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# FROM DROPS TO GELS: A PARADIGM SHIFT IN OPHTHALMIC DRUG DELIVERY SYSTEMS

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## ABSTRACT

"Ophthalmic in situ gels have brought a significant breakthrough in ocular drug delivery. A major emphasis needs to be on addressing the challenges posed by the eye's inherent protective barriers. Traditional methods, like eye drops and ointments, frequently experience swift drug clearance caused by tear turnover and blinking, resulting in low bioavailability and the need for frequent applications. In contrast, in situ gel formulations are initially delivered as liquids but convert into gels upon exposure to certain physiological conditions, such as changes in temperature, pH, or ion concentration in the eye. This transition from sol to gel enables extended contact between the drug and ocular tissues, improving therapeutic efficacy and decreasing the need for frequent administration. The article discusses the range of polymers utilized to develop these systems, including temperature-sensitive polymers like poloxamer, pH-sensitive carbopol, and ion-sensitive gellan gum. These materials enable controlled and sustained drug release, effectively overcoming the limitations associated with traditional delivery methods. The extended retention time afforded by in situ gels makes them particularly effective for treating chronic eye conditions, such as glaucoma, uveitis, and diabetic retinopathy, where it is essential to maintain stable therapeutic levels. Despite their potential benefits, in situ gels also encounter challenges, including stability issues and limitations on the amounts of drug that can be effectively delivered. Nonetheless, ongoing research is focused on optimizing these systems to enhance patient adherence and minimize systemic side effects, indicating a promising future for advancements in ophthalmic care."

**KEYWORDS:** In-situ ocular gels, biodegradable, Occular drug delivery, controlled drug release, patient compliance, drug retention.

## INTRODUCTION

The eye is a crucial sensory organ responsible for converting light into electrical signals that the brain processes and interprets.[1] Delivering drugs to the eye presents significant challenges for pharmaceutical researchers due to the eye's unique structural and functional barriers, which limit the penetration of external substances. Traditionally, ocular drug administration has been confined to topical applications, systemic distribution, or direct injections into or around the eye.[2] However, conventional forms such as solutions, suspensions, and ointments come with limitations, including rapid elimination from the eye surface, variable drug absorption, and blurred vision.[3] To address these issues and enhance ocular bioavailability, recent advancements in controlled and sustained drug delivery have emerged in pharmaceutical research.[4] Among these innovations is the development of ophthalmic in-situ gels, representing a promising approach for more effective ocular drug delivery.[5]

## EYE ANATOMY

Anatomically eye has two major areas: (1) The anterior segment involving the cornea, conjunctiva, iris, pupil, ciliary body, anterior chamber, aqueous humour, lens, and trabecular meshwork. (2) The posterior segment including vitreous humor, sclera, retina, choroid, macula and optic nerve. (As shown in Fig. 1).[6]

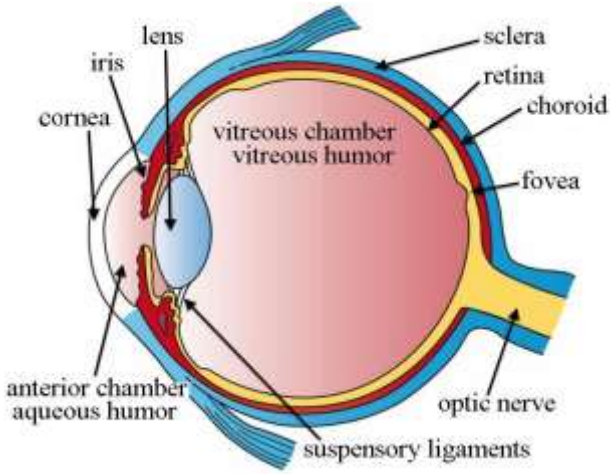



**Figure 1: Ocular system's anatomy includes two main segments: the anterior segment, which comprises the conjunctiva, ciliary body, iris, pupil, anterior chamber, cornea, and lens, and the posterior segment, containing the sclera, choroid, retina, macula, and optic nerve.**

The cornea is the transparent and clear avascular part of the ocular system which is the anterior of the eye. Anatomically, the cornea comprises of five major layers. The Corneal epithelium is the first layer, which is the most exterior.[7] The other layers include Bowman's membrane, stroma, Descemet's membrane and the endothelium layer.[6] Corneal permeability is the most essential factor that determines drug concentration in aqueous humor. For most hydrophilic drugs, the epithelium is a rate-limiting barrier to the transcorneal diffusion of drugs.[8] The stroma is hydrophilic in nature and acts as a barrier to the diffusion of highly lipophilic drugs.[8] The corneal stroma mainly consists of charged and highly organized hydrophilic collagen that inhibits the diffusion of hydrophobic molecules.[9]

Conjunctiva is a clear thin membrane that covers the sclera. It lines the inner surface of the eyelid. It is made of stratified epithelium (non-keratinized) and goblet cells. It protects the eyes by secreting mucus that prevents entry of microorganisms and lubricates the eyes.[6]

In humans, the conjunctiva covers a large surface area, enhancing drug absorption through this tissue, making it more permeable to drugs than the cornea. However, drug absorption via the conjunctiva remains limited because the conjunctival blood capillaries and lymphatic vessels cause significant drug loss into the systemic circulation, ultimately reducing ocular bioavailability.[10]

