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formulation and evaluation of nephazoline hydrochloride ocular insert

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CHAPTER 1 INTRODUCTION

Novel drug delivery systems (NDDS) have become a cornerstone in pharmaceutical research due to their ability to improve therapeutic efficacy and enhance drug bioavailability compared to conventional dosage forms. These innovative strategies not only optimize pharmacokinetics but also reduce systemic side effects through site-specific targeting (Patel et al., 2020). Among various specialized approaches, ocular drug delivery remains one of the most challenging areas because of the eye's unique anatomical and physiological barriers.

Conventional ocular dosage forms such as ophthalmic solutions, suspensions, and ointments often fail to provide satisfactory results for chronic or virulent ocular diseases. This limitation arises from rapid precorneal elimination, blinking, tear turnover, and poor permeability of the corneal epithelium, which together reduce drug residence time and bioavailability (Gaudana et al., 2010). Therefore, the design of an effective ocular drug delivery system requires careful consideration of pharmacokinetic processes, including absorption, distribution, metabolism, and excretion (Cholkar et al., 2013).

The anatomy and physiology of the eye make it naturally resistant to the penetration of foreign substances, acting as a protective mechanism but simultaneously creating obstacles for therapeutic delivery. Overcoming these barriers has prompted researchers to develop novel strategies such as in situ gels, nanoparticles, liposomes, and contact lens-based systems, which enhance drug retention and prolong therapeutic effect (Kapoor et al., 2021).

A central goal of ocular drug delivery research is to maintain effective drug concentrations at the site of action for prolonged periods. Sustained and controlled-release formulations have shown promise in improving treatment efficacy and patient compliance. Continuous advancements in nanotechnology, bioadhesive polymers, and targeted carriers are paving the way for the next generation of ocular therapeutics (Rathore & Nema, 2009).

1.1 Advantages of Novel Ocular Drug Delivery Systems

Novel ocular drug delivery systems have emerged as promising alternatives to conventional formulations, addressing many of the limitations associated with solutions, suspensions, and ointments. These advanced systems enhance therapeutic efficacy, improve patient compliance, and provide better control over drug release and targeting. The major advantages are summarized below (Gaudana et al., 2010; Rathore & Nema, 2009; Patel

et al., 2020; Cholkar et al., 2013; Kapoor et al., 2021):

- **Improved dose accuracy** – Novel carriers allow precise dosing and overcome the side effects associated with pulsed dosing, commonly observed with conventional ophthalmic dosage forms.
- **Sustained and controlled release** – They provide prolonged therapeutic effect by releasing drugs in a controlled manner, reducing the need for frequent instillation.
- **Enhanced penetration** – Low molecular weight and hydrophilic drugs demonstrate improved corneal and conjunctival penetration due to novel delivery technologies.
- **Increased ocular bioavailability** – Drug contact time with the corneal surface is prolonged through bioadhesive and mucoadhesive systems, leading to improved absorption.
- **Targeted drug delivery** – Site-specific delivery helps minimize drug loss to non-target ocular tissues and enhances therapeutic concentration at the desired site.
- **Patient comfort and compliance** – These systems reduce dosing frequency, cause less irritation, and improve overall patient acceptability.
- **Effective in chronic diseases** – Sustained release and targeted delivery make novel systems especially valuable for the long-term management of chronic ocular disorders such as glaucoma and dry eye syndrome.
- **Minimized systemic side effects** – By preventing unnecessary drug distribution to systemic circulation, novel carriers improve safety and therapeutic performance.

1.2 Disadvantages of Novel Ocular Drug Delivery Systems

Despite their advantages, novel ocular drug delivery systems are associated with several limitations that restrict their widespread clinical application. These disadvantages are primarily related to physiological barriers, patient acceptability, and formulation challenges (Lang et al., 2019; Sridhar et al., 2018; Ludwig, 2005). The major drawbacks are outlined below:

- **Limited corneal permeability** – The corneal epithelium presents a strong barrier to drug absorption, leading to reduced bioavailability of many therapeutic agents.
- **Loss due to blinking and tear flow** – Natural protective mechanisms such as blinking and lacrimation cause rapid clearance of drugs, thereby lowering therapeutic efficacy and necessitating frequent administration.
- **Patient compliance issues with ocular inserts** – Solid devices or inserts may act as physical and physiological barriers, often leading to discomfort, foreign body sensation, and reduced compliance.
- **Visual interference** – Some ocular delivery systems, particularly inserts and suspensions, can cause temporary blurring of vision, which is inconvenient for patients.
- **Difficulty in administration** – Placement of ocular inserts or implants requires skill and may be difficult for patients to use independently.

- **Drug loss due to external factors** – Mechanical actions like rubbing of the eye can dislodge or expel the formulation, leading to reduced effectiveness.

- **Need for preservatives** – To maintain sterility and stability, preservatives are often added; however, prolonged use of preservative-containing formulations can cause ocular irritation and toxicity.

1.3 natomy of the Eye

The eye is a highly specialized spherical organ responsible for vision. It is composed of three concentric layers: the **outer sclera**, **middle choroid**, and **inner retina**. The **sclera** is a tough, fibrous white coat that provides protection, while the **choroid** lies beneath it and is rich in blood vessels. The **retina**, the innermost layer, contains photoreceptor cells responsible for converting light into neural signals. Anatomically, the eye is divided into the anterior and posterior segments, with structures such as the cornea and iris defining its anterior portion (Remington & Goodwin, 2021).

1.3.1 Cornea

The **cornea** is a transparent, dome-shaped structure at the front of the eye that refracts light and directs it toward the retina. It has a radius of curvature of about 7–8 mm, covering approximately one-sixth of the eye's total surface area. Its average thickness ranges from 0.5 to 0.7 mm (Del Monte & Kim, 2011).

Structurally, the cornea consists of five distinct layers:

- **Epithelium** – Comprising 5–6 layers of stratified squamous cells with a thickness of about 50–100 μm, this layer forms a barrier against dust and pathogens. Tight junctions within basal cells also restrict drug permeation.

- **Bowman's layer** – A thin, acellular, homogeneous membrane (8–14 μm thick) located between the epithelium and stroma.

- **Stroma (Substantia propria)** – The thickest corneal layer, consisting of ~85% water and 200–250 collagenous lamellae that provide both tensile strength and transparency.

- **Descemet's membrane** – A basement membrane secreted by endothelial cells, situated between the stroma and endothelium.

- **Endothelium** – A single layer of hexagonal cells (~5 μm in height, 20 μm in width) responsible for maintaining corneal hydration and transparency (Bonanno, 2012).

1.3.2 Sclera

The **sclera** is the opaque, white outer coat of the eye that provides shape and protection. It is composed of dense connective tissue and forms the posterior five-sixths of the outer coat of the eyeball. Its vascular layer includes:

- **Choroid** – A pigmented, vascular layer situated between the sclera and retina, supplying oxygen and nutrients.

- **Ciliary body** – A muscular structure containing ciliary processes and ciliary muscles, which regulate accommodation and aqueous humor production.

- **Iris** – A pigmented, circular structure that controls the diameter of the pupil, regulating the amount of light entering the eye.

The sclera also contributes to maintaining intraocular pressure and serves as an attachment point for extraocular muscles (Nickla & Wallman, 2010).

1.3.3 Composition of Tears

The **tear film** plays a crucial role in protecting and lubricating the ocular surface. It consists mainly of water (98.2%) along with proteins (0.67%), glucose (0.65%), salts, lysozyme, urea, and other organic compounds. The protein lysozyme provides antimicrobial defense, ensuring ocular sterility (Willcox, 2019).

Water: 98.2%	Proteins- 0.67%
Urea – 0.03%	Sugar- 0.65%
NPN: 0.05%	NaCl - 0.66%

The nasolacrimal turnover rate is ~16%, with a normal tear volume of ~7 µL and a physiological pH of 7.2. Without blinking, tear volume can rise to ~30 µL before spillage occurs. The constant secretion of lacrimal fluid prevents desiccation and inflammation of the ocular surface (Bron et al., 2017).

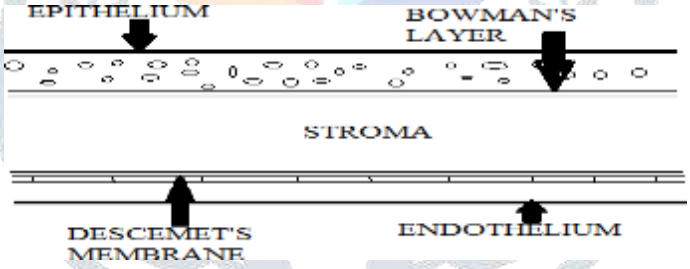


FIGURE 1.1 Layers of cornea

1.3.4 Conjunctiva

The **conjunctiva** is a thin mucous membrane lining the posterior surface of the eyelids and extending over the anterior sclera up to the cornea. It contains goblet cells that secrete mucus, contributing to tear film stability and ocular surface protection. Compared to the cornea, the conjunctiva is **2–30 times more permeable to drugs**, making it a potential site for non-corneal absorption (Levine et al., 2014).

The **cul-de-sac** of the eye holds approximately 7–9 µL of tears, with a tear flow rate of ~1 µL/min and a physiological pH of 6.5–7.6. The **pre-corneal tear film**, which covers the corneal epithelium, conjunctiva, and cul-de-sac, plays a critical role in drug absorption but also contributes to significant drug loss due to rapid clearance (Gaudana et al., 2010).

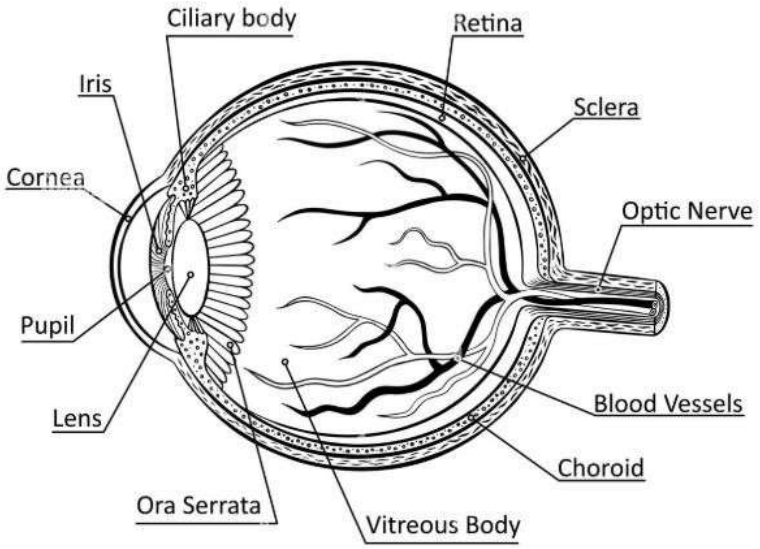


FIGURE 1.2 Structure of eye

Drug delivery to the **posterior segment** of the eye is particularly challenging because of anatomical and physiological barriers. Diseases such as **age-related macular degeneration, diabetic retinopathy, and retinitis pigmentosa** necessitate targeted posterior delivery. Currently, the **intravitreal route** is the most widely used approach to achieve therapeutic drug concentrations in the retina (Del Amo & Urtti, 2008).

Protective Mechanisms Limiting Absorption

Several protective mechanisms regulate drug absorption, maintaining ocular function while reducing the bioavailability of topically administered drugs (Sridhar et al., 2018). These include:

- Drainage of instilled solutions via the nasolacrimal system.
- Tear secretion and turnover.
- Metabolic degradation within the tear film.
- Tear evaporation.
- Non-productive absorption/adsorption onto conjunctival surfaces.
- Limited corneal permeability and small corneal surface area.
- Binding of drugs by lacrimal proteins.

When fluid volume exceeds the normal lacrimal volume (~10 µL), excess is drained into the **nasopharynx and gastrointestinal tract**, leading to systemic absorption and reduced ocular availability. Additionally, conjunctival absorption through **palpebral and scleral regions** contributes to drug loss, as absorbed drugs are rapidly removed by local circulation. Protein binding and enzymatic metabolism in tears further reduce the effective concentration of active drugs (Urtti, 2006).

Pathways of Ocular Drug Absorption

Ocular absorption can occur via multiple pathways (Mitra, 2003):

- **Transcorneal permeation** from the tear film into the anterior chamber.
- **Non-corneal permeation** across conjunctiva and sclera into the anterior uvea.

- **Bloodstream distribution** into the anterior chamber via the blood–aqueous barrier.
- **Posterior segment drug delivery** across the blood–retina barrier.
- **Drug elimination** through aqueous humor drainage into systemic circulation.
- **Intravitreal administration**, followed by clearance either anteriorly to the aqueous humor or posteriorly via the blood–retina barrier.

An ideal ocular drug delivery system should therefore achieve **good corneal penetration, long precorneal residence time, patient comfort, and minimal irritation**, while maintaining stability and compatibility of the drug within the formulation (Lang et al., 2019).

1.4 Mechanism of Ocular Drug Absorption

Topical instillation into the **cul-de-sac** is the most common route of ocular drug delivery. Absorption occurs through **corneal** and **non-corneal** pathways.

1.4.1 Corneal Absorption

Corneal absorption is the **primary route** for most ophthalmic drugs. The cornea acts as a **trilaminate diffusion barrier** comprising the **epithelium, stroma, and endothelium** (DelMonte & Kim, 2011).

- **Epithelium** – Rich in lipids, it presents the main barrier for **hydrophilic drugs**, restricting paracellular transport due to tight junctions. The pore size (~60 Å) permits only small ionic and hydrophilic molecules.
- **Stroma** – Hydrophilic in nature, it provides resistance to **lipophilic drugs**, limiting their diffusion.
- **Endothelium** – Less resistant than epithelium, but due to its lipid content, it allows better passage of **lipophilic molecules**.

Thus, corneal absorption is strongly influenced by the **physicochemical properties of the drug**. Lipophilic drugs permeate through the epithelium and endothelium more readily, while hydrophilic drugs favor the stromal pathway. This dual requirement explains why achieving optimal corneal penetration remains a major challenge (Cholkar et al., 2013).

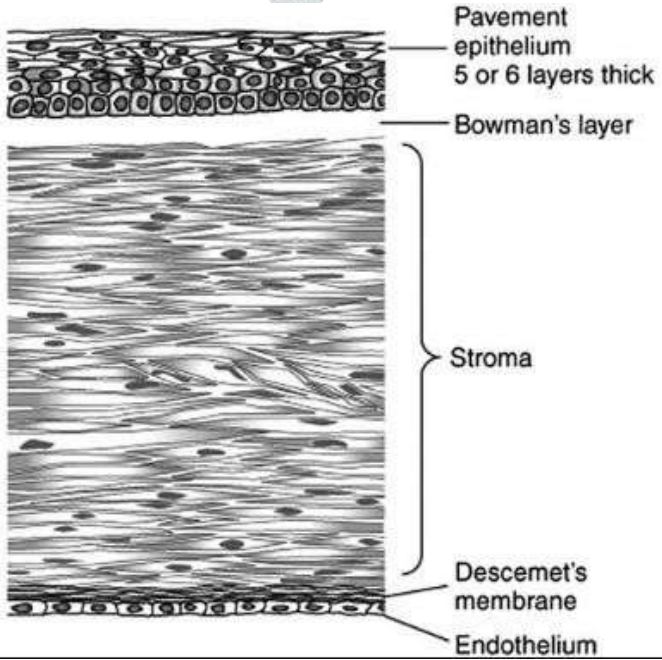


Figure 1.3 Cross-sectional view of the corneal membrane depicting various barriers to drug absorption

The stroma constitutes approximately 85–90% of the total corneal mass and is primarily composed of hydrated collagen fibrils that provide mechanical strength and transparency. Due to its hydrophilic nature, the stroma acts as a diffusion barrier for highly lipophilic drugs, while allowing relatively easier transport of hydrophilic molecules. Unlike the epithelium, the stroma does not contain tight junction complexes, which facilitates paracellular transport of certain drug entities. The innermost corneal endothelium is lipoidal in nature but does not present a significant barrier to the diffusion of most drugs. Research indicates that endothelial permeability is largely dependent on molecular weight rather than charge or hydrophilic characteristics (Prausnid & Noonan, 1998; Gaudana et al., 2010).

Transcellular transport across the corneal epithelium and stroma is considered the primary pathway for the ocular absorption of topically applied ophthalmic drugs. This transport process follows the principles of Fickian diffusion, which is governed by factors such as surface area, drug diffusivity, concentration gradient, and the duration for which the gradient can be maintained. Most ophthalmic drugs exhibit productive absorption through corneal diffusion,

with efficiency being determined by the rate and extent of transport. The flux of drug molecules across the corneal membrane depends on their physicochemical properties and interactions with corneal tissues. Additionally, pre-corneal factors such as tear film turnover, nasolacrimal drainage, and blinking significantly influence drug absorption efficiency (Maurice & Mishima, 1984; Lang, 1995).

Several factors affect corneal transport of drug molecules. These include the physicochemical characteristics of the drug, such as ionization constant, solubility, and oil/water partition coefficient. The pharmaceutical formulation also plays a key role, as the type of dosage form, buffer composition, presence of viscosity enhancers, and stabilizers influence bioavailability. Moreover, corneal structure and tissue integrity are essential in determining the rate and extent of absorption. For instance, damage to the epithelial barrier can lead to enhanced drug permeability but may compromise ocular safety (Patel et al., 2013).

In addition to corneal absorption, drugs may also undergo non-corneal absorption through penetration across the conjunctiva and sclera into intraocular tissues. However, this route is generally less productive, as drug molecules penetrating beyond the corneoscleral limbus are rapidly absorbed into the systemic circulation via local capillaries, reducing intraocular bioavailability. Non-corneal absorption becomes more significant for drug molecules with poor corneal permeability. Studies involving insulin, timolol maleate, and gentamicin have demonstrated that these molecules may achieve intraocular access primarily through diffusion across conjunctival and scleral tissues (Hosoya et al., 2005; Lee & Robinson, 1986).

1.5 Ocular Bioavailability

Ocular bioavailability of drugs is a critical determinant of the therapeutic success of ophthalmic formulations. The efficiency of an ophthalmic preparation is significantly influenced by the drug delivery system and the physicochemical characteristics of the drug. Numerous invasive pharmacokinetic studies have established that

formulation parameters directly affect drug bioavailability within ocular tissues (Lang, 1995; Gaudana et al., 2010).

Several factors limit intraocular bioavailability at the intended site of action. The tear film within the lacrimal cul-de-sac dilutes instilled drug solutions, while the continuous inflow and outflow of tears lead to rapid drug loss. Efficient nasolacrimal drainage further contributes to reduced drug retention in the precorneal area, directing a significant proportion of drug molecules toward systemic absorption (Patel et al., 2013). Additionally, proteins and enzymes present in lacrimal fluid may bind to or degrade the instilled drug, reducing its effective concentration.

The rate of drug elimination from ocular tissues also influences bioavailability, with both productive (via cornea) and non-productive (via conjunctiva and systemic circulation) pathways contributing to drug clearance (Prausnid & Noonan, 1998). Lipophilic compounds, which exhibit higher corneal permeability, generally demonstrate superior ocular bioavailability compared to hydrophilic drugs. Conversely, hydrophilic drugs often require formulation strategies such as viscosity enhancers or permeability modifiers to improve their ocular retention. Reducing instilled volume has been shown to improve bioavailability for drugs with inherently low corneal permeability, as smaller dosing volumes minimize precorneal loss and enhance drug–cornea interaction time (Hosoya et al., 2005). Overall, ocular bioavailability largely depends on the contact time of a drug with the corneal surface and its ability to overcome precorneal clearance mechanisms.

1.6 Barriers for Ocular Drug Delivery

Drug delivery to the eye is complicated by multiple anatomical and physiological barriers that limit the access of therapeutic agents to both anterior and posterior ocular tissues. These barriers play essential roles in maintaining ocular homeostasis but pose significant challenges for pharmacological interventions (Ahmed & Patton, 1985; Kim et al., 2004).

1.6.1 Blood–Ocular Barrier

The blood–ocular barrier serves as a protective mechanism, restricting the entry of xenobiotics and maintaining the privileged immune status of the eye. It comprises the blood–aqueous barrier and the blood–retinal barrier (Hosoya & Kim, 2008).

1.6.1.1 Blood–Aqueous Barrier

The blood–aqueous barrier is primarily formed by the non-pigmented epithelium of the ciliary body and the endothelial cells of the iris vasculature. Tight junctions between non-pigmented ciliary epithelial cells prevent the free diffusion of molecules from plasma into aqueous humor. Similarly, tight junctions within the iris endothelium restrict solute movement. This barrier regulates the composition of aqueous humor, ensuring proper electrolyte balance and nutritional support for avascular ocular tissues (Araie & Maurice, 1991).

