ISSN:2394-2371
CODEN (USA):IJPTIL

REVIEW PAPER

In-Situ Gels in Ocular Drug Delivery: Current Role and Recent Advances

Subham Kumar[1], Shabana Zaffar[2] , Anish Menon[3], Mukesh Sharma[4*]

[1]Assistant Professor, School of Pharmacy and Research, Dev Bhoomi Uttarakhand University, Dehradun, Uttarakhand, 248007, India

[2]Research Scholar, Arya College of Pharmacy, Arya Main Campus, Kukas, Jaipur, Rajasthan, 302038, India

[3]Research Scholar, Amity Institute of Pharmacy, Lucknow, Amity University Uttar Pradesh, Sector 125, Noida, 201313, India.

[4]Professor, Arya College of Pharmacy, Arya Main Campus, Kukas, Jaipur, Rajasthan, 302038, India.

*Corresponding Author: **Dr. Mukesh Sharma**

ABSTRACT

The ocular drug delivery is always challenging for formulation scientists due to its anatomical and physiological barriers, akin to pre-corneal residence time, tear washing, excessive lachrymation and drainage along with unproductive absorption by conjunctiva. Apart from that drug's physio-chemical properties such as lipophilic and hydrophilic nature of drug also act as hindrance in drug availability. Conventional dosage forms such as solutions, eye drops and ointment were found to be less efficient in bypassing these barriers, thus research was directed in a way of overcoming these barriers. As a result, many technologies were developed over the years from microemulsion to nanocarriers were tested and prepared. *In-situ* gelling technology is one of the kind due to several advantages it became popular among the researchers and was also developed for ocular administration of drugs. The review also gives an insight to recent advancements of *In-situ* gels in delivering drugs in ocular region with mechanism, preparation, and evaluation. *In-situ* gels could be considered as a potential candidate and future for ocular drug delivery.

Keywords: - *In-situ* Gels, Ocular, Conventional, Lipophilic, Hydrophilic, Preparation, Evaluation, Recent Advancements.

INTRODUCTION

Ocular drug delivery is an exigent field, as the eyes of human beings are an isolated organ that makes it difficult to administer drugs. Eye drops and other traditional ophthalmic formulations face challenges in delivering effective doses of medication. Their residence time on the eye's surface is brief due to the continual production and drainage of tears. Tears are consistently replenished, flushing out the medication. Additionally, absorption across the conjunctiva (the membrane lining the eyelids) is inefficient, limiting the amount of drug that can reach its intended target within the eye. There are

***CORRESPONDING AUTHOR**
Dr Mukesh Sharma
Professor, Arya College of Pharmacy, Arya Main Campus, Kukas, Jaipur, Rajasthan, 302038, India
E.Mail: mukesharya9829@gmail.com
Article Published: April – June 2024
CITE THIS ARTICLE AS
Kumar S.,et al. In-Situ Gels in Ocular Drug Delivery: Current Role and Recent Advances. Int. J. Pharm. Technol. Biotechnol. 2024; 11(2):01-21.

two main categories for administering drugs to the eye. One category targets the anterior (front) portion of eye, including the cornea, conjunctiva (membrane lining the eyelids), and iris. The other category aims to deliver medication to the posterior (back) segment of eye, such as the retina, choroid (vascular layer), and vitreous humor (gel-like fluid filling the eye). The intended area of action within eyes determines which ocular drug delivery is required [1-3].

The eye's unique physiology and anatomy make it difficult to deliver drugs effectively. Traditional eye drops formulations face several challenges. The medication tends to get rapidly flushed out by the continual production and drainage of tears from the eye's surface. As a result, frequent re-dosing is necessary to maintain therapeutic levels. However, this dosing regimen can lead to poor patient adherence and suboptimal absorption of the drug into the eye. [4,5]. To overcome these limitations, ocular drug delivery systems should be designed with specific properties. They need sufficient adhesion or viscosity to resist being quickly washed away by tears. Additionally, they require an optimal balance of lipophilic (fat-soluble) and hydrophilic (water-soluble) characteristics. This balance allows the medication to penetrate through the tear film barrier and subsequently permeate across the cornea to reach the intended targets within the eye. [6,7].

While designing ocular drug delivery systems, it is crucial to consider the intricate structure of the cornea, which serves as a natural barrier. The cornea is a meticulously organized tissue composed of three main layers. The cornea, the transparent front part of the eye, is a multi-layered structure. Its outermost layer is referred to as the epithelium, which interfaces with the conjunctiva, the membrane that lines the inner surfaces of the eyelids. Underneath the epithelium lies the stroma, forming the central layer of the cornea. The innermost layer is known as the endothelium. Each of these distinct corneal layer functions as a selective barrier, regulating and controlling the permeation of various drug molecules through the cornea. These barriers modulate the passage of both lipophilic (fat-soluble) compounds and hydrophilic (water-soluble) compounds, presenting challenges for effective drug delivery to the interior of the eye. Overcoming these barriers is a key challenge in achieving effective drug delivery to the intended targets within the eye. [6,8,9-11]. Additionally, the epithelium's intercellular tight connections restrict the diffusion of hydrophilic compounds (size > 100 Da) via the paracellular pathway. [8] Polymers utilised in ophthalmology , the temperature, pH, and ionic strength are three environmental cues in the eye that cause an in-situ gel system to go through a sol-gel transition [1,4]. This allows the gel to adhere to the ocular surface and extend the precorneal residence time of the drug, enhancing its bioavailability [3].

The focus of more recent studies on ocular medication delivery systems is on creating new methods. that incorporate multiple drug delivery technologies to extend the contact time of the vehicle at the ocular surface and slow down the elimination of the drug. One more recent drug delivery technique being investigated for ocular applications is in situ gel systems. [5].

A HUMAN EYE: UNDERSTANDING ANATOMY AND PHYSIOLOGY

Ocular drug delivery is one of the most challenging areas of pharmaceutical science, due to the unique anatomy of the eye and the permeability of the cornea. For treating conditions affecting the eye, administering medications topically (i.e., applying them directly to the eye's surface) is generally the preferred route compared to systemic delivery methods like oral or intravenous administration. However, the challenge with topical ocular drug delivery is that the medication must be able to penetrate through the various protective barriers of the eye to reach the intended interior targets. Simply applying the drug topically to the eye's exterior is often insufficient for achieving the desired therapeutic effect within the eye itself. To be truly effective, topically administered ophthalmic formulations must possess the ability to permeate through the eye's multilayered defenses and reach the specific ocular tissues or structures requiring treatment. [12].

