CODEN [USA]: IAJPBB ISSN : 2349-7750

INDO AMERICAN JOURNAL OF
PHARMACEUTICAL SCIENCES
SJIF Impact Factor: 7.187
https://doi.org/10.5281/zenodo.17228219

https://www.iajps.com/volumes/volume12-september-2025/25-issue-09-september-25/

Available online at: http://www.iajps.com *Review Article*

A COMPREHENSIVE REVIEW ON "UNLOCK SUPERIOR EYE HEALTH: WHY *INSITU*-GELS ARE A GAME CHANGER

Archana AS[1], Prof.(Dr.) John Wesley[2], Prof. (Dr.) Mathan S[3], Prof. (Dr.) Shaiju S Dharan[4]

[1] M.Pharm Student, Department Of Pharmaceutics, Ezhuthachan College of Pharmaceutical Sciences, Neyyattinkara

[2]Department of Pharmaceutics, Ezhuthachan college of Pharmaceutical Sciences Neyyatinkara

[3]Professor, Head of the Department, Vice Principal, Department Of Pharmaceutics, Ezhuthachan College of Pharmaceutical Sciences, Neyyattinkara

[4]Principal, Ezhuthachan College of Pharmaceutical Sciences, Neyyattinkara

Mail ID : asa659704@gmail.com

Abstract:

The conventional treatment of ophthalmic diseases primarily focused on the topical application of eye drops. However, these formulations often exhibit low bioavailability and limited therapeutic efficacy due to rapid precorneal elimination mechanisms such as drainage and tear turnover. To address these challenges, in situ gelling systems have been developed. These systems are administered as liquid drops but undergo a sol-to-gel transition upon contact with the ocular surface, typically triggered by physiological factors like pH, temperature, or ionic strength. This transition enhances the residence time of the drug in the precorneal area, thereby improving its bioavailability and therapeutic response. In this context, the present study focuses on the formulation and evaluation of an ophthalmic delivery system for insitu activated gel system. These drug delivery systems are based on the principle of pH-triggered in situ gelation, using polymers such as polyacrylic acid (Carbapol 940) as gelling agent and HPMC K4M and HPMC K15M) as viscosity enhancers. This approach aims to provide a sustained release of the drug, thereby prolonging its therapeutic effect and enhancing patient compliance.

Corresponding author:

Archana AS,

M.Pharm Student,
Department Of Pharmaceutics,
Ezhuthachan College of Pharmaceutical Sciences,
Neyyattinkara

QR CODE

Please cite this article in press *Archana AS* ***et al., A Comprehensive Review On "Unlock Superior Eye Health: Why Insitu-Gels Are A Game Changer., Indo Am. J. P. Sci, 2025; 12(09).***

INTRODUCTION:

Eye disorders and the resulting visual impairments are increasingly recognized as global public health challenges, with significant implications for both physical and psychological health. At present, nearly 90% of available ophthalmic therapies are formulated as eye drops; widely used in the treatment of various ocular conditions including infections, cataracts, inflammation, dry eye disease, and conjunctivitis. Administering topically remains the most employed common route due to its non-invasing nature and easy for application [1]. Effective drug delivery to the eye remains a challenge due to anatomical and physiological barriers, including the cornea, tear film, and blood-retina barrier, as well as continuous ocular motion that limit drug retention. In situ gel technology represents a promising alternative, offering sustained release, improved absorption, and enhanced patient adherence [2]. In situ gel systems, initially formulated as free-flowing liquids, are particularly advantageous for ocular drug delivery due to their ability to transition into gels upon exposure to physiological conditions. The polymers utilized in these systems typically demonstrate pseudo plastic behaviour, wherein their viscosity decreases under shear stress such as that caused by blinking allowing for uniform distribution across the ocular surface. Gel formation is induced by external stimuli, including variations in pH, ionic strength, or temperature, and the manufacturing process for these systems is relatively straight forward. Thermo responsive in situ gels, for instance, incorporate polymers that remain in a liquid state below the lower critical solution temperature (LCST) and undergo gelation when this threshold is surpassed. Conversely, when the temperature falls below the upper critical solution temperature (UCST), the gel reverts to a sol state [3].

Anatomy of human eye

The human eye is structurally divided into two major parts;the anterior segment and posterior segment. The anterior segment includes cornea, conjunctiva, iris, pupil, ciliary body, anterior chamber, aqueous humor, lens, and trabecular meshwork. In contrast, the posterior segment consists of the vitreous humor, sclera, retina, choroid, macula, and optic nerve [4].The outermost layer consists of the cornea and sclera, providing protection and structural integrity. The middle layer, which includes the iris and pupil, is rich in blood vessels and plays a critical role in supplying nutrients to the eye. The inner layer is the retina, which is responsible for detection of light and transferring visual information. The anterior chamber lies between the cornea and iris, while the posterior chamber is located between the iris and the lens. These chambers are filled with aqueous humor, helps to nourish internal ocular structures and maintain intraocular pressure. The vitreous chamber which is situated in the third chamber, located in between lens and retina, containing vitreous humor—a gel substance that occupies the eye's figure and enabling the light pathway transmitting to the retina. Visual information is then passed to the brain through the optic nerve, which extends from the exterior part of the eye through the optic foramen. This nerve provides as the primary portion for visualising images from the retina to the visual processing centres of the brain. Externally, the eyelids serve as protective structures. The inner surface of the eyelid is lined by the conjunctiva, a mucous membrane that connects the eyelid to the eye. Tear glands located in the upper eyelid secrete fluids essential for lubrication. The thin layered parts of eye contains of cornea, iris, and pupil. The sclera, the white, portion of the eye, surrounding most of the eyeball and also acts as a protective sheet for the optic nerve. The colored portion, which is the iris, located beneath the cornea, to control the amount of light entering into the eye by regulating the pupil's size. The pupil allows as light entry point into the eye. The retina, a light-sensitive layer at the back of the eye, contains photoreceptor cells called rods and cones. These cells detect light and convert it into electrical signals, which then transmitted to the brain via the optic nerve [5].

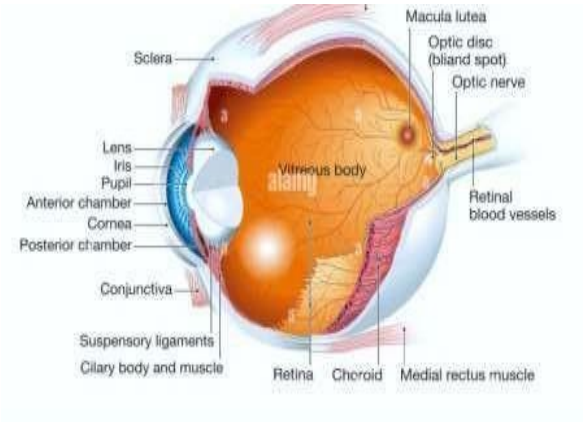

Fig 1: alamy.com*anatomy of eye

CHALLENGES IN OPHTHALMIC DRUG DELIVERY SYSTEM

To sustain therapeutic drug concentrations in the tear film or target tissues, frequent application of eye drops is often required. Low bioavailability of ocular drugs primarily results from precorneal loss mechanisms such as solution drainage, tear production and dynamics, dilution, turnover, absorption by the conjunctiva, non-productive drug absorption, and limited residence time in the conjunctival sac, and the corneal epithelial barrier's low permeability. These anatomical and physiological factors pose considerable challenges

to delivering drugs effectively to the anterior segment via topical administration. For a topical ocular formulation to be effective clinically, it must strike an optimal balance between lipophilic and hydrophilic properties while also maximizing the drug's retention time on the eye surface [7].