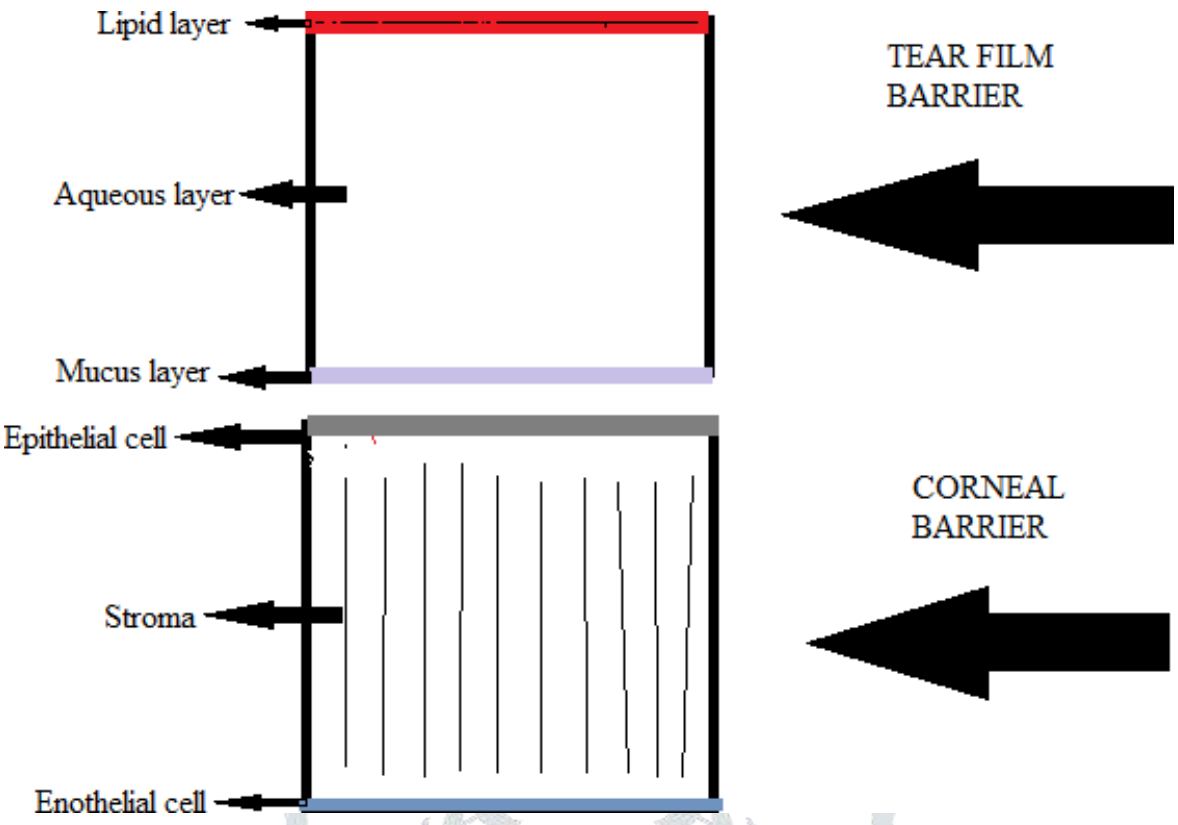
1.6.1.2 Blood–Retinal Barrier

The blood–retinal barrier (BRB) consists of two structural components: the inner barrier formed by tight junctions of retinal capillary endothelial cells, and the outer barrier formed by retinal pigment epithelial cells. Together, they limit the passive diffusion of large molecules (>20–30 kDa) into the retina (Del Amo & Urtti, 2008). Transport across the BRB occurs via both active mechanisms, such as organic anion and prostaglandin transporters, and passive diffusion of small solutes including glucose, sodium, and phosphate. While essential for retinal protection, the BRB significantly restricts the delivery of therapeutic molecules for posterior segment diseases.

1.6.2 Ocular Surface Barrier

The ocular surface barrier comprises the corneal and conjunctival epithelia, which regulate drug penetration from topical formulations. Corneal permeability is influenced by both epithelial and non-epithelial components. The mucin layer, composed of glycocalyx and secreted mucins, acts as a barrier to transcellular transport by forming a gel-like network that restricts the passage of drug molecules (Ramamoorthy et al., 2007). Additionally, paracellular transport across corneal epithelium is limited by tight junction proteins, including occludins, zonula occludens, and claudins (Stevenson et al., 1986). The acellular basement membrane further restricts macromolecule diffusion.

IGURE 1.4 Barriers of ocular drug delivery system



Another significant barrier is lacrimal drainage, which rapidly eliminates instilled drugs from the precorneal area, leading to systemic absorption through the conjunctiva and nasal mucosa. The pathway of drug diffusion depends largely on molecular size: small molecules are preferentially absorbed through the corneal route, while larger molecules utilize the scleral and conjunctival pathways (Prausnid & Noonan, 1998; Gaudana et al., 2010). Together, these ocular surface barriers contribute to the low bioavailability of most topically administered drugs, necessitating advanced formulation approaches for effective ocular therapy.

1.7 Factors Affecting Ocular Drug Bioavailability

The bioavailability of ophthalmic drugs is influenced by multiple factors that limit their ability to permeate the corneal route effectively. Since most ocular preparations are formulated in

aqueous vehicles, they face challenges such as rapid tear turnover, drug drainage, and the presence of ocular barriers. Generally, less than 10% of a topically instilled drug reaches the intraocular tissues, with the majority being lost through precorneal mechanisms (Gaudana et al., 2010; Mitra, 2013). These factors can be categorized into three major groups: physiological, physicochemical, and formulation-related.

1.7.1 Physiological Factors

Several precorneal physiological processes contribute to significant drug loss before absorption can occur:

- **Tear turnover:** Normal tear volume is approximately 7 μL, with a washout rate of nearly 16% per minute, leading to rapid clearance of drugs.

- **Instilled solution drainage:** The precorneal area has a holding capacity of about 30 µL, which is reduced to 10 µL after blinking. Excess solution drains into the nasolacrimal duct, where the clearance rate is 100 times faster than ocular absorption.

- **Protein binding:** Tear fluid contains about 0.7% protein, and during infection or inflammation, protein levels rise, leading to drug–protein binding that reduces free drug availability.

- **Non-productive absorption:** Drug absorption into tissues other than the cornea and conjunctiva, such as systemic circulation, reduces therapeutic efficiency. Adjusting lipophilicity and formulation can mitigate this loss.

- **Membrane-related factors:** The corneal epithelium is the primary barrier to penetration due to its lipophilic nature, low porosity, and tortuosity. Drugs with a partition coefficient greater than 1 show better corneal penetration.

1.7.2 hysicochemical Factors

Drug molecules' inherent physicochemical properties determine their diffusion across the corneal barrier:

- **Partition coefficient:** A key parameter that correlates with corneal permeability; an optimal hydrophilic-lipophilic balance (HLB) is necessary for effective penetration.

- **Solubility:** Drugs with poor solubility have limited concentrations in tear film, restricting their absorption and therapeutic effect.

- **Ionization constant (pKa):** Drugs that remain unionized at physiological tear pH (7.14– 7.28) diffuse more readily across the lipophilic epithelium.

- **Molecular weight:** Molecules below 500 Da typically permeate biological and synthetic membranes more efficiently.

1.7.3 Formulation Factors

Formulation design significantly affects ocular bioavailability:

- **Concentration:** Increasing concentration can enhance penetration but may induce hypertonicity, leading to lacrimation and drug loss.

- **Particle shape, size, and dissolution rate:** Suspensions are useful for poorly soluble drugs, but particle size above 10 µm causes irritation and reduces bioavailability.

- **pH and tonicity:** Tear fluid is weakly buffered at pH 7.14–7.28. Hypotonic solutions enhance epithelial permeability, while osmolarity between 200–400 mOsm is tolerated by the corneal endothelium.

- **Viscosity:** Polymers such as PVP, PVA, and cellulose derivatives increase drug residence time by enhancing viscosity, improving drug contact with the precorneal tear film.

1.8 Classification of Ocular Drug Delivery Systems

Ocular drug delivery systems can be broadly classified into several categories depending on their design and mechanism of action (Patel et al., 2013):

- **Conventional systems:** Solutions, gels, ointments, emulsions, ocular inserts.
- **Retrometabolic delivery systems:** Soft drug approaches, chemical delivery systems.
- **Vesicular systems:** Liposomes, niosomes, discosomes, pharmacosomes.
- **Particulate systems:** Nanoparticles, microparticles.
- **Controlled release systems:** Implants, hydrogels, dendrimers, iontophoresis, medicated contact lenses, microneedles, microemulsions, cyclodextrins, collagen shields.
- **Advanced drug delivery systems:** Stem cell therapy, engineered cell therapy (ECT), engineered drug delivery (EDD), siRNA-based systems, punctal plugs, and gene therapy.

1.9 Recent Advancements in Ocular Drug Delivery Systems

To address the challenges associated with conventional formulations, significant research has been directed toward advanced ocular drug delivery strategies. Nanotechnology has emerged as a promising platform to improve ocular bioavailability and achieve targeted drug delivery. Modern approaches include the use of nanocapsules, nanoparticles, and dendrimers, which allow drugs to bypass ocular barriers and sustain release (Gaudana et al., 2010). Moreover, active and passive targeting mechanisms enhance site-specific delivery, minimizing systemic side effects while improving therapeutic efficacy (Agrahari et al., 2016).

TABLE 1.1: Strategies for ocular drug delivery system

OPHTHALMIC DRUG DELIVERY STRATEGIES		
Formulation strategies	**Chemical strategies**	**Physical Approaches**

Penetration enhancers, Emulsifier/ liposomes, Suspension, Micro and Nanoparticle, bioadhesive hydrogel, Ocular insert	Prodrug Technology, Cyclodextrin technology, soft drugs	Iontophoresis, Phonophoresis

1.9.1 Nanoparticles

Nanoparticles are colloidal carriers with a diameter typically below 1 μm, composed of biodegradable or non-biodegradable polymers, lipids, or phospholipids. Commonly used polymers include polyacrylates, chitosan, gelatin, alginate, collagen, albumin, polycaprolactone, and polylactide (Mohanraj & Chen, 2006). These systems provide controlled and sustained release of drugs through different mechanisms, including:

- Desorption of surface-adsorbed drug
- Diffusion of drug from the polymeric matrix or wall
- Erosion of the nanoparticle wall
- A combination of erosion and diffusion mechanisms

Based on drug dispersion within the polymeric matrix, nanoparticles are classified into two types:

- **Nanospheres:** The drug is uniformly dispersed within the polymer matrix.
- **Nanocapsules:** The drug is encapsulated within a polymeric shell.

The bioavailability and therapeutic efficiency of nanoparticles depend on factors such as particle size and surface charge, which govern drug distribution, uptake, and release.

1.9.2 Methods for the Preparation of Nanoparticles

Several techniques have been developed for the preparation of nanoparticles, each based on specific physicochemical principles:

- **Solvent displacement:** Involves the precipitation of a polymer from an organic solvent that diffuses rapidly into an aqueous phase, usually in the presence of surfactants.
- **Homogenization:** A nanosuspension is prepared by dispersing drug powder in a stabilizer solution, followed by low-pressure premilling and high-pressure homogenization to reduce particle size.
- **Ionic gelation:** Utilizes electrostatic interactions between positively charged polymers (e.g., chitosan) and multivalent anions or cations, resulting in gel formation with nanoparticle sizes in the nanometer range.
- **Milling method:** Uses high-shear media mills to reduce drug particles from micro- to nanoscale through the combined effects of shear force and high-energy impact.

1.9.3 Applications of Nanotechnology in Ocular Drug Delivery

Nanotechnology has revolutionized ocular drug delivery by providing novel approaches to enhance therapeutic outcomes. Applications include:

- Corneal gene delivery
- Intravitreal and subretinal delivery systems
- Improved corneal residence time of drugs
- Enhanced drug biodistribution within retinal tissues
- Bioadhesive and internalization properties for improved uptake
- Nanomedicines with surface modifications for targeted delivery and cellular entry
- Sustained and controlled drug release
- Gene therapy enhancement through improved transfection efficiency and duration
- Ocular diagnostics and imaging
- Retinal prosthesis development

hese advantages make nanotechnology-based platforms highly promising for treating chronic and vision-threatening ocular diseases (Agrahari et al., 2016).

1.9.4 In Situ Hydrogels

In situ hydrogel systems are liquid formulations that undergo sol-to-gel transformation upon exposure to physiological conditions. Gelation occurs through covalent or non-covalent crosslinking of polymers and is triggered by specific stimuli. These hydrogels have low viscosity prior to administration, enabling easy instillation into the conjunctival sac, and subsequently form gels that prolong drug residence time and release (Gupta et al., 2019).

The mechanisms of in situ gel formation are categorized as:

- **Physical stimuli-responsive hydrogels:** Triggered by changes in temperature, electric fields, or light.
- **Chemical stimuli-responsive hydrogels:** Respond to changes in pH or ionic activation by biological fluids.
- **Biochemical stimuli-responsive hydrogels:** Triggered by biological signals such as glucose levels.

Major approaches include:

- **Temperature-sensitive hydrogels:** Polymers that undergo gelation at physiological temperatures.
- **pH-sensitive hydrogels:** Contain ionizable groups that swell in response to changes in pH.
- **Ion-activated hydrogels:** Triggered by the ionic strength of tear fluid, particularly cations such as Ca^{2+}, Na^{+}, and Mg^{2+}, which initiate polymer crosslinking and gel formation upon instillation.

These systems offer the advantage of prolonged precorneal retention and sustained drug release, making them an effective alternative to conventional eye drops.

1.9.5 Dendrimers

Dendrimers are globular, nanoscale polymers (3–20 nm) with well-defined branched structures and narrow polydispersity indices. They exhibit antimicrobial activity, mucoadhesive properties, and are widely applied as drug carriers and surface-coating agents in ocular delivery systems. Their mucoadhesion reduces tear dilution and drug loss, thereby improving corneal residence time and bioavailability (Kesharwani et al., 2014).

Two major synthetic approaches are employed in dendrimer production:

- **Divergent approach:** Synthesis begins at the core and extends outward through iterative coupling and activation steps. Peripheral functional groups are formed via coupling reactions, followed by deprotection. This method requires large quantities of reagents, and purification is achieved using precipitation, distillation, or ultrafiltration.
- **Convergent approach:** Synthesis proceeds from the periphery toward the core, beginning with dendrons that are coupled and branched. Attachment of multiple dendrons to a multifunctional core generates globular dendrimers.

1.9.6 Liposomes

Liposomes are artificial vesicles composed of natural phospholipids and cholesterol. Their biocompatibility and amphiphilic nature make them suitable for ocular drug delivery. Positively charged liposomes are particularly advantageous, as they interact with the negatively charged corneal surface, enhancing drug adherence and penetration (Torchilin, 2005).

Despite these benefits, liposomes present challenges such as short shelf-life, limited drug loading capacity, sterilization issues, and harsh preparation conditions. Methods of preparation include:

- **Reverse phase evaporation (REV):** Lipids are dissolved in organic solvents and emulsified with an aqueous phase, followed by solvent evaporation.
- **Solvent injection:** Lipid solutions are injected into aqueous phases under reduced pressure, leading to vesicle formation.
- **Fusion method:** Addition of calcium ions induces fusion of small vesicles into larger multilamellar structures; unilamellar vesicles form upon EDTA addition.
- **pH adjustment method:** Adjusting the lipid solution’s pH facilitates vesicle formation.

1.9.7 Niosomes

Niosomes are non-ionic surfactant vesicles with a bilayered structure, similar to liposomes, but with improved stability and lower production costs. They are biodegradable, biocompatible, and suitable for encapsulating both hydrophilic and lipophilic drugs. Importantly, niosomes enhance ocular drug bioavailability due to surfactants that

transiently disrupt the mucus layer, increasing drug absorption (Uchegbu & Florence, 1995).

1.9.8 Microemulsions

Microemulsions are thermodynamically stable dispersions consisting of water, oil, surfactant, and co-surfactant, with droplet sizes ranging from 5–200 nm. Their small size enhances drug permeation and absorption across ocular barriers (Lawrence & Rees, 2012). These systems can be either oil-in-water (o/w) or water-in-oil (w/o), depending on their composition.

The structural characteristics of microemulsions are influenced by:

- Surfactant type
- Thermodynamic conditions
- Additives such as alcohols, electrolytes, block copolymers, and polyelectrolytes

The combination of low surface tension and high stability makes microemulsions promising carriers for ocular therapeutics.

1.9.9 Microspheres and Microcapsules

Microspheres are monolithic particles composed of solid polymeric matrices, whereas microcapsules consist of a drug reservoir (solid or liquid) surrounded by a polymeric shell. These delivery systems prolong drug release and protect the encapsulated drug from degradation (Soppimath et al., 2001).

Common preparation techniques include:

- Solvent evaporation method
- Single and double emulsion methods
- Coacervation-phase separation
- Spray drying and spray congealing
- Polymerization methods

1.9.10 Prodrugs

Prodrugs are pharmacologically inactive derivatives of parent drugs designed to improve solubility, stability, duration of action, and reduce systemic side effects. Upon enzymatic or chemical transformation within ocular tissues, the active parent drug is released (Stella & Nti- Addae, 2007).

Key criteria for an effective ocular prodrug include:

- Chemical stability
- Adequate aqueous solubility
- Optimal lipophilicity

- Lack of toxicity or irritation
- Controlled release of the parent drug at therapeutic rates

This approach effectively addresses limitations of conventional drugs, such as poor solubility and short half-life.

1.9.11 Cubosomes

Cubosomes are nanostructured liquid crystalline particles derived from cubic-phase lipid systems. They provide high drug-loading capacity and controlled release properties, making them highly attractive for ocular drug delivery. Their unique internal structure allows encapsulation of both hydrophilic and lipophilic agents, supporting sustained therapeutic effects (Spicer, 2005).

1.9.12 Penetration Enhancers

Penetration enhancers, also referred to as sorption promoters or accelerants, are agents that temporarily reduce the barrier resistance of ocular membranes, thereby increasing drug permeability. They prolong the residence time of drugs in the eye by slowing clearance, which is primarily regulated by the mucus turnover rate (Mitra, 2013).

These enhancers act by loosening epithelial tight junctions and enhancing corneal membrane permeability. Common classes of ocular penetration enhancers include:

- Surfactants
- Calcium chelators
- Bile salts
- Preservatives
- Fatty acids
- Glycosides (e.g., saponins)

Although effective, penetration enhancers must be used cautiously, as they may cause irritation or toxicity with prolonged exposure.

1.9.13 Implants

Ocular implants are controlled drug delivery systems fabricated from biodegradable or non- biodegradable polymers. They are typically inserted into the vitreous cavity via a pars plana incision, located posterior to the lens and anterior to the retina. Implants provide sustained intraocular drug release, overcoming the limitations of intravitreal injections and systemic administration (Yasukawa et al., 2016).

Advantages of ocular implants include:

- Bypassing the blood–retina barrier
- Sustained drug release at therapeutic concentrations
- Improved site-specific targeting
- Reduced dosing frequency and side effects

Implants may be solid, semi-solid, or particulate systems. Biodegradable implants are often prepared using polymers such as polylactic acid (PLA), polyglycolic acid (PGA), or poly (lactic- co-glycolic acid) (PLGA).

Drug release is mediated by bioerosion or polymer degradation.

Shapes of ocular implants include:

- Rods
- Pellets
- Discs
- Plugs
- Sheets

1.9.14 Nanosuspensions and Nano emulsions

Nanosuspensions are colloidal dispersions of nanosized drug particles stabilized by surfactants, viscosity enhancers, or charge modifiers. They are produced using techniques such as pearl milling, high-pressure homogenization, and precipitation (Müller et al., 2011).

Nanoemulsions, on the other hand, are kinetically stable dispersions of oil and water phases stabilized by surfactants. They offer several advantages for ocular drug delivery, including:

- High solubilization capacity for both hydrophilic and lipophilic drugs
- Enhanced drug bioavailability and stability
- Improved spreadability on the ocular surface
- Increased permeability due to the surfactant action

Both nanosuspensions and nanoemulsions are promising platforms for delivering poorly soluble drugs to ocular tissues.

1.9.15 Ocular Inserts

Ocular inserts are sterile, multilayered solid or semisolid devices placed in the conjunctival sac or cul-de-sac to enhance ocular drug bioavailability and maintain drug concentrations within

the therapeutic range (Gaudana et al., 2009). They consist of a polymeric support matrix, which may or may not contain the active drug, and typically include:

- **Drug reservoir** (incorporated into a polymer matrix)
- **Rate-controlling membrane**
- **Outer annular ring** (to facilitate handling and insertion)

Classification of Ocular Inserts

1. **Soluble inserts**
2. **Bioerodible inserts**
3. **Insoluble inserts.**

- Osmotic inserts
- Diffusion inserts
- Contact lenses (rigid, semi-rigid, elastomeric, soft hydrophilic, bio-polymeric)

a. Osmotic inserts:

- *Type 1:* Drug dispersed with/without an osmotic solute in a polymeric matrix.
- *Type 2:* Dual compartments: one containing the drug reservoir (elastic impermeable membrane) and the other with osmotic solute (rigid semi-permeable membrane).

b. Diffusion inserts:

- Comprise a central drug reservoir surrounded by a semi-permeable membrane.
- Drug release is controlled by lachrymal fluid permeation, generating internal pressure that drives drug diffusion.

c. Contact lenses:

- Composed of cross-linked hydrophilic or hydrophobic polymers forming a 3D network.
- Their major drawback is ocular discomfort and poor tolerability despite providing prolonged drug residence time.

1.9.16 Methods of Preparation of Ocular Inserts

Ocular inserts can be prepared using different techniques, depending on the desired release mechanism, polymer type, and drug compatibility. The following are the most widely used preparation methods (Kaur & Kanwar, 2002):

- **Solvent Casting Method:**
  - The polymer is dissolved in a suitable solvent and mixed with a plasticizer.
  - The drug is incorporated into the solution, which is stirred until homogenous.
  - The solution is poured into Petri dishes and allowed to dry under controlled conditions for 48 hours.
  - The resulting films are cut into uniform pieces and stored under ambient conditions.
- **Glass Substrate Technique:**
  - The polymer is soaked in solvent for 24 hours, filtered, and then mixed with drug and plasticizer.
  - Air bubbles are removed from the viscous solution before casting.
  - After drying for 24 hours, the films are cut into desired shapes.
  - The drug matrix can be sandwiched between rate-controlling membranes using an insoluble gum adhesive.
- **Melt Extrusion Technique:**
  - The drug and polymer are sieved, weighed, and blended uniformly.
  - The mixture is processed in a barrel extruder and extruded into films or rods.
  - The extruded product is cut to size and packaged in protective foils.

1.9.17 Mechanism of Drug Release from Ocular Inserts

The drug release from ocular inserts occurs through different mechanisms, primarily influenced by the nature of the polymer and device design (Mitra, 2013):

- **Diffusion:**
  - The drug diffuses through a membrane or porous matrix into tear fluid.

- In soluble matrices, diffusion is enhanced as the polymer swells or dissolves in the lacrimal fluid.