The front, transparent, avascular portion of the eye is called the cornea. It has five layers: the epithelium (outermost layer), Descemet's membrane, Bowman's membrane, stroma, & endothelium (innermost layer) [13]. The primary determinant of medication dosage in the aqueous humour is corneal permeability. [2].

Epithelium acts as a barrier that limits rate drug release to trans corneal diffusion for the majority of hydrophilic medicines. [14]. Although the stroma is hydrophilic, it also acts as a barrier to medications that are extremely lipophilic [15]. The middle layer of the cornea, known as the stroma, primarily consists of collagen fibers that are hydrophilic (water-attracting) in nature. These collagen fibers carry an electrical charge and are arranged in a highly organized manner. This structural composition impedes the diffusion and penetration of hydrophobic (water-repelling) drug molecules through the corneal stroma. Covering the sclera, the opaque white portion of the eye's outer surface, is a delicate see-through membrane known as the conjunctiva. This thin, translucent layer also extends inward to line the inner surfaces of the upper and lower eyelids. The conjunctiva forms a protective barrier over portions of the eye while still allowing light to pass through its transparent structure. It comprises a stratified (multi-layered) epithelium that lacks keratinization, as well as specialized goblet cells. The conjunctiva plays a protective role for the eyes by secreting mucus. This mucus serves two

key functions: preventing the entry of microorganisms and providing lubrication to the ocular surface. [2].

The conjunctiva, the membrane covering the sclera and lining the eyelids, has a significantly larger surface area compared to the cornea in humans. Specifically, the conjunctival surface area exceeds that of the cornea by approximately 17 times. This increased surface area theoretically allows for greater absorption of topically applied drugs through the conjunctival pathway when compared to corneal absorption. However, while drug permeability tends to be higher across the conjunctiva relative to the cornea, the overall conjunctival absorption of medications is still relatively low. This limitation arises from the presence of blood capillaries and lymphatic vessels within the conjunctiva. A considerable portion of the drug absorbed through the conjunctiva enters the systemic circulation via this blood and lymphatic channels, thereby reducing the amount of drug that ultimately reaches the intended targets within the eye. Consequently, the overall ocular bioavailability achieved through the conjunctival route remains suboptimal [16].

Within the eye, there is a clear fluid called the aqueous humor that fills both the posterior and anterior chambers. This fluid is not vascularized, meaning it does not contain blood vessels, which allows it to maintain transparency for optimal light transmission. The aqueous humor serves as a source of nutrients for the avascular cornea. It is characterized by a relatively high concentration of ascorbate (vitamin C), approximately 15 times higher than the levels found in blood plasma. Additionally, the aqueous humor has a slightly basic pH of around 7.2. The primary functions of the aqueous humor are threefold. Firstly, it delivers essential nutrients to the non-vascular tissues within the eye. Secondly, it facilitates the removal of metabolic waste products from these avascular tissues. Thirdly, and perhaps most importantly, the aqueous humor plays a crucial role in regulating and maintaining the intraocular pressure within the eye. This pressure is responsible for preserving the convex curvature of the cornea, which is essential for proper visual acuity and focus [16,17].

The opaque, white part of the outer layer of the eye is called the sclera. It has an elastic network of collagen fibers, providing structural support and protection. In contrast to the transparent cornea, the sclera generally exhibits higher permeability to various solutes, particularly hydrophilic (water-soluble) compounds. This increased permeability is attributed to the sclera's structure, which allows diffusion primarily through an aqueous medium containing proteoglycan or via leaky spaces within the collagen fiber network, rather than requiring passage across cellular membranes. While the sclera's primary function is to serve as a protective outer coating for the eye, it also plays a crucial role in maintaining intraocular pressure. Additionally, the sclera provides an attachment site for the extraocular muscles

responsible for controlling eye movements. Despite its relatively high permeability compared to other ocular tissues, the sclera is not a preferred route for drug delivery due to its location away from the primary sites of action within the eye [13,14]. Situated at the rear of the eye, the layer of retina is a complex, multilayered structure made up of different kinds of cells and fibers. It contains vascular elements (blood vessels), glial cells (which provide support and insulation for neurons), neural cells (nerve cells), and nerve fibers. The intricate structure of the retina is a major obstacle, especially when it comes to getting higher molecular weight medications into the inner workings of the eye. The retina's multilayered architecture and diverse cellular makeup make it challenging for high-molecular-weight drug molecules to effectively penetrate and reach their intended targets within or beyond the retinal tissue. When developing drug delivery systems for ophthalmic applications, a significant challenge arises in the need to bypass the formidable barrier posed by retinal tissue. This hurdle becomes particularly critical for therapeutic interventions aimed at treating conditions that involve the posterior segment of the eye, the region located beyond the retina. Effectively overcoming the retinal barrier's resistance to drug permeation is a crucial consideration that must be addressed during the formulation design process. Strategies to enhance drug transport across the complex, multilayered retinal structure are essential for ensuring adequate drug levels reach the intended targets within the posterior ocular compartments [15,16].

Due to effective tear drainage and blinking, drug concentration is reduced by 10-fold in cases where the medication is given as an infusion. This means that the drug only reaches the ocular tissue for a very short time. Additionally, compared to elimination, absorption happens far more slowly. For many drugs, the elimination rate constant (Kloss) is about 0.5-0.7/min, while the absorption rate constant (Kabs) is about 0.001/min. The percentage of the administered dosage absorbed by the eye is determined by addition of two rate constraints [12].

THE IN-SITU GELLING VEHICLE

Innovative formulations known as "in situ gel-forming delivery systems" were liquids before application and solidify at their intended site in response to environmental cues like Ionic strength, temperature, and pH. This technology was first proposed in the early 1980s, and since then, it has been extensively investigated and developed for various applications.

Gelation occurs when polymer chains crosslink, and this crosslinking can be achieved through either covalent or non-covalent bonds. In the context of *In-situ* gel-forming systems, these are characterized by low-viscosity solutions that, in response to the physiological environment within the conjunctival cul-de-sac, undergo a phase transition to form viscoelastic gels. The speed that in situ

formation of gel takes place is important because, the development of a more potent gel, the fluid mechanics of the eye initiate the formation of a solution and a less viscous gel. Both natural and synthetic polymers are utilized in the formulation of in situ gels, serving various functions in the creation of these ocular drug delivery systems [13,18].

ROLE OF IN-SITU GELS FOR DELIVERING ACTIVE AGENTS IN OCULAR REGION [7,13,19]

- Less blurred vision than with ointments
- Decreased medication outflow via the nasolacrimal duct, a process which may result in unfavourable systemic side effects.
- Consistent and extended drug release with a relatively stable plasma profile.
- Decreased need for frequent administration, contributing to enhanced patient adherence and comfort.
- Typically, they offer better comfort compared to insoluble or soluble inserts.
- Enhanced local bioavailability as a result of prolonged presence in the precorneal area, improving absorption.