The aqueous humor is a clear fluid that fills both the posterior and anterior chambers of the eye. This nonvascular, transparent structure is essential for light transmission and supports corneal nutrition.[6] It contains a high concentration of ascorbate—about 15 times that found in plasma—and has a pH of 7.2.[7] Its primary roles include nutrient supply, waste removal from nonvascular tissues, and regulating intraocular pressure, which maintains the cornea's convex shape.[11]

The sclera, the opaque, white outer layer of the eye, is composed of elastic collagen fibers.[6] Compared to the cornea and conjunctiva, the sclera allows greater permeability for solutes, particularly hydrophilic compounds. This increased permeability is due to transport through aqueous pathways within the proteoglycan-rich collagen network rather than movement across cellular membranes. The sclera also serves as a protective layer, helping to regulate intraocular pressure and providing attachment points for the eye's extraocular muscles.[10][8] The retina, with its complex, multi-layered structure of vascular, glial, neural cells, and nerve fibers, presents a significant barrier for delivering drugs with large molecular weights into the eye.[7] [10]

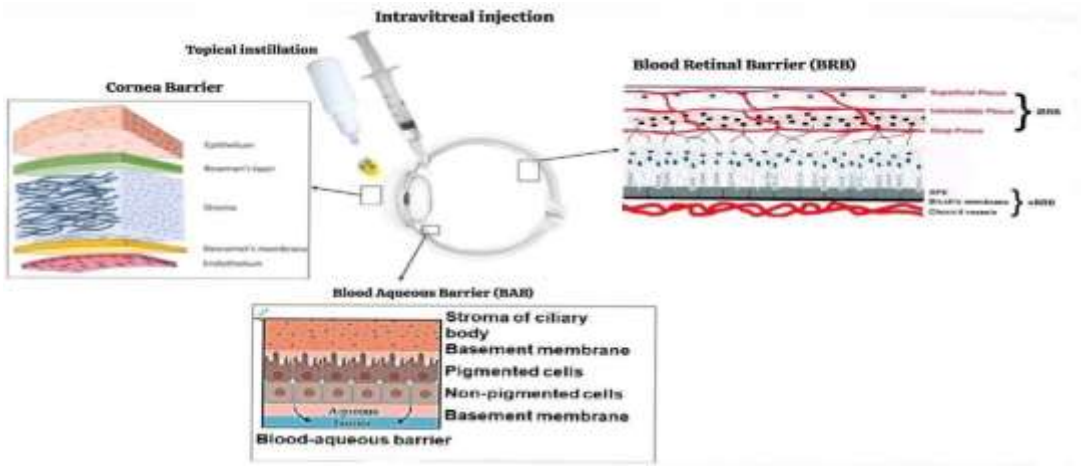



**Figure 2: ocular drug delivery faces challenges from key barriers: the corneal barrier, with its tightly joined epithelial layers and stroma; the blood-retinal barrier, formed by retinal capillaries; and the blood-aqueous barrier, created by ciliary body epithelium and iris endothelium.**

## OCULAR SUSTAINED DRUG DELIVERY SYSTEMS (OSDDS)

OSDDS are designed to provide controlled and prolonged release of drug directly to the eye, addressing a limitation of conventional of eye drops, which are rapidly cleared from ocular surface. OSDDS are formulated to enhance therapeutic efficacy, improve patient compliance and limit the dosing frequency by maintaining therapeutic drug concentration in the target tissue for extended periods.[12]

• Key types of occular sustained drug delivery system include.

1. **Inserts and implants**

- **Occular Inserts:** These are solid or semisolid placed in a conjunctival sac, slowly releasing the drug. An example is the occusert system for pilocarpine delivery for glaucoma treatment.
- **Biodegradable impact:** These implants the release of drug as they degrade within the eye over weeks or months, such as retisert (Fluocinolone acetonide) for uveltis treatment.

2. **Microspheres and Nanoparticles**

- **Microspheres:** These are spehrical particles that can encapsulate the drugs, allowing the gradual release of drug when injected into the eye. they are useful for targeting posterior segment.
- **Nanoparticles:** smaller than microspheres, nanoparticles offer increased surface area for drug release and can penetrate the deeper occular tissue for sustained release.

3. **Hydrogels:** Hydrogels are cross linked polymers that can swell and release the drug gradually when applied as eye drops or occular Inserts. They provide a sustained release due to their ability to retain moisture and hold drugs for extended periods.

4. **Contact Lens based drug delivery**

Specially designed contact lenses are used to deliver drugs to the eye in a sustained manner. Drug - loaded contact lenses ensure prolonged contact with the cornea, improving compared to eye drop.

5. **Liposomes:** liposome drug delivery system are encapsulate drugs within liquid bilayers allowing for slow sustainable release of drug when applied to the eye. Liposome are versatile and biocompatible.

6. **In situ gels:** These are liquid formulation that turn into gels when applied to the eye. The gel formation prolong drug retention time, allowing drug release over time.

These systems are especially important for treating chronic eye conditions such as glaucoma, diabetic retinopathy, uveitis and macular degeneration, where prolonged drug delivery system is needed for optimal outcomes

## TRIGGERING FACTORS AND APPROACH OF FORMATION OF IN SITU OPTHALMIC GEL

Ophthalmic in situ gels are liquid formulation that transform into gel upon instillation in the eye, prolonging the retention time of drug and enhancing the bioavailability. The transition from liquid to gel is triggered by specific stimuli in the environment. These triggering factor include.