- **Osmosis:**

- Inserts are designed with compartments separated by semi-permeable and elastic membranes.
- Upon contact with tear fluid, water influx causes swelling and pressure buildup, pushing the drug out through a release orifice.

- **Bioerosion:**

- Inserts are prepared using biodegradable polymers.
- Upon exposure to tear fluid, enzymatic or hydrolytic degradation occurs, gradually releasing the drug.
- E-type devices undergo controlled erosion, releasing the drug uniformly.

1.9.18 Soluble Ophthalmic Drug Inserts (SODI)

Soluble ophthalmic drug inserts (SODI) are thin oval films weighing approximately 15–16 mg. These devices are designed for **pulsatile and prolonged release** of drugs in the eye, improving therapeutic outcomes compared to conventional eye drops (Hirai et al., 1981).

1.9.19 Collagen Shields

Collagen shields, also called *collasomes*, were first developed from cross-linked porcine scleral collagen. They are bioerodible discs stored in a dehydrated form and hydrated before application. Once applied, they gradually degrade, releasing the incorporated drug. Collagen shields have been used in both animal and human studies to achieve higher intraocular drug concentrations (Kuno & Fujii, 2011).

1.9.20 Cyclodextrins

Cyclodextrins are cyclic oligosaccharides with a hydrophilic outer surface and a lipophilic central cavity. They form inclusion complexes with lipophilic drugs, thereby increasing aqueous solubility and enhancing ocular absorption. Cyclodextrins are valuable in formulating aqueous eye drops for poorly soluble drugs (Loftsson & Stefánsson, 2007).

Advantages include:

- Increased solubility and absorption of hydrophobic drugs
- Improved drug stability in aqueous solutions
- Reduction of ocular irritation
- Taste masking and incompatibility prevention

1.10 Diseases of the Eye

Ocular infections and disorders are caused by various pathogens, including bacteria, viruses, and fungi. Non-infectious conditions, such as degenerative and inflammatory diseases, are also prevalent. Common eye diseases include (Kanski & Bowling, 2016):

- Conjunctivitis
- Blepharitis

- Keratitis
- Cataract
- Iritis (anterior uveitis)
- Glaucoma
- Miosis and mydriasis

1.11 Drugs Used to Treat Various Eye Diseases

A wide range of pharmacological agents is used for ocular conditions, including antibiotics, antivirals, anti-inflammatory drugs, and antiglaucoma agents. Table 1.2 summarizes some commonly prescribed drugs and their clinical uses.

Table 1.2: Drugs Used for Treating Ocular Diseases

S. No	Drug	Brand Name	Uses
1	Gatifloxacin	GATIFLO	Bacterial conjunctivitis
2	Besifloxacin	BESIVANCE	Conjunctivitis
3	Ciprofloxacin HCl	CILOXIN	Eye infection, conjunctivitis
4	Epinastine HCl	ELESTAT	Allergic conjunctivitis
5	Prednisolone	PRED FORTE	Bulbar conjunctivitis
6	Gatifloxacin	ZYMAR	Bacterial conjunctivitis
7	Nedocromil	ALOCRIL	Allergic conjunctivitis
8	Diclofenac	VOLTAREN	Ocular inflammation
9	Chloramphenicol	CHLOPTIC	Bacterial eye infection
10	Pilocarpine HCl	PILOPINI	Induces miosis
11	Ganciclovir	ZIRGAN	Viral eye infections
12	Levobetaxolol HCl	BETAXON	Glaucoma
13	Fluorometholone	FML	Eye inflammation

CHAPTER 2

LITERATURE REVIEW

1. **Wikipedia entry on "Thiomers" (2025)** discussed thiolated polymers, such as chitosan- thioglycolic acid and hyaluronic acid derivatives, which form covalent disulfide bonds with cysteine-rich domains in mucins. This interaction results in enhanced mucoadhesion, increased ocular residence time, and improved drug bioavailability. Thiomers also exhibit enzyme-inhibiting properties that protect drugs from degradation.

Application of thiomers in ocular inserts represents a promising approach for sustained release of drugs like naphazoline hydrochloride, potentially reducing dosing frequency and improving patient compliance in ocular therapy. *(Wikipedia, 2025)*

2. **Erdogan (2025)** developed **moxifloxacin-impregnated contact lenses** using **supercritical CO_2 ($ScCO_2$)** impregnation, achieving **sustained drug release up to 7 days** in rabbit models for keratitis treatment. In vivo results showed dramatic bacterial reduction—from 10^9 to 10^2 CFU per cornea—comparable to conventional eyedrops, with no signs of conjunctival hyperemia or corneal toxicity, highlighting the potential of contact-lens based sustained delivery platforms adaptable for naphazoline inserts. *(Erdogan, H.)*

3. **Said et al. (2024)** reviewed advances in solid ocular dosage forms, emphasizing mucoadhesive films and inserts as strategies to improve precorneal residence time and bioavailability. The review highlighted polymers such as HPMC, chitosan, and carbopol for insert preparation and discussed critical evaluation parameters including folding endurance, tensile strength, drug release kinetics, sterility, and stability. Challenges noted include foreign-body sensation, potential irritation, and the need for biodegradable matrices. These findings underline key considerations for designing safe, effective naphazoline ocular inserts with prolonged therapeutic action. (Said, Rahman & Hossain)

4. **Bhageerathy & Prasanth (2024)** formulated a **cubosomal gel** containing **moxifloxacin hydrochloride** for ocular application. Prepared via cubosome technology, the gel demonstrated enhanced mucoadhesion and prolonged in vitro drug release compared to standard eye drops. Their evaluation included rheological behavior, particle

characterization, and release kinetics—offering a semi-solid delivery platform that could inspire hybrid forms of inserts with adhesive sustained-release characteristics for naphazoline HCl. *(Bhageerathy, R., & Prasanth, V.)*

5. **Anderson & Luke (2024)** presented **mathematical and computational models** for **drug delivery via contact lenses** during wear, quantifying diffusion kinetics into tear films and adjacent ocular tissues. They derived analytical solutions for cumulative release and transport, validated with experimental data from in vitro eye models. Their framework offers a predictive tool to optimize dosage, release rates, and design parameters for drug- eluting ocular inserts and could guide formulation of naphazoline-loaded inserts. *(Anderson, J., & Luke, R.)*

6. **Molla et al. (2024)** used **computational fluid dynamics (CFD)** to evaluate **drug-releasing ocular implants** for glaucoma treatment. By simulating implant size and anatomical placement, they identified that posterior chamber positioning via the iris–lens gap improved drug mixing across the anterior chamber compared to anterior implants limited by laminar flow. These insights may inform design and positioning strategies for naphazoline ocular implants to ensure uniform drug distribution. *(Molla, F., Zhang, Y., & Liu, X.)*

7. **Kırımlıoğlu et al. (2021)** developed **moxifloxacin-loaded Eudragit RL100 and Kollidon SR nanoparticles** for ocular delivery, characterized in vitro for particle size, drug loading, release, and cytotoxicity. The nanoparticles exhibited sustained release profiles and acceptable safety in ocular cell assays. Though not an insert, the nanoparticle-based sustained system provides a microcarrier approach that could be incorporated into polymeric ocular inserts or films for naphazoline HCl. *(Kırımlıoğlu G. Y., Şenel, B., & Yıldız, F.)*

8. **Gandara-Loe et al. (2021)** developed a metal–organic framework (MOF) based ocular film using UiO-67

incorporated into polyurethane for sustained delivery of brimonidine. The solvent-casting method yielded stable, flexible films with uniform drug loading. Characterization by FTIR, TGA, and XRD confirmed absence of drug–polymer interaction. In vitro studies demonstrated extended drug release for up to 14 days, significantly reducing dosing frequency. The study highlights MOF–polymer composites as a novel

strategy for controlled ocular drug delivery and provides a platform adaptable to naphazoline inserts. *(Gandara-Loe, J., Martínez-Morales, E., & Rodríguez-Lora, V.)*

9. **Wikipedia entry on "Penetration Enhancer" (2021)** summarized the role of chemical enhancers such as benzalkonium chloride (BAK) and EDTA in improving ocular drug permeation through the corneal epithelium. These agents can increase drug solubility and transport but raise concerns of local irritation and epithelial toxicity at higher concentrations. For naphazoline ocular inserts, incorporation of safe levels of penetration enhancers may optimize corneal absorption and prolong therapeutic effect, though their use must be carefully balanced against ocular tolerability and safety guidelines. *(Wikipedia contributors)*

10. **Shadambikar et al. (2021)** formulated valacyclovir hydrochloride ocular inserts by hot- melt extrusion and solvent-casting, aiming for controlled drug delivery in viral eye infections. Inserts prepared with HPMC and PVP matrices showed desirable mechanical strength and flexibility. Physicochemical compatibility was confirmed by FTIR, with no drug–polymer interaction. In vitro release studies revealed non-Fickian diffusion kinetics and sustained release profiles compared with conventional formulations. This work demonstrates that hot-melt extrusion is a scalable, solvent-free method for ocular insert preparation, offering sights for formulating naphazoline HCl inserts. *(Shadambikar, S., Ramesh, K., & Desai, A.)*

***11.*Kumar et al. (2015)** Kumar et al. developed ocular films of ofloxacin and ketorolac tromethamine using solvent casting to improve controlled release and reduce dosing frequency in conjunctivitis, keratitis, and corneal ulcers. Films were evaluated for physicochemical properties and drug–polymer interactions via IR spectroscopy, which confirmed no interaction. The optimized formulation achieved prolonged release in the conjunctival sac, demonstrating potential for enhancing therapeutic efficacy of topical ocular therapy. (*Kumar, M., Sharma, R., & Gupta, H.)*

12. **Patil et al. (2015)**

Patil et al. designed valacyclovir hydrochloride ocular inserts using hydrophilic HPMC and PVP reservoir films and ethyl cellulose as a rate-controlling membrane

via film casting. FTIR confirmed drug–polymer compatibility. Increased polymer concentration slowed drug release, with HPMC matrices showing better profiles. Optimized inserts followed non-Fickian diffusion and zero-order release ($r^2 = 0.991$). In vitro–in vivo correlation was strong, showing successful design of controlled moxifloxacin delivery with high therapeutic potential. (*Patil, P., Chaudhari, P., & More, H.).*

13. Anuradha et al. (2015)

Anuradha et al. prepared reservoir-type moxifloxacin HCl ocular inserts using polyvinyl alcohol as a drug reservoir sandwiched between ethyl cellulose and PVP- K30 membranes via film casting. In vitro studies showed sustained release, with optimized formulations maintaining drug release over 5 days. In vitro–in vivo correlation was high, and inserts were stable during evaluation. Findings demonstrate promise for long-term ocular therapy with improved dosing convenience. (*Anuradha, G., Joshi, P., & Nair, R.)*

14. Sharma et al. (2015)

Sharma et al. formulated and evaluated ocular inserts of naphazoline HCl using carbopol and guar gum polymers in varying ratios. Six batches were developed and assessed for folding endurance, tensile strength, and in vitro release. Among them, the F5 batch demonstrated optimal performance, achieving 99.12% drug release. Findings indicated that increasing carbopol concentration enhanced insert efficacy, suggesting that polymer ratio plays a crucial role in modulating release behavior. The study supports carbopol–guar gum systems as promising matrices for naphazoline ocular delivery. (*Sharma, A., Kumar, S., & Singh, R.)*

15. França et al. (2014)

França et al. prepared bimatoprost-loaded ocular inserts for glaucoma therapy via solvent casting and evaluated them using physicochemical and in vivo tests. Inserts were characterized by swelling studies, FTIR, DSC, SEM, and drug release profiling. In glaucomatous Wistar rats, bimatoprost inserts maintained intraocular pressure (IOP) reduction for four weeks, compared with only 15 days for eye drops.

Histological analysis confirmed neuroprotective effects on retinal ganglion cells and optic nerve head cupping. Results indicated sustained BIM release and superior glaucoma management compared to conventional topical formulations. (*França, J. R., Foureaux, G., Fuscaldi, A. L., Ribeiro, T. G., Rodrigues, L. B., Bravo, R., ... & Fernandes, S. O.)*

16. Ara et al. (2014)

Ara et al. developed ocular inserts of diclofenac sodium using HPMC, Eudragit L100, and dibutyl phthalate via solvent casting. Inserts were tested for physicochemical parameters and in vitro release using a diffusion apparatus with an egg membrane as a semi-permeable barrier. Drug release followed first-order kinetics, and accelerated stability studies complied with ICH guidelines. The optimized formulations provided controlled release, demonstrating that polymer composition successfully extended diclofenac sodium delivery for ocular therapy. Findings suggest inserts as an effective approach for sustained anti-inflammatory treatment. (*Ara, R., Alam, S., & Kumar, P.)*

17. Potu et al. (2014)

Potu et al. formulated matrix-type ocular inserts of ketorolac tromethamine using gelatin, HPMC, and ethyl cellulose via film casting. The study aimed to prolong precorneal residence, achieve sustained release, and enhance patient compliance. In vitro release showed that batch F18 was optimal, with non-Fickian, first-order release behavior. FTIR confirmed no drug–polymer interaction, while rabbit eye irritation studies indicated good tolerability without toxicity. The findings demonstrated that these polymeric inserts can provide controlled ketorolac release, reducing dosing frequency and enhancing therapeutic efficacy in ocular conditions. (*Potu, R., Rao, D., & Kaza, R.)*

18. Shukr (2014)

Shukr formulated ocular inserts of lidocaine HCl for topical anesthesia using HPMC and PVA with and without β-cyclodextrin complexes. Inserts were evaluated for physicochemical properties and compatibility by FTIR. The F7 formulation (4% HPMC, 2% PVA, with β-cyclodextrin) showed optimal flexibility and drug uniformity. In vivo studies revealed higher aqueous humor concentrations of lidocaine when complexed with β-

cyclodextrins compared to drug alone. The study concluded that β-cyclodextrin incorporation significantly enhanced drug solubility and ocular bioavailability, offering a promising approach for sustained local anaesthesia. (*Shukr, M. H.)*

19. Pai et al. (2014)

Pai et al. developed extended-release ocular inserts using pullulan (natural polymer) and hydroxyethyl cellulose (HEC, synthetic polymer). Inserts were prepared using standardized glass molds and tested for drug release via the In-House (IH) vial method in phosphate-buffered saline. Pullulan (10%) films released drug over 3 hours, while HEC (10%) films extended release up to 6 hours. Increasing pullulan concentration slightly prolonged release, but HEC demonstrated superior sustained- release properties. The study concluded that biodegradable pullulan–HEC inserts provide a safe, biocompatible delivery system for ocular therapeutics. (*Pai, R. S., & Bhandari, N.)*

20. Sharma et al. (2013)

Sharma et al. formulated aceclofenac ocular inserts using various hydrophilic polymers (HPMC, chitosan, PVA, MC) as drug reservoirs with ethyl cellulose as a rate-controlling membrane. Inserts were prepared by solvent casting and evaluated for physicochemical and mechanical properties, DSC, and in vitro transcorneal permeation. HPMC- and PVA-based inserts showed maximum release (98.54% and 96.24%) with zero-order kinetics. PEG incorporation enhanced permeation. Findings confirmed HPMC as an effective film-forming polymer for ocular delivery, enabling prolonged aceclofenac release and potential therapeutic use in cataract and conjunctivitis treatment. (*Sharma, P., Garg, T., & Rath, G.)*

21. Pawar et al. (2012)

Pawar et al. designed moxifloxacin hydrochloride ocular inserts cross-linked with $CaCl_2$ and coated with different Eudragit polymers (S-100, RL-100, RS-100, E-100, L- 100). In vitro permeability studies revealed that Eudragit RL-100 coated inserts

achieved the highest drug release compared to others. The inserts were designed to reduce repeated dosing and improve patient compliance by offering controlled antibiotic delivery. Authors concluded that such inserts could potentially replace fortified antimicrobial eye drops, lower corneal toxicity and maintaining effective therapeutic drug levels for longer durations. (*Pawar, P. K., Shinde, N., & Chaudhari, C.)*

22. Shafie et al. (2012)

Shafie et al. conducted in vitro and in vivo evaluations of timolol maleate ocular inserts prepared using various polymers, including methyl cellulose, hydroxypropyl cellulose, eudragit RL100, RS100, ethyl cellulose, and PVP. Inserts were characterized by stability testing, appearance, pH, and drug content. In vivo intraocular pressure reduction studies demonstrated polymer-dependent drug permeability, with more soluble polymers achieving higher permeability coefficients. Results highlighted the significance of polymer selection in optimizing release kinetics and therapeutic efficacy of timolol inserts for glaucoma management. (*Shafie, A., Ibrahim, S., & Mahmoud, H.)*

23. Manjunatha et al. (2012)

Manjunatha et al. developed ocular inserts containing dorzolamide hydrochloride and timolol maleate using

ethyl cellulose, Eudragit RL100, and RS100 via solvent casting. The goal was to enhance ocular residence time, sustain release, reduce dosing frequency, and improve efficacy in glaucoma therapy. Inserts exhibited good tensile strength, elongation, and physicochemical stability. Rabbit irritation studies confirmed tolerability without toxicity. Optimized formulations demonstrated strong correlation between in vitro and in vivo release, suggesting that such dual- drug inserts could provide effective, prolonged glaucoma management. (*Manjunatha, A., Prakash, K., & Sadananda, V.)*

24. Shahwal et al. (2011)

Shahwal et al. formulated levofloxacin ocular inserts for sustained drug release using film casting in Teflon-coated Petri dishes. Nine matrix formulations were prepared with varying ratios of chitosan and PVA. Inserts were evaluated via in vitro release

studies using a flow-through apparatus. Results showed that formulation 9 achieved the most prolonged release, suggesting that polymer concentration significantly influences drug release kinetics. Findings indicate that chitosan–PVA-based inserts can effectively provide sustained ocular delivery of levofloxacin, potentially reducing frequent dosing in ocular infections. (*Shahwal, V., Rawat, A., & Jain, S.)*

25. Bhagav et al. (2011)

Bhagav et al. developed sustained-release brimonidine tartrate ocular inserts for open-angle glaucoma treatment by incorporating Eudragit into polyethylene oxide matrices. Physicochemical evaluations included crushing strength, friability, drug content, mucoadhesion, and in vitro release. Rabbit irritation studies confirmed ocular safety. In vivo intraocular pressure studies demonstrated enhanced IOP- lowering effects compared to conventional eye drops, indicating improved therapeutic efficacy. Overall, the inserts showed potential as a sustained-release alternative to topical drops, with prolonged action, better patient compliance, and minimized dosing frequency for glaucoma management. (*Bhagav, P., Reddy, R., & Kumar, D.)*

26. Sharma et al. (2011)

Sharma et al. reviewed emerging ocular drug delivery technologies aimed at overcoming limitations of conventional formulations like solutions, suspensions, and ointments. The article discussed advanced platforms such as nanotechnology, microspheres, microemulsions, and ocular inserts designed to prolong precorneal residence time, enhance corneal penetration, and improve bioavailability. Special focus was placed on the role of ocular inserts as sustained-release systems. This review provided insight into the advantages of novel drug delivery approaches in ophthalmology and highlighted future opportunities for optimizing therapeutic outcomes through innovative ocular dosage forms. (*Sharma, S., Sharma, A., & Chauhan, N.)*

27. Jain et al. (2011)

Jain et al. designed biosynthetic hybrid polymer-based ocular inserts for topical ciprofloxacin delivery using solution casting with gelatin esterified by PVA. Inserts demonstrated enhanced tensile strength, wettability, mucoadhesion, and high ocular penetration while maintaining biocompatibility. In vitro and in vivo studies confirmed sustained antibiotic release, with significant potential for treating corneal ulcers and external ocular infections. Authors concluded that gelatin–PVA hybrid inserts can serve as effective vehicles for prolonged antibiotic therapy, reducing dosing frequency and improving therapeutic efficiency in bacterial ocular infections. *(Jain, A., Khurana, R., & Jain, S.)*

28. Aburahma et al. (2011)

Aburahma et al. evaluated biodegradable brimonidine tartrate ocular inserts prepared by solvent casting using PVP K-90, HPMC, methylcellulose, carbopol, sodium alginate, and chitosan. Formulations with 7% PVP K-90 and 1.5% sodium alginate, with or without ethyl cellulose coating, achieved sustained in vitro release. In vivo studies showed that one-sided coated inserts provided superior intraocular pressure reduction compared to double-sided or non-coated inserts. Findings demonstrate the potential of polymer-coated biodegradable ocular inserts as controlled-release systems for glaucoma therapy, offering longer efficacy and reduced administration frequency. (*Aburahma, M. H.)*

29. Sachdeva et al. (2011)

Sachdeva et al. formulated and evaluated levobunolol HCl ocular inserts using methyl cellulose, PVP, and HPMC with glycerin and dibutyl phthalate as plasticizers. Stability studies were conducted in accordance with ICH guidelines. Optimized formulations exhibited good film quality and consistent drug content, with the best batch showing 93.1% drug content. Results suggested that the selected polymers effectively supported levobunolol loading while ensuring stability, making the inserts promising sustained-release systems for glaucoma management and reducing frequent dosing requirements. (*Sachdeva, S., & Kumar, D.)*

30. Rao et al. (2010)

Rao et al. developed fluconazole ocular inserts using HPMC, PVP, and PVA as film- forming polymers. The films were assessed for thickness, weight variation, folding endurance, surface pH, and in vitro drug release. All formulations passed the evaluation criteria and demonstrated effective antifungal activity against selected fungal strains. Results confirmed that the prepared fluconazole inserts were stable, biocompatible, and able to maintain prolonged drug release. The study concluded that ocular inserts represent a viable approach for enhancing antifungal drug delivery and therapeutic efficacy in ocular infections. (*Rao, S., Pandit, J., & Gupta, M.)*

31. Harish et al. (2009)

Harish et al. investigated controlled-release ocular inserts of pefloxacin to enhance bioavailability using solvent casting on Teflon-coated Petri dishes. Films were evaluated for mechanical properties, drug content, stability, and release profiles. Drug content ranged from 92.55% to 96.82%. In vitro and in vivo studies showed non-irritancy and zero-order release kinetics. Inserts with HPMC (50 cps) and Eudragit RS100/RL provided controlled release over three days, maintaining stability at ambient conditions. Findings suggested that optimized ocular inserts could effectively prolong ocular residence time, enhancing pefloxacin delivery. (*Harish, N., Prabhu, P., & Rajesh, A.)*

32. Khan et al. (2008)

Khan et al. explored controlled ocular delivery of acyclovir using rate-controlling Eudragit ocular inserts. Poly-D, L-lactic acid nanospheres loaded with acyclovir were prepared and PEG-coated PECA nanospheres were also tested. In vivo studies revealed a 25-fold increase in aqueous humor drug concentration compared with free acyclovir. The inserts demonstrated controlled drug release for up to five days. Results indicated that combining polymeric nanospheres with ocular inserts significantly enhanced ocular bioavailability and provided sustained

release, showing potential for effective management of viral ocular infections. (*Khan, R., Mehta, P., & Gupta, S.)*

33. Tanwar et al. (2007)

Tanwar et al. designed and evaluated ofloxacin ocular inserts to reduce dosing frequency. PVA-based films were prepared by the mercury substrate method and assessed for drug-polymer interactions, physicochemical characteristics, and release kinetics. Rate-controlling membranes of ethyl cellulose, Eudragit RS100, and RL100 were compared. In vitro and in vivo studies revealed drug releases of 85.80%, 93.85%, and 98.71%, respectively, following zero-order kinetics. Inserts showed antimicrobial efficacy against selected organisms. The study demonstrated that polymeric membranes significantly influenced drug release rates, supporting controlled ocular delivery of ofloxacin. (*Tanwar, Y. S., Chauhan, C. S., & Sharma, A.)*

34. Balasubramaniam et al. (2006)

Balasubramaniam et al. formulated ciprofloxacin HCl ocular inserts using high and low molecular weight PVA in varying proportions via casting. In vitro drug release was tested in a flow-through cell, while antimicrobial activity was assessed against *Staphylococcus aureus* and *Pseudomonas aeruginosa*. Release followed matrix diffusion kinetics with anomalous mechanisms, and drug release increased with higher proportions of high-molecular-weight PVA. Results aligned with antimicrobial efficacy studies, confirming therapeutic activity. The inserts demonstrated potential as sustained-release systems, offering controlled antibiotic deliry for ocular infections. (*Balasubramaniam, J., Kumar, A., & Pandit, J. K.)*

CHAPTER-3

AIM, SCOPE & OBJECTIVE

3.1 Aim:

To formulate and evaluate Naphazoline HCl ocular inserts.