***IN-SITU* GELLING MECHANISMS**

The mechanism related with swelling:

Certain materials have the ability to undergo a gel formation process directly at the site of application. This process, known as in situ gelation, involves the material absorbing water or moisture from its immediate surroundings. As the material imbibes this moisture, it undergoes a volumetric expansion, allowing it to occupy and fill a desired space or cavity. The in situ gel formation mechanism enables the material to transition from a solution or semi-solid state to a gel-like consistency upon exposure to the aqueous environment at the application site.. A prime illustration of this phenomenon can be observed with glycerol mono-oleate, a polar lipid that swells when exposed to water, resulting in the development of lyotropic liquid crystalline phase structures. Notably, glycerol mono-oleate exhibits bio adhesive characteristics and is susceptible to enzymatic degradation within a living organism [13].

The mechanism related with diffusion:

This technique makes use of the spontaneous process of solvent diffusion in the nearby biological tissue milieu from a polymer-based solution. When the solvent progressively permeates the tissue and leaves the polymer solution, it triggers a phase change within the polymer matrix. This

change causes the polymer to precipitate or solidify into a more solid-like structure or depot. The underlying principle relies on the controlled exchange of solvent between the polymer formulation and the adjacent tissue, facilitating the desired transformation of the polymer from a solution state to a more solidified or gel-like state. N-methyl pyrrolidone (NMP) is one solvent that can be utilised in this procedure [15]**.**

Chemical Reaction Mechanism:

In situ gelation through chemical reactions encompasses various mechanisms, such as enzymatic changes, photo-initiated reactions, and the formation of inorganic particles from extremely concentrated ionic solutions [15,19]. These mechanisms are depicted in Fig.1.

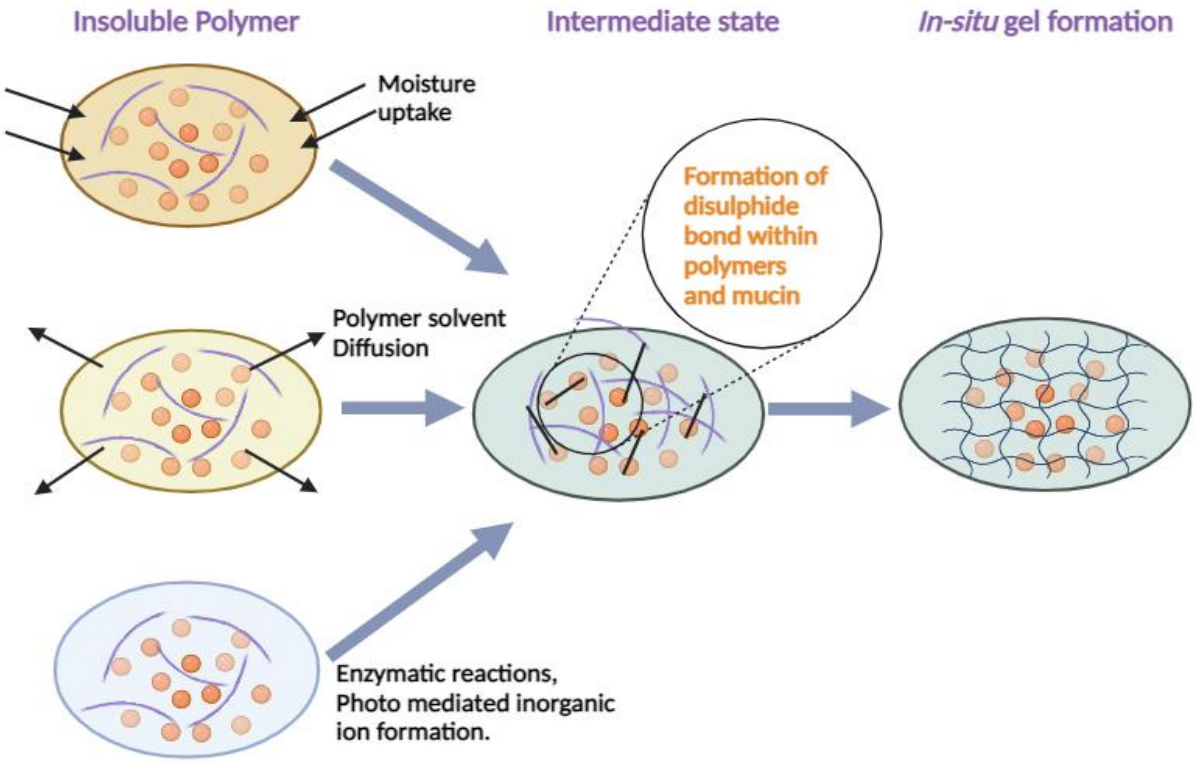

Fig.1. Different mechanisms involved in formation of *In-Situ* gels.

POLYMERS USED IN *IN-SITU* GELS

Carbopol:

Carbomer, also referred to as an acrylic acid polymer, is a type of polymer that exhibits pH-sensitive behavior and the ability to adhere to mucosal surfaces (mucoadhesive properties). The mucoadhesive nature of carbomer arises from its capability to interact with mucin, a key component of

mucus, through four distinct mechanisms: electrostatic attraction, hydrogen bonding, hydrophobic interactions, and inter-diffusion of polymer and mucin molecules. Another pH-responsive polymer commonly used is Carbopol. This polymer undergoes a gelation process when its carboxylate functional groups partially dissociate in an aqueous environment, leading to repulsive forces between the negatively charged groups. In its acidic form, the Carbopol molecule adopts a tightly coiled conformation. However, as the pH increases, the molecule gradually unfolds and swells due to the dissociation of these carboxylate groups. To trigger and facilitate this gel formation process, neutralizing agents, such as sodium hydroxide, triethanolamine, or potassium hydroxide, are introduced, which aid in the dissociation and subsequent swelling of the Carbopol polymer. [21].