1. **Temperature - Triggered system**

- **Mechanism -** These gels remain in a liquid state at room temperature but undergo a sol-to-gel transformation upon contact with the eye's higher physiology temperature approximately 33- 37°C.
- **Polymer used -** like ***poloxamer*** (Pluronic F-127) and ***poly(N - isopropylacrylamide (PNIPA)*** are thermosensitive and are commonly used in temperature-sensitive in situ gels.
- **Example :** when applied, the formulation remains fluid at room temperature but gels upon warming to body temperature, providing sustained drug release.[13]

2. **pH - Triggered Systems**

- **Mechanism:** These formulations are sensitive to the pH of the environment. The eye's tear fluid has slightly alkaline pH (around 7.4) and when a pH - sensitive formulation is introduced into this environment, the change in pH triggers the gelation.
- **Polymer Used:** like ***carbopol*** and ***polycarbophil*** are commonly used in pH sensitive system. They are in liquid state at lower pH(below 7) and form a gel at the physiological pH of the eye.
- **Example:** A drug solution that remains liquid in its container but gels upon exposure to the eye's alkaline pH, ensuring prolonged retention and drug release.[14]

3. **Ion - Triggered Systems**

- **Mechanism:** These Gels respond to changes in ion concentration. When instilled in the eye, the electrolytes in tear fluid (such as sodium, calcium, or magnesium ions) induce the Sol-to- gel transition.
- **Polymer used:** Like ***gellan gum (Gelrite)*** and ***sodium alginate*** are commonly used in ion- sensitive gels. These polysaccharides gel in response to the divalent cations present in tears.
- **Example:** A solution containing gellan gym remains liquid in the bottle but forms a gel upon contact with the tear fluid, where ions like calcium act as a crosslinker to induce gelation.[15]

4. **Enzyme triggered systems**

- **Mechanism:** Enzyme triggered gels depend on specific enzymes present in the occular environment to initiate the gelation process. These systems are designed to respond particular enzymes, creating a sustained release profile profile.
- **Polymer Used:** Enzyme sensitive polymer can be synthesised to respond to enzymes like lysozyme in tears. They can less common compared to the other triggers but hold potential for precision drug delivery
- **Example:** A liquid that respond to enzymatic activity in the eye, initiating crosslinking and gel formation to release the drug gradually.[16]

Each of these triggering mechanisms enhances the drug's residence time in the eye, overcoming challenges like rapid tear turnover and drainage, leading to more. Effective and sustained drug delivery.

## ADVANTAGES OF IN SITU GEL[17]

- **Improved Drug Retention**: The gel formed in situ remains in the eye longer than liquid drops, enhancing drug retention and allowing prolonged drug contact with ocular tissues.
- **Controlled Drug Release**: In situ gels enable sustained and controlled drug release, which can reduce dosing frequency and improve therapeutic efficacy.
- **Reduced Drainage**: The gel structure minimizes the rapid drainage associated with traditional eye drops, increasing the drug's bioavailability.
- **Enhanced Patient Comfort**: The liquid form of in situ gels before administration provides easier instillation, while the gel transformation reduces discomfort and irritation compared to more viscous solutions.
- **Increased Stability and Protection**: In situ gels protect the drug from rapid degradation, improving stability and providing a protective barrier against environmental factors.
- **Minimized Systemic Side Effects**: By prolonging local action and reducing the need for frequent application, in situ gels can help minimize systemic absorption and potential side effects.
- **Adaptable to Various Triggers**: In situ gels can be tailored to respond to physiological triggers such as temperature, pH, or ion concentration, making them versatile for various drug delivery needs.

## DISADVANTAGE OF IN SITU GEL[19]

- **Formulation Complexity**: Developing in situ gels requires precise formulation to ensure they respond accurately to physiological triggers like temperature, pH, or ions, which can make the manufacturing process more complex and costly.
- **Variable Gelation Time**: The rate at which the gel forms may vary depending on the individual's physiological conditions, potentially leading to inconsistent drug release and therapeutic effects.
- **Stability Issues**: Some in situ gel formulations may be sensitive to storage conditions, which can affect their stability and the reliability of their gelation response.
- **Potential for Blurred Vision**: Due to their gel-like consistency post-application, in situ gels may cause temporary blurred vision, which can be uncomfortable and inconvenient for users.
- **Compatibility Concerns**: Certain polymers and excipients used to achieve in situ gelation may not be compatible with all active drugs or might cause irritation in some users.

- **Limited Drug Loading Capacity**: In situ gels may have a lower drug loading capacity compared to other delivery forms, which could limit their effectiveness for delivering larger doses.
- **Challenges in Sterilization**: Ensuring sterility in the formulation of in situ gels can be more challenging, especially when using sensitive polymer materials that may degrade with conventional sterilization methods.