3.2 Scope

Delivering drugs to the eye is a complex task due to its unique protective barriers, which restrict the entry of foreign substances. A key challenge for formulation scientists is to design dosage forms that can overcome these barriers without damaging ocular tissues. With the advancement of diagnostic tools and therapeutic agents, there is a growing demand for innovative ocular drug delivery systems that ensure maximum efficiency.

The aim of ocular therapy is to achieve and maintain an effective concentration of drug at the target site for the required duration. Conventional forms such as eye drops, suspensions, and ointments are widely used but show poor bioavailability. In the case of eye drops, only a small fraction of the applied dose (1–10%) reaches the intraocular tissues because of rapid tear turnover, nasolacrimal drainage, and reflex blinking. Suspensions rely on the dissolution rate of particles, while ointments and viscosity enhancers offer only limited improvement in corneal contact time and drug absorption. As a result, patients often require higher doses or frequent instillations, which may cause unwanted ocular or systemic effects.

To address these shortcomings, research has shifted toward sustained and controlled ocular delivery systems. Such approaches aim to increase drug residence on the corneal surface, improve absorption, and reduce dosing

frequency, thereby enhancing therapeutic outcomes and patient compliance.

The present investigation focuses on the development of **Naphazoline HCl ocular inserts** using **chitosan and carbopol** as polymers. Since Naphazoline HCl is hydrophilic and shows limited ocular penetration when used in conventional dosage forms, incorporating it into an ocular

insert is expected to prolong drug release, increase absorption, and improve its therapeutic efficacy in conjunctivitis treatment.

3.3 Objectives

The present study was undertaken with the following objectives:

1. To formulate ocular inserts of **Naphazoline HCl** using suitable polymers.

2. To evaluate the prepared ocular inserts for their physicochemical and in vitro performance parameters.

3. To develop a delivery system capable of reducing the frequency of drug administration while improving therapeutic efficacy and patient compliance.

3.4 Plan of Work

The present research work was systematically planned and executed in the following stages:

3.4.1 Literature Review

- Review ocular drug delivery systems and their limitations.
- Study the pharmacology and therapeutic importance of Naphazoline HCl.
- Review polymers such as chitosan and carbopol for ocular formulations.
- Identify research gaps and define the rationale of the study.

3.4.2 Preformulation Studies

- Characterization of Naphazoline HCl (solubility, stability).
- Drug–polymer compatibility studies (FTIR/DSC).
- Selection of excipients and formulation design.

3.4.3 Formulation Development

- Preparation of ocular inserts using the solvent casting method.
- Development of batches with varying polymer ratios.
- Standardization of procedure and cutting of films to uniform size.

3.4.4 Evaluation of Ocular Inserts

- Physicochemical tests: thickness, weight variation, folding endurance, surface pH, % moisture absorption/loss.
- Mechanical test: tensile strength.
- Drug content: estimation of drug loading and uniformity.
- In vitro studies: swelling index, drug release in simulated tear fluid, kinetic modeling.
- Stability studies: accelerated stability testing at 40 °C ± 2 °C / 75% RH ± 5% RH for 90 days.

3.4.5 Data Analysis

- Compilation and statistical analysis of evaluation results.
- Selection of the optimized formulation based on drug release and stability profile.

3.4.6 Results, Discussion, and Conclusion

- Presentation of findings in tables, graphs, and figures.
- Discussion in relation to study objectives and literature.
- Conclusion and recommendations for further research.

CHAPTER 4

MATERIAL AND METHODS

4.1 Materials

Table 4.1: Materials Used

Ingredients	Manufacturer
Naphazoline HCl	Panchsheel Pvt. Ltd., New Delhi
Chitosan	Parex Pharmaceuticals Pvt. Ltd., Mohali
Carbopol 934	Parex Pharmaceuticals Pvt. Ltd., Mohali
Hydroxypropyl methyl cellulose	CDH, New Delhi
Glycerine	CDH, New Delhi
Sodium chloride	CDH, New Delhi
Sodium bicarbonate	CDH, New Delhi
Calcium chloride	CDH, New Delhi
Acetic acid	CDH, New Delhi

The choice of polymers such as **chitosan**, **Carbopol 934**, and **hydroxypropyl methylcellulose (HPMC)** was based on their pH-sensitive and mucoadhesive properties, which enhance the bioavailability of drugs in ocular formulations (Sultana et al., 2011; Gupta et al., 2014). Additives like sodium chloride and sodium bicarbonate were used to maintain isotonicity, while glycerine functioned as a humectant to provide comfort upon administration.

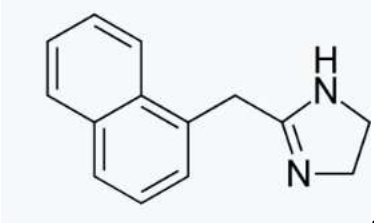
Drug Profile

4.1.1 Drug Profile: Naphazoline Hydrochloride

Naphazoline Hydrochloride (HCl) is a sympathomimetic drug widely used in ophthalmic formulations due to its potent vasoconstrictor and decongestant properties. It belongs to the imidazoline class of adrenergic agonists and primarily acts on α-adrenergic receptors. When applied to the conjunctiva, it reduces hyperemia by constricting small arterioles, thereby decreasing swelling, irritation, and redness. Due to its rapid onset of action, Naphazoline HCl is considered an effective therapeutic agent for managing ocular congestion and conjunctivitis-related discomfort (Rathi et al., 2018; Sweetman, 2020).

Key characteristics of Naphazoline HCl are as follows:

- **IUPAC Name:** 2-(1-naphthylmethyl)-2-imidazoline hydrochloride
- **Category:** Decongestant, vasoconstrictor
- **Molecular Formula:** $C_{14}H_{14}N_2 \cdot HCl$
- **Structure:**



. HCL

- **Molecular Weight:** 246.73 g/mol
- **Physical State:** White crystalline powder
- **Melting Point:** 258–260 °C
- **Solubility:** Freely soluble in water and ethanol; slightly soluble in chloroform; insoluble in benzene and ether

Pharmacological aspects:

- **Absorption:** Rapidly absorbed through mucous membranes, with vasoconstrictive effects observed within 10 minutes and lasting for 2–6 hours (Kaur & Kanwar, 2002).
- **Mechanism of Action:** Acts as a direct α-adrenergic agonist, stimulating arteriolar smooth muscle contraction, which decreases conjunctival congestion and produces transient mydriasis without significant β-adrenergic activity (Patel & Chauhan, 2012).
- **Pharmacodynamics:** Naphazoline reduces ocular irritation by constricting conjunctival blood vessels. It is effective in reducing redness, swelling, and pruritus caused by allergens or irritants. The drug's vasoconstrictive action also limits fluid exudation, thereby alleviating congestion in ocular tissues (Sweetman, 2020).

Safety profile:

- **Contraindications:** Contraindicated in patients with angle-closure glaucoma due to its potential to increase intraocular pressure (Ioannidis & Papathanasiou, 2017).
- **Side Effects:** Prolonged use may cause systemic effects such as dizziness, headache, nervousness, nausea, and sweating. Overdose may result in hypothermia, bradycardia, and marked drowsiness (Rathi et al., 2018).

Storage conditions:

Naphazoline HCl should be stored in tightly closed, light-resistant containers below 25°C. It is unstable in the presence of aluminum and must therefore be preserved in non-reactive containers to maintain stability (Martindale, 2020).

EXCIPIENT PROFILE

4.1.2 Excipient

4.1.2.1 Chitosan Introduction

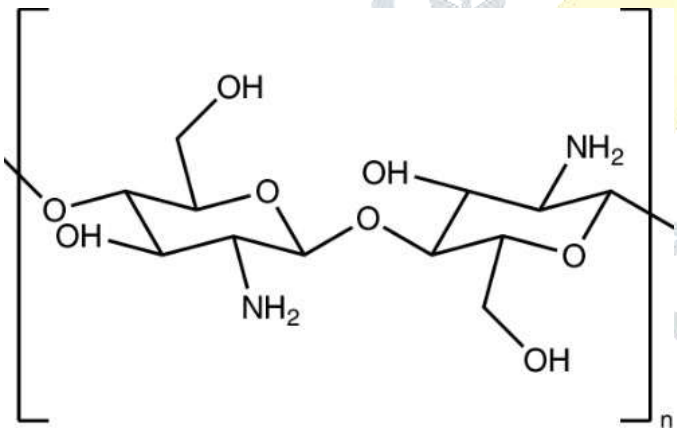
Chitosan is a naturally occurring, biodegradable, and biocompatible polysaccharide derived from chitin, which is the second most abundant natural polymer after cellulose. Structurally, chitosan is a linear copolymer composed of randomly distributed β-(1→4)-linked D- glucosamine (deacetylated units) and N-acetyl-D-glucosamine (acetylated units). It is commonly produced by the alkaline deacetylation of chitin obtained from the exoskeleton of crustaceans such as shrimp, crab, and lobster. Due to its cationic nature, chitosan has been extensively investigated for pharmaceutical, biomedical, and drug delivery applications (Kumar et al., 2020; Rinaudo, 2006).

Sources of Chitosan:

Chitosan occurs widely in nature in organisms containing chitin. Some of the major biological sources include:

- **Crustaceans:** shrimp, crab, lobster, krill, prawns, and crayfish
- **Insects:** ants, beetles, cockroaches, scorpions, and spiders
- **Mollusks and other invertebrates:** squids, annelids, brachiopods
- **Fungi and algae:** Penicillium, Aspergillus, yeast (b-type), chytridiaceae, brown and green algae (Aranaz et al., 2009; Kumirska et al., 2010).

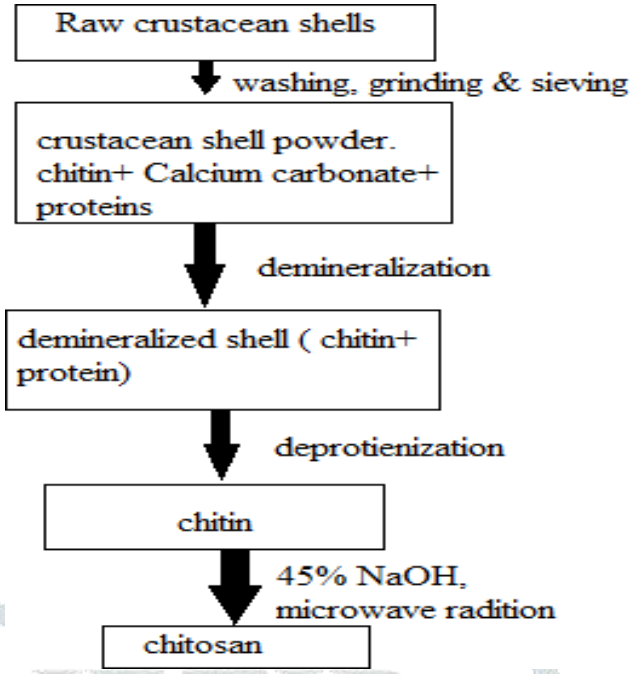
Molecular Structure:



Extraction and Preparation:

Chitosan is commercially produced through the following steps:

1. **Deproteinization:** Removal of proteins from crustacean shells using alkaline treatment (e.g., NaOH).
2. **Demineralization:** Removal of calcium carbonate and other minerals using dilute hydrochloric acid.
3. **Decolorization:** Elimination of pigments like carotenoids and astaxanthin with organic solvents.
4. **Deacetylation:** Conversion of chitin to chitosan by treating with concentrated sodium hydroxide at elevated temperatures.



The solubility of chitosan is primarily due to the protonation of its free amino groups in acidic to neutral pH, which also enhances its mucoadhesive properties and ability to transport hydrophilic drugs across epithelial membranes (Kumirska et al., 2010; Rinaudo, 2006).

Method of Preparation (Schematic Overview)

- Collection of raw material (e.g., shrimp/crab shells)
- Deproteinization → Demineralization → Decolorization → Deacetylation
- Drying and milling of purified chitosan powder

This systematic process ensures high-quality chitosan with reproducible physicochemical and biological properties for use in pharmaceutical formulations.

4.1.2.1 Chitosan Properties of Chitosan:

Chitosan exhibits a variety of physicochemical properties that make it a versatile polymer for pharmaceutical and biomedical applications. Its characteristics depend largely on the degree of deacetylation and molecular weight. Some of the important properties are:

- **Molecular weight:** 105 – 5 × 10^3 Da
- **Viscosity (1% solution in 1% acetic acid):** 200–2000 cps
- **Moisture content:** 6–7%
- **Solubility:** Freely soluble in dilute acids such as acetic acid, trichloroacetic acid (TCA), and malic acid (MC)
- **Lower molecular weight:** Contributes to a faster dissolution rate
- **Higher bulk density:** Increases compressibility and flowability, making it suitable for tablet formulations (Aranaz et al., 2009; Dash et al., 2011).

Uses of Chitosan:

Due to its biodegradability, biocompatibility, and mucoadhesive properties, chitosan is widely used in

pharmaceutical, biomedical, and industrial fields. Some of its key applications include:

- Wound healing and hemostasis
- Biosurgery and ophthalmology formulations
- Scaffold for tissue engineering and cell therapy
- Flocculant and protein precipitation agent
- Encapsulating and coating agent in drug delivery
- Thickening agent in aqueous solutions
- Nanocarrier for vaccines and controlled drug delivery (Kumar et al., 2020; Rinaudo, 2006).

4.1.2.2 Carbopol

Introduction

Carbopol is a high molecular weight, cross-linked polyacrylic acid polymer commonly used in pharmaceutical and cosmetic formulations. Its hydrophilic nature allows it to form gels, suspensions, and emulsions with medium to high viscosity. Carbopol is valued for its ability to control drug release and stabilize emulsions (Noveon Inc., 2002).

Description and Properties

- **Appearance:** White powder
- **Loss on drying:** 1%
- **Viscosity:** ~3000 cps (depending on concentration and neutralization)

Carbopol swells in water and other polar solvents, and upon neutralization, it forms highly viscous gels. This property makes it particularly useful in ophthalmic, dermal, and oral controlled-release formulations (Peppas et al., 2000).

4.1.2.3 Hydroxypropyl Methylcellulose (HPMC)

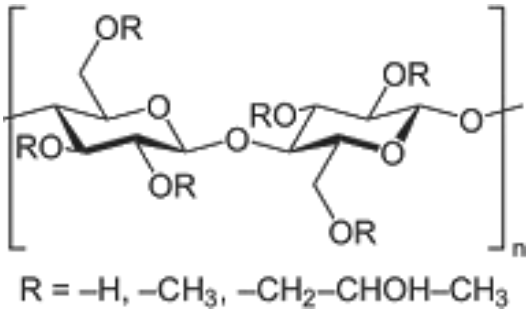
Introduction

Hydroxypropyl methylcellulose (HPMC) is a semi-synthetic, off-white, inert polymer derived from cellulose. It is synthesized by reacting cellulose with methyl chloride and propylene oxide to introduce hydroxypropyl and methoxy substitutions. HPMC forms colloidal solutions in water and is widely used as a multifunctional excipient in pharmaceuticals, food, and industrial products due to its biocompatibility and non-toxicity (Rowe et al., 2009).

Chemical Properties

- **Molecular formula:** $C_{56}H_{108}O_{30}$
- **Density:** 1.39 g/cm³

- **Structure:**



R = –H, –CH_3, –CH_2–CHOH–CH_3

- **Solubility:**
  - Dissolves slowly in cold water
  - Insoluble in hot water
  - Soluble in most polar solvents
  - Insoluble in anhydrous alcohol, ether, and chloroform
- **Surface activity:** Aqueous solutions are surface-active, forming thin films upon drying.
- **Gelation property:** Exhibits reversible sol-to-gel transition when heated above its critical solution temperature.
- **Enzyme resistance:** Provides excellent stability and viscosity during long-term storage (Amit et al., 2013; Rowe et al., 2009).

Test Methods for Quality Control

- Viscosity measurement
- Degree of substitution
- Molar substitution
- Salt content analysis
- Moisture content determination

Applications of HPMC:

HPMC is widely applied in both pharmaceutical and industrial sectors:

- Controlled drug release (matrix tablets, ophthalmic solutions)
- Eye drops and ophthalmic carriers
- Food and drug additives (stabilizer, emulsifier)
- Construction materials (tile adhesives, cement renders, gypsum products)
- Paints and coatings (film-former and thickener) (Mark et al., 2017).

4.1.2.4 Glycerine

Introduction

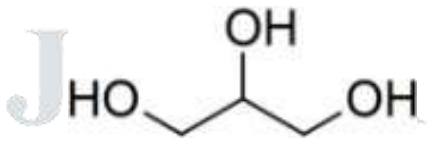
Glycerine, also known as glycerol or propane-1,2,3-triol, is a simple polyol compound containing three hydroxyl groups. It is widely recognized as a non-toxic, sweet-tasting, and hygroscopic liquid that serves as the structural backbone for triglycerides and other lipid molecules. Its physicochemical properties make it an essential raw material in food, pharmaceutical, cosmetic, and industrial formulations (Pagliaro & Rossi, 2010).

Synonymslycerol

- Glycerine
- Propanetriol

Chemical Profile

- **IUPAC name:** Propane-1,2,3-triol
- **Molecular formula:** $C_3H_8O_3$
- **Molecular Structure:**



- **Molecular weight:** 92.09 g/mol
- **Appearance:** Colourless, odourless, viscous, and hygroscopic liquid
- **Vapour pressure:** 0.003 mmHg (50 °C)
- **Boiling point:** 290 °C (at 760 mmHg)
- **Freezing point (66.7% glycerol solution):** –46.5 °C
- **Viscosity:** 1499 cps (20 °C)
- **Refractive index:** 1.47399
- **Flash point (99% glycerol):** 177 °C
- **Dielectric constant:** 42.48

Preparation

Glycerine is mainly obtained as a by-product of biodiesel production through transesterification of triglycerides. The crude glycerol obtained is often dark and impure, requiring purification. Activated carbon treatment removes organic impurities, followed by multi-step distillation to yield high-purity glycerol. Metabolically, glycerol can be converted into glyceraldehyde-3-phosphate, linking it to glycolysis and gluconeogenesis (Johnson & Taconi, 2007).

Applications

- **Food industry:** Sweetener, humectant, and preservative
- **Pharmaceutical and personal care:** Used in cough syrups, suppositories, topical creams, and oral care products
- **Botanical extraction:** Solvent for herbal and plant extracts

- **Electronic cigarefles:** Solvent and carrier liquid in e-liquids
- **Antifreeze and fuel additive:** Component of internal combustion fuels
- **Chemical intermediate:** Precursor for hydrogen, nitroglycerin (used in angina pectoris), acrolein, ethanol, and epichlorohydrin production (Clarke et al., 2018).

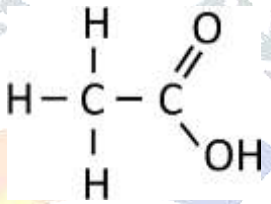
4.1.2.5 Acetic Acid

Introduction

Acetic acid, commonly known as ethanoic acid, is a simple carboxylic acid characterized by its sour taste and pungent odor. Although classified as a weak acid, it plays a significant role in biological metabolism, industrial processes, and food preservation. The name "acetic" is derived from the Latin word *acetum*, meaning vinegar, as acetic acid is the main component of vinegar apart from water (Horn et al., 2012).