A

nterior segment drug delivery challenges

When a drug is applied to the eye, it must first overcome precorneal barriers such as the tear film and conjunctiva before it can reach the corneal epithelium. These initial barriers significantly hinder the drug's ability to penetrate ocular tissues. As a result, precorneal loss mechanisms are a major contributor to the limited bioavailability observed in many topical ophthalmic formulations [8].

Posterior segment drug delivery system

This barrier is more permeable to lipophilic molecules, which largely dictates the extent of drug penetration into the back of the eye. Major challenge in posterior segment drug delivery is maintaining effective therapeutic levels over an extended period while minimizing the frequency of dosing. Drugs may be cleared from the eye via two primary routes: the anterior pathway where drugs move into the aqueous humor and are drained through the trabecular meshwork and through the posterior route. These elimination pathways further complicate sustained drug delivery to the posterior segment [9].

BARRIERS OF OCULAR DRUG DELIVERY SYSTEMS

Precorneal Barriers

i. Volume of Cul-de-sac

The cul-de-sac refers to the shallow space located in the lower eyelid, where the palpebral and bulbar conjunctiva converge, and also includes a deeper recess within the upper eyelid. ocular conditions such as inflammation or allergic reactions can reduce the volume capacity of the cul-de-sac [10].

ii. Loss of drug from lacrimal fluid

Currently one of the primary challenges in the ocular drug delivery is the rapid drainage of administered ocular solutions. Drug loss from the tear film may occur due to reflex tearing, solution outflow, and absorption by the conjunctiva that does not contribute to therapeutic effect. Furthermore, enzymatic metabolism and protein binding within the tear film can further limit the amount of drug available for effective absorption [11].

Corneal barriers

The corneal region acts as a protective membrane barrier against so many chemical and mechanical reactions while at the same time also playing a crucial role in focusing light in to the retina. The epithelial layer in the cornea consists five to seven tightly joined cell layers, serving as a primary barrier to hydrophilic drugs and large molecular compounds. The stroma, a dense, water-rich layer, restricts the penetration of lipophilic substances. The endothelium maintains corneal transparency and facilitates the selective passage of hydrophilic drugs and macromolecules into the aqueous humor. Overall, factors such as molecular weight, charge, ionization state, and Lipophilicity significantly affect corneal drug permeability. Consequently,trans-corneal transport is considered the rate-limiting step in the movement of drugs from the tear film into the aqueous humor [12].

Blood ocular barriers

The BAB, located in the front part of the eye, regulates the internal ocular environment by limiting the entry of many substances. It selectively permits small, lipophilic drugs to pass through, which are typically cleared from the anterior chamber more rapidly than larger, water-soluble molecules. The BRB is found in the back portion of the eye and is consists of retinal endothelial cells and retinal pigment epithelial cells. Its major role is to protect the retina from harmful agents, including water and various plasma components [13].

ROUTES FOR OCULAR DRUG DELIVERY

1. Topical administration

Topical application is the most widely used method for delivering drugs to the eye, accounting for over 95% of commercially available ocular formulations [14]. While it is a non- invasive approach, its effectiveness is limited by poor bioavailability—typically less than 5%—due to inadequate corneal penetration and a short duration of contact with the eye surface [15]. Additional factors such as tear production, blinking, and drug drainage into the systemic circulation via the nasolacrimal duct further reduce drug absorption. As a result, higher and more frequent dosing is often required, which can lead to adverse side effects and may negatively impact patient adherence to the treatment regimen[15][12].

2. Intracameral injections

Intracameral injections refer to the direct administration of antibiotics into the anterior chamber or vitreous body of the eye. This procedure is commonly performed following cataract surgery as a preventive measure against endophthalmitis, an infection that can develop postoperatively [16].

3. Intravitreal injections

Intravitrealinjection focuses administering medication straight into the vitreous humor which is near to the retina at the back of the eye. A novel

strategy for managing glaucoma includes a single injection of microspheres composed of vitamin E and poly (lactic-co-glycolic acid), encapsulating glial cell line-derived neurotropic factor. This method achieved sustained drug release for up to six months. Comparable outcomes were observed with intravitreal delivery of polymer-free dexamethasone dimer implants [17].

4. Retro bulbar route

This route delivers the medication by the insertion of a needle through the eyelid and orbital fascia, placing the drug directly into the gap behind the eyeball. Administering amphotericin B via retro bulbar injection has demonstrated greater antifungal effectiveness compared to intravenous delivery [18]. Chlorpromazine is administered via retro bulbar injection as a treatment option for relieving pain in blind, non-seeing eyes [19]. To manage macular oedema resulting from retinal vein occlusion, triamcinolone can be administered via the retro bulbar route [20].

5. Subconjunctival injection

In the management of uveitis, steroids formulated in pegylated liposomes and administered via Subconjunctival injection have demonstrated prolonged anti-inflammatory effects and targeted delivery to ocular tissues for at least one month [21]. The use of Subconjunctival injections to deliver brinzolamide encapsulated in PLGA nanoparticles effectively managed intraocular pressure for up to 10 days [22]. Subconjunctival injection of human mesenchymal stromal cells significantly reduced corneal inflammation and squamous metaplasia in mice affected by graft-versus-host disease [23].

6. Juxta scleral injections

Juxtascleral injections are employed to address certain conditions affecting the posterior segment of the eye that are not responsive to traditional topical treatments. This method is utilized in managing cystoid macular oedema, ocular trauma, and diabetic-related eye diseases. A novel therapy for age-related macular degeneration (AMD) involves juxtascleral delivery of anecortave cortisone, which has demonstrated sustained release within the choroid and retina for up to six months. Additionally, advanced trans-scleral micro needles have been developed to deliver adeno-associated viruses for gene therapy targeting retinal disorders [24].

7. Irrigated eye solutions

These solutions are prepared aseptically and do not contain preservatives. Surgeons use them as balanced salts to remove blood and cellular debris while maintaining proper hydration within the eye [25]. Examples include adding ketorolac (0.3% w/v) and phenylephrine (1% w/v) to irrigation fluids helps reduce the duration of cataract surgery and prevents pupil constriction [26].

8. Iontophoresis

This type of drug delivery technique which utilizes, electric voltage gradient to facilitate the movement of medication into the posterior part of the eye, bypassing barriers that limits drug penetration. These innovative systems have demonstrated the ability to deliver approximately twice the amount of therapeutic agents to the posterior ocular tissues compared to traditional suprachoroidal injection methods, potentially improving treatment outcomes for retinal and choroidal diseases [27]. Combining iontophoresis drug delivery with contact lens technology has significantly enhanced the efficiency of ocular drug administration, achieving drug uptake into the choroidal capillaries 550 to 1300 times faster than conventional methods. Additionally, short-duration iontophoresis using an acyclovir prodrug has been shown to substantially improve both drug permeation and bioavailability, offering a promising strategy for enhancing ocular drug delivery to posterior segment tissues [28].