## CLASSIFICATION OF OPHTHALMIC DRUG DELIVERY SYSTEM[20]

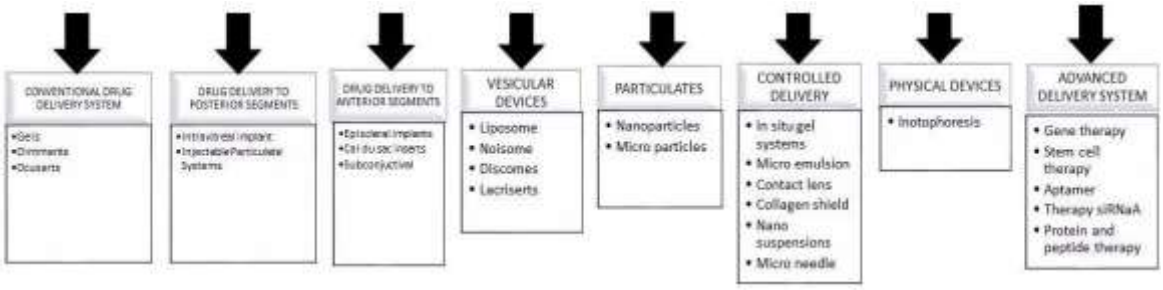



**Figure 3: Classification of Ophthalmic drug delivery system.**

## OCULAR ABSORPTION

1) Systemic Administration

The eye contains multiple barriers to prevent the entry of unwanted substances, including the blood-eye barrier. The aqueous humor, a clear fluid essential for maintaining intraocular pressure, is produced by the ciliary epithelium through the ciliary process. Acting as an ultra-filter, the ciliary epithelium restricts the transport of large molecules, like antibiotics and proteins. During the production aqueous humor, only low molecular weight substances can typically pass through. In cases of inflammation caused by infection or ocular disease, the blood-aqueous humor barrier may be compromised, allowing certain drugs to reach the aqueous humor and, subsequently, the front parts of the eye. Another significant barrier, the blood- vitreous humor barrier, is highly viscous, making drug diffusion through it extremely challenging. Effective drug delivery to the posterior segment of the eye remains a complex and demanding task.[21,22]

2) Local Administration

For a drug to be effective within the eye, it must pass through the eye's protective barriers and layers, rather than remaining on the surface. Generally, the transcorneal route is recognized as the primary pathway for drug transport into the eye. However, the non-corneal route also plays a significant role in drug absorption in the ocular region, as seen with certain

drugs like timolol. Additionally, many agents used to treat eye conditions exhibit high permeability through the sclera. Tears, which help keep the cornea clear, healthy, and moist, are distributed by the eyelids during blinking, which can alter the rate and pattern of transcorneal drug absorption.[23]

## POLYMERS USED IN THE FORMULATION OF IN-SITU GELS

A polymer is a large molecule (macromolecule) composed of repeating structural units. These subunits are connected by covalent chemical bonds.[24]

### Ideal Characteristics of Polymers[25]

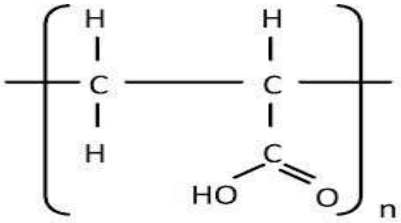
The polymers used for in-situ gelling systems should have following characteristics:

- Polymers must be non-toxic, non-irritating, and safe for ocular tissues to prevent adverse reactions upon application.
- Ideal polymers should break down into non-toxic byproducts after delivering the drug, reducing the need for removal from the application site.
- They should undergo a sol-to-gel transition in response to physiological triggers like pH changes, temperature variations, or ion concentrations.
- The polymer should have a controlled and predictable gelation time to ensure effective drug release and retention at the target site.
- For ocular applications, the polymer gel should be transparent to avoid impairing vision.
- The gel formed should be strong enough to remain intact at the application site but not so rigid as to cause discomfort.
- Polymers should have characteristics that enable controlled and sustained release of the drug, enhancing therapeutic efficacy.
- The polymer solution should be of low enough viscosity to allow for easy application but able to form a stable gel once triggered.

### 1. Carbopol

It is a pH sensitive polymer. It is also called as carbomer, acritamer, acrylic acid polymer etc.[26]

**Structure of Carbopol**



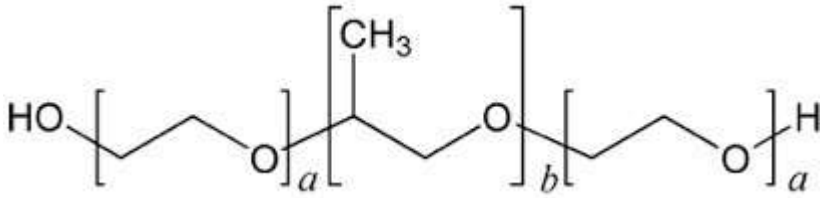

**Properties of Carbopol**[26]

1. **High Viscosity**: Carbopol is known for its excellent thickening ability, which makes it suitable for forming gels with a range of viscosities depending on concentration and pH.
2. **pH-Sensitive Gelation**: Carbopol undergoes sol-to-gel transformation in response to pH changes. It remains in a liquid state in acidic conditions and transitions to a gel at higher, more neutral pH levels, making it ideal for in situ gelling systems.
3. **Biocompatibility**: Carbopol is generally safe for use in pharmaceutical and cosmetic formulations, with low toxicity and non-irritating properties at appropriate concentrations.
4. **Good Bioadhesive Properties**: Carbopol adheres well to mucosal surfaces, which helps improve drug retention and prolongs drug contact time, making it effective in ocular and other mucosal applications.
5. **High Clarity**: When hydrated, Carbopol forms a transparent gel, which is important for applications like ocular gels where visual clarity is essential.
6. **Excellent Stability**: It has good chemical stability and can maintain its properties under various storage conditions, though it may require preservatives in certain formulations to prevent microbial growth.
7. **Controlled Drug Release**: Due to its matrix structure, Carbopol allows for a controlled release of the drug, which can be tailored by adjusting its concentration and cross-linking density.
8. **Non-Ionic Nature**: Carbopol does not interfere with ionic ingredients in formulations, making it versatile and compatible with a wide range of drugs and excipients.
9. **Shear-Thinning Behavior**: Carbopol gels exhibit pseudoplastic or shear-thinning behavior, meaning they become less viscous under stress (like during blinking), which is beneficial for ease of spreading on the ocular surface.

