to be completely understood. Normal tension glaucoma is thought to be related at least in part to decreased blood flow to the optic nerve. This may eventually cause neuronal damage. In addition, these eyes appear to be more susceptible to pressure related damage within the normal or high normal range and therefore a pressure lower than normal is often necessary to prevent further visual loss.\(^ {111}\)

**Drug-induced glaucoma**

Several therapeutic classes of drugs, such as those with anti-cholinergic, adrenergic, or corticosteroid effects, have been implicated in inducing or worsening glaucoma. Medications affect open angle and closed angle glaucoma differently.\(^ {112}\) Drugs that dilate the pupil, for instance, may precipitate an acute attack of angle closure glaucoma but usually do not produce harmful effects in those with open angle
glaucoma. Dilation of the pupil in angle closure glaucoma may cause the peripheral iris to bulge forward, blocking the trabecular meshwork. The aqueous humor is prevented from reaching the outflow channels, which results in increased IOP. Because excessive resistance to outflow in open angle glaucoma is caused primarily by changes within the trabecular outflow channels, dilation of the pupil usually will not increase the intraocular pressure.

1.7.6 Pharmacotherapy of glaucoma

Prevention or modification of risk factors, particularly the raised intraocular pressure is the primary goal in the management of Glaucoma. The disease is to be managed by laser therapy or by conventional surgery as the case may be.

Antiglaucoma agents

Depending on their route of administration, anti-glaucoma agents may be.

Topical drugs

- **Cholinergic agents**: Pilocarpine, cabachol, demecarium bromide and echothiophate iodide.
- **Adrenergic agonist**: Epinephrine, dipivefrin, brimonidine and metoprolol.
- **β-blockers**: Timolol, carteolol, betaxolol, levobunolol and metoprolol.
- **Prostaglandin analogs**: PGF₃₅, latanoprost, unoprostone and PHXA-85.
- **Carbonic anhydrase inhibitors**: Dorzolamide and brinzolamide.
Systemic drugs

- **Carbonic anhydrase inhibitors**: acetazolamide and methazolamide.
- **Osmotic agents**: Glycerine, mannitol and urea.

Miscellaneous drugs include forskolin, ethacrynic acid, steroid antagonists, cannabinoids, angiotension converting enzyme inhibitors, atrial natriuretic peptide and neuroprotective agents.

**Mechanism of action of antiglaucoma agents**

The anti-glaucoma agents act on the aqueous humor dynamics to reduce the intraocular pressure by three mechanisms.\(^{114}\)

- Decrease aqueous production is the ciliary body.
- Increase aqueous humor outflow through the trabecular meshwork.
- Increase aqueous humor outflow via the uveoscleral pathway.

**Glaucoma treatment**

The global burden of glaucoma possess a challenge to the researchers, ophthalmologists, and general practitioners to detect, prevents and effectively treat this visual disability and make safer drugs available to making at an affordable price.

**Laser Treatment**

For patients who cannot tolerate medications or for whom medication alone has not been adequate, laser treatment continues to be an excellent alternative. It should be noted that laser may also be used as primary treatment. The advantage of
this approach is that if adequate pressure lowering is achieved with laser treatment alone, the need for taking a daily medication may be delayed, along with the associated side effects. The effect of laser treatment is typically not permanent and many patients will eventually require medications. The most common laser treatments for glaucoma are selective laser trabeculoplasty (SLT) and argon laser trabeculoplasty (ALT).

**Glaucoma Risk**

A risk factor is something that increases your likelihood of getting a disease or condition. It is possible to develop glaucoma with or without the risk factors. However the more risk factors you have the greater your likelihood of developing glaucoma.¹¹⁵

**1.8 RATIONALE OF THE STUDY**

Drug delivery in ocular therapeutics is a challenging problem and a difficult task to scientist working in the multidisciplinary areas pertaining to the age. Current trends in ocular therapeutics and drug delivery suggest that the existing dosage forms should be replaced by novel drug delivery systems that offer novelty and improved therapy. The main objective of drug delivery system to the eye is to improve existing ocular dosage forms and exploit newer drug delivery system for improving the therapeutic efficiency. Topical application of eye drops is the most common method of administering drugs to the eye in the treatment of ocular diseases.¹¹⁶ Although topical and localized applications are still in acceptable and preferred route, such dosage forms are no longer sufficient to overcome the various ocular diseases such as
glaucoma, due to poor bioavailability and efficient mechanisms protecting the eye from harmful materials and agents. This includes reflex, blinking, lacrimation, tear turn over and drainage of tear results in the rapid removal of drug from the eye surface. Similarly, frequent instillation of concentrated medication is required at the site of action which is a patient compliance.

Glaucoma is an eye disease, characterized by higher level of intraocular pressure. This can permanently damage vision in the affected eyes and lead to blindness if left untreated. Open angle glaucoma, the most common form of glaucoma, accounts of at least 90% of all the chronic glaucoma, create a major problem of public health and it is the second leading cause of blindness in the world. It is estimated that the number of people with glaucoma will be nearly 79.6 million worldwide by 2020 as cited in WHO. This alarmingly large number of anticipated patients requires urgent improvement in current therapeutic approaches adopted for the treatment of this disease. Even though, the currently available eye drops for glaucoma treatment reduces its disability. Their long term effectiveness and efficacy are being questioned due to poor patient compliance.