TOPICAL OPHTHALMIC DRUG FORMS

Liquid Ophthalmic Drug Forms

a) Eye Drops

These formulations are isotonic and sterile solutions of pH with 7.4. When determining whether to buffer the drug, it's important to consider both the chemical stability of the active compound and how well the eye tissue can tolerate the formulation. If the pH falls outside the 4 to 8 range which is generally acceptable for ocular use it can lead to discomfort, irritation, and potentially reduced drug effectiveness due to increased tear production [29].

b) Ophthalmic solutions

They are sterile, water-based preparations commonly used for purposes such as washing and rinsing the eyes. These solutions may include excipients to help adjust properties like ph, osmolality, and viscosity. When packaged for multiple uses, preservatives are often added to maintain sterility over time [30].

c) Micro emulsions

They are considered a promising option for drug delivery due to their low production cost, ease of sterilization, and high stability. The mechanism works by allowing the Nano droplets, which act as a drug reservoir along with the internal phase of the micro emulsion, to adhere to the corneal surface, thereby minimizing drug loss due to overflow[31]. Micro emulsion formulations have been developed for several active compounds,

including difluprednate [32], cyclosporine A [33], flurbiprofen axetil and a flurbiprofen prodrug [34].

d) Prodrugs

A prodrug is a strategy used to enhance corneal permeability. Prodrugs have been developed for several ophthalmic agents, including epinephrine, phenylephrine, timolol, and pilocarpine. Example includes dipivefrine, a diester formed from epinephrine and pivalic acid exhibits a 17 times increase in corneal permeability when compared to epinephrine. This improvement is largely due to its significantly greater Lipophilicity (approximately 600 times higher) at pH 7.2. [35].

e) Cyclodextrin

Cyclodextrin are ring-shaped oligosaccharides that can form inclusion complexes with active pharmaceutical ingredients, enhancing the water solubility of poorly soluble, hydrophobic drugs without altering their molecular structure. These compounds act as carriers, keeping hydrophobic drugs dissolved and facilitating their delivery to biological membranes. For ophthalmic applications, achieving effective drug bioavailability typically requires cyclodextrin concentrations below 15% in aqueous eye drop formulations [36]. The most commonly used type for ocular delivery is 2-hydroxypropyl-β-cyclodextrin, known for being non-irritating [37].

Semisolid Ophthalmic Drug Forms

a) *In Situ* Gels (Sol-to-Gel Systems)

In situ gels are liquid formulations that can transform into a gel upon exposure to certain external stimuli such as changes in pH, temperature, or the presence of specific ions. This transformation helps reduce the rate at which the drug is washed away from the eye's surface, thereby enhancing the bioavailability of the active compound. Polymers commonly used in these systems include gellan gum, poloxamer, Carbapol, HPMC, chitosan and cellulose acetate phthalate. Research into in situ gels has explored their use with various active ingredients, such as ciprofloxacin hydrochloride, timolol maleate, fluconazole, ganciclovir, and pilocarpine [29] [31] [36].

b) Eye Ointments

Ophthalmic ointments are semisolid preparations intended for external application, typically made from a hydrocarbon base that melts or softens at temperatures close to that of the human body. Once applied, the ointment breaks down into small droplets that remain in the conjunctival sac for an extended period, helping to enhance the drug's bioavailability. [29].

Solid Ophthalmic Drug Forms

a) Drug-Loaded Contact Lenses

Contact lenses can serve as drug delivery systems by absorbing water-soluble medications on their surface, which are then gradually released onto the eye over an extended period. The most commonly used material for manufacturing these lenses was cross-linked poly (2- hydroxyethyl methacrylate), in combination with small quantity of ethylene glycol di methacrylate [54]. More recently, research has focused on developing lenses made from silicone-based materials. Drugs that have been studied for release from contact lenses include timolol, ciprofloxacin, dexamethasone, and cyclosporine [61].

b) Ocular inserts

Ocular inserts are solid or semisolid drug delivery systems that offer significant advantages over traditional ophthalmic formulations. Unlike conventional eye drops, they are less affected by natural eye defence mechanisms such as drainage through the nasolacrimal duct. These inserts remain in the conjunctival sac for extended periods and exhibit improved stability. Key benefits include precise dosing, the ability to release medication at a consistent rate over time, and reduced systemic absorption [62]. Ocular insert, composed of a copolymer made from ethylene and vinyl acetate, and delivers pilocarpine as the active agent [29] [31] [40].

Soluble Ophthalmic Drug Inserts (SODI)

They are oval-shaped, small wafer like inserts which dissolve in the eye. They consist of materials such as acrylamide, N-vinylpyrrolidone, and ethyl acrylate. Once it placed in the conjunctival sac, they get hydrated by the tear fluid, causing them to soften and adhere to the surface of the eye. This dosage form was initially created for use by astronauts in zero-gravity environments. SODI release medication in an intermittent, uncontrolled manner but provide an extended duration of action. Various active pharmaceutical ingredients investigated for use in SODI systems include neomycin, kanamycin, atropine and pilocarpine [41] [42].

Minidiscs

Minidiscs, a kind of Ocular Therapeutic System, which are specialized drug delivery systems designed to similar to that contact lenses with a convex exterior and a concave inner surface that conforms to the eye. These tiny discs, typically 4-5 mm in diameter, are formulated using key copolymers such as α-ω-bis (4-methacryloxy)-butyl poly (dimethylsiloxane) and poly (hydroxyethyl methacrylate). They can be either hydrophilic or hydrophobic, allowing for controlled and prolonged drug release [40] [43].

Artificial Tear Inserts
Artificial Tear Inserts are long, rod-shaped pellets made from hydroxypropyl cellulose and free of preservatives. Marketed under the brand name Lacrisert, they are used to manage dry eye syndrome. Once it is placed in the conjunctival sac, they absorb moisture from the surrounding tissues and forms a hydrophilic layer that helps maintain the tear film and keeps the cornea hydrated [31].

Collagen Shield
These drug delivery systems are derived from porcine scleral tissue, in which its collagen closely resembles to human cornea. Shields are stored in hydrated and dried forms before application to the eye [31]. Studies conducted on both animals and humans have demonstrated that these shields can serve as drug delivery systems for medications such as gentamicin (an antibiotic), dexamethasone (an anti-inflammatory), and antiviral agents.
Compared to traditional eye drops and contact lenses, collagen shields have shown the ability to deliver higher concentrations of medication to the cornea and aqueous humor [31] [43].

New Ophthalmic Delivery System (NODS)
It consists of solid paper-like handle connected to a polyvinyl alcohol "flag" that contains the active drug. This flag is then attached to the handle using a membrane that dissolves in fluid. When the device is placed in the conjunctival sac the drug-part film seperates from the handle and get dissolves in tear film releasing the medication. This delivery system enables precise dosing directly to the eye and significantly enhances the drug's bioavailability—up to eight times higher than traditional eye drops in the case of pilocarpine. Known as NODS, this system is preservative-free and sterilized using gamma radiation [44- 46].

