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A Comprehensive Review On Ophthalmic In Situ Gelling System

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ABSTRACT

The eye is one of the most delicate organs in our body. The eye is a complex organ characterized by its low permeability, short precorneal residence time, and small area for absorption, which pose significant barriers to drug delivery. Typically, less than 10% of a drug administered penetrates the eye. Traditional ocular delivery systems are also constrained, with significant drug loss due to tears and blinking, leading to blurred vision and untimed release events without sustained action, resulting in suboptimal outcomes in ocular therapy. To overcome such challenges, in situ ophthalmic gels have been developed. These gels' ability to transition from a liquid to a gel state allows for sustained drug release at the target site. In situ gel systems are in solution form before administration and then convert to a gel under physiological conditions (pH, temperature, or ionic concentration). This review discusses the anatomy and physiology of the eye, the challenges of ocular drug delivery, types of in situ gelling systems, mechanisms of gel formation, types of smart polymers, and methods for evaluating polymeric in situ gels.

Keywords: Ocular drug delivery, in situ gel, sol-gel transition, smart polymers, sustained release.

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INTRODUCTION

For pharmaceutical scientists, one of the most fascinating and difficult areas is ocular medication delivery. Ophthalmic in situ gels employ a variety of polymers. Hydrogels are typically utilized. The viscosity of the solution will rise due to these polymers. For pharmaceutical scientists, one of the most fascinating and difficult areas is ocular medication delivery. The field has greatly improved during the past ten to twenty years.¹ Because of the delicate nature of the application site and its numerous restrictions, care must be taken when developing new products.² The physiology of the eye states that this organ is impervious to outside substances. It is challenging to formulate a medication that can pass through the eye's protective layers and reach the site of action with a high enough concentration.¹ Innovative drug delivery techniques sought to get past the biological barrier that can prevent effective drug administration into the eyes.³ One of the biggest challenges for formulators during formulation is overcoming the protective barrier without causing harm to the permanent tissue. Common conditions that can be treated with topical medication delivery include glaucoma, trachoma, keratitis, conjunctivitis, and blepharitis.⁴ Poor bioavailability, increased precorneal elimination, and considerable variability in efficacy are the main drawbacks of conventional formulations such solutions, suspensions, emulsions, ointments, etc.^{5,6} For ophthalmic chemotherapy, the most popular formulation is optical application due to its ease and safety.

Anatomy of Eye

The anterior segment of the human eye comprises the cornea, conjunctiva, iris, pupil, ciliary body, anterior chamber, aqueous humor, lens, and trabecular meshwork, while the posterior segment consists of the vitreous humor, sclera, retina, choroid, macula, and optic nerve. The cornea is the eye's outermost membrane. The epithelium, Bowman's layer, stroma, Decemet's membrane, and endothelium are the five layers that make up this clear, transparent, thin vascular tissue. The clear liquid that fills the eye's anterior and posterior chambers is known as aqueous humor. It is the cornea's main source of nourishment.^{7,10} The iris is a thin, circular, contractile curtain that sits in front of the lens. Behind the cornea, however, is a variable-sized diaphragm that works to control the pupil's size and the amount of light that enters the eye. The iris sphincter and dilator muscle help with this adjustment. The central layer of the eye contains a ring of smooth muscles called the ciliary muscle, which regulates space for viewing objects at different distances. The lens is a thin, clear covering that encloses a transparent biconvex structure. It is a pliable entity made up of tissue layers encased in a capsule. Very thin fibers known as zonules defer it from the ciliary muscles. Beginning at the cornea's edge, the conjunctiva is a mucous membrane that runs along the inside of

the eyelids, sclera, and limbus. By lubricating the eyes and secreting mucus that stops germs from entering, it protects the eyes. The sclera, sometimes known as the "white of the eye," is the protective outer covering of the eye that keeps the eye's form. It serves as the interior organs' main defence. The choroid, a highly vascularized tissue that sits between the retina and the sclera, contrasts with the sclera. The choroid, the second layer of the eye between the sclera and the retina, is a thin, highly vascular membrane with a dark brown colour and a pigment that absorbs excess light to prevent impaired vision. It has the blood arteries that provide the retina's outer layers with nutrition. The retina is a multi-layered, intricate structure made up of nerve fibers, vascular glial cells, and neural cells. It can be found at the rear of the eye. This structure is sensitive to light because it has photosensitive cells that absorb light and transform it into electrical impulses. After passing via the optic nerve, these impulses are transformed into images in the brain. Distributed between the retina and lens, the vitreous humor is a smaller area in front that includes a transparent, thin, jelly-like fluid that resembles water.^{7,8,9,10}