2. **Poloxamer**

It is a temperature sensitive polymer. It is commercially called as Pluronic.®

**Structure of poloxamer**




**Properties of Poloxamer**

**1) Thermo-Sensitive Gelation**: Poloxamer solutions transition from sol to gel as temperature increases. They are liquid at lower temperatures (e.g., room temperature) and gel at body temperature, which is beneficial for in situ applications like ocular, nasal, and topical drug delivery.

**2) Biocompatibility and Non-Toxicity**: Poloxamers are generally biocompatible, non-toxic, and well- tolerated by tissues, making them safe for pharmaceutical and medical applications.

**3) Good Solubility**: Poloxamers are highly water-soluble, which allows for easy preparation of aqueous solutions that can be administered as liquid drops or injections before gelling in situ.

**4) Shear-Thinning Behavior**: Poloxamers exhibit pseudoplasticity, meaning they become less viscous under shear (such as during application or blinking), aiding in ease of application and spreadability.

**5) High Clarity**: Poloxamer gels are transparent, which is particularly advantageous for ocular applications, as they do not obscure vision.

**6) Sustained Drug Release**: The gel matrix formed by Poloxamer can provide a controlled release of drugs, enhancing therapeutic effects and reducing the frequency of administration.

**7) pH Stability**: Poloxamers are generally stable across a wide range of pH levels, adding to their versatility and compatibility with various active pharmaceutical ingredients.

**8) Low Immunogenicity**: Poloxamers typically do not provoke immune responses, which is important for patient safety, especially in sensitive areas like the eye.

**9) Ease of Sterilization**: Poloxamer solutions can be sterilized by autoclaving, which simplifies the formulation process for applications requiring sterility.

**10) Solubilizing Agent**: Poloxamer can improve the solubility of poorly soluble drugs, making it useful in formulations for drugs with low water solubility.[28]

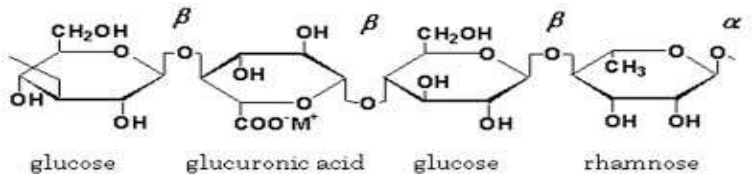
**Uses of Poloxamer**

It can be used as Gelling Agent, Emulsifying Agent and Solubilizing Agent.

**3. Gellan gum**

It is an ion-sensitive polymer. It is also known as Gelrite® (trade name).

**Structure of gellan gum**




**Properties of Gellan Gum**

**1) Ion-Sensitive Gelation**: Gellan gum can undergo sol-to-gel transformation in the presence of cations like calcium, sodium, or potassium, making it ideal for ion-sensitive in situ gelling systems used in ocular, nasal, and oral drug delivery.

**2) Biocompatibility and Biodegradability**: Derived from natural sources, gellan gum is biocompatible and biodegradable, which ensures it is safe for various applications, including ophthalmic and mucosal drug delivery.

**3) Excellent Mucoadhesive Properties**: Gellan gum adheres well to mucosal surfaces, which enhances drug retention and prolongs drug action, particularly in the ocular and gastrointestinal areas.

**4) High Clarity**: Gellan gum forms transparent gels, making it suitable for ocular applications where visual clarity is essential.

**5) Thermal Stability**: Gellan gum exhibits good stability across a range of temperatures, contributing to the durability of its gel structure during storage and application.

**6) Controlled Drug Release**: Due to its gel matrix, gellan gum can provide a sustained and controlled release of drugs, optimizing therapeutic effects and reducing dosing frequency.

**7) Adjustable Gel Strength**: The gel strength can be controlled by adjusting the concentration of gellan gum or the type and amount of cations present.

**8) pH Stability**: Gellan gum is relatively stable across a wide pH range, making it compatible with different drugs and suitable for varied formulations.

**9) Ease of Sterilization**: Gellan gum formulations can be sterilized by autoclaving, facilitating its use in sterile applications such as ocular gels.

**10) Good Film-Forming Ability**: Gellan gum can form thin films upon drying, which can be beneficial in drug delivery applications where a protective coating or barrier is needed.

**Uses of Gellan Gum**

a) Thickening Agent.

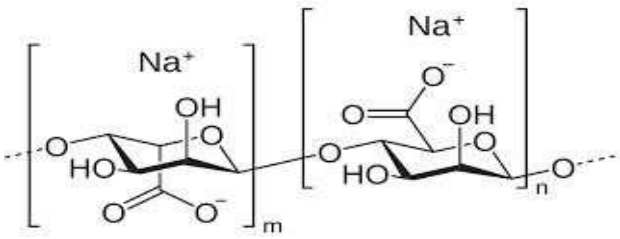
b) Gelling Agent.

c) Stabilizing Agent.