Mini tablets
Mini tablets are solid, biodegradable drug delivery systems that, once placed in the conjunctival sac, transform into a gel. This gel formation prolongs the contact time between the drug and the eye's surface, thereby enhancing the bioavailability of the active ingredient [47, 49]. Their formulation, often containing mucoadhesive polymers, allows for extended contact with the corneal surface [48, 49]. The formulation of Minitablets intended for ocular application commonly utilizes various polymers, particularly cellulose-based derivatives such as hydroxypropyl methylcellulose (HPMC), hydroxyethyl cellulose (HEC), sodium carboxymethyl cellulose, and ethyl cellulose. Other frequently used materials include acrylate polymers like polyacrylic acid and its cross-linked variants (e.g., Carbapol or Carbomer), chitosan, and starches such as drum-dried waxy maize starch. These formulations are often supplemented with excipients like mannitol, which acts as a solubilizing agent, as well as lubricants such as sodium stearyl fumarate and magnesium stearate. Minitablets are typically produced through either direct compression or an indirect process, which involves compressing preformed granules. The indirect approach offers the benefit of a dry granulation step that improves powder flow ability especially important when working with bio adhesive polymers and facilitates production beyond the laboratory scale. Active pharmaceutical ingredients used in ocular Minitablets include piroxicam, timolol, ciprofloxacin, gentamicin [47-51].

Multi compartment Drug Delivery Systems
Nanoparticles and Micro particles
Polymeric solid-based multi compartment drug delivery systems represent a promising approach for ocular administration. These systems can be categorized based on the size of the polymeric carriers: nanoparticles, typically ranging from 10 nm to 1000 nm and micro particles, which for ocular use usually range in size from 1 to 5 micro meters[29][31]. Nanoparticles are polymer-based carriers constructed using biodegradable and biocompatible materials, which may be either natural or synthetic in origin. These carriers often possess mucoadhesive characteristics [52-54].

For ocular delivery applications, various materials have been utilized in the formulation of these systems, including Poly (Alkyl Cyanoacrylate), Polylactic Acid, Poly (E- Caprolactone), Poly (Lactic-Co-Glycolic Acid), Chitosan, Gelatin, Sodium Alginate, and Albumin. These Nano particulate systems are typically categorized into two types: Nano spheres, which are solid, dense polymer matrices where the drug is uniformly dispersed; and Nano capsules, which function as reservoirs, enclosing the drug either in solid or liquid form within a polymeric shell [53-55]. Once Nano spheres or Nano capsules are administered into the conjunctival sac, drug absorption occurs either through diffusion or as a result of polymer degradation [29].

Liposomes
The effectiveness of active ingredient delivery via liposomes is influenced by several factors, including their encapsulation efficiency, size, surface charge, stability within the conjunctival sac, and interaction with the corneal surface [54]. Positively charged liposomes tend to adhere more strongly to the negatively charged corneal epithelium and conjunctival mucin compared to their neutral or negatively charged counterparts. This enhanced interaction helps prolong the

retention time of the active compound at the application site [55]. To improve the adhesion of neutral and negatively charged liposomes, strategies such as incorporating them into mucoadhesive gels or coating them with mucoadhesive polymers have been suggested. Liposomal formulations have been explored for ocular delivery of drugs such as acyclovir, pilocarpine, acetazolamide, chloramphenicol [56] and ciprofloxacin [57].

Dendrimers

Dendrimers are largely fanned, globular, monodisperse, three- dimensional polymer structures characterized by specific size, shape, and molecular mass (57- 58). They can serve as carriers by recapitulating active constituents within their polymer matrix or forming electrostatic or covalent bonds with face- bound medicines due to the presence of multitudinous functional groups similar as carboxyl, hydroxyl, and amine groups. PolyAMidoAMine(PAMAM) in dendrimers, are used as carriers for ophthalmic medicines, dragging the duration of active component's efficacy and improves their bioavailability. Studies have shown that PAMAM, used as carriers for ophthalmic medicines, can extend the duration of active constituents' efficacy and enhance the bioavailability. The enhanced bioavailability of such substances after the incooperation to eye may be attributed to the encapsulation of the medicine within these structures, results in slower release of the active constituents (58- 59).

REVOLUTIONIZING THE EFFECT OF *INSITU* ACTIVATED OPHTHALMIC GELS A SMART APPROACH TO OCULAR DRUG DELIVERY

Conventional eye drops often face challenges in maintaining effective drug concentrations in the eye due to rapid precorneal drainage and the natural blinking reflex. These factors can lead to diminished drug retention and reduced therapeutic efficacy. Additionally, while eye ointments can enhance drug retention, they may cause temporary blurred vision, potentially affecting patient adherence to treatment regimens. Therefore, developing advanced drug delivery systems that improve ocular bioavailability without compromising visual clarity is essential for effective eye care [60-61].

Effective ocular drug delivery is hindered by several physiological barriers, including the limited volume of the conjunctival sac, rapid precorneal drainage, nasolacrimal drainage, and dilution by tear fluid. These factors contribute to the low ocular bioavailability and short duration of action of conventional topical formulations such as solutions and suspensions. Additionally, the cornea presents a significant obstacle to drug permeation due to its tight epithelial junctions, which restrict Para cellular transport and limit the absorption of therapeutic agents[62-63].

***Insitu* gels**

In situ gelling systems are innovative ophthalmic formulations that, upon ocular administration, transition from a free-flowing liquid to a gel under physiological conditions such as changes in temperature, pH, or ionic strength. This transformation enhances the residence time of the drug on the ocular surface, thereby improving bioavailability and therapeutic efficacy. The polymers used in these systems often exhibit pseudo plastic behaviour, meaning their viscosity decreases under shear stress such as during blinking allowing the formulation to spread uniformly across the eye surface. Consequently, *in situ* gels serve as effective vehicles for sustained drug delivery, offering advantages over conventional eye drops and ointments by prolonging drug contact time without compromising visual clarity [64].

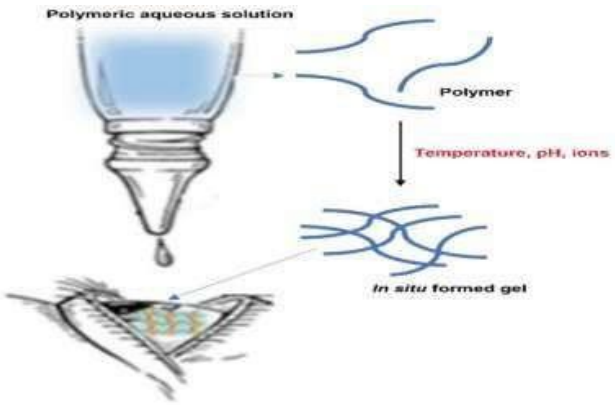

Fig 2 : MDPI*

According to the mechanism sol-to-gel transformation on the ocular surface, in situ gel systems can be classified as follows:

•PH-sensitive systems—utilizing agents such as cellulose acetate phthalate (CAP) latex, Carbapol, polymethacrylic acid (PMMA), polyethylene glycol (PEG), and pseudo latexes.

