In Situ Ocular Gels: A Overview

Dheeraj Singh

Gopinath E

Vineeth Chandy

T.john college of pharmacy

Abstract

The pharmaceutical scientist faces one of the most intriguing and difficult tasks: ocular medication delivery. Due to rapid precorneal drug loss (through dilution and drainage from the eye), high variability in efficiency, and blurred vision, among other factors, conventional ophthalmic formulations (solutions, suspensions, and ointments) have poor bioavailability. Therefore, it was necessary to develop an advanced drug delivery system. The bioavailability of a given medicine is impacted by both static and dynamic obstacles. Prior to administration in the body, polymeric systems are in solution form to address the disadvantages of conventional drug therapy; however, after administration, these systems go through gelation. In situ gels are liquid preparations that, after being injected into the eye, transition into a viscous gel as a result of the changes in the eye's environment. This innovative drug delivery technology encourages the crucial ease and convenience of administration, delivery of an exact dose, and extension of the drug's residence period in contact with mucosa. The main criteria for an effective control release product centre on improving patient compliance, good stability, and biocompatibility traits, which make the in situ gel dosage forms particularly dependable. This overview will outline the fundamental physiology and anatomy of the human eye, as well as the numerous techniques for creating in-situ gels and the few methods that are employed in their creation. These systems are tested for drug content, clarity, pH, gelling ability, viscosity, change in temperature.in vitro drug release research, texture analysis, sterility testing, isotonicity evaluation, accelerated studies, and irritancy test.

KEYWORDS: *in Situ gel. temperature sensitive, . nanosuspension. implants. iontophorosis*

INTRODUCTION

The most reachable body part for topical medication delivery is the eye. The main issue with drug instillation in ocular administration. Eye formulations cannot stay in the eye for a longer period of time and cannot demonstrate their intended effects because of the protective mechanisms of the eye, nasolacrimal drainage, tear drain away blood barriers, endothelium, and blood barrier found in the structure of the eye. Because they are in solution form, the formulation's primary downside is that they drain from the eye. As a result, the contact time and residence time are reduced. Traditional ocular delivery methods, such as suspensions, ointments, and solutions, fail to lengthen the contact period, which has a negative impact on bioavailability. substitution of formulations, such as collagen shields nanocarriers, microspheres, penetration enhancer, and occuserts. to boost the outcome and obtain the most effective result Effective formulation using a novel strategy that lengthens the dosage form's residence time and enhances its therapeutic impact. Gels depend on PH, ion sensitivity, and thermosensitivity. Polymers have a significant role in emerging techniques. Before administration, polymers are in solution form, but when they come into contact with body heat, they change into gel. As a result, the drug's residence time increases, providing a superior therapeutic impact[1].

PHYSIOLOGY OF EYE

Overall, the eye serves as a biological camera, absorbing light and translating visual information into nerve signals that are sent to the brain. The cornea is the initial part of the eye where light enters and is refracted to start the focusing process. Photon then passes through the pupil, where the size of the pupil and the amount of light entering the eye are determined by the iris's muscular contractions. The lens further distorts the light as it travels through it, bringing it into focus on the retina. The lens can adapt to different changes in vision due to the ciliary muscles' contractions pulling on the zonular fibres and the lens. The ciliary muscles relax to allow the lens to take on a broad shape while viewing objects that are close to the eye. The lens's broad design enables it

to refract light to a high degree in order to focus on the retina. In order to concentrate light from distant objects on the retina, the ciliary muscles pull on the lens to flatten it, lowering the degree of refraction. After travelling through the lens, light then proceeds into the vitreous humour and the retina. The retina's photoreceptor cells are trained to recognise light and respond by sending nerve signals. Rods are the photoreceptors that are more numerous, sensitive, and developed for seeing in low light. In low light, they produce grayscale images, but in daylight or in a room with artificial lighting at night, they are blinded by light. Cones can distinguish between different colours and are designed specifically for detecting light in brighter environments. Red, green, and blue cone cells are capable of detecting particular light colours or wavelengths. All of the colours that the human eye is able to perceive are created by the interaction of the three different types of cone cells. After the photoreceptors have detected light, the cells create an action potential that is transmitted to the bipolar cells and ganglion cells in the retina. These cells send the signal to the optic nerve, which carries it to the brain for processing. The choroid absorbs light that has already passed through the retina[2]. The choroid shields the eye from surplus light, which would otherwise develop into afterimages. High intensity lights have the power to overcome the choroid's absorptive properties, giving eyes the "red eye" that is seen in photographs[3].