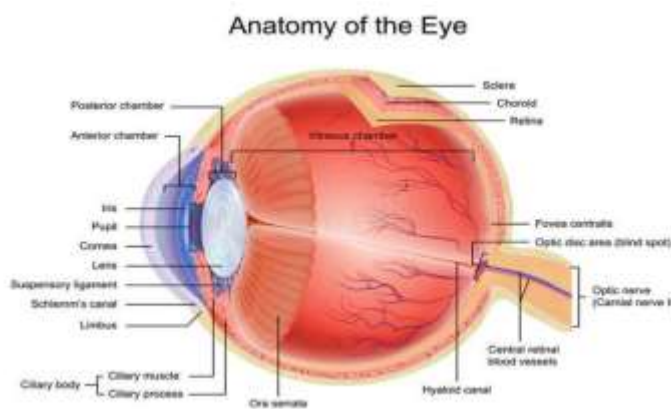


Figure: 1: Anatomy of eye¹⁰

THE BARRIERS

Drug loss from the ocular surface

The drug's dosage form in the ocular system causes some of the drug to be wiped off from its surface by the flow of lacrimal fluid, with a washout rate of only around 1 $\mu\text{l}/\text{min}$. In contrast, the majority of the drug is rapidly removed through the nasolacrimal duct in a matter of minutes. The systemic absorption of the drug, as opposed to its ocular absorption, is another source of drug elimination. Systemic absorption occurs either after the fluid enters the nasal cavity or primarily through the conjunctival sac to the nearby blood capillaries¹¹.

Lacrimal fluid-eye barriers

The corneal epithelium that is present in the eye may limit the amount of medication that is absorbed from the lacrimal fluid. The drug's paracellular penetration is restricted by corneal

epithelial cell-derived tight junctions. Compared to hydrophilic medicines, lipophilic medications exhibit greater permeability in the cornea. To put it another way, the conjunctiva has a leaky epithelium in comparison to the cornea. It also has a twenty-fold larger surface area than the cornea, which facilitates rapid systemic absorption.

Blood-ocular barriers

The bloodstream contains blood-ocular barriers that shield the eye from xenobiotic. The blood-retina barrier and the blood-aqueous barrier are its two components. Endothelial cells in the uvea, or the middle layer of the eye beneath the sclera, iris, ciliary body, and choroid, make up the anterior blood-eye barrier. This barrier reduces the admission of plasma albumin into the aqueous humor and inhibits the entry of hydrophilic medications found in plasma. The retinal pigment epithelium (RPE) and retinal capillaries make up the posterior barrier, which forms a tight wall connection between the eye and the plasma stream. The choroidal extravascular space has easy access to medications because of the choroid vasculature's substantial blood flow and leaky walls, but the presence of RPE and retinal endothelium again restricts their distribution in the retina¹².

ROUTES OF OCULAR DRUG DELIVERY

The various possible routes for ocular drug delivery are described below:

Intravitreal route:

This method involves administering the drug by injections into the eye's vitreous fluid. Numerous eye conditions can be cured with this method of administration; figure 2 illustrates how it is delivered through the eyes.

Intracameral route:

In this mode of delivery, a medicine acts on either the anterior or posterior chambers of the eye. In order to demonstrate it, an anesthetic substance is typically injected into the anterior chamber of the eye during surgery.

Perilocular route:

This method of administration involves putting the medication around the eye. Peril ocular steroid injection, which involves applying steroids all over the eye to treat intraocular inflammation or swelling, can help to explain it¹³.

Suprachoroidal route:

This administration method targets the area of the eye that lies above the choroid. The term "suprachoroidal space" refers to the area that exists between the choroid and the sclera.

Subconjunctival route:

This method involves administering the medication to the mucous membrane, which includes the inner surface of the eyelids and the open region of the eyeball.

Topical route:

The greatest examples of ophthalmic dosage forms for topical medication administration in the eye are eye drops, as opposed to ointments, gels, and emulsions, which are used to treat conditions affecting the anterior segment of the eye. Because it is easier to administer and less expensive, it is the most practical way to deliver drugs to the eye.

Systemic route:

Common barriers to the systemic delivery of ophthalmic drugs are blood-aqueous barrier and blood-retinal barrier (BRB) for the anterior segment and posterior segments of eye, respectively¹⁴.