**4. Sodium alginate**

It is an ion-sensitive polymer which can be used in controlled drug release. It is also referred to as algin, alginic acid, sodium salt, E401, Kelcosol, Keltone, Protanal, sodium polymannuronate.[26]

**Structure of Sodium Alginate**




**Properties of Sodium Alginate**

**1) Ion-Sensitive Gelation**: Sodium alginate gels in the presence of divalent cations like calcium, transitioning from sol to gel, which is ideal for in situ gelling applications in drug delivery systems such as ocular and oral.

**2) Biocompatibility and Biodegradability**: Sodium alginate is biocompatible and biodegradable, making it safe and environmentally friendly for pharmaceutical applications, especially for sensitive areas like the eye.

**3) Mucoadhesive Properties**: It adheres well to mucosal surfaces, enhancing drug retention and prolonging the duration of drug action at the site of application, which is especially useful in ocular and gastrointestinal drug delivery.

**4) High Viscosity**: Sodium alginate provides excellent viscosity control, which can be tailored by adjusting the concentration, making it suitable for formulations requiring specific thickness levels.

**5) pH Stability**: Sodium alginate is stable over a wide range of pH levels, making it compatible with various drugs and enhancing its versatility across different formulations.

**6) Controlled Drug Release**: The gel matrix formed by sodium alginate allows for sustained and controlled release of drugs, optimizing therapeutic effects and potentially reducing the frequency of administration.

**7) Good Film-Forming Ability**: Sodium alginate can form thin, flexible films when dried, useful for applications requiring protective coatings or sustained-release layers.

**8) Thermal Stability**: It is stable across a range of temperatures, which enhances the stability and shelf- life of formulations containing sodium alginate.

**9) High Water Retention**: Sodium alginate has a strong water-binding capacity, which helps maintain moisture and is beneficial in formulations designed for hydration, such as ocular and skin applications.

**10) Ease of Sterilization**: Sodium alginate-based formulations can be sterilized, making it suitable for sterile pharmaceutical applications such as eye drops and wound dressings.[24]

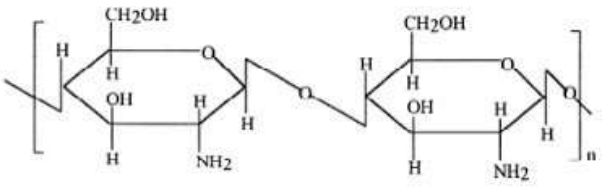
**Uses of Sodium Alginate[26]**

a) Thickening Agent.

b) Suspending Agent.

**5. Chitosan**

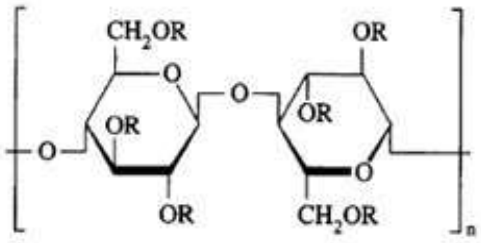
**Structure of Chitosan**




**Properties of Chitosan**

1) Chitosan has mucoadhesive properties because of electrostatic interactions between positively charged amino groups and negatively charged mucin.[27]
2) It is called as ophthalmic vehicle.[29]
3) It is biodegradable, biocompatible and non-toxic polymer.[29]
4) It exhibits pseudoplastic and viscoelastic behavior.[29]
5) It has good antibacterial property
6) It has good bioadhesive properties.[27,29]
7) It can convert into a hydrogel at ocular pH(pH 7.4).[30]

**5. Hydroxypropyl methyl cellulose** It is a temperature sensitive polymer.[26] **Structure of HPMC**



**Properties of HPMC**

1) It is a water soluble polymer.[31]
2) It has good solubility characteristics in organic and aqueous solvent system.
3) It is non-interfering with drug availability.
4) It is flexible and has no taste or odour.
5) It shows stability in the presence of heat, light, air, or reasonable levels of moisture.
3) It increases its viscosity when temperature increases.[27]
4) It shows phase transition between 75°C and 90°C. These temperatures can be lowered by chemical or physical modifications.[33]

**Uses of HPMC[33]**

a) Thickening Agent.
b) Suspending Agent.
c) Stabilizing Agent.

**Table no. 1: Polymers used for in-situ gelling formulations.[27]**

| POLYMERS | NATURE | INTERNAL CHARGE | AQUEOUS SOLUBILITY | MUCOADHESION |
|---|---|---|---|---|
| Carbomer | Synthetic | Anionic | Insoluble | Excellent |
| Polyacrylic acid | Natural | Anionic | Insoluble | Excellent |
| Chitosan | Natural | Cationic | Soluble | Good |
| Xanthan Gum | Natural | Anionic | Insoluble | Poor |
| Methyl Cellulose | Natural | Non-ionic | Soluble | Poor |
| Xyloglucan | Natural | Anionic | Soluble | Poor |
| Poloxamer | Synthetic | Non-ionic | Soluble | Good |
| Sodium Alginate | Natural | Anionic | Soluble | Good |
| HPMC | Natural | Non-ionic | Soluble | Poor |