Poloxamer:

This polymer exhibits temperature sensitivity and is commonly known as Pluronic. At room temperature (around 25°C), poloxamer takes on the characteristics of a viscous liquid, but as the temperature rises (to approximately 37°C), it undergoes a transformation into a transparent gel. In its lower temperature state, forms micellar subunits. When the temperature increases, there is a concurrent rise in viscosity, leading to swelling and the formation of a larger, cross-linked micellar network [21]**.**

Gellan Gum:

It is occasionally referred to as Gelrite® in trade, is an ion-sensitive polymer. It achieves in situ gelation through cation-induced cross-linking involving both mono- and divalent cations (such as Ca^{2+}, Mg^{2+}, K^{+}, Na^{+}) with negatively charged helices. When it comes to gelation, divalent ions especially Ca3 are more potent than monovalent cations. By prolonging the duration of drug residence at its absorption site, this gelation process improves medication bioavailability. [22]**.**

Sodium Alginate:

Sodium alginate is another example of an ion-sensitive polymer, also referred to by various names such as algin, alginic acid, sodium salt (E401), Kelcosol, Keltone, Protanal, and sodium polymannuronate. Its monomers, composed of G-L glucuronic acid (G) and β-D mannuronic acid (M), form blocks that alternate between M-G and G-M. When the polymer's G block interacts with calcium ions, it leads to the formation of a uniform gel. The tensile strength and porosity of the resultant hydrogel are influenced by variables and kind of cross-linker utilised, plus the concentration of the alginate solution [23]**.**

Chitosan:

The ionised sialic acid residues in mucin and amino acids that are positively charged in chitosan interact ionic to produce mucoadhesive properties. Its hydrophilic, bio adhesive, and well-dispersed properties make it a useful viscosity-enhancing ingredient in artificial tear compositions **[20,21].**

Hydroxy Propyl Methyl Cellulose (HPMC):

HPMC, also known as Hypromellose or Methocel, is a temperature-sensitive polymer. Gelation in HPMC solutions primarily occurs due to interactions between compounds with methoxy substitution that are hydrophobic. The macromolecules in question are hydrated at low temperatures and exhibit only weak polymer-polymer interactions, such as simple entanglement. As the temperature increases, the polymers gradually lose their hydration, leading to a decrease in relative viscosity. As the polymer undergoes a controlled dehydration process, reaching a state of partial but not complete dehydration, intermolecular associations begin to form between the polymer chains. This process leads to the gradual development of an interconnected, infinite network structure within the polymer system. This sol-gel transition, where a polymer solution transforms into a gel-like state, has been exploited in the design of in situ gelling systems for various applications. These in situ gelling systems are characterized by exhibiting relatively low viscosity at room temperature (around 23°C), which facilitates their administration or application. However, upon exposure to physiological conditions, such as the body temperature of 37°C, these systems undergo a phase transformation, forming soft, gel-like structures. This temperature-induced gelation process occurs due to the intermolecular associations and network formation within the polymer chains at the higher temperature [24].

STRATEGIES FOR *IN-SITU* GELLING VEHICLE

There are three main strategies for In-Situ Gels namely, temperature triggered, pH sensitive and Ion induced. Generally, they change the sol-to-gel form by converting initial liquid state to gel system by an external stimulus i.e., temperature, pH and ion concentration as demonstrated in Fig 2.

System for in-situ gelling triggered by temperature:

Sensitive to temperature *In-situ* gels are one of the classes for environment responsive polymer structures that have been studied the most in drug delivery research. Within this gelation system, the polymers maintain a liquid state at room temperature (around 20-25°C) but transition into a gel state at physiological temperatures (approximately 35-37°C) [25]. Polymer solutions that undergo gelation in response to temperature changes are formulated to exist as liquids below a specific lower critical temperature. As the environmental temperature increases beyond an upper critical threshold, the polymer chains begin to unravel and aggregate into micelle structures. This aggregation process leads to

the formation of an entangled polymeric network, causing the solution to transition from a liquid into a gel state. The transformation is marked by a gradual breakdown of the polymer chains and increased micellar clustering as the temperature rises [17,25].

The temperature at which the phase transition occurs for ideal temp-triggered in situ gelling liquids should be greater than room temperature (25°C).. This makes it easy to administer the medication to the eye, and even at low concentrations (e.g., 5% w/v), it will gel at the precorneal temperature (35°C) without being affected by the dilution effects of tear fluid [22].

System for in-situ gelling triggered by pH:

Some polymeric formulations are engineered to undergo a liquid-to-gel transition triggered by variations in pH levels. These are known as pH-responsive in situ gelling systems. When introduced to the specific pH conditions present in tear film coating the eye's surface, the solutions solidify into gel-like structures due to the pH change. The phase transformation from a fluid state to a semi-solid gel state occurs in response to the new pH environment encountered. Two prominent examples of polymers employed in such pH-responsive ocular gelling systems are cellulose acetate phthalate and Carbopol. These polymers exhibit pH-dependent conformational changes and intermolecular interactions, which drive the solution-to-gel transition when introduced to the specific pH conditions of the tear film. [26] Certain polymers designed for pH-triggered in situ gelling systems contain weakly acidic or basic functional groups integrated into their molecular structure. These functional groups could either donate or accept protons (hydrogen ions) in response to changes in the surrounding pH environment. When the pH reaches specific levels, various intermolecular forces come into play, including electrostatic attractions, hydrophobic interactions, and hydrogen bonding. These forces drive a process of interpenetration and conformational rearrangement within the polymer chains, ultimately leading to swelling of the polymer network. As a result of this pH-induced swelling phenomenon, the polymer system undergoes a phase transition from a solution state (sol) to a gel-like state. The shift in pH acts as the trigger for this sol-gel transformation by initiating the intricate interplay of intermolecular forces and conformational changes within the polymer structure. The pH responsiveness of these polymers allows them to transition from a low-viscosity solution to a gel upon exposure to the desired pH conditions, such as those encountered in the tear film or other ocular environments [27].

System for in-situ gelling triggered by ion:

When subjected to the ionic concentration present in tear fluids, the solution's viscosity rises in ion-triggered In-situ gelling systems [22]. This gelation process, where a solution transforms into a gel-like state, is driven by the osmotic forces present in the surrounding environment. It is commonly

referred to as osmotically induced gelation. Ocular drug delivery methods employ specific polymers that are engineered to exhibit ionic species responsiveness. The functional groups of these ion-sensitive polymers can interact and create crosslinks with the divalent (double-charged) and monovalent (single-charged) cations found in the tear film on the surface of the eye. The formation of these ionic crosslinks between the polymer chains and the cations in the tear film plays a crucial role in extending the residence time of the drug delivery system on the ocular surface. This increased retention time is achieved by the gel-like network structure that develops because of the ionic crosslinking process. The extended contact between the drug formulation and the ocular tissues facilitated by this mechanism can potentially increase the drug's therapeutic effectiveness and bioavailability after administration [4,28].