•Thermo sensitive systems—involving materials like chitosan, pluronics, tetronics, xyloglucans, and hydroxypropyl methylcellulose (HPMC).

• Ion-activated systems—which undergo gelation through osmotic induction, using substances such as Gelrite, gellan gum, hyaluronic acid, and alginates.

Procedure

Initially, buffer salts are dissolved in 75 mL of

purified water. To this solution, Methocel K4M or k15M is added and allowed to hydrate fully. Subsequently, Carbapol® 940 is gradually incorporated into the mixture and permitted to hydrate overnight. The solution is then stirred using an overhead stirrer. In a separate container, drug is dissolved in purified water, followed by the addition of benzalkonium chloride (BKC) as a preservative. This drug solution is then filtered through a 0.2-µm cellulose acetate membrane filter to ensure sterility. The filtered drug solution is combined with the Carbapol-HPMC mixture under constant stirring until a homogeneous solution is achieved. Purified water is added to adjust the final volume to 100 ml. The prepared formulations are transferred into 5-mL amber glass vials, sealed with gray butyl rubber stoppers, and secured with aluminum caps. To ensure sterility, the final product undergoes terminal sterilization by autoclaving at 121°C and 15 psi for 20 minutes.

The gelling ability of prepared formulation was measured by introducing 100 µL of the formulation into a vial containing 2 mL of freshly made artificial tear fluid (ATF), which equilibrated at body temperature 37°C. The composition of the ATF used was sodium chloride (0.670 g), sodium bicarbonate (0.200 g), calcium chloride•$2H_2O$ (0.008 g), and purified water to make up 100.0 g. Viscosity measurements were conducted using a Brookfield Synchrolectric viscometer (RVT model) equipped with a small volume adapter. The viscosity measured rpm [65].

Mechanism of gelling system

In-situ gel formation can be initiated through various mechanisms, such as changes in temperature, pH levels, or ionic concentrations. Thermo sensitive systems rely on polymers that remain in liquid form below their lower critical solution temperature (LCST) but transform into a gel as the temperature rises to or surpasses the LCST. PH-sensitive gels involve polymers with acidic or basic groups in their structure that respond to shifts in environmental pH, typically forming gels as the pH increases. Ion-sensitive gels, sometimes referred to as Osmotically triggered systems, respond to the presence of cations like sodium (Na^+), calcium (Ca^{2+}), and magnesium (Mg^{2+}) found in tear fluid, which induce gelation by altering the ionic environment. Additional gelation triggers include enzymatic reactions and light-activated polymerization [66].

P^H-sensitive in situ gelling systems

pH-sensitive in situ gelling systems are widely utilized in ocular drug delivery due to their ability to undergo sol-to-gel transitions in response to pH changes, thereby enhancing drug residence time and bioavailability. For instance, polyacrylic acid (Carbapol® 940) serves as a gelling agent, while hydroxypropyl methylcellulose (HPMC K4M &K15M) acts as a viscosity enhancer. This combination results in formulations that are therapeutically effective, stable, non-irritant, and provide sustained drug release over extended periods compared to conventional eye drops. Another example includes cellulose acetate phthalate (CAP), a polymer that remains in solution at an acidic pH (approximately 4.5) and undergoes gelation when exposed to the neutral pH of tear fluid (around 7.4). This pH-triggered gelation mechanism facilitates prolonged ocular drug delivery, although the initial low pH may cause transient discomfort. These pH-sensitive in situ gelling systems offer significant advantages in ocular drug delivery, including improved drug bioavailability, reduced dosing frequency, and enhanced patient compliance [67-68].

Temperature triggered system

Thermo sensitive in situ gels are designed to utilize Poloxamer as a vehicle for ophthalmic drug delivery, capitalizing on its sol-to-gel transition properties. The gel forming temperature of graft copolymers can be fixed by assessing temperature at which immobility of the meniscus in each solution is noted first. For instance, Poloxamer 407 (Pluronic F127®), a polyoxyethylene-polyoxypropylene block copolymer, exhibits a solution viscosity that increases when its temperature is raised to the eye's temperature [69-70]

Ion-activated in situ gelling system

Ion-activated in situ gelation utilizes alginate (Kelton) as the primary gelling agent, combined with HPMC (Methocel E50Lv) to enhance viscosity. Gelrite, known for forming gels in response to mono- or divalent cations naturally present in tear fluid, can be used independently or in combination with sodium alginate for ophthalmic formulations [71-72].

EVALUATION TESTS FOR *INSITU* ACTIVATED OPHTHALMIC GELLING SYSTEMS

Physical parameters

The *in situ* gel formulation was evaluated based on its physical characteristics, including transparency, pH level, gel-forming ability, and drug content analysis.

Estimation of gelling capacity

A drop of the formulation is added to a vial containing 2.0 ml of freshly prepared simulated tear fluid. The formation of the gel is then visually observed, and required time for gelation is recorded [67-73].

Rheological evaluation

Viscosity of formulations was determined using instruments such as Brookfield Viscometer and Cone and Plate Viscometer. Samples were introduced into the viscometer's sampling tube for measurement. According to previous studies, formulations should exhibit a viscosity range of 5 to 1000 mpas prior to gelation, while post-gelation upon activation by ions in the ocular environment viscosity should increase significantly, ranging between approximately 50 and 50,000 mpas. Measurements were carried out at both ambient temperature (25°C) and physiological temperature (37°C ± 0.5°C), maintained using a circulating water bath connected to the viscometer. During testing, spindle angular velocity was varied incrementally at speeds of 20, 30, 50, 60, 100, and 200 rpm. The results indicated that all formulations demonstrated Newtonian flow behaviour before gel formation, and exhibited pseudo plastic characteristics after gelation in simulated tear fluid[74-75].

In Vitro Drug Release Studies

The in vitro release profile formulation can evaluated by using Franz diffusion cell. At the donor compartment, the gel s placed and receptor compartment was filled with freshly formulated simulated tear fluid (STF). A dialysis membrane with a pore size of 0.22 µm was positioned between the two compartments. The entire setup was maintained on a thermostatically controlled magnetic stirrer, with the temperature stabilized at 37°C ± 0.5°C. At regular intervals of one hour over a six-hour period, 1 ml of the receptor medium was withdrawn and immediately replaced with an equal volume of fresh medium to maintain sink conditions. Each collected sample was diluted to 10 ml using the appropriate solvent in a volumetric flask and analysed using a UV spectrophotometer at the relevant wavelength, employing a reagent blank for baseline correction. Drug concentration was calculated using a standard calibration curve, and the percentage of cumulative drug release (%CDR) was determined. The release data were further analysed using mathematical models to identify the best fit, including the Korsmeyer–Pappas model and Fickian diffusion mechanisms, to understand the kinetics of drug release [67].

Texture analysis

The in situ gel's formulation parameters, firmness, and bio adhesiveness was measured by usage of a texture profile analyzer, which primarily asses the strength of the gel and the ease of invivo application A higher degree of adhesiveness is desirable to ensure prolonged contact with the mucosal surface [76].