IN SITU GELLING SYSTEM

Due to increased tear production, traditional ophthalmic administration methods such eye drops sometimes have poor absorption and therapeutic response. As a result, the medication is quickly eliminated from the ocular cavity. Poor patient compliance results from the need to frequently administer eye drops in order to maintain the medication concentration in the afflicted site. In an effort to boost the medicine's bioavailability, additional drug is being added to the formulation, but if the drug solution drains off, it could be harmful. To lessen infections brought on by many types of bacteria, fungi, and viruses as well as to relieve intraocular tension in glaucoma, local ophthalmic drug delivery systems can be constructed utilising numerous classes of medications, such as anti-infective, anti-inflammatory, and autonomic medicines. occuserts. ointments, suspensions, in situ gels, etc are just a few of the newer types of ophthalmic drug delivery systems that have been created to prolong ocular contact duration and improve ophthalmic bioavailability[4].

One of the best revolutionary drug delivery systems has evolved as the "in situ gel" system. With its unique characteristic of "Sol to Gel" transition, the in situ gelling system aids in the controlled and prolonged release of the medications as well as increased patient comfort. A formulation known as an in situ gelling system is one that, before being absorbed by the body, is in solution form. Nevertheless, depending on the physiological setting, it will transform into gel. Temperature, pH changes, solvent exchange, UV light, and the presence of certain molecules or ions are only a few of the variables that affect the sol to gel transition. For the production of sustained delivery vehicles for bioactive compounds, drug delivery systems with the aforementioned qualities of "sol to gel transition" can be exploited widely. The "in situ gelling system" has many benefits, such as simplified dosage administration, decreased administration frequency, and even protection of medicine against changes in ambient conditions. A variety of organic and inorganic polymers go through in situ gel formation and may be applied by oral, ophthalmic, transdermal, buccal, intraperitonial, parenteral, injectable, rectal, and vaginal routes. Using the changes in physiological individuality has been made possible by recent developments in in situ gels. For better drug absorption as well as patient convenience and compliance, in various areas of the digestive tract. Some of the natural polymers utilised for in situ gelling systems include pectin, gellan gum, chitosan, alginic acid, guar gum, carbopal, xyloglucan, xantham gum, HPMC, and poloxamer.
The in situ gelling mechanism has many uses and benefits in modern life. This review primarily focuses on an introduction to in situ gel, its mechanism, the different polymers employed, and its applications[5].

MODEL OF IN SITU GELS
In situ gels work by using the following mechanisms:

- **According to a physical mechanism**

1 **Swelling**: In this in-place gel production technique, the material collects water from the environment and expands to fill the necessary space. One polar lipid that does this is glycerol mono-oleate, which expands in water to form lyotropic liquid crystalline phase structures. It can be destroyed in vivo by enzymatic action and has some bioadhesive characteristics[6].

2 **Diffusion**: In this technique, the solvent from the polymer solution diffuses into the tissue around it, precipitating or solidifying the matrix of the polymer. It has been demonstrated that a good solvent for this system is N-methyl pyrrolidone (NMP)[7].

- **Based on the mechanics of a chemical reaction**

Precipitation of inorganic solids from supersaturated ionic solutions, enzymatic processes, and photo-initiated processes are a few examples of the chemical reactions that lead to in situ gelation[8].

ADVANTAGES

- The frequency of dosing is reduced, and it eliminates the negative effects of pulsed dosing caused by conventional methods.
- As a result of systemic absorption, the drug's decreased nasolacrimal drainage may result in negative side effects[9].
- Less doses administered every interval compared to premade gel. Patient comfort and compliance are increased due to the decreased amount and frequency of applications.
- Improved precorneal absorption and residence duration, increasing bioavailability[10].
- To improve a drug's therapeutic effectiveness and patient compliance[11].