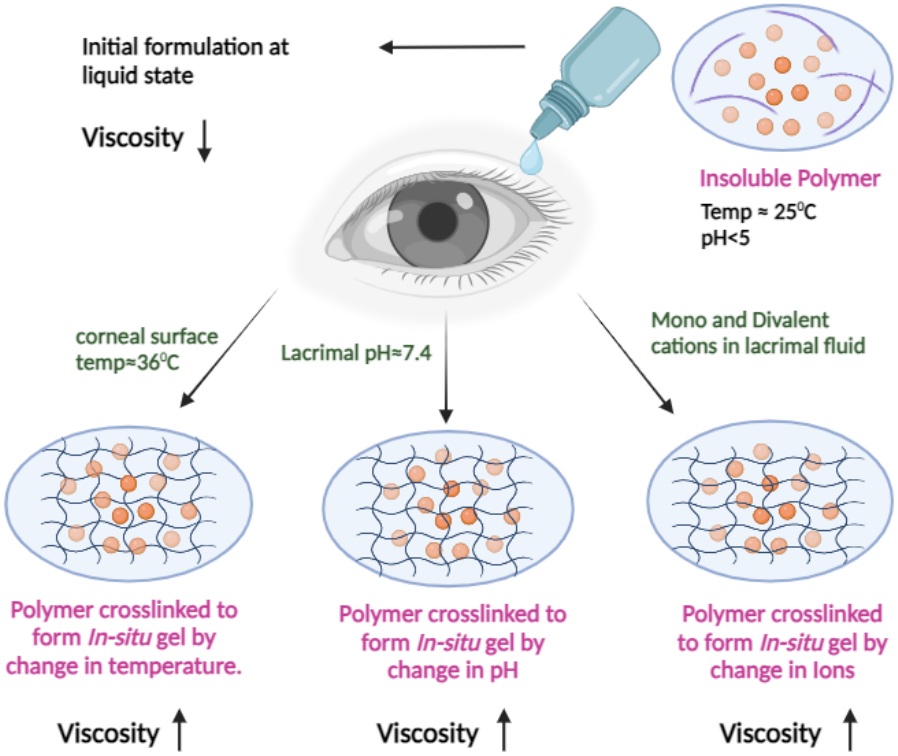

Fig.2. *In-situ* gel formation: (a) Temperature triggered *In-situ* system (b)Ion triggered *In-situ* gel formation (c) pH triggered *In-situ* gel formation.

EVALUATION OF OCULAR IN SITU GEL

Clarity and Aesthetic Appearance:

To find any particle debris, the created in situ formulation's clarity and visual appeal are assessed in luminescent light on both white and black backgrounds. [29].

pH Measurement:

The pH of the formulation is crucial as it affects the solubility and stability of the drug in ophthalmic formulations. It should be adjusted to ensure both formulation stability and patient comfort. pH is measured using a digital pH meter [30].

Gelling potential:

To evaluate the gelation ability of an ocular formulation designed for in situ gel formation, a specific testing procedure is employed. In this test, a small drop of the formulation is introduced into a vial containing a freshly prepared solution that mimics the composition of human tear fluid. The vial contains approximately 2.0 milliliters of this simulated tear fluid solution. After introducing the formulation drop, the time required for the formulation to undergo a transition from its initial state to a gel-like consistency is carefully monitored and recorded. This measured time provides an indication of the gelling capacity and kinetics of the formulation when exposed to an environment that simulates the tear film on the ocular surface [31].

Isotonicity:

Ensuring the isotonicity of ophthalmic formulations is a critical consideration to avoid potential tissue damage or irritation to the eye. Isotonicity refers to the osmotic pressure exerted by dissolved salts in an aqueous solution. For eye drops and other ocular formulations, it is essential to maintain an osmotic pressure within a specific range that is compatible with the eye's natural environment. This optimal range is typically between 290 and 310 milliosmoles per kilogram. To ensure that ophthalmic formulations fall within this desired isotonic range, their osmotic pressure is measured using a specialized instrument called an osmometer. By accurately determining the osmotic pressure of the formulation, appropriate adjustments can be made to achieve isotonicity and minimize the risk of tissue irritation or damage upon administration to the eye [32].

Texture Analysis:

The physical characteristics of the in-situ gel formulation, including its consistency, firmness, and cohesiveness, are evaluated using a specialized instrument called a texture profile analyzer. This analytical technique provides valuable insights into the gel's strength and its suitability for administration to the eye. Specifically, it measures properties such as hardness, compressibility, and adhesiveness of the gel. These measured properties can be correlated with key parameters that influence the gel's performance and ease of use. For instance, the hardness and compressibility data can indicate how readily the gel can be extracted from its container for administration. The adhesiveness property can be linked to the gel's ability to spread evenly across the corneal surface and adhere to the mucous

layer lining the eye. This adherence is crucial for prolonging the residence time of the gel formulation on the ocular surface, thereby enhancing the duration of drug delivery. By assessing these textural characteristics, formulators can optimize the in-situ gel's properties to achieve desirable handling characteristics, spreadability, and prolonged retention on the eye, ultimately enhancing the efficacy and convenience of the ocular drug delivery system. [33-35].

Rheological Studies:

The primary tool used to determine the viscosity of ophthalmic in in situ gels is a Brookfield viscometer. Viscosity is determined by progressively increasing the angle of rotation from 0.5 to 100 rpm both before and after gelation. A cone rheometer is used to better evaluate the qualities of rheology. Viscosity is measured by applying an increasing shear rate from 0 to 100 s^{-1} at both 25°C and 35°C (the surface temperature of the eye). Three duplicates of each rheology test are run in order to do statistical analysis. To prepare the in-situ gel systems, the combinations that showed the lowest starting viscosity and the largest viscosity rise upon adding simulated tear fluid (STF) were selected. [31, 33, 35].

Stability Studies:

Stability studies for the *In-situ* gel are conducted following the guidelines set by the International Conference on Harmonization (ICH) at 40°C and 75% relative humidity. Three sets of formulations undergo these stability studies. Samples are withdrawn at the 0th, 1st, and 3rd months, with 0.1 mL of each sample analyzed for drug content using high-performance liquid chromatography (HPLC). Additionally, other stability parameters are determined alongside drug content analysis [34,35].