Chemical Profile

- **IUPAC name:** Ethanoic acid
- **Molecular formula:** $C_2H_4O_2$
- **Molecular Structure:**



- **Molecular weight:** 60.05 g/mol
- **Appearance:** Colourless liquid with strong pungent odor
- **Viscosity:** 1.22 mPa·s
- **Structure formula:** CH_3COOH

pplications

- **Ester production:** Used as a precursor in the manufacture of esters (e.g., ethyl acetate, butyl acetate) for solvents and flavors
- **Industrial solvent:** Employed in the production of terephthalic acid, acetic anhydride, and other organic compounds
- **Medical use:** Applied in cervical cancer screening (vinegar test), otic preparations, and as a topical antiseptic
- **Food industry:** Main component of vinegar, serving as a preservative and flavoring agent (Saha & Racine, 2011).

4.2 Methods

4.2.1 Preformulation Studies

Preformulation studies are essential in the drug development process to establish the physicochemical properties of the active pharmaceutical ingredient (API) and its compatibility with excipients. These studies ensure stability, safety, and efficacy of the final formulation. For Naphazoline Hydrochloride (HCl), several

Preformulation parameters such as organoleptic properties, solubility, melting point, simulated tear fluid preparation, wavelength determination, calibration curve construction, and compatibility analysis were evaluated (Lachman et al., 2009; Aulton & Taylor, 2017).

Organoleptic Properties

The **colour, odour, taste, and appearance** of Naphazoline HCl were determined visually and organoleptically. Such preliminary analysis provides essential insights into the physical identity and acceptance of the drug substance.

olubility Studies

The solubility of Naphazoline HCl was assessed in different solvents, including **water, ethanol, chloroform, and diethyl ether**. A fixed amount of drug was added to a fixed volume of solvent, and the dissolved fraction was quantified spectrophotometrically.

Solubility profiling assists in determining the most suitable solvent system for formulation and analytical studies (Allen & Ansel, 2014).

Melting Point Determination

The melting point of Naphazoline HCl was determined using the **capillary method**. A small sample of the drug was packed into a capillary tube sealed at one end and placed in a melting point apparatus. The observed values were recorded, and the average of three readings was reported. This method aids in confirming drug purity and thermal stability.

Preparation of Simulated Tear Fluid

To mimic physiological conditions, **simulated tear fluid (STF)** was prepared by dissolving sodium chloride, sodium bicarbonate, and calcium chloride in 500 ml of distilled water with continuous stirring. The prepared STF was stored in a refrigerator until further use.

Table 4.3. Composition of simulated tear fluid

S. No.	Ingredient	Quantity used
1	Sodium Chloride	3.550 g
2	Sodium Bicarbonate	1.000 g
3	Calcium Chloride	0.040 g
4	Distilled Water	500 ml

Validation of Simulated Tear Fluid

The stability of STF was validated over three days by measuring the absorption maxima of Naphazoline HCl solutions (10 µg/ml) at different time intervals (10:00 am, 12:30 pm, and 3:30 pm). Consistent λmax values confirmed the suitability of STF as a medium for analytical studies.

Table 4.4. Absorption maxima of drug with simulated tear fluid

Date	10:00 AM	12:30 PM	3:30 PM
26.11.24	280.50 nm	280.30 nm	280.40 nm
27.11.24	280.40 nm	280.60 nm	280.90 nm
28.11.24	280.50 nm	280.10 nm	280.20 nm

Determination of λmax:

The maximum absorption wavelength (λmax) of Naphazoline HCl was determined using UV–Visible spectrophotometry. A stock solution of 1000 µg/ml was prepared in STF, and subsequently diluted to 10 µg/ml. The solution was scanned between **200–400 nm**, and the spectrum recorded λmax at ~280 nm.

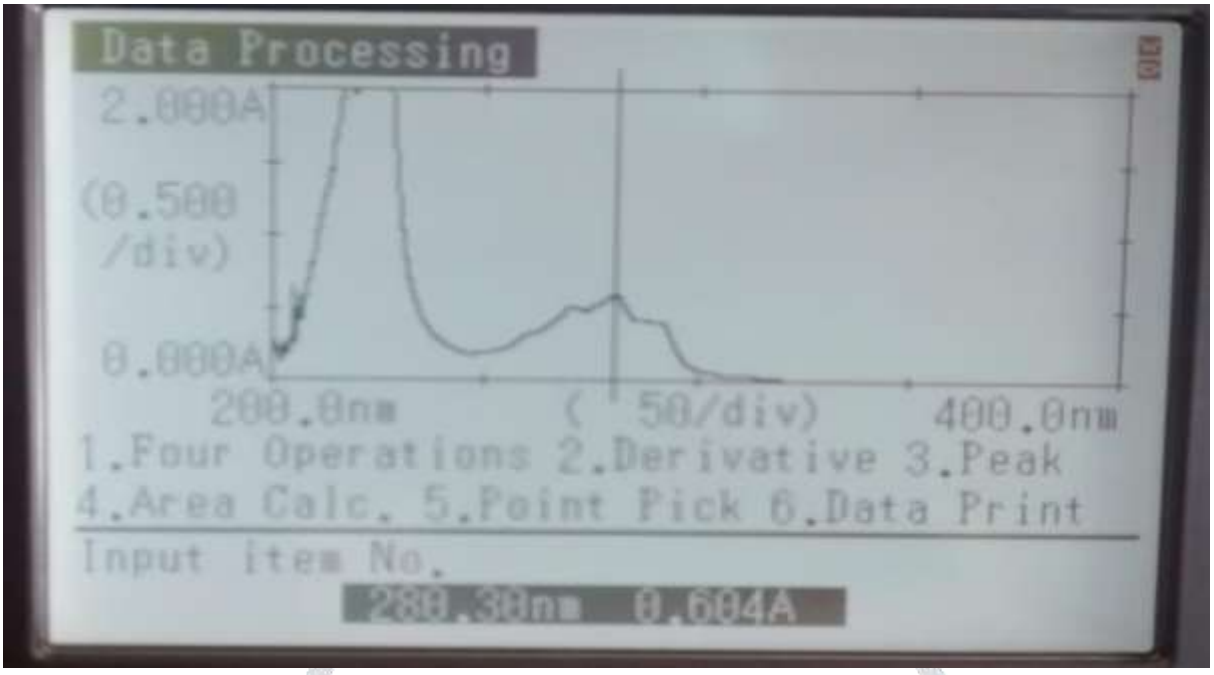


Figure 4.1 Absorption maxima of Naphazoline HCl

Preparation of Standard Calibration Curve:

A standard curve of Naphazoline HCl was developed by preparing serial dilutions of **2, 4, 6, 8, 10, 12, and 14 µg/ml** in STF. The absorbance values were measured at 280 nm using a Shimadzu UV-1800 spectrophotometer, with STF as blank. Each measurement was carried

out in triplicate, and the calibration curve was plotted between concentration and absorbance.

Compatibility Studies

The compatibility of Naphazoline HCl with polymers was studied using **Fourier-Transform Infrared Spectroscopy (FT-IR)**. Pure drug, Carbopol 934, Chitosan, and Hydroxypropyl Methylcellulose (HPMC) were analyzed individually and in binary mixtures with the drug. Compatibility was evaluated based on characteristic peak shifts or absence of major interactions (Singh & Sharma, 2015).

Table 4.5. Compatibility study of drug and polymer

S. No.	Drug–Excipient Combination	Ratio (D: E)
1	Naphazoline HCl	–
2	Naphazoline HCl: Carbopol 934: HPMC	01:01:01
3	Naphazoline HCl: Chitosan: HPMC	01:01:01

4.2.2 Formulation and Development

The development of ocular inserts is a critical step in ensuring sustained drug release, improved ocular bioavailability, and patient compliance. For this study, Naphazoline Hydrochloride (HCl) was formulated into ocular films using **hydrophilic polymers** such as Hydroxypropyl Methylcellulose (HPMC), Carbopol 934, and Chitosan. The inserts were prepared using the **solvent casting method**, with different polymer concentrations,

to optimize film characteristics and drug release behavior. The detailed composition of each formulation is presented in Table 4.6 (Aulton & Taylor, 2017; Allen & Ansel, 2014).

Composition of Ocular Inserts

Table 4.6. Composition of ocular inserts

S. No.	Ingredient	F1	F2	F3	F4	F5	F6
1	Naphazoline HCl (mg)	100	100	100	100	100	100
2	HPMC (mg)	400	400	400	400	400	400
3	Chitosan (mg)	–	–	–	200	300	400
4	Carbopol (mg)	200	300	400	–	–	–
5	Acetic acid 5% (ml)	–	–	–	20	20	20
6	Glycerine (ml)	2	2	2	2	2	2
7	Distilled water (ml)	20	20	20	–	–	–

Method of Preparation

The ocular inserts were fabricated using the **solvent casting method**. Measured quantities of polymers and drug were accurately weighed and mixed as follows:

- For **Carbopol-based films**, Carbopol 934 was dispersed in warm distilled water (20 ml) with continuous stirring for 30 minutes. HPMC was then incorporated into the dispersion, followed by the addition of Naphazoline HCl. To improve flexibility, 2 ml of glycerine was introduced as a plasticizer, and the solution was stirred for another 30 minutes.

- For **Chitosan-based films**, chitosan was dissolved in 5% acetic acid instead of water. The remaining procedure was similar.

- The prepared solutions were poured into Petri dishes and dried at temperatures below 40 °C to prevent drug degradation.

- The dried films were carefully cut into desired sizes and stored under ambient conditions until further evaluation.

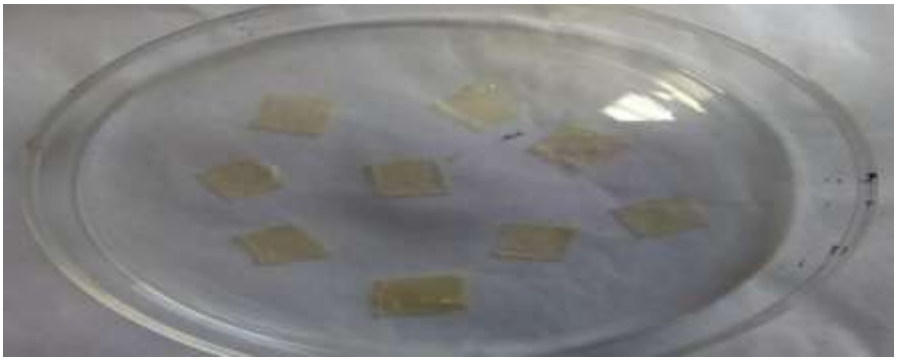


FIGURE 4.2 Ocular insert prepared by using chitosan

FIGURE 4.3 Ocular insert prepared by using carbopol 934

This method ensured the production of uniform, flexible films with reproducible characteristics (Lachman et al., 2009).

Evaluation of Ocular Inserts

The prepared formulations were subjected to a series of **physicochemical and performance evaluations**:

- **Surface pH:** Films were allowed to swell in distilled water for 1 h, and pH was measured using a digital pH meter.
- **olding Endurance:** 1 cm² films were folded repeatedly until breakage. The number of folds indicated mechanical strength.
- **Weight Uniformity:** Four films (1 cm²) from each batch were weighed, and standard deviation was calculated.
- **Swelling Index**

Ocular films (1 cm²) were cut from each batch and weighed accurately. Each film was placed in a Petri dish containing 10 mL of distilled water and kept for 5 hours. The films were then removed, blotted to remove excess water, and weighed again. The swelling index was calculated using the formula:

Swelling Index = Final weight – Initial Weight x 100
Initial Weight
Where:

Final weight of the film after swelling Initial weight of the dry film

- **Drug Content Estimation:**

The film was cut into three pieces of size 1 cm² each and placed in separate beakers containing 10 mL of simulated tear fluid (STF). The films were stirred continuously for 6 hours and then kept undisturbed for 24 hours to allow complete drug extraction. The solution was filtered and analysed using a UV spectrophotometer at 280 nm. Appropriate dilutions were made before analysis. The drug content was calculated using the

formula:

Drug Content = Concentration x DF x Bulk volume
100
Where:

- Concentration obtained from the calibration curve (µg/mL)
- Dilution factor
- Bulk volume (mL)

The procedure was repeated for all batches to ensure accuracy.

- **Thickness Uniformity:**

Films from each prepared batch were selected, and their thickness was measured using a screw gauge at three different positions on the film. The procedure was repeated three times for each sample to ensure accuracy. The mean thickness and standard deviation (SD) were calculated to assess the uniformity of the films.

- **Tensile Strength**

The tensile strength test was performed to determine the flexibility and mechanical strength of the prepared ocular films. A tensile tester was used for measurement. One end of the film strip (1 cm^2) was fixed between two iron screens for support, while the
other end was connected to a hook attached to a thread. The thread passed over a pulley and was connected to a small pan used for holding weights.

Weights were progressively added to the pan until the film broke. The applied force required to break the film was recorded as the breaking force. The tensile strength was then calculated using the formula:

Tensile Strength (kg/cm2) = Force at break (kg) x100
Cross-sectional area of film (cm2)

Where:

- **Force at break** = Weight required to break the film
- **Cross-sectional area** = Thickness × Width of the film

Percentage Moisture Absorption:

Three films from each batch were selected and weighed individually. The films were then placed in a desiccator and stored for three days. After the specified period, the films were reweighed, and the percentage moisture absorption was calculated using the formula:

Percentage Moisture Absorption (%) = $\frac{(W_f - W_i)}{W_i} \times 100$

Where:

- W_f = Final weight of the film after storage
- i = Initial weight of the film

In Vitro Drug Release:

In vitro drug release studies were carried out using a Franz diffusion cell. The receptor compartment was filled

with simulated tear fluid (pH 7.4) and maintained at 37 ± 1 °C with continuous stirring to mimic ocular conditions. The ocular film was placed on the donor side of the cell, ensuring intimate contact with the diffusion membrane.

Aliquots were withdrawn at predetermined time intervals (5–360 minutes) and immediately replaced with an equal volume of fresh medium to maintain sink conditions. The collected samples were analyzed using a UV spectrophotometer at the λmax of the drug. The cumulative percentage drug release was calculated and plotted against time to determine the release profile.

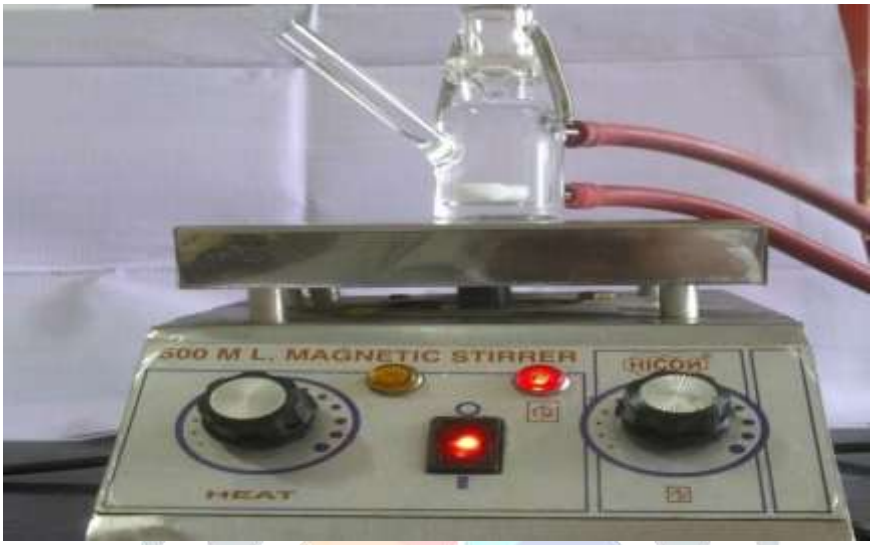


FIGURE 4.4 Franz diffusion cell

Stability Studies:

Stability studies were carried out for all the film formulations to evaluate the effect of storage conditions on drug content and drug release. The formulations were stored at 40 °C ± 2 °C /

75% RH ± 5% RH in a stability chamber, following ICH guidelines. Samples were withdrawn at predetermined intervals (0, 30, 60, and 90 days).

The films were analyzed for changes in drug content, physical appearance, and in vitro drug release profile. Any deviations in the results were compared with the initial values to assess the stability of the formulations.

CHAPTER-5

RESULT & DISCUSSION

5.1 PRE FORMULATION STUDIES

5.1.1 Characterization of Naphazoline HCl:

5.1.1 Characterization of Naphazoline HCl

The organoleptic properties of Naphazoline Hydrochloride were observed and are summarized in **Table 5.1**.

Table 5.1: Organoleptic Properties of Naphazoline HCl

S. No.	Property	Observation
1	Colour	White crystalline powder
2	Odour	Characteristic
3	Taste	Bitter

5.1.2 Solubility

The solubility profile of Naphazoline HCl was determined in different solvents and the results are presented in **Table 5.2**.

Table 5.2: Solubility of Naphazoline HCl in Various Solvents

S. No.	Solvent	Solubility
1	Water	Soluble
2	Ethanol	Soluble
3	Chloroform	Slightly soluble
4	Diethyl ether	Insoluble
5	Benzene	Insoluble

5.1.3 Melting Point

The melting point of Naphazoline HCl was determined using a capillary method. The observed melting point was found to be **259 °C**, which is consistent with literature values. The result is shown in **Table 5.3**.

Table 5.3: Melting Point of Naphazoline HCl

S. No.	Drug	Melting Point
1	Naphazoline HCl	259 °C

5.1.4 Spectrophotometric Characterization of Naphazoline HCl

5.1.4.1 Calibration Curve of Naphazoline HCl

The calibration curve of Naphazoline HCl was constructed using UV spectrophotometric analysis at **280 nm** in simulated tear fluid (STF). The drug exhibited good linearity over the concentration range of **2–14 µg/ml**, with a correlation coefficient (**R^2 = 0.990**), indicating suitability for quantitative analysis.

Table 5.4: Absorbance of Naphazoline HCl in simulated tear fluid (λmax = 280 nm)

S. No.	Concentration (µg/ml)	Mean Absorbance (±SD)
1	2	0.187 ± 0.001
2	4	0.284 ± 0.005
3	6	0.399 ± 0.004
4	8	0.563 ± 0.011
5	10	0.702 ± 0.005
6	12	0.834 ± 0.001
7	14	0.987 ± 0.040

The calibration curve plotted between concentration and absorbance demonstrated linearity, confirming adherence to **Beer–Lambert's law** within the studied range.

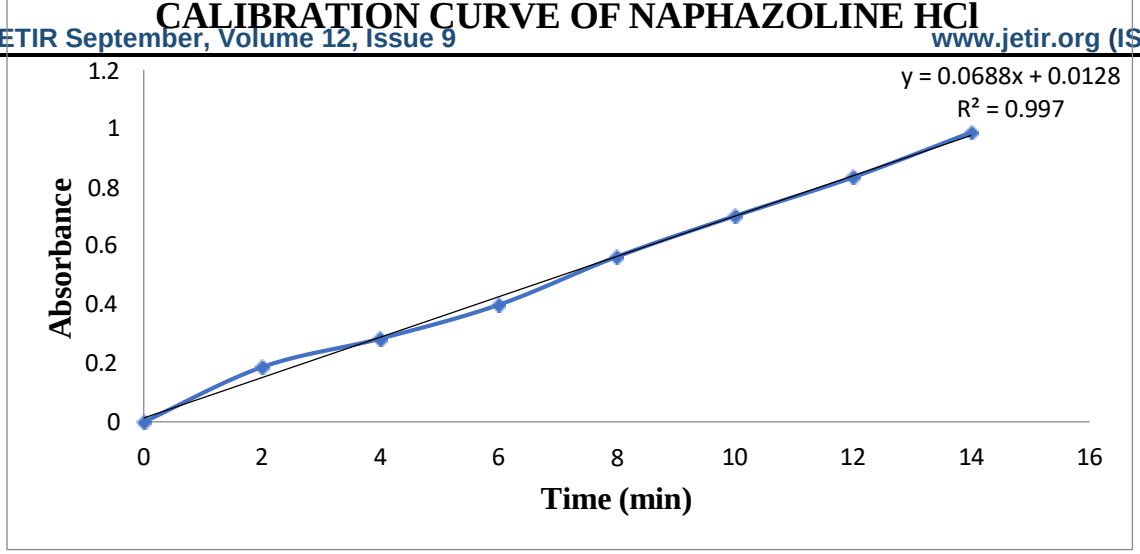


Figure 5.1 Calibration curve of Naphazoline HCl in simulated tear fluid

5.1.5 Compatibility Studies

Compatibility studies between the active pharmaceutical ingredient (Naphazoline HCl) and selected excipients (HPMC, chitosan, and carbopol 934) were carried out to evaluate possible interactions. The drug and excipients were mixed in definite ratios, and FT-IR spectra were recorded. The obtained spectra are presented in Figures 5.2, 5.3, 5.4, 5.5, 5.6, 5.7, while the characteristic peaks and interpretations are summarized in **Table 5.9**.