Dorzolamide is a Carbonic Anhydrase Inhibitor (CAI) used in the treatment of glaucoma. Carbonic anhydrase is responsible for generation of tricarbonate anions secreted by the ciliary process into the posterior chamber of the eye. Inhibition of CA results in reduction of IOP. Orally administrated CAIs, such as acetazolamide are very effective ocular hypotensive agents but their oral administration results in systemic side effects including general malaise depression, loss of appetite, fatigue, weight loss, gastro intestinal disturbances, parenthesis and renal calculi. Dorzolamide is
reported to have 20 times higher potency than acetazolamide and is topically active. When dorzolamide solution is instilled in ocular cul de sac, common side effects observed are bitter taste in mouth, blurred vision, redness, burning, stinging upon and dryness of eyes with sensitivity to sunlight and tearing. These side effects could be due to exposure of concentrated solution of Dorzolamide to eyes and would be more severe when eye drops are instilled frequently to achieve the desired pharmacological effects.\textsuperscript{121} Ophthalmic drug delivery is one of the most interesting and challenging endeavors ever faced by the pharmaceutical scientists. The anatomy, physiology and biochemistry of the eye render this organ exquisitely impervious to foreign substances. The challenge to the formulator is to circumvent the protective barrier of the eye without causing any permanent tissue damage. The primitive ophthalmic dosage forms like solution, suspension and ointment are clearly no longer sufficient to combat some present virulent diseases. The major problem encountered with solution is the precorneal lachrymal fluid by solution drainage, lacrimation and nonproductive absorption by the conjunctiva, which may lead to undesirable side effects.\textsuperscript{122} It has been reported that bioavailability particularly for ocular solutions ranges from 1 to 10\% of total administrated dose. Rapid clearance kinetics resulting from reflux, tearing and blinking where half life of instilled isotonic solutions was found to be only 15 sec in humans. It must be noted that this high drainage rate is due to the tendency of the eye to maintain its residence volume at 7-10 µl permanently, whereas volumes topically instilled range from 20 to 50 µl. Ointments increase the contact time, minimize the dilution by tears and resist nasolachrymal drainage, however they are responsible for blurring vision. Suspensions show high variability due to inadequate
dosing, mainly due to lack of patient compliance inadequate shaking before use. Ophthalmic inserts constitute psychological and physiological barrier to use.123.

Due to various disadvantages associated with conventional drug delivery systems, attention has been focused on developing controlled and sustained drug delivery system in order to reduce the frequency of dosing or to increase the effectiveness of the drug by localization at its site of action, decreasing the dose required or providing uniform drug delivery. This problem can be overcome by using vesicular system.

At present no available drug delivery system achieves the site specific delivery with controlled release, kinetics of drug in predictable manner. Drug targeting is the ability to direct therapeutic agent specifically to desired site of action. Paul Ehlich in 1909 initiated the era for development of targeted delivery. When he envisaged a drug delivery mechanism that would target directly to disease cell, since then number of carriers were utilized to carry drug at the target organ tissue, which include immunoglobulins, serum proteins, synthetic polymers, liposomes, erythrocytes, microspheres, niosomes and nanoparticles.

Vesicular drug delivery system using colloidal particulate carriers (liposomes or niosomes) have distinct advantages over conventional dosage forms because colloidal particles can act as drug containing reservoirs.124 Modification of the particle composition or surface can adjust the affinity for the target site and the drug release rate.
The slow drug release from carrier system may reduce the toxicity of the drug and hence these carriers play an important role in drug delivery. Vesicular systems not only provide sustained and controlled release of the medication at the corneal surface but also prevent metabolism of the drug at tear/ corneal epithelium surface by various enzymes including esterases and oxido reductases.  

The evolution of niosomal drug delivery technology has shown promising approach in ocular drug delivery. Niosomes (non-ionic surfactant vesicles) are microscopic lamellar structure formed on admixture of non ionic surfactant of the alkyl or dialkyl poly glycerol ether class and cholesterol with subsequent hydration in aqueous media. It is droppable, biocompatible and biodegradable in nature. It reduces the toxicity of drug and also facilitates prolonged and controlled drug action at the corneal surface along with controlled ocular delivery through prevention of drug metabolism mediated by enzymes. However disadvantage of pre corneal and nasolachrymal drainage are more often associated with such niosomal system in the ophthalmic drug delivery.

Therefore in-situ gel forming systems have been developed to prolong the pre corneal residence time of a drug and improved ocular bioavailability. By employing one polymer system it forms stiff gel upon instillation in the eye for that higher concentration of polymer is required but as the concentration of polymer increases, its acidic nature also increases which may cause stimulation in the eye tissue. Therefore in order to reduce the total polymer content without comprising the gelling properties, combination of polymers are used in delivery systems. The main idea is that the aqueous composition of polymers should reversibly gel upon variation in pH. But the
drug release rate from these system i.e pH triggered *in-situ* gel was not found to be sustained release type.\(^\text{129}\) So in order to overcome the disadvantages associated with individual system the idea is to combine the two systems (Niosomes & *in-situ* gel) together to make niosomal *in-situ* gel system which is able to overcome the usual barriers of conventional therapies along with controlled and direct delivery of drug to the site of actions.\(^\text{130}\)

Hence the research work is focused to develop and characterize novel niosomal *in-situ* gel drug delivery system for the reduction in intra ocular pressure in the field of ocular therapeutics.

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