RECENT ADVANCEMENT

Xiaomin *et al.*, 2020, Researchers investigated the development of a pH-sensitive in-situ gel for ophthalmic drug delivery loaded with bear bile extract (Xiaomin et al., 2020). The in-situ gel exhibited excellent stability across a range of pH values (5.0 to 8.0) for up to five days. Interestingly, the bear bile extract was found to slightly reduce the gel's ability to form. The viscosity of the gel decreased as the shear rate increased. Examination of the freeze-dried gel revealed a three-dimensional network structure at physiological pH. In-vitro studies demonstrated sustained drug release for up to 160 minutes, while in-vivo studies showed a three-fold increase in retention time compared to conventional eye drops. Biocompatibility testing confirmed the formulation's safety and compatibility with ocular tissues. These findings suggest that pH-sensitive in-situ gels hold promise as a novel approach for delivering ophthalmic medications for improved treatment of eye diseases [3]**.**

Destruel et al., 2020, prepared ophthalmic preparation containing gellan gum and hydroxyethyl cellulose for preparing *In-situ* gels. In this investigation, innovative in-situ gelling delivery systems were formulated, incorporating a combination of phenylephrine hydrochloride and tropicamide. These in-situ gelling delivery systems displayed physicochemical attributes well-suited for ophthalmic applications. They exhibited the right viscosity, effective in-situ gelation capabilities, and demonstrated shear-thinning behaviour, which is advantageous for ocular administration [36]**.**

Sun *et al.,* 2021, demonstrated In-situ Gel of SLN loaded with Tacrolimus. In this research, Tacrolimus-loaded Solid Lipid Nanoparticles (SLN) incorporated into in-situ gels were prepared through a combination of homogenization and probe sonication methods. The average particle size of these Tacrolimus-loaded SLN in-situ gels measured at 122.3±4.3 nm. Interestingly, the introduction of in-situ gel did not increase the particle size compared to Tacrolimus-loaded SLNs, and there was no significant difference between the two. Viscosity measurements indicated that Tacrolimus-loaded SLN in-situ gels exhibited characteristics of pseudoplastic systems, with a noticeable increase in viscosity as the temperature rose, ultimately forming a rigid gel at 32°C. In vitro and in vivo investigations demonstrated a sustained drug release model for Tacrolimus from these SLN-loaded in-situ gels. In contrast to standard eye drops and SLNs, Tacrolimus-loaded SLN in-situ gels demonstrated favourable pharmacodynamics, according to an animal model investigation. These findings imply that SLN in-situ gels filled with tacrolimus could be a perfect ocular medication delivery method. [37].

In a recent study published in 2021, Wang and colleagues reported the development of an innovative composite drug delivery system designed for ophthalmic applications. This system combines the use of carbon dots (CDC-HP) synthesized through a one-step hydrothermal process involving hyaluronic acid and carboxymethyl chitosan as precursors. These carbon dots were subsequently incorporated into a thermosensitive gel matrix composed of Poloxamer 407 and Poloxamer 188 using a swelling technique. The researchers conducted a comprehensive characterization of the physicochemical properties of the synthesized carbon dots. In vitro studies demonstrated that the resulting composite drug delivery system, termed DS-CDC-HP-Gel, exhibited sustained drug release kinetics over a 12-hour period. Additionally, ex vivo fluorescence distribution studies using ocular tissue models confirmed the system's potential for both drug delivery and bioimaging applications within the eye. These findings suggest that the composite system could potentially improve the precorneal residence time of the encapsulated drug, thereby enhancing its therapeutic efficacy. This innovative ophthalmic drug delivery system offers several advantages, including ease of administration, improved patient compliance due to reduced dosing frequency, and the ability to deliver both anti-

inflammatory drugs (NSAIDs) and antimicrobial agents. The development of this multifunctional nanocarrier paves the way for a new generation of ocular drug delivery systems [5].

Soliman *et al., 2019, developed* Poloxamer-based in situ gels are being explored as potential vehicles for ocular drug delivery. These gels are known for their stability under steam sterilization and their compatibility with corneal tissues, which has been extensively studied. By blending Poloxamers P407 and P188 in different ratios, it is feasible to develop formulations that gel at physiological temperatures. In vitro studies have shown that these in situ gels can sustain drug release for various medications, thus prolonging drug activity and enhancing bioavailability. However, it is imperative to evaluate the impact that various formulation constituents and tear fluids have on the mechanical, rheological, and thermoresponsive characteristics of polymers. Through non-invasive or minimally invasive methods, this research area shows promise for delivering sustained medication delivery to the posterior section of the eye, potentially eliminating the need for frequent intravitreal (IVT) injections in the treatment of posterior eye disorders. [1].

Cardoso *et al., 2021,* In-situ gelling microemulsions, which are intended for topical ocular administration of model pharmaceuticals, such as betamethasone and loxifloxacin, have been effectively produced by the researcher. The nanoformulations have been optimized with desirable physicochemical parameters, including an ideal gelling temperature. These microemulsions have demonstrated a controlled release profile, which allows for extended control over the lipophilic drug betamethasone. Furthermore, when applied to the cornea under static conditions, these formulations have shown to enhance the drug's penetration. This research improved the efficacy of topical ocular drug delivery, particularly for drugs that require extended release and enhanced penetration. [38]**.**

Sustained ocular delivery of desmopressin acetate was demonstrated by Lie *et al.*, 2022, thermosensitive *In-situ* gels formulation, Rheological studies revealed that the optimized gels were pseudoplastic fluids with desirable thixotropic properties. Scanning calorimetry analysis confirmed the uniform distribution of desmopressin acetate within the gel matrix. According to in vivo research, the newly created gel had an antidiuretic effect comparable to that of ophthalmic drops since it greatly increased the residence time and ocular accessibility of desmopressin acetate. **[**39]**.**

Ciprofloxacin-loaded bilosomes were meticulously prepared and integrated into in-situ gels for ocular administration, specifically designed for the treatment of ocular microbial infections. In their study, Alsaiden *et al., 2022,* discovered that Ciprofloxacin-loaded bilosomes in-situ gels exhibited sustained release of Ciprofloxacin, with a notably higher flux compared to both pure Ciprofloxacin and Ciprofloxacin in-situ gels. Importantly, these Ciprofloxacin-loaded bilosomes in-situ gels showed no

indications of toxicity, as confirmed through corneal hydration studies, histology, and the HET-CAM test. Moreover, they demonstrated superior antibacterial efficacy against Pseudomonas aeruginosa and Staphylococcus aureus when compared to pure Ciprofloxacin. In conclusion, biosomes and *In-situ* gels could represent an innovative approach to enhance corneal residency time and the therapeutic effectiveness of Ciprofloxacin [40].

Aslzad *et al., 2022,* created hybrid chitosan/dialdehyde starch in situ gel-forming hydrogels for betamethasone ocular administration. The simultaneous utilization of dialdehyde starch (DAS) and chitosan (CS) in this hybrid system enabled the development of in situ hydrogels with a rapid gelation time of less than 1 minute. This quick gelation is highly favorable for ocular drug delivery purposes [41].