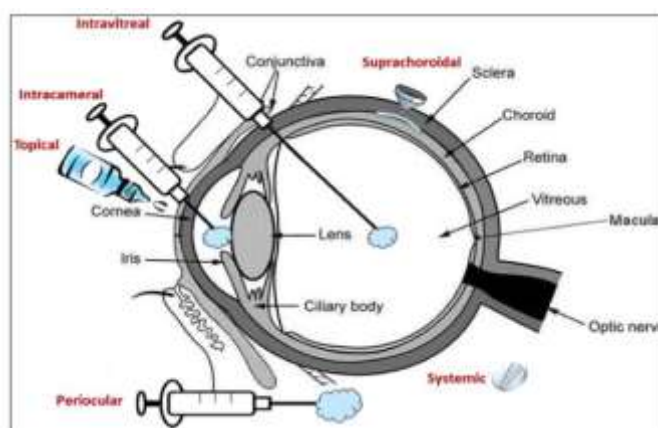


Figure 2: Intravitreal route¹⁴

Classification of Ocular Drug Delivery System:

Ocular drug deliveries consist of following types of dosage forms:-

- 1) Semisolid -Gel, Ointment.
- 2) Solid -Ocular Inserts.
- 3) Liquid –Solution, Suspension.
- 4) Intraocular –Implant, Injections

Advantages of ocular drug delivery systems:

The advantages of ocular drug delivery systems have been summarized below:

1. They provide consistency and precision in the dosage rate. It is possible to prevent pulsed dosing of traditional systems.
2. Drugs can be released gradually and under supervision.
3. They improve the ocular bioavailability of medications by lengthening the corneal contact time, which is accomplished by the drug's efficient adhesion to the corneal surface.
4. The ocular globe should be targeted in order to prevent the loss of ocular tissues.

5. Drainage, lacrimation, and conjunctival absorption are some of the protective ocular barriers that they avoid.
6. Additionally, they provide comfort, increase therapeutic medication performance, and increase patient compliance.
7. They offer improved delivery system housing.
8. They allow people to administer medications on their own.
9. Absorption is quicker and there are fewer systemic and ocular side effects¹⁵.

Disadvantages of ophthalmic drug delivery systems:

The major drawbacks of ophthalmic drug delivery systems are as follows:

1. The medication solution and ocular surface have a brief contact time.
2. Insufficient bioavailability
3. Dissolved drug instability.
4. Preservative usage¹⁶.

Limitations of ocular drug delivery:

Ocular delivery of drugs suffers from the following limitation:

1. During an emergency, the dosage form cannot be stopped.
2. Interference with vision.
3. Encounters challenges when removing and placing the dose form.
4. The medicine may occasionally be lost when you sleep or touch your eyes¹⁶.

Suitable characteristics of polymers:

An essential ingredient in the manufacture of in situ and preformed gel is a polymer. The suitable polymer characteristics for in situ gels given below:

1. It should be possible for the polymer to stick to the mucosal membrane.
2. It should work nicely together and shouldn't be irritant.
3. Do not show any toxic effect.
4. It ought to be tolerant.
5. It must be biocompatible.
6. In order to reduce viscosity during eye blinking, the polymer should be able to decrease viscosity as the shear rate increases.

Polymers used as in situ gelling agents are:

- Gellan gum
- Alginic gum
- Carbomer

- Pectin
- Xylogulan
- Xanthan gum
- Chitosan

IN SITU GELLING SYSTEM:

Drug delivery systems that are in solution form before to being supplied to the body but go through gelation in situ thereafter to create a gel triggered by an external stimulus like pH, temperature, etc., and release the drug in a controlled or prolonged manner are known as in situ gel forming systems. Early in the 1980s, the unique idea of creating in situ gel was initially put out. Gelation happens when polymer chains are cross-linked, which can be accomplished by either non-covalent (physical cross-linking) or covalent (chemical) bond formation. Low viscosity liquids that undergo phase transition in the conjunctival cul-de-sac to create viscoelastic gels as a result of conformational changes of polymers in response to the physiological environment are known as in situ gel-forming systems. Because the fluid mechanism of the eye produces a solution or weak gel between instillation in the eye and before a strong gel forms, the velocity of in situ gel formation is crucial. It is possible to create in situ gels using both natural and synthetic polymers^{17, 18, 19}.