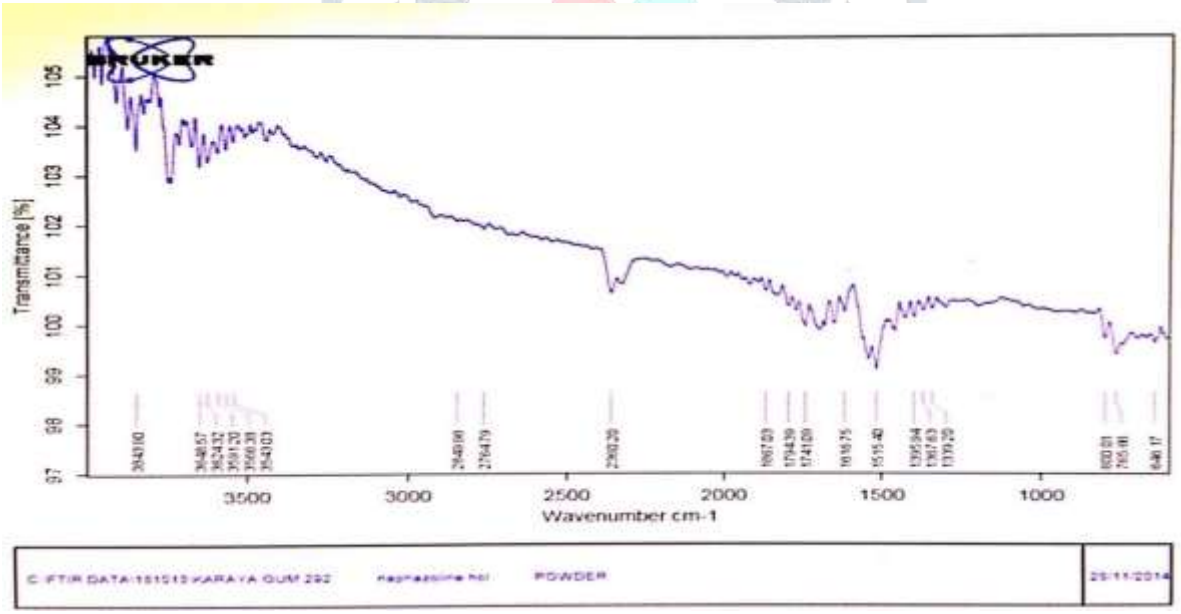


FIGURE 5.2 IR spectra of Naphazoline HCl

TABLE 5.5 Different functional groups of Naphazoline HCl with their range

Wavenumber (cm^{-1})	**Functional Group Assignment**	**Observation / Interpretation**
2360.2	–COOH (carboxylic group)	Characteristic stretching vibration present
1515.4	C–C (aromatic ring)	Confirms aromatic nucleus in drug structure
1367.63	$–NO_2$ (stretching)	Indicates presence of nitro group
3566.38	–OH (hydrogen bonded)	Broad peak confirming hydrogen bonding
3649.57	–OH (dilute, free hydroxyl group)	Sharp peak due to non-hydrogen bonded hydroxyl

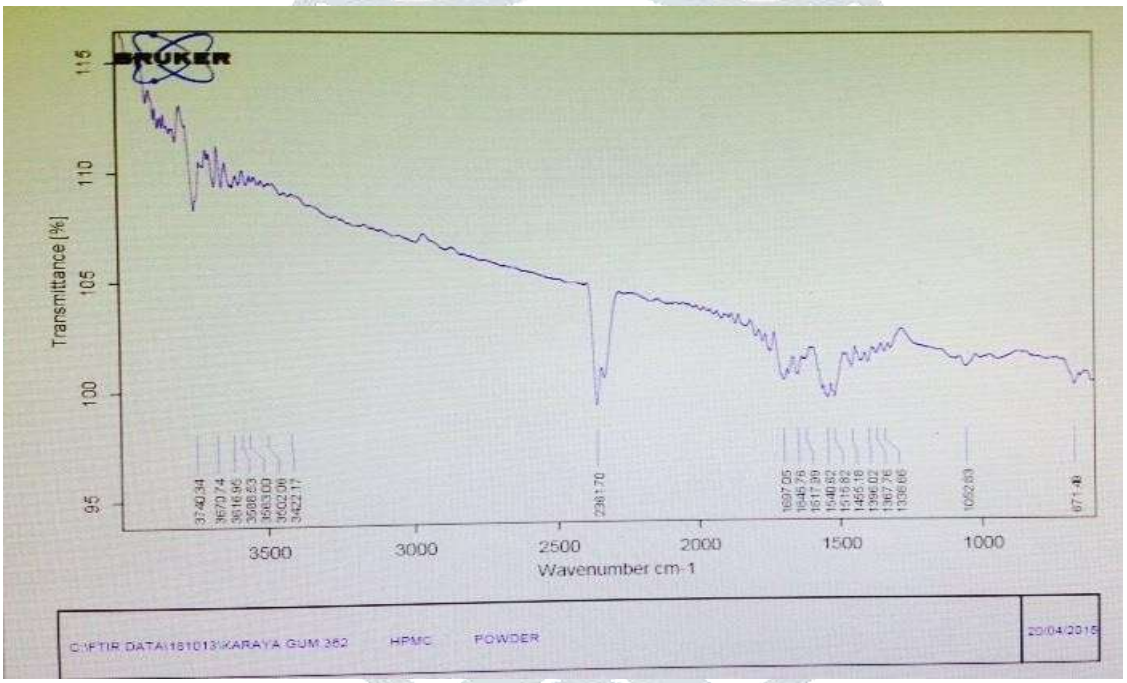


FIGURE 5.3 IR spectra of HPMC

TABLE 5.6 Different functional groups of HPMC with their range

Wavenumber (cm^{-1})	**Functional Group Assignment**	**Observation / Interpretation**
2361.7	$–NH_2$ (N–H stretching)	Indicates amino functional group
1515.82	C–C (aromatic ring)	Confirms aromatic moiety
1697.05	C=O (stretching)	Characteristic carbonyl stretching peak
671.49	–CH (alkyl group)	Presence of aliphatic C–H bending

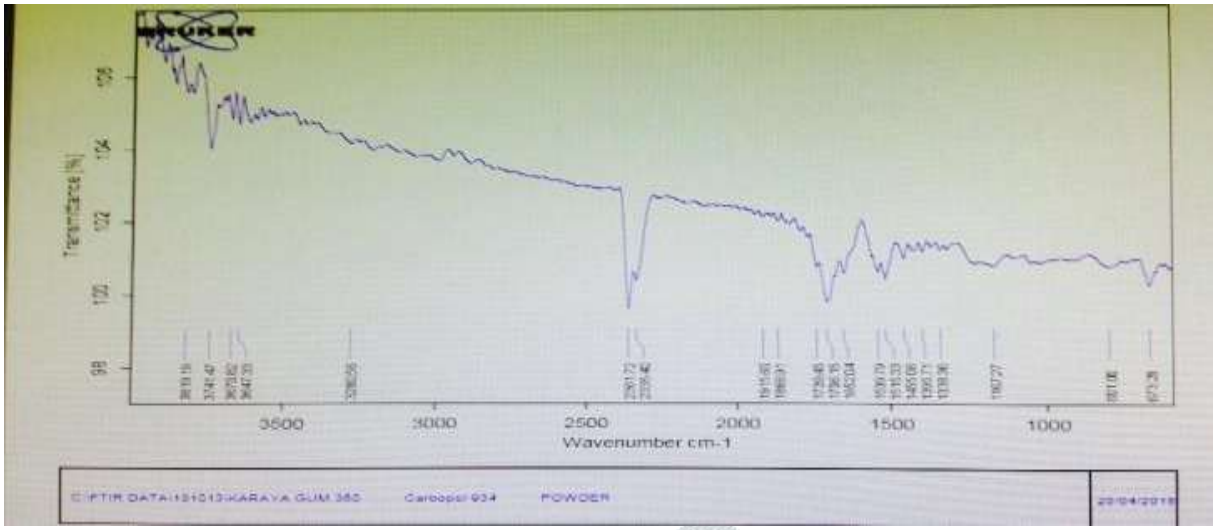


FIGURE 5.4 IR spectra of carbopol 934

TABLE 5.7 Different functional groups of Carbopol 934 with their range

Wavenumber (cm^{-1})	**Functional Group Assignment**	**Observation / Interpretation**
3741.47	–OH (hydroxyl stretching)	Broad band, confirms hydroxyl group presence
2361.72	–COOH (carboxylic acid group)	Indicates acidic functional group
2335.4	$–NH_2$ (N–H stretching)	Suggests presence of amino group
1706.15	C=O (unsaturated aliphatic carbonyl)	Strong absorption, confirms carbonyl moiety
1515.33	C–C (aromatic ring)	Aromatic skeletal vibration
673.28	–CH (alkyl group)	C–H bending, confirms aliphatic group presence

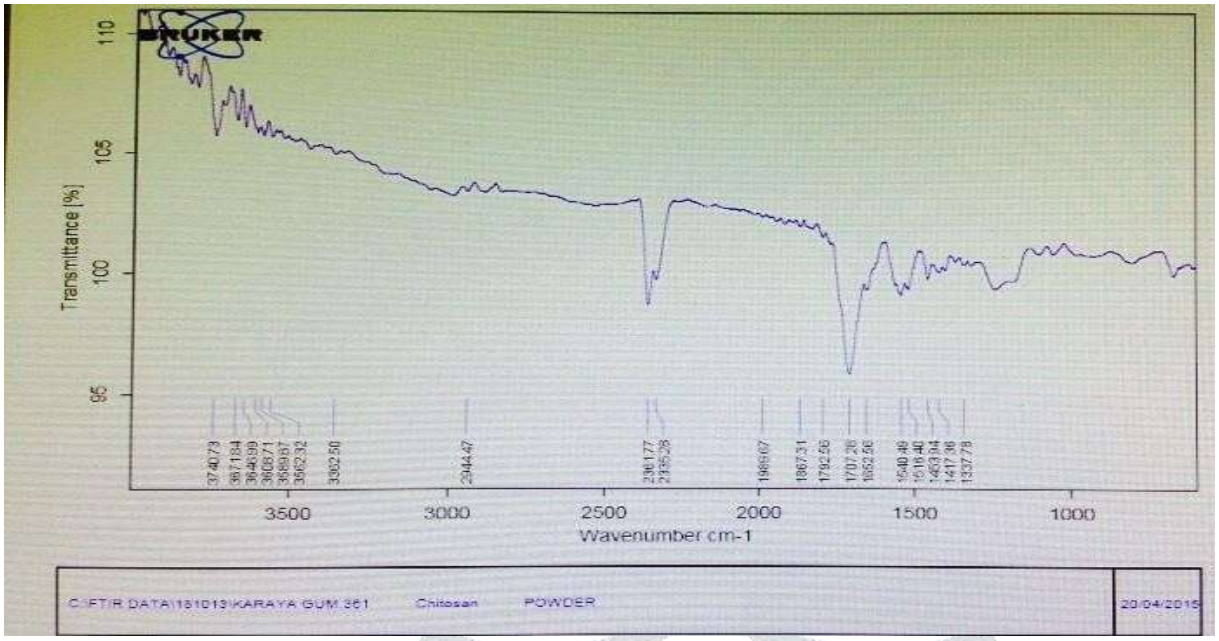


FIGURE 5.5 IR spectra of chitosan

TABLE 5.8 Different functional groups of chitosan with their range

Wavenumber (cm^{-1})	**Functional Group Assignment**	**Observation / Interpretation**
3671.84	Free –OH group	Strong, broad band indicating hydroxyl functionality
2361.77	–COOH (carboxylic acid group)	Confirms presence of acidic functional group
1707.28	C=O (imides, six- membered cyclic)	Sharp peak, characteristic of imide group
1540.49	C–NO_2 (nitro group, asymmetric stretch)	Distinct band confirming nitro functionality
1453.94	–NO_2 (symmetric stretching)	Supports presence of nitro substitution
1337.78	C–O (tertiary alcohol group)	Indicates presence of alcohol functionality

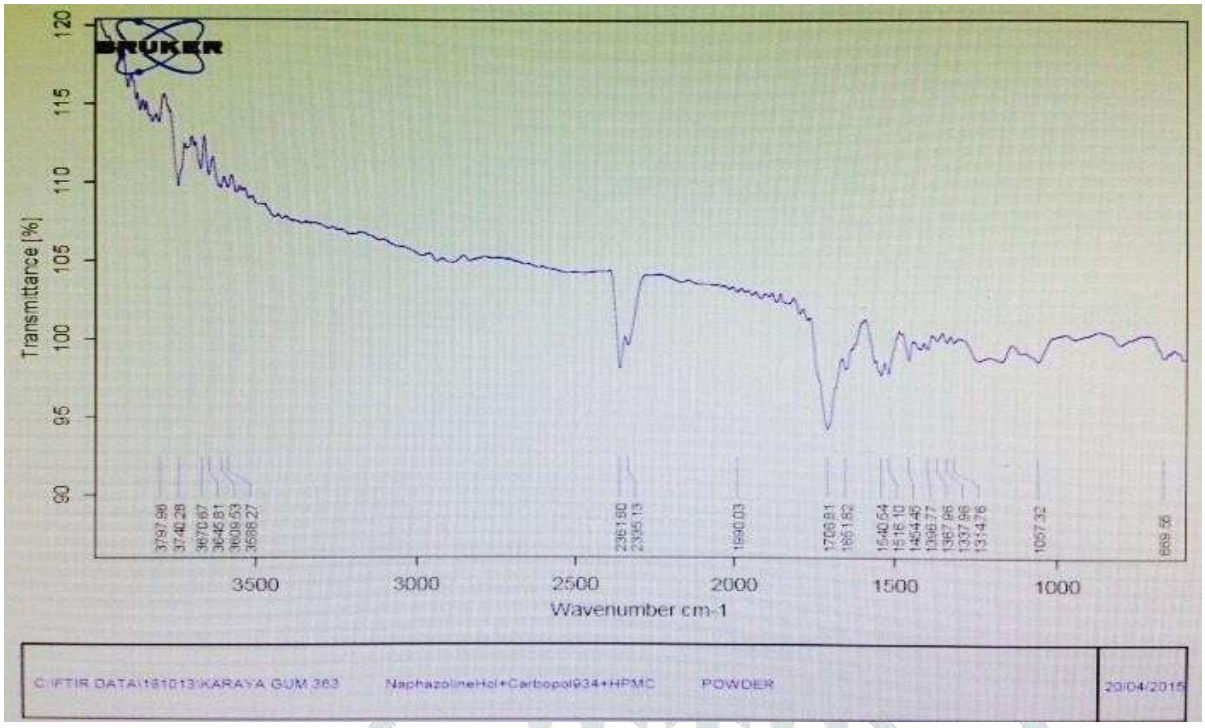


FIGURE 5.6 IR spectra of Naphazoline HCl with HPMC and carbopol 934

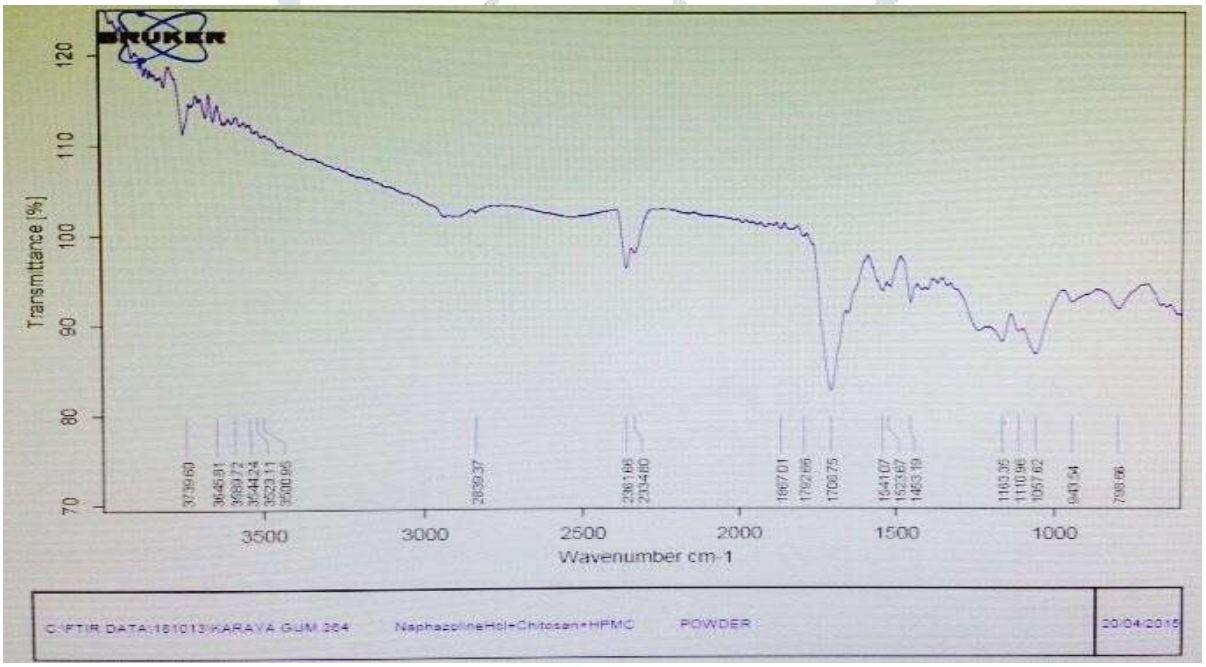


FIGURE 5.7 IR spectra of Naphazoline HCl with HPMC and chitosan

Table 5.9 Different functional groups of drug and polymer with their range

Table 5.9: Comparative FTIR Spectral Data of Naphazoline HCl and Its Formulations

Functional group present	**Wave numbers (cm^{-1})**			**Observation / Interpretation**
	Naphazoline HCl	**Naphazoline HCl + HPMC + Carbopol 934**	**Naphazoline HCl + HPMC + Chitosan**	
-COOH	2360	2361	2361	Retained in formulations, no major shift (stable interaction)

-C-C (aromatic)	1515	1515	1523	Slight shift in chitosan blend, indicating mild polymer– drug interaction
-NO_2 (stretch)	1367	1367	1453	Shift observed with chitosan, suggesting hydrogen bonding/interaction
-OH	3649	3645	3645	Minor shift, indicating possible H-bonding with polymers
-CH	765	669	798	Peak shifts reflect polymeric influence on CH vibrations

5.2 FORMULATION

5.2.1 Surface pH:

The variation in polymer concentration caused only slight changes in the pH of the formulations. The pH values were found to be in the range of **6.8 ± 0.01 to 7.1 ± 0.03**, which is near neutral. Since the pH was almost neutral, the risk of ocular irritation is minimal. In all formulations, the concentration of **drug (Naphazoline HCl), HPMC, glycerine, and water** was kept constant, while the concentrations of **Carbopol 934** and **Chitosan** were varied. The results are represented in **Figure 5.8**.

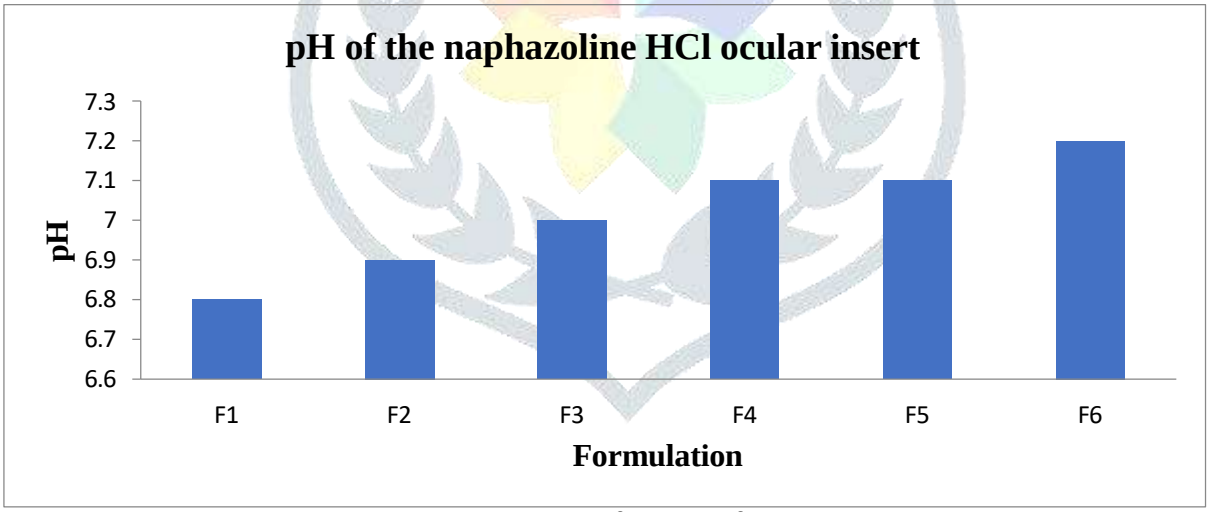


Figure 5.8: pH of various formulations

5.2.2 Folding Endurance

Folding endurance indicates the mechanical strength and flexibility of ocular films. A high value reflects flexibility, while a low value indicates brittleness. All formulations showed satisfactory flexibility, as none of the films exhibited cracks even after **300 folds**. This demonstrates the good mechanical strength of the prepared films.

5.2.3 Weight Uniformity

All formulations exhibited uniformity in weight, ranging from **0.046 ± 0.05 g to 0.053 ± 0.09 g**. Films prepared using **Chitosan** showed slightly higher weights compared to those prepared with **Carbopol 934**, which may be attributed to the higher molecular weight and density of Chitosan. The results are depicted in **Figure 5.9**.

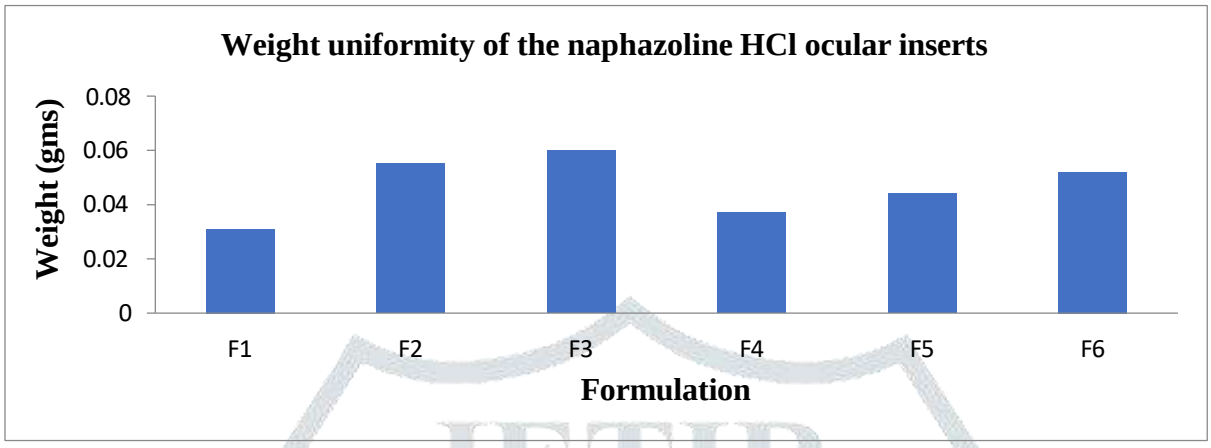


Figure 5.9: Weight uniformity of formulations

5.2.4 Swelling Index

The swelling index study indicated that an increase in polymer concentration directly enhanced the swelling capacity of the ocular inserts. For carbopol-based inserts, the maximum swelling was observed in formulation **F3**, while the minimum swelling was recorded in **F1**. In the case of chitosan-based inserts, formulation **F6** exhibited the highest swelling index, whereas the lowest was observed in **F3**. This suggests that polymer type and concentration significantly influence the hydration and swelling behavior of the ocular inserts, which in turn may affect drug release characteristics. The results are presented in **Figure 5.10**.