IMPORTANCE OF IN SITU GELLING SYSTEM

- Because of their unique "Sol-Gel transition," in-situ gels after delivery encourage the controlled and prolonged release of the medication.
- There is no drug accumulation and no negative effects because in-situ gels are accurate at dosing and release medications in a controlled manner
- Greater drug interaction with tissue and longer drug residence duration as a result of gel formation.
- The physical simplicity of in-situ gel systems makes them simple to administer, which enhances patient comfort and compliance[12].
- It aids in the monitoring and assistance of medicines' distinctive "Sol-Gel" transition.
- Symptoms or medications will not be gathered; only a tiny amount of the medication is required.
- The best measuring structures for liquids are those that can still control discharge while maintaining consistent contact with the cornea of the eye.
- The nasolacrimal canal may experience negative effects from decreased essential intakes of wasted medicines. With its peculiar modification, it facilitates the assisted and controlled entry of medications. Sol-Gel[13].

IDEAL CHARACTERSTICS OF IN SITU GEL

- It has to be capable of adhering to the mucous membrane.
- The production of tears should be affected.
- It should have excellent optical clarity and tolerance.
- Stability when exposed to heat, light, air, or a suitable amount of moisture[14].
- It possesses viscoelastic and pseudoplastic characteristics.
- It has bio adhesive properties and is antimicrobial.
- By reaching ocular pH, it can change into a hydrogel[15].

METHODS

- **TEMPERATURE TRIGGERED SYSTEM**

The most often researched category of environment-sensitive polymer systems in drug delivery research is undoubtedly temperature-sensitive hydrogels. An appealing method to approach in-situ formation is to use a biomaterial whose transition from sol-gel is driven by increase in temperature. The optimal critical temperature range for such a system is ambient and physiological temperature, such that clinical manipulation is facilitated and no external source of heat other than that of the body is necessary for trigger gelation. Tolerable system should be able to take into account slight variations in local temperature, such as those that could occur in appendages near the skin's surface or the oral cavity Engineering of thermoresponsive sol-gel polymeric systems can be divided into three primary categories. Negatively thermosensitive, positively thermosensitive, and thermally reversible gels are the three categories into which temperature-sensitive hydrogels are divided for convenience. Hydrogels that are negatively temperature sensitive have lower critical solution temperatures (LCSTs) and shrink when heated above them. For this, low critical temperature polymers (LCST) that transition between ambient and physiologic temperature are utilised. Poly(N-isopropyl acrylamide) is among the most

studied polymers that show useful LCST transition (PNIPAAm). At its low LCST, PNIPAAm is a water-soluble polymer, but as it rises above LCST, it becomes hydrophobic, causing it to precipitate out of the solution at the LCST. Pluronics are triblock copolymers of poly (ethylene oxide), poly (propylene oxide), and poly (ethylene oxide) (PEO-PPOPEO), which are fluid at low temperatures but turn into thermosensitive gels when heated due to a disorder-order transition in micelle packing. This property makes these polymers suitable for in situ gelation. An upper critical solution temperature (UCST) governs the contraction of a positive temperature sensitive hydrogel when it cools below the UCST.Positive temperature dependence of swelling is observed in polymer networks of poly(acrylic acid), poly(acrylamide), and poly(acrylamide-co-butyl methacrylate). The thermoreversible gels known as Pluronics®, Tetronics®, and poloxamer are the most often used ones. They are made of poly(ethylene oxide)-bpoly(propylene oxide)-bpoly(ethylene oxide). At room temperature, polymer solution flows the body as a solution, they undergo an irreversible sol gel transition and quickly solidify into a stable gel. It persists at the injection site and offers absorption times of less than a week to many months. A device like that would be simple to insert into desired body cavity[16.]

- **pH TRIGGERED SYSTEM**

pH fluctuations can also cause gel to develop in situ in response to physiological cues. Every pH-sensitive polymer has a pendant acidic or basic group that reacts to changes in the pH of the environment by either accepting or releasing protons. Polyelectrolytes are polymers having many ionizable groups. When weakly acidic (anionic) groups are present in the polymer, hydrogel swelling increases when the external pH rises, while it decreases when weakly basic (cationic) groups are present. PAA (Carbopol®, carbomer) or its derivatives constitute the basis for the majority of anionic pH-sensitive polymers. Similar to how hydrogel is formed at neutral pH conditions by low viscosity polyvinylacetal diethylaminoacetate (AEA) solutions at pH 4. Drugs created as liquid solutions have a number of drawbacks, such as poor bioavailability and a tendency to be rapidly eliminated by tear fluid[17].