CLASSIFICATION OF IN-SITU GEL

1. Based on physical stimuli. a. Temperature induced in situ gel system. b. pH induced in situ gel systems
2. Based on physical mechanism a. Swelling. b. Diffusion.
3. Based on chemical reaction a. Ion Cross Linking. b. Enzymatic Cross Linking.
4. Below describes the classification of in situ gel:-

1. Based on physical stimuli

a. Temperature induced in situ gel system:

When the temperature rises, certain hydrogels and polymers that are temperature responsive will change from sol to gel. There is no need for an external temperature to initiate sol to gel conversion because the body temperature is adequate. The configured system should be able to withstand slight temperature variations. Three types of temperature-sensitive hydrogels are distinguished: thermally reversible gels, positively thermosensitive gels, and negatively thermosensitive gels. Certain hydrogels have a lower critical solution temperature and are negative temperature sensitive, meaning they become insoluble when heated. If heated over this temperature, they will contract. A temperature adjustment improves the gelling of these solutions and prolongs the release of the medication. A change in temperature causes a change in the

hydration state, which results in a volume phase transition when the polymer molecule's intra- and intermolecular hydrogen bonds are preferred over water solubilization. Drug polymers, which are in solution form at room temperature and turn into gel at body temperature, can be used to produce this state. The upper critical solution temperature is the point at which certain polymers become soluble when heated. The volume phase transition brought on by the shift in hydration state results in intermolecular and intermolecular hydrogen bonding in the polymer, which makes the molecule insoluble^{20,21}.

Eg: poloxamer- it is a thermosetting polymer, when concentration of poloxamer is increased the contact time and elasticity of the drug is increased and sol to gel conversion is decreased^{18,22}.

b. pH induced in situ gel systems:

In this instance, a pH shift causes the sol to gel transition. The polymers that exhibit a pH-dependent transition and contain basic or acidic groups that either release or receive protons when the pH changes. When the pH rises, weakly acidic (anionic) groups swell, whereas weakly basic (cationic) groups do the opposite at lower pH. Polymers that are sensitive to anionic pH, such as carbopol, carbomer, and its variants. The formulation is in solution form at pH 4.4, but when it is injected into the eye, its pH shifts from 4.4 to 7.4; as a result, the formulation transforms from sol to gel^{18,20}.

Eg: cross e linked polyacrylic, derivatives of carbomer etc.

2. Based on physical mechanism:

a. Swelling:

When materials absorb water from their surroundings and expand to create the appropriate area, in situ conversion of sol to gel may also occasionally take place. For example, myverol 18-99 is a polar lipid that, when swollen in water, forms a lyotropic liquid crystalline structure.

b. Diffusion:

By diffusing the solvent from the polymer solution into the surrounding tissues, the diffusion process causes the polymer matrix to precipitate or solidify. The solvent for a system is N methyl pyrrolidine, for instance.

3. Based on chemical reaction:-

a. Ion Cross Linking:

When several ions are present, polymers may experience a phase transition. A subset of polysaccharides are classified as ion-sensitive. I-carrageenan primarily forms flexible gels in the presence of Ca^{2+} , whereas k-carrageenan creates rigid, fragile gels due to a minor amount of K^{+} . Gellan gum, commercially marketed under the name Gelrite®, is an anionic polysaccharide that

undergoes in situ gelling when mono and divalent cations such as Ca^{2+} , Mg^{2+} , K^{+} , and Na^{+} are present. Divalent cations such as Ca^{2+} can induce the low methoxy pectins to gel. Similarly, when divalent or polyvalent cations are present, alginic acid gels. For instance, Ca^{2+} from interaction with the alginate chains' guluronic acid block^{18,21}.

b. Enzymatic Cross Linking:

Natural enzyme-catalyzed in situ formation has not received much attention, yet it seems to offer some benefits over chemical and photochemical methods. For instance, an enzymatic process can function effectively in physiological settings without the use of potentially hazardous substances like initiators and monomers. Hydrogels that have been studied for their ability to release insulin are used in intelligent stimuli responsive delivery systems. When blood glucose levels rise, cationic pH-sensitive polymers that contain immobilized insulin and glucose oxidase can swell, pulsatilely releasing the trapped insulin. The mixes can be administered prior to gel formation because varying the enzyme dosage also offers a suitable mechanism for regulating the rate of gel formation^{10,20,23}.

EVALUATION OF IN-SITU GEL

Clarity test:

Visual inspection of the formulations under light or against black and white backgrounds is frequently used to assess the clarity of the formulations both before and after gelling. Furthermore, a swirling motion is frequently used to start the materials moving. Additionally, any undesired particles scattered throughout the solution or the development of turbidity are monitored^{24, 25, 26}.