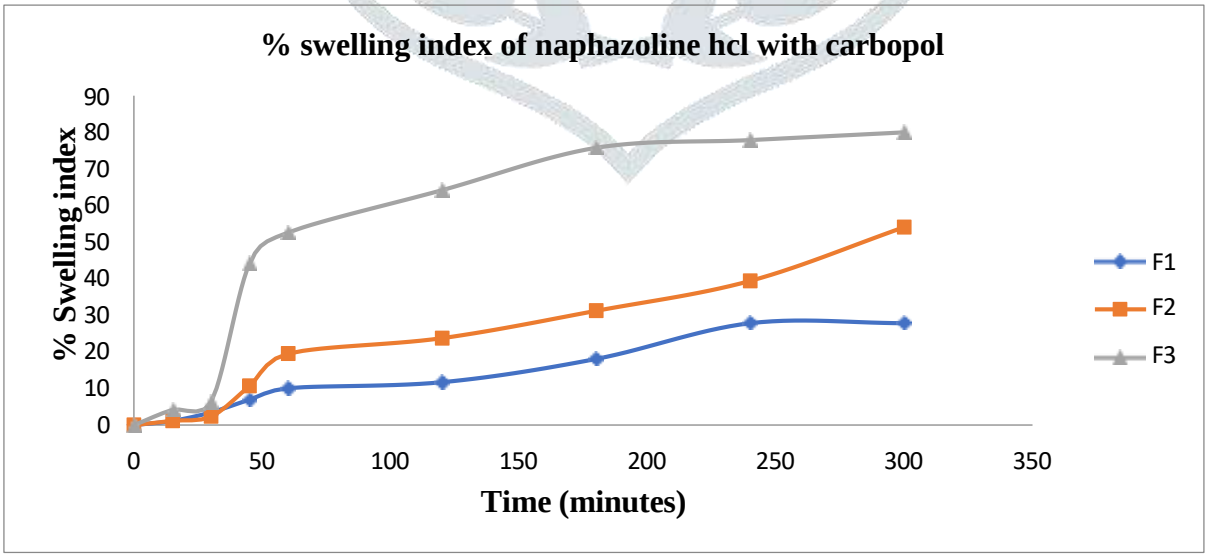


Fig5.10 % Swelling index of ocular insert with carbopol

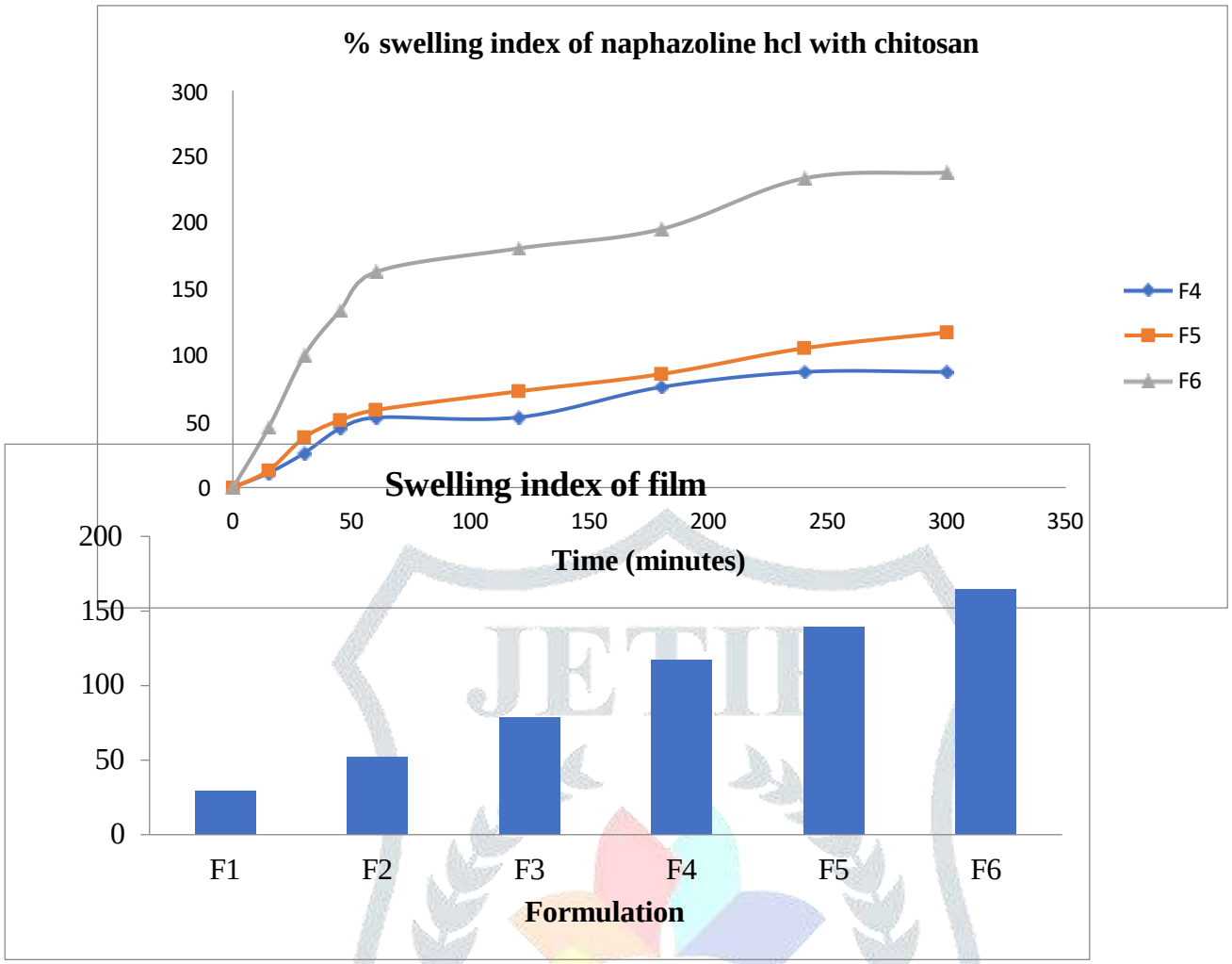


Fig5.11 % Swelling index of ocular insert with chitosan

Comparative Swelling Index

On comparison between carbopol- and chitosan-based ocular inserts, it was observed that the maximum swelling index was obtained in the formulation prepared using **chitosan** as the polymer. This indicates the superior hydration and water uptake ability of chitosan

compared to carbopol. The comparative swelling index values of both polymers are illustrated in **Figure 5.12**.

Figure 5.12: % Swelling index of different formulation

% Swelling index

TABLE 5.10: Swelling index of ocular inserts

TIME (min)	F1	F2	F3	F4	F5	F6
0	0	0	0	0	0	0
15	1.16	1.17	4.21	11.04	13.04	45.58
30	1.49	2.35	6.31	26.04	18.04	100.00
45	6.97	10.71	44.21	44.29	51.08	133.82
60	10.11	19.52	52.63	53.10	58.69	163.23
120	11.74	23.76	64.21	53.12	72.82	180.88
180	18.11	31.23	75.78	76.04	85.86	195.50
240	27.9	39.41	77.89	87.5	105.43	233.82
300	27.9	54.11	80.00	87.5	117.39	238.23

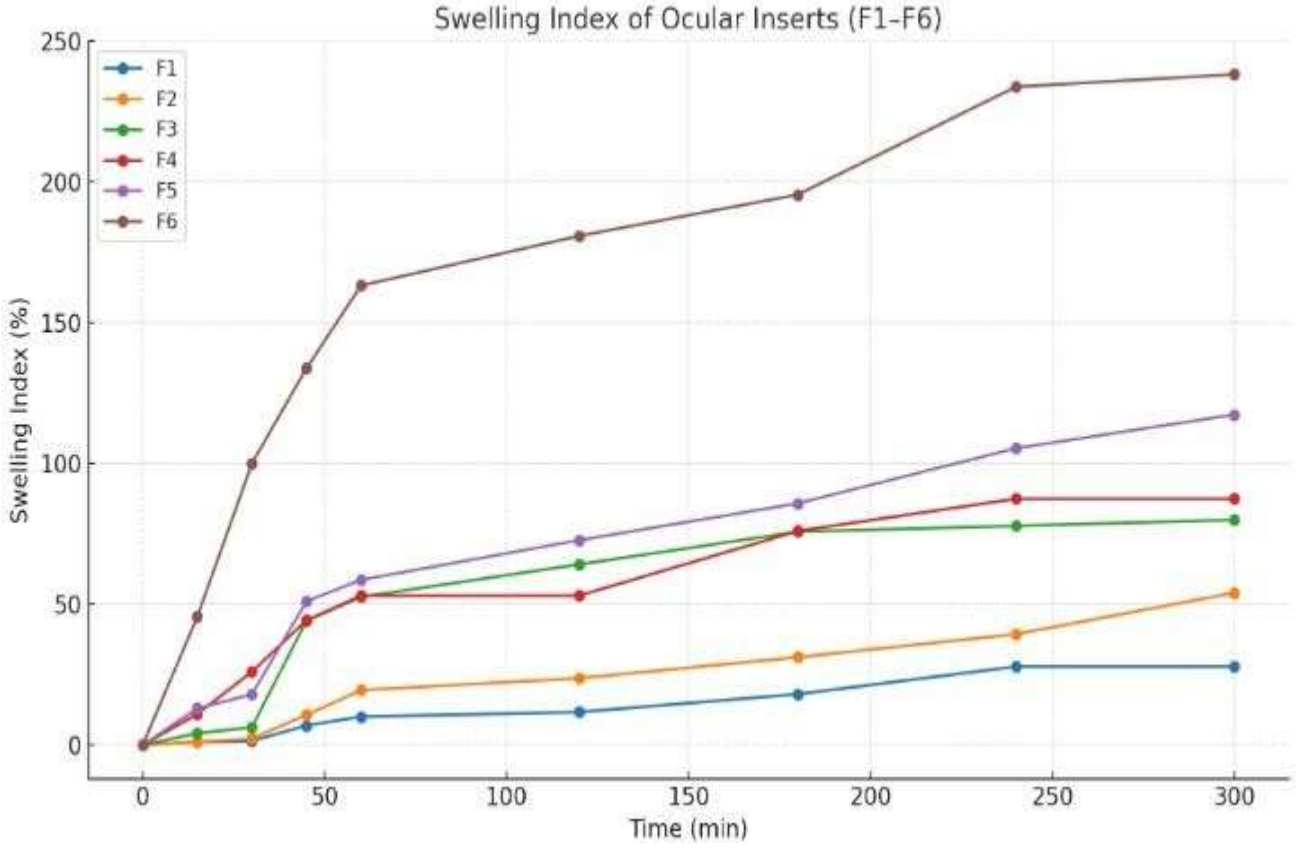


Figure 5.12: Swelling index of ocular inserts (F1–F6)

This graph clearly shows that among all formulations, **F6 exhibited the maximum swelling index**, followed by F5 and F4. Inserts prepared using **chitosan as the polymer demonstrated greater swelling ability** compared to those formulated with carbopol. This indicates higher water uptake capacity, which enhances drug release and mucoadhesion.

5.2.5 Drug Content

Estimation of drug content was carried out to assess the uniform distribution of drug within the ocular inserts. Triplicate readings were taken for each formulation, and the drug content of all batches was found to range between **78.3% and 89.3%**, indicating satisfactory uniformity.

Among the six formulations, **batch F6 exhibited the highest drug content (89.3%)**, whereas **batch F1 showed the lowest (78.3%)**. On comparing polymer types, it was observed that **chitosan-based ocular inserts demonstrated higher drug content (up to 89.3%)** than carbopol-based formulations, suggesting better entrapment efficiency.

The results are graphically represented in **Figure 5.13**.

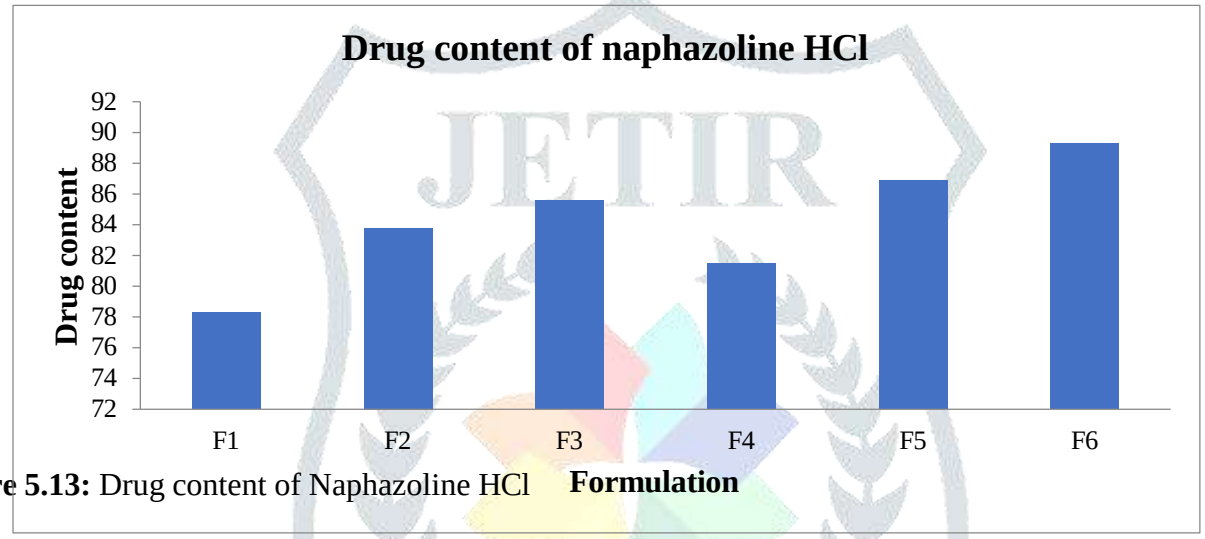


Figure 5.13: Drug content of Naphazoline HCl

5.2.6 Thickness Uniformity

The thickness of the ocular inserts was measured to ensure uniformity, as variation in polymer concentration directly influences film thickness. The values were found to be in the range of **0.181 ± 0.15 mm to 0.199 ± 0.05 mm**, indicating good consistency across all formulations.

Among the six batches, **F3 exhibited the minimum thickness (0.181 ± 0.15 mm)**, while **F6 showed the maximum thickness (0.199 ± 0.05 mm)**. The results suggest that an increase in polymer weight corresponds to a slight increase in film thickness

The comparative results are represented in **Figure 5.14**.

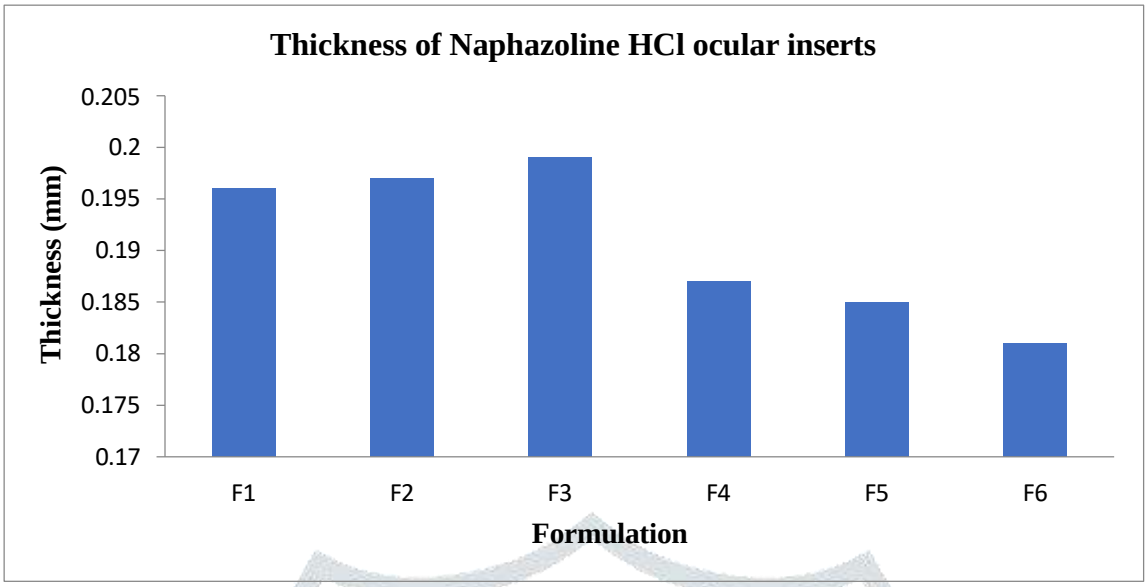


Figure 5.14 Thickness of different formulated ocular inserts

5.2.7 Tensile Strength

Tensile strength is a critical parameter that determines the mechanical integrity and handling properties of ocular inserts. The results indicated that all prepared films possessed satisfactory tensile strength, with values ranging from **4.82 ± 0.05 to 5.38 ± 0.06 kg/cm²**.

Among the six batches, **F1 exhibited the highest tensile strength (5.38 ± 0.06 kg/cm²)**, while **F6 showed the lowest tensile strength (4.82 ± 0.05 kg/cm²)**. This variation can be attributed to the difference in polymer composition and concentration.

The findings confirm that both **chitosan and carbopol-based ocular inserts demonstrate adequate tensile strength**, ensuring their stability during handling and application.

The comparative results are illustrated in **Figure 5.15**.

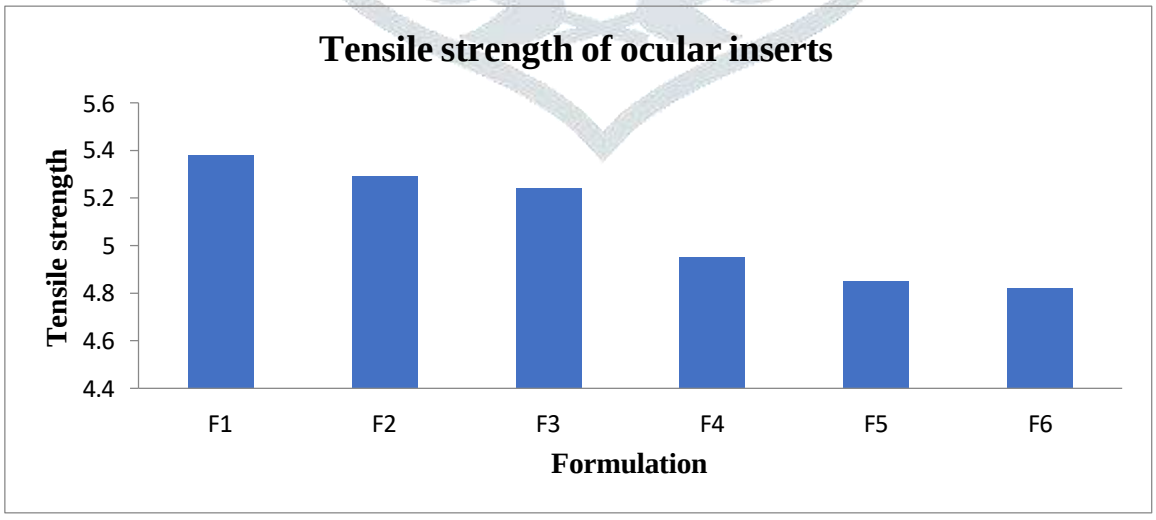


Figure 5.15 Tensile strength of prepared of ocular inserts

5.2.8 Percentage Moisture Absorption

Moisture absorption studies were carried out to assess the hygroscopic nature and stability of the prepared ocular inserts. The results indicated that **carbopol-based inserts exhibited higher moisture uptake** compared to chitosan-based inserts, with a noticeable weight gain observed after three days.

The percentage moisture content ranged from **0.082 ± 0.05 to 0.107 ± 0.06%**, demonstrating that the films were **minimally affected by atmospheric moisture**. This low hygroscopicity suggests a **reduced risk of deterioration during storage**, thereby ensuring better stability of the formulations.

The comparative findings are presented in **Figure 5.16**.