Xu et al. (2023) developed an ion-sensitive in-situ gel for ocular delivery of Brimonidine Tartrate to address the limitations of currently available commercial Brimonidine eye drops, such as rapid depletion, short duration of effectiveness, and limited safety. Researchers have developed and optimized an ion-sensitive in-situ gelling ophthalmic formulation containing the drug Brimonidine. This formulation offers several advantages, including ease of preparation, convenience of use, and good fluidity at room temperature, making it suitable for large-scale industrial manufacturing. Additionally, the formulation exhibits robust stability characteristics and can facilitate rapid drug release upon intraocular administration, ensuring a quick onset of therapeutic action. In vivo studies have demonstrated that this Brimonidine in-situ gel formulation can significantly extend the retention time of the drug in the eye, leading to enhanced bioavailability of Brimonidine compared to conventional formulations. Notably, the optimized formulation exhibits the dual beneficial attributes of both rapid and sustained drug release profiles. It is anticipated that this novel Brimonidine in-situ gel preparation has the potential to be further developed into a new commercial drug product, offering a safer, more effective, and more convenient dosing option for a wide range of patients requiring ophthalmic treatment. Importantly, the intraocular bioavailability achieved with this in-situ gel formulation surpasses that of traditional commercial eye drop formulations, making it a promising alternative for ocular drug delivery [42].

CONCLUSION

The field of ocular drug delivery is rapidly evolving, driven by researchers' efforts to address the challenges associated with delivering therapeutic agents to the eye. Advancements in our understanding of the principles governing ocular drug absorption and distribution, coupled with technological innovations, have significantly improved the efficacy of ophthalmic drug delivery systems. A key focus

in the development of successful controlled-release products has been enhancing patient compliance. In this regard, in situ gelling systems offer a promising solution by providing ease of administration and improving patient adherence. In recent years, in situ gelling systems have garnered significant attention from researchers due to their ability to deliver precise and reproducible drug quantities, extend the precorneal residence time, facilitate sustained drug release, enable drug delivery to deeper ocular tissues, and reduce the frequency of administration. Additionally, these systems can incorporate drug-loaded nanoparticles, liposomes, or other colloidal drug carriers, further enhancing and improving sustained drug delivery. The use of biodegradable and water-soluble polymers in the formulation of in situ gels has the potential to increase the acceptance and effectiveness of these systems as drug delivery platforms. Recent advancements in ophthalmic in situ gelling drug delivery systems offer several advantages, including improved drug targeting, increased bioavailability, and reduced side effects. These benefits could translate into improved therapeutic outcomes for patients requiring ocular drug delivery. Moreover, the ease of commercialization of in situ gelling systems provides advantages from an industrial perspective, making them an attractive option for pharmaceutical companies. Overall, the future of ocular drug delivery appears promising, with in situ gelling systems emerging as a viable and effective solution for delivering drugs to the eye.

ACKNOWLEDGMENT

The authors are grateful to Mr. Sanjay Bansal, Chancellor, Dev Bhoomi Uttarakhand University and to School of Pharmacy and Research, Dehradun, Uttarakhand, to Dr. Arvind Agarwal, Hon'ble President, Arya College of Pharmacy, Arya Main Campus, Kukus, Jaipur (RAJ.), and to Dr. Ashok K. Chauhan, Hon'ble Founder President, Amity University Uttar Pradesh, and to Amity Institute of Pharmacy, Lucknow (U.P.) for providing facilities to the authors for writing this review.

CONFLICT OF INTEREST

No conflicts of interest are disclosed by the authors.

REFERENCES

1. Soliman KA, Ullah K, Shah A, Jones DS, Singh TR. Poloxamer-based in situ gelling thermoresponsive systems for ocular drug delivery applications. Drug Discov. Today. 20191;24(8):1575-86.
2. Tuwar A, Mahajan N, Gondkar S, Bachhav R. An overview of ophthalmic in-situ gel. World J. Pharm. Res.2023;12(12):421-433

3. Ni X, Guo Q, Zou Y, Xuan Y, Mohammad IS, Ding Q, Hu H. Preparation and characterization of bear bile-loaded pH sensitive in-situ gel eye drops for ocular drug delivery. Iran. J. Basic Med. Sci. 2020;23(7):922.
4. Sheshala R, Kok YY, Ng JM, Thakur RR, Dua K. In Situ Gelling Ophthalmic Drug Delivery System: An Overview and Its Applications. Recent Pat Drug Deliv Formul . 2015;9(3):237-48.
5. Wang L, Pan H, Gu D, Sun H, Chen K, Tan G, Pan W. A novel carbon dots/thermo-sensitive in situ gel for a composite ocular drug delivery system: characterization, ex-vivo imaging, and in vivo evaluation. Int. J. Mol. Sci. 2021;22(18):9934.
6. Imperiale JC, Acosta GB, Sosnik A. Polymer-based carriers for ophthalmic drug delivery. J Control Release. 2018;10; 285:106-41.
7. Wu Y, Liu Y, Li X, Kebebe D, Zhang B, Ren J, Lu J, Li J, Du S, Liu Z. Research progress of in-situ gelling ophthalmic drug delivery system. Asian J. Pharm Sc. 2019;14(1):1-5.
8. Janagam DR, Wu L, Lowe TL. Nanoparticles for drug delivery to the anterior segment of the eye. Adv. Drug Deliv. Rev.2017;122:31-64.
9. Sandri G, Bonferoni MC, Chetoni P, Rossi S, Ferrari F, Ronchi C, Caramella C. Ophthalmic delivery systems based on drug–polymer–polymer ionic ternary interaction: In vitro and in vivo characterization. Eur J Pharm Biopharm. 2006;62(1):59-69.
10. Lalu L, Tambe V, Pradhan D, Nayak K, Bagchi S, Maheshwari R, Kalia K, Tekade RK. Novel nanosystems for the treatment of ocular inflammation: Current paradigms and future research directions. J Control Release. 2017;268:19-39.
11. Sánchez-López E, Espina M, Doktorovova S, Souto EB, García ML. Lipid nanoparticles (SLN, NLC): Overcoming the anatomical and physiological barriers of the eye–Part II-Ocular drug-loaded lipid nanoparticles. Eur J Pharm Biopharm. 2017;110:58-69.
12. Cao SL, Zhang QZ, Jiang XG. Preparation of ion-activated in situ gel systems of scopolamine hydrobromide and evaluation of its antimotion sickness efficacy. Acta Pharmacol. Sin. 2007;28(4):584-90.
13. Patil RN, Kumar RS. In situ gelling system: novel approach for ophthalmic drug delivery. World J Pharm Pharm Sci. 2014;30;3(7):423-40.
14. HB N, Bakliwal S, Pawar S. In-situ gel: new trends in controlled and sustained drug delivery system. Int. J. Pharmtech Res. 2010;2(2):1398-408.