**ROUTES OF ADMINISTRATION IN EYE**

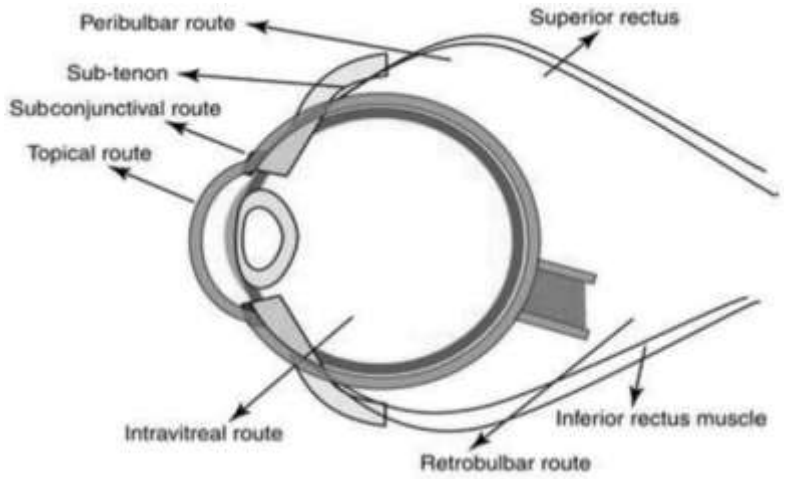



**Figure 4: routes of administration in eye.**

1. **Topical Administration:** The most common route, involving the application of eye drops, ointments, or gels directly to the conjunctiva or cornea. It primarily treats conditions affecting the anterior (front) segment of the eye, such as conjunctivitis, glaucoma, or dry eye.[34],[35]
2. **Intravitreal Injection:** A direct injection into the vitreous humor of the eye, typically used to treat conditions in the posterior (back) segment, such as age-related macular degeneration, diabetic retinopathy, and retinal vein occlusion. Intravitreal injections ensure high drug concentration in the retina and vitreous.[36]
3. **Subconjunctival Injection: -** Injection into the space beneath the conjunctiva, delivering drugs to the anterior part of the eye while avoiding the tear drainage system. It is often used for treating inflammation and infections or providing anesthesia during eye surgery.[37]
4. **Periocular Administration**: Injection around the eye, including routes such as sub-Tenon's, per bulbar, and retro bulbar. These routes are often chosen for delivering anesthesia before ocular surgery or for treating inflammation in the posterior segment.
5. **Intracameral Injection**: Injection directly into the anterior chamber of the eye, often used during eye surgeries, such as cataract surgery, to deliver antibiotics or other medications to prevent infection and inflammation.
6. **Systemic Administration**: Involves oral or intravenous (IV) delivery of drugs. This route is used when a medication needs to reach the eye from the bloodstream, typically for infections, inflammatory conditions, or vascular diseases involving the retina.
7. **Suprachoroidal Administration**: A newer route involving injection into the suprachoroidal space, between the sclera and choroid. It is used to deliver drugs to the posterior segment of the eye, especially in treating retinal and choroidal diseases.

**8. Intraocular Implants**: Sustained-release implants surgically placed inside the eye to provide long- term drug release, especially for chronic posterior segment conditions like uveitis and macular edema. These implants reduce the need for frequent dosing.

**IN SITU GELLING SYSTEM**

In situ gel-forming systems are drug delivery systems initially in liquid form that transform into gels upon administration in the body. This gelation process occurs in response to external triggers like temperature or pH, enabling controlled or sustained drug release. Introduced in the early 1980s, this innovative approach uses cross-linking of polymer chains, achieved through either chemical (covalent) or physical (non-covalent) bonds. These systems are low-viscosity solutions that, upon reaching the conjunctival sac, undergo phase changes to become viscoelastic gels, adapting to the physiological environment. The rate of gel formation is critical, as the initial solution or weak gel interacts with eye fluids before a strong gel forms.[38]

In situ Ophthalmic gels both natural as well as synthetic polymers can be used.[39]

**MECHANISM OF IN SITU GELLING TECHNOLOGY SITU GEL TECHNOLOGY**

In situ gelling technology is based on the concept of applying a solution that transforms into a gel upon exposure to physiological conditions, allowing for sustained and controlled drug delivery. This transformation is typically triggered by specific environmental stimuli, leading to a sol-to-gel phase transition at the application site. The key mechanisms for in situ gelation include.[40, 41, and 42]

**pH-Triggered Gelation**: In this approach, the formulation remains in a sol state at a certain pH but gels when exposed to physiological pH (usually around 7.4 in the eye). Polymers like Carbopol utilize this mechanism, remaining liquid at lower pH and forming a gel at neutral or slightly basic pH, which is beneficial for ocular and mucosal applications.[42]

**Temperature-Triggered Gelation**: Temperature-sensitive polymers such as Poloxamers (Pluronic) exhibit sol-to-gel transition in response to body temperature. These formulations are liquid at room temperature and rapidly gel upon reaching body temperature (37°C), making them useful for ease of administration and prolonged action in ocular, nasal, and injectable formulations.[42]

**Ion-Triggered Gelation**: Some polymers, like gellan gum and sodium alginate, gel in response to the presence of specific ions such as calcium, sodium, or potassium. These ions, present in tears or bodily fluids, interact with the polymer chains to induce cross-linking and gel formation. This ion-sensitive mechanism is ideal for ocular applications, where ion concentrations are predictable and conducive to gelation.[41]

**Photo-Triggered Gelation**: In certain advanced formulations, light-sensitive polymers gel in response to specific wavelengths of light. This method, though less common in ocular applications, is being explored for precise control over gelation in other fields, such as wound care and targeted drug delivery.[41]

**Enzyme-Triggered Gelation**: In enzyme-responsive systems, specific enzymes present at the application site trigger the gelation process. These systems are particularly beneficial for targeted delivery in areas with predictable enzyme concentrations, although they are less commonly used in ophthalmic applications.