- **ION ACTIVATED SYSTEM**

In the presence of different ions, polymers can occasionally change from sol to gel. Ion-sensitive polymers include some types of polysaccharides. The pace of gelation is thought to be dependent on the osmotic gradient across the gel surface. The sol to gel transition in the eye may be impacted by the solution's osmolality. In most cases, mono- or divalent cations are present in tear fluid, forming a transparent gel of aqueous polymer solution. An anionic polysaccharide called gellan gum undergoes gelling in the presence of monovalent and divalent cations. The sol to gel transition is typically brought on by the Na, Ca, and Mg ions found in tear fluid. Alginic acid gels in the presence of divalent cation (Ca)[18].

TECHNIQES FOR CREATING IN SITU GELS

- **DENDRIMERS**

The chemical structure of dendrimers, which are big and complicated molecules, is clearly defined. With superior reported water solubility, bioavailability, and biocompatibility, dendrimers can be employed successfully for a variety of drug delivery methods. When dendrimers with carboxylic and hydroxyl surface groups were present, the residence time was longer. Vandamme created and assessed poly (amidoamine) dendrimers containing fluorescein for regulated ocular drug administration and identified the impact of size, molecular weight, and the quantity of amine, carboxylate, and hydroxyl surface groups in many series of dendrimers. For solutions with dendrimers that have carboxylic and hydroxyl surface groups, the residence period was longer[19].

- **MICRO-EMULSION**

A micro emulsion is a dispersion of water and oil stabilised by a surfactant and a co-surfactant to lower interfacial tension. It is often distinguished by small droplet size (about 100 nm), higher thermodynamic stability, and a clear appearance. The stability of the system can be affected by the choice of the aqueous phase, organic phase, and surfactant/co-surfactant systems[20].

- **NANOSUSPENSION**

Since they increased not only the pace and extent of ophthalmic drug absorption but also the intensity of drug action with much longer duration of medication impact, nanosuspensions have emerged as a promising method for the effective delivery of hydrophobic medicines. Techniques such as media milling and high-pressure homogenization have been employed in the production of nanosuspensions for commercial purposes[21].

- **IMPLANTS**

Implants are a reliable method of medicine delivery for long-term eye conditions including cytomegalovirus (CMV) retinitis. In the past, nonbiodegradable polymers were utilised, but their insertion and removal required surgery. Poly Lactic Acid (PLA), a biodegradable polymer, is now safe and effective for drug delivery in the vitreous cavity and exhibits no adverse effects. Fluocinolone acetonide intravitreal implants have been created for the treatment of posterior segment and have been shown to regulate retinal ocular inflammation[22].

- **IONTOPHOROSIS**

Visual iontophoresis has drawn a lot of attention due to the non-intrusive nature of medicine delivery to both the front and back of the eye. To boost ionised drug penetration into ocular tissues, linked electric current is necessary. The potential adverse effects of intraocular infusions and implants can be avoided with this method of transportation. It is safe, rapid, and simple to administer visual iontophorosis, and it helps to concentrate medication at a specific eye spot. Comparatively speaking to eye drops, the delivery of antiinfection medicines by the iontophoresis approach has significantly reduced bacterial settlements in the cornea. Tobramycin, gentamicin, and ciprofloxacin are a few examples of anti-toxins that have been successfully used in the past, however vancomycin cannot be because of its large atomic weight.

CONCLUSION

The current review comes to the conclusion that the "in situ gel" system has become one of the best innovative drug delivery methods. The in situ gelling system aids in the controlled and sustained release of the medications, as well as increased patient comfort. It is possible to administer medications by oral, ophthalmic, transdermal, buccal, intraperotonial, parenteral, injectable, rectal, or vaginal routes using a variety of natural and synthetic polymers that go through in situ gel formation. In situ gel system research has a lot of potential for developing cutting-edge drug delivery strategies.

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