Texture analysis:

The texture profile analyzer, which shows gel strength and application ease, is used to assess the cohesion, firmness, and consistency of in situ gel. For the gel to remain in close contact with the mucous surface in vivo, the polymer must have a high adhesiveness value^{6,27}.

pH:

In ocular formulations, pH has an impact on the drug's stability and solubility. It should be such that the patient won't experience any irritation during administration and that the formulation will be stable at that pH. The digital pH meter is used for the measurement²⁸.

Isotonicity evaluation:

Isotonicity is preserved in ophthalmic medicines to avoid tissue damage or ocular discomfort. A few drops of blood are added to the formulation, which is then examined under a 45x magnification microscope and contrasted with commercially available formulations^{29, 30, 31}.

Histological study:

In order to assess the impact of in situ formulation on corneal structure and investigate the possibility of irritation, corneas are extracted from the eyes of a recently slaughtered goat and incubated in formulation for five hours at 37°C. The positive control is 0.1% (w/w) sodium dodecylsulfate (SDS) solution in phosphate buffer saline (PBS). After the corneas have been incubated, they are promptly fixed in formalin (8%, w/w) and cleaned with PBS. After dehydrating in an alcohol gradient, tissues are submerged in molten paraffin and hardened into blocks. Cutting cross sections and staining them with hematoxylin and eosin (H&E) are done. To check for any changes, cross sections are examined under a microscope³².

Drug Content:

It is calculated by diluting 1 milliliter of the formulation with 100 ml of distilled water. 1 ml was taken out and diluted with distilled water to make 10 ml. The concentration was measured using UV visible spectroscopy at 200–400 nm¹⁷.

Homogeneity:

Examine the particle roughness under the light by sandwiching the preparation between two glasses³³

Gelling capacity:

By adding a drop of the formulation to a vial with 2.0 ml of freshly made simulated tear fluid, the gelling capacity of the formulation is ascertained, and the gelling time is recorded³⁴.

Gelling strength:

The gelling agent, a certain amount of "gel" made in a beaker from the "sol" form, is what gives the gelling strength, which was measured by a Rheometer. A probe is pushed slowly through the "gel" that contains the beaker to be lifted at a certain rate. The depth of the "gel" surface's immersion is used to measure the weight on the probe^{35,36}.

Rheological studies:

The Brookfield viscometer is primarily used to measure the viscosity of in situ ophthalmic gels. Viscosity is determined both before and after gelation by progressively increasing the angular velocity from 0.5 to 100 rpm³⁷.

Ocular irritancy test:

Male albino rabbits weighing between one and two kilograms are used in these investigations. The modified Draize technique is employed to assess the possibility of ocular discomfort. After administration, the formulation is put in a lower cul-de-sac and its irritancy is measured one, two, forty-eight, seventy-two, and one week later. Then periodically checks the rabbits for eye redness, edema, and wetting^{38, 39, 40}.

In vitro drug release study:

Franz diffusion cells are used in in vitro drug release studies. Artificial tear fluid (ATF) that has just been prepared is put into the receptor compartment. The dialysis membrane sits between the donor and receptor compartments. To replicate in vivo circumstances, the entire assembly is kept on a thermostatically controlled magnetic stirrer, and the medium's temperature is kept at $37^{\circ}\text{C} \pm 0.5^{\circ}\text{C}$. At 20 rpm, the medium is continually churned. The donor compartment is filled with 1 milliliter of the formulation. At predefined intervals, the sample (0.5 ml) is removed and replaced with ATF. Samples are examined using an HPL or a UV spectrophotometer^{41, 42}.

Antifungal studies:

First, sabouraud dextrose dissolves in hot water (i.e., media). After 15 to 20 minutes of autoclaving, the organisms (e.g., *Aspergillus fumigatus*, *Candida albicans*, etc.) are transferred to the media in sequence. A sample is then taken using a micropipette and left for 30 minutes. The diameter of the zone or zones of inhibition was measured following a 24-hour incubation period at 25°C , and the results were compared with both positive and negative controls⁴³.

Accelerated Stability Studies:

To ascertain the formulation's physical stability under accelerated storage circumstances, a stability study for in situ formulation is conducted in accordance with ICH criteria. For six weeks of stability tests, every formulation was examined for visual appeal, clarity, pH, and medication retention¹⁷.

CONCLUSION

The field of ocular medication administration is difficult, and most scientists are working hard to address the various issues related to this delivery. Continuous technological advancements and a growing understanding of the mechanisms and processes influencing the absorption and disposal of ocular drugs have undoubtedly improved the effectiveness of ocular drug delivery systems.

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