Evaluation of Isotonicity

Maintaining Isotonicity is a crucial aspect of ophthalmic formulations, as it helps prevent irritation and potential damage to ocular tissues. Therefore, all such preparations undergo Isotonicity testing to ensure they meet the required standards for drug release, gelling properties, and viscosity. In this evaluation, the formulations are combined with a few drops of blood and examined microscopically at 45X magnification, with the results compared against a commercially available ophthalmic product [77].

Drug-Polymer Interaction and Thermal Characterization

Fourier Transform Infrared (FTIR) spectroscopy is commonly used to assess potential interactions between drugs and polymers. The KBr pellet method enables identification of the types of bonding or interactions that occur during the gelation process. Thermal analysis techniques such as Thermogravimetric Analysis (TGA) can be applied to *in situ* forming polymer systems to determine the water content in hydrogels. Additionally, Differential Scanning Calorimetry (DSC) is utilized to detect any thermal behaviours changes by comparing the thermo grams of formulations with those of the pure active pharmaceutical ingredients [76].

Ocular irritation test

The Draize test is utilized to assess the potential for ocular irritation of ophthalmic products before they are released to the market. In this irritation study test, 100 µl of the test sample is applied to the lower portion of the conjunctival sac of rabbit eye. Observations are made at specific intervals 1 hour, 24 hours, 48 hours, 72 hours, and one week post-application.

The study uses three male rabbits weighing between 1.5 and 2 kg. The sterile formulation is administered 2 times daily for seven days. Following this, a cross-over study is conducted, with a three-day washout period using saline between phases. Throughout the study, the rabbits are regularly monitored for signs of irritation such as redness, swelling, and excessive tearing [78-79].

Accelerated Stability Studies

For short-term accelerated stability testing, formulations are stored in amber-colored vials sealed with aluminum foil and kept at 40 ± 2 °C and 75 ± 5% relative humidity, following the guidelines set by the International Conference on Harmonisation (ICH). At monthly intervals, samples are evaluated for various parameters including clarity, pH, gelling ability, drug content, rheological properties, and in vitro drug release [77].

CONCLUSION:

The field of ophthalmic drug delivery is rapidly evolving, presenting researchers with numerous challenges in overcoming limitations associated with ocular drug administration. Advances in the understanding of ocular pharmacokinetics and drug absorption, combined with progress in formulation technologies, have significantly improved the effectiveness of ophthalmic delivery systems. A key goal in developing controlled-release formulations is enhancing patient adherence to treatment, which *in situ* gelling systems successfully address. These polymer-based gels offer several benefits over traditional eye drops, including sustained drug release, improved stability, and favourable biocompatibility. The use of biodegradable and water-soluble polymers further enhances the safety and acceptability of these formulations. *In situ* gels, which transform into a gel upon administration, are particularly advantageous due to their ease of application as eye drops and their minimal interference with vision. Additionally, they provide more consistent drug release than conventional liquid formulations. Such systems are increasingly employed in the treatment of conditions like Glaucoma, Dry eye syndrome, Sjögren's syndrome, Age-Related Macular Degeneration (ARMD), and Trachoma.

REFERENCES:

1. Pandey M, Choudhury H, binti Abd Aziz A, Bhattamisra SK, Gorain B, Su JS, Tan CL, Chin WY, Yip KY. Potential of stimuli-responsive in situ gel system for sustained ocular drug delivery: Recent progress and contemporary research. Polymers. 2021 Apr 20; 13(8):1340.
2. Paul S, Majumdar S, Chakraborty M. Revolutionizing ocular drug delivery: recent advancements in in situ gel technology. Bulletin of the National Research Centre. 2023 Oct 23; 47(1):154.
3. Ahmed B, Jaiswal S, Naryal S, Shah RM, Alany RG, Kaur IP. In situ gelling systems for ocular drug delivery. Journal of Controlled Release. 2024 Jul 1; 371:67-84.
4. Mandeep S, Dhruv D, DN P. A Recent Overview: In Situ Gel Smart Carriers for Ocular Drug Delivery. Journal of Drug Delivery & Therapeutics. 2021 Nov 2; 11(6-S):195- 205.
5. Sebastian ET. The complexity and origins of the human eye: A brief study on the anatomy, physiology, and origin of the eye.
6. Alamy.com
7. Patel PB, Shastri D, Shelat P, Shukla A. Ophthalmic drug delivery system: challenges and approaches. Systematic Reviews in Pharmacy. 2010 Jul 1;1(2):113.
8. Raj VK, Mazumder RU, Madhra MO. Ocular drug delivery system: challenges and approaches. Int J Appl Pharm. 2020; 12(5):49-57.
9. Mandal S, Shiva K, Kumar KP, Goel S, Patel RK, Sharma S, Chaudhary R, Bhati A, Pal N, Dixit AK. Ocular drug delivery system (ODDS): Exploration the challenges and approaches to improve ODDS. Journal of Pharmaceutical and Biological Sciences. 2021 Jul 1; 9(2):88-94.
10. Singh V, Ahmad R, Heming T. The challenges of ophthalmic drug delivery: a review. International Journal of Drug Discovery. 2011; 3(1):56-62.
11. Ahmed S, Amin MM, Sayed S. Ocular drug delivery: a comprehensive review. AAPS Pharm SciTech. 2023 Feb 14; 24(2):66.
12. Singh M, Bharadwaj S, Lee KE, Kang SG. Therapeutic Nano emulsions in ophthalmic drug administration: concept in formulations and characterization techniques for ocular drug delivery. J Control Release. 2020; 328:895-916.
13. Ahmed S, Amin MM, El-Korany SM, Sayed S. Corneal targeted fenticonazole nitrate-loaded novasomes for the management of ocular candidiasis: preparation, in vitro characterization, ex vivo and in vivo assessments. Drug Deliv. 2022; 29(1):2428–41.
14. Duvvuri S, Majumdar S, Mitra AK. Drug delivery to the retina: challenges and opportunities. Expert opinion on biological therapy. 2003 Feb 1; 3(1):45-56.
15. Elsayed I, Sayed S. Tailored nanostructured platforms for boosting Trans corneal permeation: Box–Behngan statistical optimization, comprehensive in vitro, ex vivo and in vivo characterization. International Journal of Nano medicine. 2017 Oct 30:7947-62.
16. Chan KC, Yu Y, Ng SH, Mak HK, Yip YW, van der Merwe Y, Ren T, Yung JS, Biswas S, Cao X, Chau Y. Intracameral injection of a chemically cross-linked hydrogel to study chronic neuro degeneration in glaucoma. Acta biomaterialia. 2019 Aug 1; 94:219-31.
17. Battiston K, Parrag I, Statham M, Louka D, Fischer H, Mackey G, Daley A, Gu F, Baldwin E, Yang B, Muirhead B. Polymer-free corticosteroid dimer implants for controlled and sustained drug delivery. Nature Communications. 2021 May 17; 12(1):2875.
18. Safi M, Ang MJ, Patel P, Silkiss RZ. Rhino-orbital-cerebral mucormycosis (ROCM) and associated cerebritis treated with adjuvant retro bulbar amphotericin B. American journal of ophthalmology case reports. 2020 Sep 1; 19:100771.