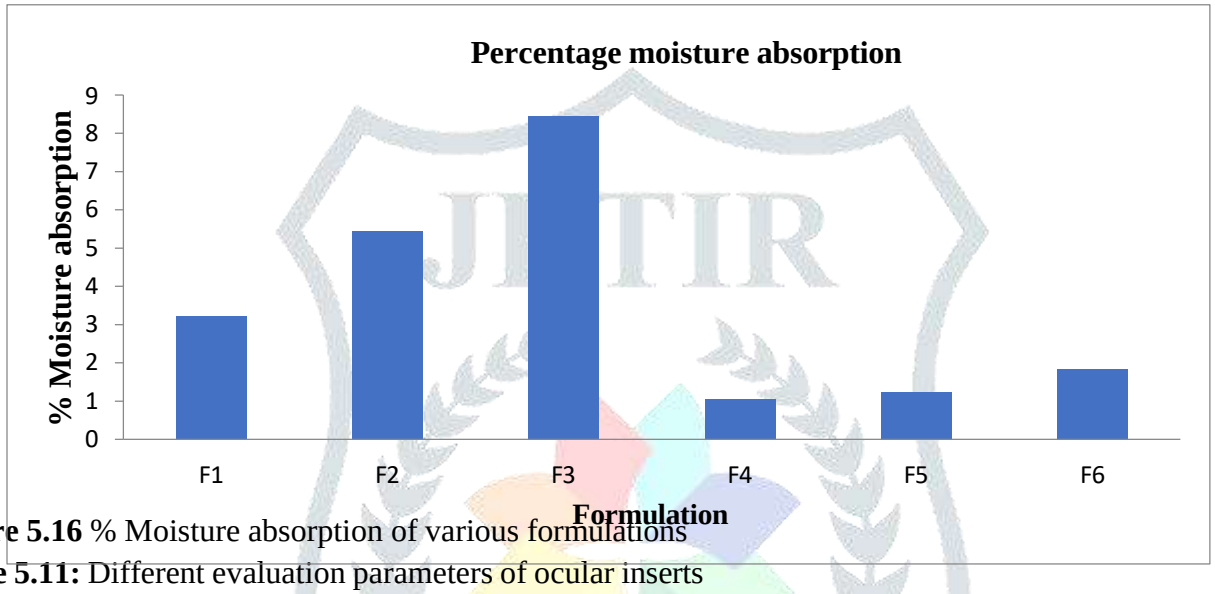


Figure 5.16 % Moisture absorption of various formulations

Table 5.11: Different evaluation parameters of ocular inserts

Parameters	Formulations					
	F1	F2	F3	F4	F5	F6
Surface pH	6.8±0.01	6.9±0.01	7.0±0.03	7.1±0.02	7.1±0.01	7.2±0.03
Folding Endurance	>300	>300	>300	>300	>300	>300
Weight Uniformity (gms)	0.031±0.05	0.055±0.05	0.061±0.06	0.037±0.09	0.044±0.07	0.052±0.08
Drug Content (%)	78.3±0.15	83.8±0.05	85.6±0.01	81.5±0.04	86.9±0.11	89.3±0.05
Thickness (mm)	0.196±0.29	0.197±0.15	0.199±0.05	0.187±0.11	0.185±0.56	0.181±0.15
Tensile Strength (Kg/mm^2)	5.38±0.06	5.29±0.05	5.24±0.06	4.95±0.06	4.89±0.05	4.82±0.05
% Moisture content	3.21±0.05	5.45±0.05	8.45±0.06	1.83±0.06	1.23±0.05	1.04±0.06

5.2.9 In-vitro Drug Release

The in-vitro release study was performed to evaluate the ability of the prepared ocular inserts to release the drug within the expected time. The results demonstrated that all formulations exhibited sustained and controlled drug release. Among the carbopol-based formulations, **F3** showed the maximum drug release, whereas in the chitosan-based formulations, **F6** exhibited the highest release profile.

On comparing both polymer systems, it was observed that chitosan-based ocular inserts provided greater drug release compared to carbopol-based inserts, suggesting better diffusion and polymeric compatibility with the drug. The detailed results of the in-vitro release study are represented graphically in **Figures 5.17, 5.18, 5.19, 5.20, 5.21, and 5.22**.

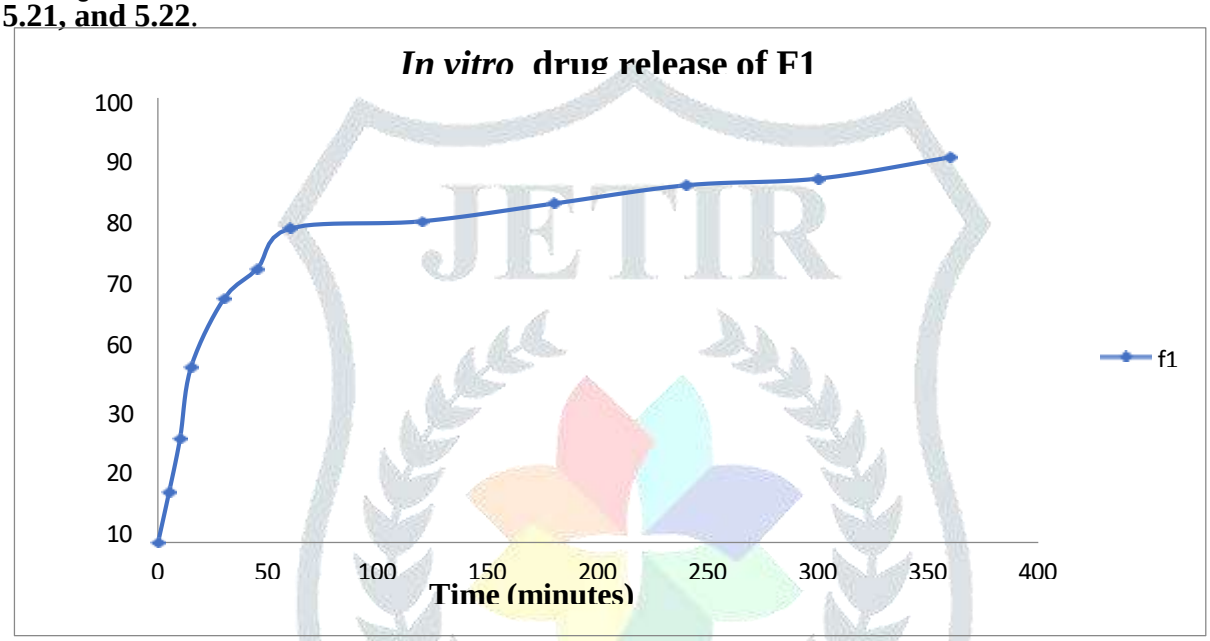


Figure 5.17 *In vitro* drug release of carbopol 934 formulated F1 formulation

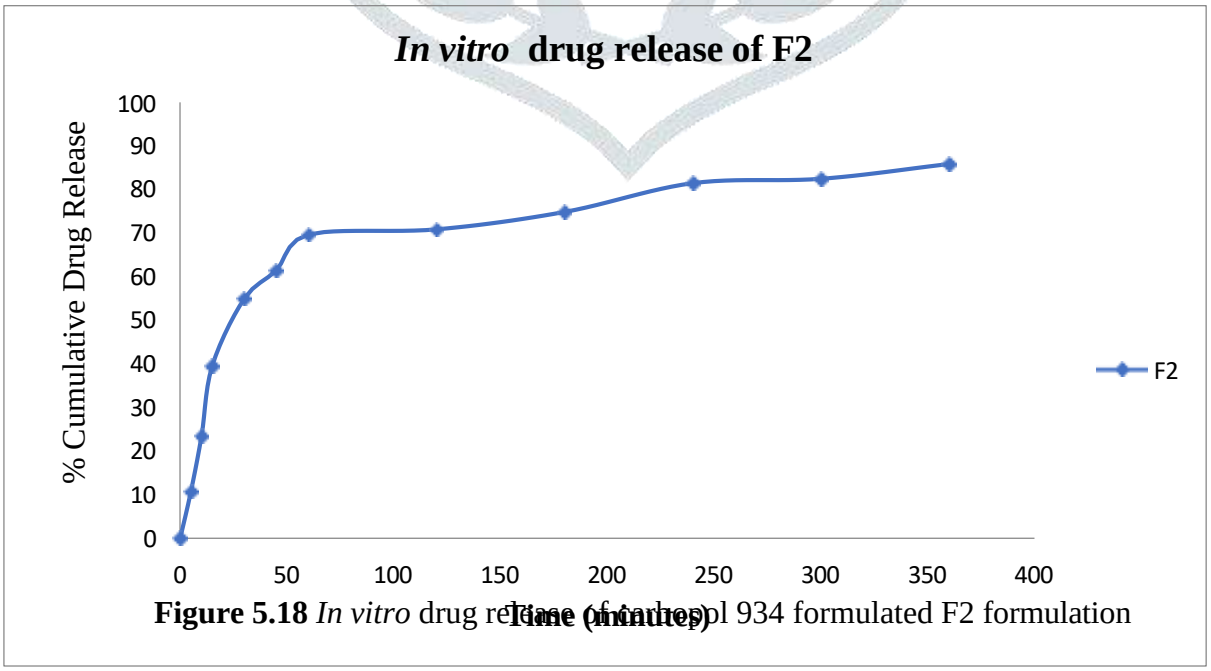


Figure 5.18 *In vitro* drug release of carbopol 934 formulated F2 formulation

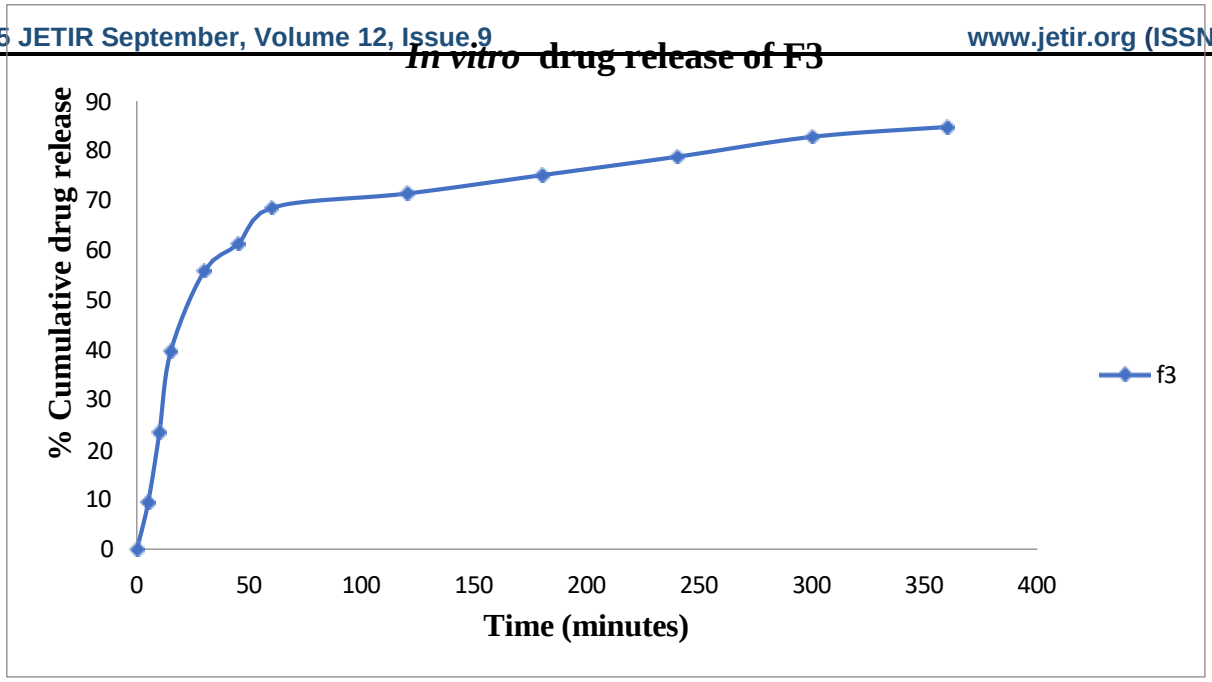


Figure 5.19 *In vitro* drug release of carbopol 934 formulated F3 formulation

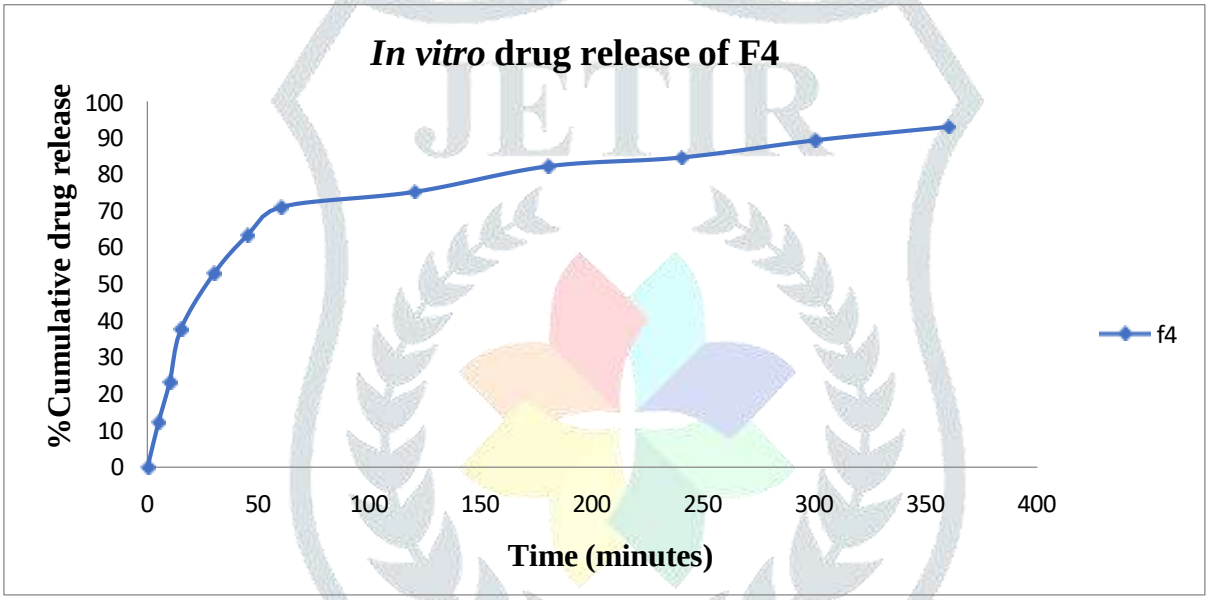


Figure 5.20 *In vitro* drug release of chitosan formulated F4 formulation

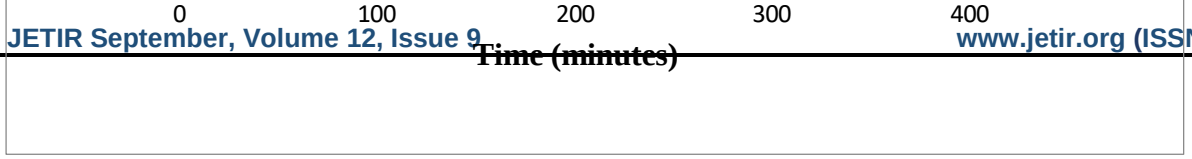


Figure 5.21 *In vitro* drug release of chitosan formulated F5 formulation

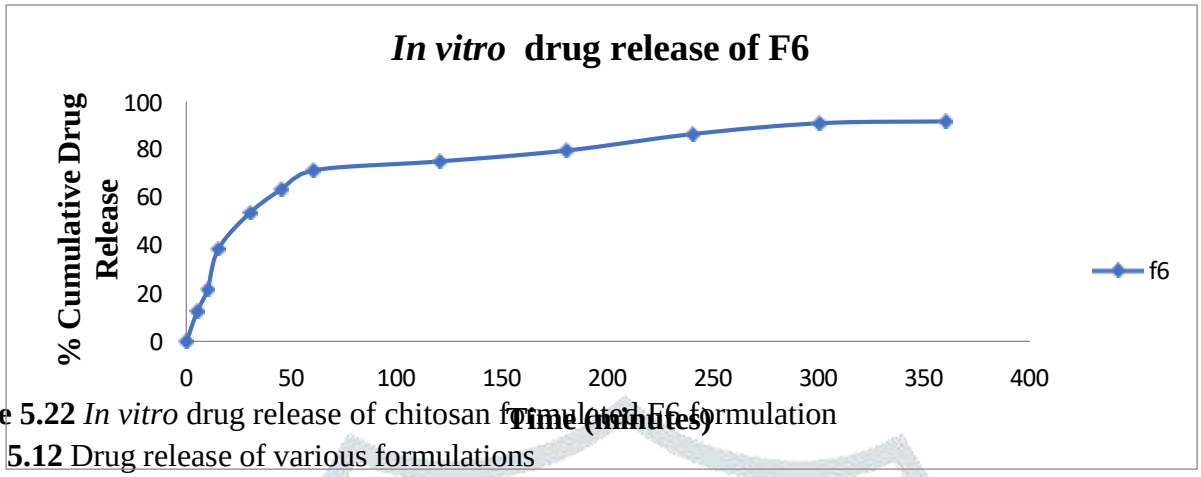


Figure 5.22 *In vitro* drug release of chitosan formulated F6 formulation

Table 5.12 Drug release of various formulations

Time (min)	F1	F2	F3	F4	F5	F6
0	0	0	0	0	0	**0**
5	9.5	10.7	11.3	12.5	14.9	**12.6**
10	19.4	20.9	23.6	23.4	22.3	**41.9**
15	30.5	34.6	39.8	37.8	38.8	**50.7**
30	48.6	50.7	56.9	53.1	52.1	**58.9**
45	54.6	58.9	61.4	60.5	63.4	**63.6**
60	70.7	63.3	70.6	69.8	67.8	**71.5**
120	72.3	70.9	71.5	73.4	72.6	**75.2**
180	76.3	74.9	75.2	82.3	81.6	**79.7**
240	80.4	81.5	82.9	84.7	85.5	**86.6**
300	81.9	82.5	84.9	89.4	88.6	**91.1**
360	86.7	85.9	90.7	93.1	92.6	**95.6**

5.2.10 Stability Studies

Stability studies of the prepared ocular inserts were carried out at **40 °C ± 2 °C** and **75% ± 5% RH** for a period of **three months** (evaluated at 0, 30, 60, and 90 days). The films were analyzed for **drug content** and **in-vitro drug release** to determine their stability under
accelerated conditions.

The results indicated that the formulations showed only minor changes in drug content and cumulative drug release over the study period, suggesting good stability. After 3 months, the drug content and % cumulative release were recorded as follows:

- **F1:** 78.0% drug content, 86.3% cumulative release
- **F3:** 85.2% drug content, 84.7% cumulative release

- **F4:** 81.2% drug content, 92.5% cumulative release
- **F6:** 89.2% drug content, 91.8% cumulative release

These findings confirm that the prepared ocular inserts maintained acceptable stability, with negligible variations in performance, throughout the study period.

Table 5.13 Comparative stability study of different formulations

Formulations	Days	Drug contents	Surface pH	% cumulative drug release after 6hrs
F1	0	78.3	6.8	86.7
	30	78.3	6.8	86.4
	60	78.2	6.8	86.4
	90	78.0	6.8	86.3
	0	85.6	6.8	84.9
F3	30	85.6	7.0	84.9
	60	85.4	7.0	84.8
	90	85.2	7.0	84.7
	0	81.5	7.0	93.1
F4	30	81.5	7.1	92.8
	60	81.2	7.1	92.7
	90	81.2	7.1	92.5
	0	89.3	7.1	91.9
F6	30	89.3	7.2	91.9
	60	89.3	7.2	91.8
	90	89.2	7.2	91.8

CHAPTER 6 CONCLUSION

The present study was undertaken to develop and evaluate ocular inserts of **Naphazoline Hydrochloride** using **chitosan** and **carbopol 934** as film-forming polymers. Different formulations were prepared by varying polymer concentrations and evaluated for physicochemical and performance parameters.

The prepared films were found to be **uniform, smooth, and transparent**, with no visible cracks or imperfections. The **pH values** ranged between 6.7 and 7.1, which falls within the physiological tear fluid range, suggesting that the formulations would not cause ocular irritation. The **thickness (0.181 ± 0.15 mm to 0.199 ± 0.05 mm)** and **weight variation (0.031 ± 0.05 g to 0.055 ± 0.05 g)** were consistent across batches, demonstrating good uniformity and reproducibility.

Moisture absorption studies revealed that carbopol-based inserts showed relatively higher water uptake compared to chitosan films. However, the overall percentage moisture absorption was low (0.082 ± 0.05 to 0.107 ± 0.06), indicating reduced susceptibility to deterioration under humid conditions.

Drug content analysis confirmed that all films contained the drug uniformly, with negligible variations between batches. Mechanical evaluations showed that the films had satisfactory tensile strength and folding endurance,

making them strong enough to withstand handling without breaking.

In vitro release studies indicated that **chitosan-based formulations released the drug more efficiently than carbopol-based formulations**, with formulation F6 showing the highest drug release (above 95%) within 6 hours. This sustained release pattern suggests the suitability of chitosan for extended ocular delivery.

tability testing for 45 days demonstrated that the ocular inserts maintained their physicochemical and drug release properties, with no significant deviations in pH, moisture content, or drug content.

Overall, it can be concluded that ocular inserts prepared using **chitosan and carbopol 934** provide an effective and sustained-release delivery system for **Naphazoline Hydrochloride**. Such inserts offer several advantages, including prolonged drug release, reduced dosing frequency, enhanced patient compliance, and minimal risk of side effects associated with conventional eye drops.

CHAPTER 7 SUMMARY

Conventional ocular dosage forms like lotions, ointments, and suspensions are widely used but often suffer from poor bioavailability due to rapid precorneal drainage and reduced contact time. This necessitates frequent dosing to achieve therapeutic efficacy.

Ocular diseases such as glaucoma, miosis, mydriasis, and conjunctivitis require more effective drug delivery systems. Polymeric ocular inserts offer advantages of prolonged drug contact time, better bioavailability, and convenient administration, with novel approaches including liposomes, niosomes, nanoparticles, and mucoadhesive systems.

In the present study, **Naphazoline HCl ocular inserts** were formulated using **HPMC (film former), carbopol 934, and chitosan (mucoadhesive polymer)**, with glycerin as a plasticizer. Six formulations were developed with varying polymer concentrations. **FTIR studies confirmed no drug–excipient interaction.**

Evaluation showed:

- **H:** 6.8–7.2 (physiological range)
- **Moisture uptake:** 1.04%–3.21% (low, ensuring stability)
- **Drug content:** 78.3%–89.3%
- **In vitro release:** 86.7%–95.6%, with **F6 showing maximum release and content.**

Overall, the formulated inserts provided satisfactory physicochemical properties and sustained release, meeting the project's objectives.

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1. References

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