15. Nerkar TS, Gujarathi NA, Rane BR, Bakliwal SR, Pawar SP. In-situ gel: novel approach in sustained and controlled drug delivery system. Pharma science monitor. 2013;4(4):1-8.
16. Parekh HB, Jivani R, Jivani NP, Patel LD, Makwana A, Sameja K. Novel insitu polymeric drug delivery system: a review. J. drug deliv. ther.2012;2(5):136-145.
17. Cao Y, Zhang C, Shen W, Cheng Z, Yu LL, Ping Q. Poly (N-isopropylacrylamide)–chitosan as thermosensitive in situ gel-forming system for ocular drug delivery. Journal of controlled release. 2007 Jul 31;120(3):186-94.
18. Mali MN, Hajare AA. In situ gel-forming systems for sustained ocular drug delivery. Eur. Ind. Pharm. 2010;5:17-20.
19. Menon A, Neha M, Ocular Drug Delivery System: Challenges and Recent Advancements, *Eur. Chem. Bull. 2023;12(10):1423-1450.*
20. Nanjawade BK, Manvi FV, Manjappa AS. In situ-forming hydrogels for sustained ophthalmic drug delivery. J Controlled Release 2007; 122:119-13
21. Tinu TS, Litha T, Kumar Anil B. Polymers used in ophthalmic in situ gelling system. Int J Pharm Sci Rev Res. 2013;20(1):176-83.
22. Boddeda B, Ratna JV, Battu H. A review on mucoadhesive polymers in ophthalmics. Int J Pharm Sci Rev Res. 2014;24(1):237-45.
23. Champalal KD, Sushilkumar P. Current status of ophthalmic in-situ forming hydrogel. Int J Pharm Bio Sci. 2012;3(3):372-88.
24. Gambhire SA, Bhalerao KA, Singh SU. In situ hydrogel: different approaches to ocular drug delivery. Int J Pharm Pharm Sci. 2013;5(2):27-36.
25. Meshram S, Thorat S. Ocular in Situ gels: Development, evaluation and advancements. Sch. Acad. J. Pharm. 2015;4:340-6.
26. Ma WD, Xu H, Wang C, Nie SF, Pan WS. Pluronic F127-g-poly (acrylic acid) copolymers as in situ gelling vehicle for ophthalmic drug delivery system. Int. J. Pharm. 2008;350(1-2):247-56.
27. Devasani SR, Dev A, Rathod S, Deshmukh G. An overview of in situ gelling systems. Pharmaceut Biolog Evaluat. 2016;3(1):60-9.
28. Kumar D, Jain N, Gulati N, Nagaich U. Nanoparticles laden *in situ* gelling system for ocular drug targeting. J Adv Pharm Technol Res. 2013; 4(1):9-17.

29. Darwhekar G, Jain P, Jain DK, Agrawal G. Development and optimization of dorzolamide hydrochloride and timolol maleate in situ gel for glaucoma treatment. Asian J. Pharm. Anal.2011;1(4):93-7.

30. Pawar SD, Pawar R, Gadhve M. Controlled release in situ forming gatifloxacine HCl for ophthalmic drug delivery. Int Res J of Phar. 2012;3:86-9.

31. Laddha UD, Mahajan HS. An insight to ocular in situ gelling systems. Int. j. adv. pharm.2017;6(2):31-40.

32. Singh V, Bushetti SS, Raju SA, Ahmad R, Singh M. Glaucoma: A treatment by hydrogel. Pharm Sci Monitar. 2010;2:285-94.

33. Geethalakshmia A, Karkib R, Sagib P, Jhac SK. Temperature triggered in situ gelling system for betaxolol in glaucoma. J. Appl. Pharm. Sci.. 2013;3(2):153-9.

34. Vodithala S, Khatry S, Shastri N, Sadanandam M. Formulation and evaluation of ion activated ocular gels of ketorolac tromethamine. Int J Curr Pharm Res. 2010;2(3):33-8.

35. Urtti A, Pipkin JD, Rork G, Sendo T, Finne U, Repta AJ. Controlled drug delivery devices for experimental ocular studies with timolol 2. Ocular and systemic absorption in rabbits. Int. J. Pharm. 1990;61(3):241-9.

36. Destruel PL, Zeng N, Seguin J, Douat S, Rosa F, Brignole-Baudouin F, Dufay S, Dufay-Wojcicki A, Maury M, Mignet N, Boudy V. Novel in situ gelling ophthalmic drug delivery system based on gellan gum and hydroxyethylcellulose: Innovative rheological characterization, in vitro and in vivo evidence of a sustained precorneal retention time. Int. J. Pharm. 2020;574:118734.

37. Sun K, Hu K. Preparation and characterization of tacrolimus-loaded slns in situ gel for ocular drug delivery for the treatment of immune conjunctivitis. Drug Des Devel Ther. 2021:141-50.

38. Cardoso CO, Ferreira-Nunes R, Cunha-Filho M, Gratieri T, Gelfuso GM. In situ gelling microemulsion for topical ocular delivery of moxifloxacin and betamethasone. J. Mol. Liq. 2022 15;360:119559.

39. Lei F, Zhang H, Luo R, Fei Q, Bai L, He N. Sustained ocular delivery of desmopressin acetate via thermoreversible in situ gel formulation: Preparation and in vitro/in vivo evaluation. J. Pharm. Investig. 2022;52(5):639-48.

40. Alsaidan OA, Zafar A, Yasir M, Alzarea SI, Alqinyah M, Khalid M. Development of Ciprofloxacin-Loaded Bilosomes In-Situ Gel for Ocular Delivery: Optimization, In-Vitro Characterization, Ex-Vivo Permeation, and Antimicrobial Study. Gels. 2022 Oct 25;8(11):687.

41. Aslzad S, Savadi P, Abdolahinia ED, Omidi Y, Fathi M, Barar J. Chitosan/dialdehyde starch hybrid in situ forming hydrogel for ocular delivery of betamethasone. Mater. Today Commun.. 2022;33:104873.

42. Xu H, Liu Y, Jin L, Chen X, Chen X, Wang Q, Tang Z. Preparation and Characterization of Ion-Sensitive Brimonidine Tartrate In Situ Gel for Ocular Delivery. Pharmaceuticals. 2023;16(1):90.