19. Anderson RL, Caplan A, Schuman JS. Ethical considerations for performing intraocular surgery on eyes with no light perception. Ophthalmology. 2019 Jan 1; 126(1):10-2.
20. Hayashi K, Hayashi H. Intravitreal versus retro bulbar injections of triamcinolone for macular oedema associated with branch retinal vein occlusion. American journal of ophthalmology. 2005 Jun 1; 139(6):972-82.
21. Wong CW, Czarny B, Metselaar JM, Ho C, Ng SR, Barathi AV, Storm G, Wong TT. Evaluation of Subconjunctival liposomal steroids for the treatment of experimental uveitis. Scientific reports. 2018 Apr 26; 8(1):6604.
22. Salama HA, Ghorab M, Mahmoud AA, Abdel Hady M. PLGA nanoparticles as Subconjunctival injection for management of glaucoma. Aaps Pharm SciTech. 2017 Oct; 18:2517-28.
23. Martínez-Carrasco R, Sánchez-Abarca LI, Nieto-Gómez C, Garcia EM, Sánchez-Guijo F, Argüeso P, Aijón J, Hernández-Galilea E, Velasco A. Subconjunctival injection of mesenchymal stromal cells protects the cornea in an experimental model of GVHD. The ocular surface. 2019 Apr 1; 17(2):285-94.
24. Yiu G, Chung SH, Moll Hoff IN, Nguyen UT, Thomasy SM, Yoo J, Taraborelli D, Noronha G. Suprachoroidal and sub retinal injections of AAV using transcleral micro needles for retinal gene delivery in nonhuman primates. Molecular Therapy Methods & Clinical Development. 2020 Mar 13; 16:179-91.
25. Sobaci G, Tuncer K, Taş A, Özyurt M, Bayer A, Kutlu U. The effect of intraoperative antibiotics in irrigating solutions on aqueous humor contamination and endophthalmitis after phacoemulsification surgery. European journal of ophthalmology. 2003 Nov; 13(9-10):773-8.
26. Walter K, Delwadia N, Coben J. Continuous Intracameral phenylephrine–ketorolac irrigation for miosis prevention in femtosecond laser–assisted cataract surgery: Reduction in surgical time and iris manipulation. Journal of Cataract & Refractive Surgery. 2019 Apr 1; 45(4):465-9.
27. Jung JH, Chiang B, Grossniklaus HE, Prausnitz MR. Ocular drug delivery targeted by iontophoresis in the suprachoroidal space using a micro needle. Journal of Controlled Release. 2018 May 10; 277:14-22.
28. Chen Y, Kalia YN. Short-duration ocular iontophoresis of ionisable acyclovir Prodrugs: A new approach to treat herpes simplex infections in the anterior and posterior segments of the eye. International journal of pharmaceutics. 2018 Jan 30; 536(1):292- 300.
29. Rathore KS, Nema RK. An insight into ophthalmic drug delivery system. Int J Pharm Sci Drug Res. 2009 Apr; 1(1):1-5.
30. Polish Pharmacopoeia, vol.8, part1, The Office for Registration of Medicinal Products, Medical Devices and Biocidal Products, Warsaw, Poland, 2008.
31. Tangri P, Khurana S. Basics of ocular drug delivery systems. International Journal of Research in Pharmaceutical and Biomedical Sciences. 2011 Oct; 2(4):1541-52.
32. Yamaguchi M, Yasueda SI, Isowaki A, Yamamoto M, Kimura M, Inada K, Ohtori A. Formulation of an ophthalmic lipid emulsion containing an anti-inflammatory steroidal drug, difluprednate. International journal of pharmaceutics. 2005 Sep 14; 301(1-2):121- 8.
33. Kapoor Y, Chauhan A. Ophthalmic delivery of Cyclosporine A from Brij-97 micro emulsion and surfactant-laden p-HEMA hydrogels. International journal of pharmaceutics. 2008 Sep 1; 361(1-2):222-9.
34. Shen J, Gan L, Zhu C, Zhang X, Dong Y, Jiang M, Zhu J, Gan Y. Novel NSAIDs ophthalmic formulation: flurbiprofen axetil emulsion with low irritancy and improved anti-inflammation effect. International journal of pharmaceutics. 2011 Jun 30; 412(1- 2):115-22.
35. Järvinen T, Järvinen K. Prodrugs for improved ocular drug delivery. Advanced drug delivery reviews. 1996 May 22; 19(2):203-24.
36. Gaudana R, Jwala J, Boddu SH, Mitra AK. Recent perspectives in ocular drug delivery. Pharmaceutical research. 2009 May; 26:1197-216.
37. Stefánsson E, Loftsson T. Cyclodextrin in eye drop formulations. Journal of inclusion phenomena and macro cyclic chemistry. 2002 Dec; 44:23-7.
38. Jung HJ, Abou-Jaoude M, Carbia BE, Plummer C, Chauhan A. Glaucoma therapy by extended release of timolol from nanoparticle loaded silicone-hydrogel contact lenses. Journal of controlled release. 2013 Jan 10; 165(1):82-9.
39. Aburahma MH, Mahmoud AA. Biodegradable ocular inserts for sustained delivery of brimonidine tartrate: preparation and in vitro/in vivo evaluation. Aaps Pharm SciTech. 2011 Dec; 12:1335-47.
40. Ratnam GV, Madhavi S, Rajesh P. Ocular drug delivery: an update review. International journal of pharmacy and biological sciences. 2011; 1(4):437-46.
41. Shivhare R, Pathak A, Shrivastava N, Singh C, Tiwari G, Goyal R. An update review on novel advanced ocular drug delivery system. World Journal of Pharmacy and Pharmaceutical Sciences. 2012 Jul 15;1(2):545-68.