## WORKING MECHANISM

The drug formulation is prepared as a low-viscosity solution, allowing easy administration as drops, spray, or injection. Once administered, the solution comes into contact with physiological stimuli (pH, temperature, ions) at the application site, initiating the gelation process. The gel forms in situ, providing a sustained-release matrix that holds the drug at the site, prolonging contact time with tissues and enabling gradual drug release. The gel matrix gradually degrades or releases the drug over time, providing sustained therapeutic effects and reducing the frequency of administration.

## EVALUATION OF OCULAR INSITU GEL

The evaluation of in situ gel formulations involves assessing parameters such as clarity, pH, gelling capacity, drug content, rheology, in vitro diffusion, isotonicity, antibacterial efficacy, in vivo ocular testing in rabbits, and stability under accelerated conditions. For effective use, the formulation must have an ideal viscosity to ensure easy administration as liquid drops, which will then quickly transition from sol to gel upon exposure to triggers like pH changes, temperature shifts, or ion exchange.[52]

### 1. Physical appearance

Testing physical appearance includes visual appearance and clarity of prepared in situ

formulation. It is checked for presence of any particulate matter under fluorescent light against a white and black back ground.[44]

**2. pH measurement**

The pH of the ocular in-situ gel-forming systems is usually measured with the help of a pH meter. pH is important to prevent ocular irritation and if the gelling mechanism is pH sensitive. Electronic precalibrated pH meters need to be used.[45]

**3. Gelling capacity**

This evaluation is essential for determining the time required for the formulation to transition from a sol to a gel state. Typically, the gelling ability of in-situ formulations is assessed using simulated tear fluid (STF). To do this, 0.5–1 ml of the formulation is introduced into 2.0–3.0 ml of STF, and the time taken for the formulation to visually transform into a gel is recorded.[46]

**4. Isotonicity**

Isotonicity evaluation for in situ ocular gels is crucial, as it ensures the formulation's compatibility with the eye's natural osmotic pressure, reducing potential irritation or discomfort upon administration. For an ocular gel to be isotonic, its osmotic pressure should match that of natural tears (typically around 290-310 mOsm/L). Testing involves comparing the osmolarity of the formulation to that of tears using instruments like osmometers. If the formulation is found to be hypertonic or hypotonic, adjustments can be made by adding tonicity agents, such as sodium chloride or dextrose, to achieve an isotonic state.[47][48]

**5. In-vitro drug release study**

In-vitro drug release study is done by utilizing the Franz diffusion cell. In the receptor compartment, freshly prepared artificial tear fluid is placed. A dialysis membrane is placed in between receptor and donor compartments. The whole assembly is kept on the thermostatically controlled magnetic stirrer to simulate in-vivo conditions and temperature is maintained at $37^{o}C \pm 0.5^{o}C$. These Samples are then analyzed for drug release over period of time, either on HPLC or Ultraviolet spectrophotometer. The best fit model is check for Krosmeyers Peppas and Fickinian diffusion mechanism for their kinetics.[49, 52]

**6. Rheological studies**

Viscosity determination of in-situ formulation is carried out on Brookfield viscometer having

a small volume adapter or cone plate viscometer. Formulation should have viscosity of 5-1000 m Pas, before gelling & about 50-50,000 m Pas after formation of gel.[50, 52]

### 7. Ocular irritancy test

The Ocular irritancy test, like Draize irritancy test is designed for the ocular irritation potential of the ophthalmic product. Normally 100µl of formulation is placed into the lower culdesac with observation of the various irritation criteria observed at a specific time interval of 1hr, 24hrs, 48 hrs, 72hrs, and 1week after administration. The study is performed on Rabbits. Rabbits are observed periodically for redness, swelling, and watering of the eye.

### 8. Accelerated stability study

The stability study for the in-situ formulation is carried out as per ICH guidelines to determine the physical stability of the formulation under accelerated storage conditions. The formulation is subjected to elevated temperatures and humidity conditions of 25±1°C/ 60%RH, 30±1°C/ 65%RH and 40 ± 2°C/ 75 ± 5 % RH. Samples are withdrawn at the end of 0, 30, 60 and 90 days and then evaluated for active drug content.[51]

### 9. Antimicrobial study

These antimicrobial efficacy tests can be done by using simple cup and plate technique. The inhibition of microbiological growth is measured by concentration of antibiotics and this has to be compared with that produced by known concentration of standard preparation of antibiotic The process should be done in the sterile area such as laminar air flow cabin. For obtaining proper results positive and negative controls should be maintained.[52]

## CONCLUSION

In ophthalmology, significant efforts have been dedicated to creating a delivery system with extended retention time in the eye, aiming to enhance ocular bioavailability. This has involved various adjustments to product formulation and composition, such as incorporating mucoadhesive polymers and modifying viscosity. A key advancement in this area has been the development of ocular in-situ gel-forming systems, which transform from a sol to a gel upon application to the eye. These systems are seen as highly promising due to their potential to improve ocular bioavailability, reduce systemic toxicity, and enhance patient compliance with sustained, prolonged drug release and reduced dosing frequency. Despite these advantages, only a limited number of drugs utilizing ocular in-situ gel technology are in clinical use. There remains a need for further research to apply this delivery system to other critical

ophthalmic drugs to advance patient care in ophthalmology.[53]

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