42. Maichuk YF. Ophthalmic drug inserts. Investigative Ophthalmology & Visual Science. 1975 Feb 1; 14(2):87-90.
43. Karthikeyan D, Bhowmick M, Pandey VP, Nandhakumar J, Sengottuvelu S, Sonkar S, Siva Kumar T. The concept of ocular inserts as drug delivery systems: An overview. Asian Journal of Pharmaceutics (AJP). 2008; 2(4).
44. Al-Tamimi DJ, Ammoo AM, Alani ME, Ibraheem JJ. Review Article Ophthalmic Dosage Forms. Karbala Journal of Pharmaceutical Sciences. 2020 Jul 1(18).
45. Kelly JA, Molyneux PD, Smith SA, Smith SE. Relative bioavailability of pilocarpine from a novel ophthalmic delivery system and conventional eye drop formulations. British journal of ophthalmology. 1989 May 1; 73(5):360-2.
46. Diestelhorst M, Krieglstein GK. The ocular tolerability of a new ophthalmic drug delivery system (NODS). International ophthalmology. 1994 Jan; 18:1-4.
47. Weyenberg W, Vermeire A, Vandervoort J, Remon JP, Ludwig A. Effects of roller compaction settings on the preparation of bio adhesive granules and ocular Minitablets. European journal of pharmaceutics and bio pharmaceutics. 2005 Apr 1; 59(3):527-36.
48. Moosa RM, Choonara YE, du Toit LC, Kumar P, Carmichael T, Tomar LK, Tyagi C, Pillay V. A review of topically administered mini-tablets for drug delivery to the anterior segment of the eye. Journal of Pharmacy and Pharmacology. 2014 Apr; 66(4):490-506.
49. Abd EL-Gawad HA, Soliman OA, Barker SA, Girgis GN. Formulation and evaluation of gel forming ocular Minitablets containing Piroxicam. British Journal of Pharmaceutical Research. 2012 Jul 1; 2(3):141.
50. Ghadjahani Y, Mahmoodi H, Mortazavi A, Jaffariazar Z. The formulation of ocular timolol maleate Minitablets. Research in Pharmaceutical Sciences. 2012 Sep 2; 7(5):394.
51. Mortazavi SA, Jaffariazar Z, Damercheli E. Formulation and in-vitro evaluation of ocular ciprofloxacin-containing Minitablets prepared with different combinations of Carbapol 974P and various cellulose derivatives. Iranian Journal of Pharmaceutical Research: IJPR. 2010; 9(2):107.
52. Nagarwal RC, Kant S, Singh PN, Maiti P, Pandit JK. Polymeric nanoparticulate system: a potential approach for ocular drug delivery. Journal of controlled release. 2009 May 21; 136(1):2-13.
53. Bucolo C, Drago F, Salomone S. Ocular drug delivery: a clue from nanotechnology. Frontiers in pharmacology. 2012 Oct 25; 3:188.
54. Sahoo SK, Dilnawaz F, Krishna Kumar S. Nanotechnology in ocular drug delivery. Drug discovery today. 2008 Feb 1; 13(3-4):144-51.
55. Mudgil M, Gupta N, Nagpal M, Pawar P. Nanotechnology: a new approach for ocular drug delivery system. Int J Pharm Sci. 2012 Feb 11; 4(2):105-2.
56. Kaur IP, Garg A, Singla AK, Aggarwal D. Vesicular systems in ocular drug delivery: an overview. International journal of pharmaceutics. 2004 Jan 9; 269(1):1-4.
57. Malik A. Tool for drug delivery. Advances in biological research. 2012; 6(4).
58. Vandamme TF, Brobeck L. Poly (amidoamine) dendrimers as ophthalmic vehicles for ocular delivery of pilocarpine nitrate and tropicamide. Journal of controlled release. 2005 Jan 20; 102(1):23-38.
59. Cheng Y, Xu Z, Ma M, Xu T. Dendrimers as drug carriers: applications in different routes of drug administration. Journal of pharmaceutical sciences. 2008 Jan 1; 97(1):123-43.
60. Nair AB, Shah J, Jacob S, Al-Dhubiab BE, Sreeharsha N, Morsy MA, Gupta S, Attimarad M, Shinu P, Venugopala KN. Experimental design, formulation and in vivo evaluation of a novel topical in situ gel system to treat ocular infections. PLoS one. 2021 Mar 19; 16(3):e0248857.
61. Sadeq ZA, Sabri LA, Al-Kinani KK. Natural polymer Effect on gelation and rheology of ketotifen loaded pH-sensitive in situ ocular gel (Carbapol). Journal of Advanced Pharmacy Education and Research. 2022; 12 (2): 45–50.https://doi. org/10.51847/zof4tcfekt. 2022.
62. El-Feky YA, Fares AR, Zayed G, El-Telbany RF, Ahmed KA, El-Telbany DF. Repurposing of nifedipine loaded in situ ophthalmic gel as a novel approach for glaucoma treatment. Biomedicine & Pharmacotherapy. 2021 Oct 1; 142:112008.
63. Chowhan A, Giri TK. Polysaccharide as renewable responsive biopolymer for in situ gel in the delivery of drug through ocular route. International journal of biological macromolecules. 2020 May 1; 150:559-72.
64. Cassano R, Di Gioia ML, Trombino S. Gel-based materials for ophthalmic drug delivery. Gels. 2021 Aug 29;7(3):130.
65. Nanjwade BK, Manjappa AS, Murthy RS, Pol YD. A novel pH-triggered in situ gel for sustained ophthalmic delivery of ketorolac tromethamine. Asian J Pharm Sci. 2009; 4(3):189-99.
66. 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 journal of pharmaceutical sciences. 2019 Jan 1; 14(1):1-5.
67. Mitan R, Gokul Gandhi Jolly R, Parikh MB, Dharmesh MM. A pH triggered in-situ gel forming ophthalmic drug delivery system for tropicamide. Drug Deliv Technol. 2007; 5:44-9.
68. Srividya B, Cardoza RM, Amin PD, Sustained ophthalmic delivery of ofloxacin from a pH triggered in situ gelling system. J Control Release 2001; 73(2-3):205-11.
69. Edsman K, Carlfors J, Petersson R. Rheological evaluation of poloxamer as an in situ gel for ophthalmic use. European journal of pharmaceutical sciences. 1998 Apr 1; 6(2):105-12.
70. El-Kamel AH. In vitro and in vivo evaluation of Pluronic F127-based ocular delivery system for timolol maleate. International journal of pharmaceutics. 2002 Jul 8; 241(1):47-55.
71. Balasubramaniam J, Kant S, Pandit JK. In vitro and in vivo evaluation of Gelrite® gellan gum-based ocular delivery system for indomethacin. ACTA PHARMACEUTICA-ZAGREB-. 2003 Dec 1; 53(4):251-62.
72. Carlfors J, Edsman K, Petersson R, Jörnving K. Rheological evaluation of Gelrite® in situ gels for ophthalmic use. European journal of pharmaceutical sciences. 1998 Apr 1; 6(2):113-9.
73. Pandit JK, Bharathi D, Srinatha A, Ridhurkar DN, Singh S. Long acting ophthalmic formulation of indomethacin: evaluation of alginate gel systems. Indian journal of pharmaceutical sciences. 2007 Jan 1; 69(1).
74. Kaur IP, Singh M, Kanwar M. Formulation and evaluation of ophthalmic preparations of acetazolamide. International journal of pharmaceutics. 2000 Apr 20; 199(2):119-27.
75. Kashyap N, Viswanad B, Sharma G, Bhardwaj V, Ramarao P, Kumar MR. Design and evaluation of biodegradable, bio sensitive in situ gelling system for pulsatile delivery of insulin. Biomaterials. 2007 Apr 1; 28(11):2051-60.
76. Sautou-Miranda V, Libert F, Grand-Boyer A, Gellis C, Chopineau J. Impact of deep freezing on the stability of 25 mg/ml vancomycin ophthalmic solutions. International journal of pharmaceutics. 2002 Mar 2; 234(1-2):205-12.
77. Rukari TG, Jadhav AS, Londhe RA, Phalke PL. A review on ophthalmic in situ gels. Am. J. Pharm. Tech. Res. 2019; 9:159-70.
78. Rathore KS, Nema RK. An insight into ophthalmic drug delivery system. Int J Pharm Sci Drug Res. 2009 Apr; 1(1):1-5.
79. Rathore KS, Nema RK. Management of Glaucoma: a review. Int. J. pharmtech res. 2009; 1(3):863-9.
80. Rukari TG, Jadhav AS, Londhe RA, Phalke PL. A review on ophthalmic in situ gels. Am. J. Pharm. Tech. Res. 2019; 9:159-70.