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# Dual Stimuli Responsive In-situ Hydrogels for Ocular Drug Delivery Recent Advances Challenges and Future Perspectives

[1]Khushi Sharma, [2]Dr. Subhranshu Panda
*[1]Corresponding Author, School of Pharmaceutical Sciences, Jaipur National University, Jaipur-Agra Bypass, near the New RTO office in Jagatpura, Jaipur Rajasthan: 302017*
*[2]Professor, School of Pharmaceutical Sciences, Jaipur National University, Jaipur, Rajasthan: 302017, India*

***Abstract*—Because of the special anatomical and physiological barriers of the eye, such as nasolacrimal drainage, fast tear turnover, and restricted corneal permeability, which together lower the bioavailability of traditional ophthalmic formulations, ocular medication delivery is still a major issue. Because in-situ hydrogels can undergo a sol-to-gel transition in response to physiological stimuli, extending precorneal residence time and improving therapeutic efficacy, they have become viable drug delivery platforms. Because they react to two physiological triggers, such as pH, temperature, or ionic strength, dual stimuli-responsive in- situ hydrogels have drawn a lot of attention among these systems. This allows for better gelation control and more accurate drug release than single stimulus-responsive systems.**

**This article offers a thorough overview of dual stimuli-responsive in-situ hydrogels for ocular drug delivery, emphasizing their formulation techniques, polymeric components, design concepts, mechanisms of responsiveness, and assessment parameters. A critical discussion is given of recent developments in the use of these systems to treat ocular conditions such as corneal inflammation, bacterial infections, dry eye syndrome, glaucoma, and allergic conjunctivitis. The benefits of dual-responsive hydrogels are emphasized, including increased ocular retention, better bioavailability, prolonged drug release, and less burst release. Key elements affecting formulation performance and drug release behavior are also investigated.**

**Polymer compatibility, drug stability, ocular discomfort, tear fluid composition variability, sterilizing requirements, manufacturing scale-up, and regulatory approval are some of the obstacles that still need to be overcome despite their promising promise. Dual-responsive ocular hydrogel systems' clinical translation and commercialization are still hampered by these restrictions.**

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**Future studies are anticipated to concentrate on the creation of sophisticated smart hydrogels, customized eye treatments, AI-assisted formulation design, 3D-printed hydrogel systems, biomimetic and bioadhesive materials, and gene and protein delivery platforms. Dual stimuli-responsive in-situ hydrogels are expected to be a key component of the future generation of ocular drug delivery systems, providing safer, more efficient, and patient-centered therapeutic options, as biomaterials research and pharmaceutical technology continue to progress.**

***Index Terms*—Dual stimuli-responsive hydrogels; i- situ hydrogel; stimuli-responsive polymers; allergic conjunctivitis; smart hydrogels**

## I. INTRODUCTION

The eye, which has anterior and posterior portions, is an essential element of the human body. One-third of the eye is made up of the anterior segment, which includes the cornea, iris, ciliary body, aqueous humor, and lens. The posterior segment, which includes the sclera, choroid, optic nerve, vitreous humor, and retina, makes up the remaining two-thirds of the eye [1]. Eye drops are often used topical preparations to treat anterior segment disorders. Due to precorneal losses from drainage, fast tear fluid turnover, and dynamics, less than 5% of medications reach the cornea and intraocular tissues following instillation. To increase the bioavailability and retention period of medications, suspensions, emulsions, and ointments are frequently utilized. However, their efficacy is limited by low stability and blurred eyesight. For individuals with chronic conditions including glaucoma and refractory chorioretinal diseases, systemic administration via intraocular injections of medications is preferred because topically applied medications typically do not reach the posterior portion of the eye [2].

Because of induced lacrimation, lacrimal drainage, poor corneal permeability, and the reduced size of the ocular cavity, developing ocular medication delivery systems has always been difficult. Consequently, a dosage form should be able to withstand lachrymal fluid dilution after instillation, not induce discomfort or blurred vision upon instillation, and prolong the drug's duration in the precorneal area [3]. When constructing an ocular pharmaceutical with high therapeutic efficacy, the most important difficulty is to achieve an ideal drug concentration at the site of action.

## II. ANATOMY OF EYE

The human eye is made up of several layers with distinct internal structures, each of which serves a particular purpose.

### 2.1. The Sclera, Cornea, and Conjunctiva

The white portion of the eye that makes up the outer layer of the eye ball and looks as an opaque, rigid white sheath is called the sclera. It maintains the shape of the eye like a rigid fibrous membrane. It continues inside the cornea and is considerably thicker in the back of the eye than in

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the front. It is made up of proteoglycans and collagen fibers that have been incorporated into the extracellular matrix. Because of diffusive transport through the leaky area of collagen fibers, the hydrophilic solutes penetrate the sclera more than the conjunctiva and cornea. Permeability across the sclera is also affected by charges (+/−) on molecules' surfaces. While hydrophilic medicines can diffuse via the ciliary body through the conjunctiva and sclera, the cornea serves as the primary route for topical medication instillation. It provides protection, keeps intraocular pressure stable, and serves as a place where the ciliary muscles can attach [4-5].

The cornea, which is transparent and clear, does not have the blood supply that is located at the front of the eye. It is made up of various components, including the endothelial layers inside, Bowman's membrane, corneal stroma, and corneal epithelium on the outside. The drug's capacity to enter and stay in the aqueous humor depends on the corneal permeability. The corneal epithelium acts as a rate-limiting barrier for the trans-corneal diffusion of lipophilic medicines. A number of ciliary nerves connect the corneal stroma, which is composed of hydrophilic collagen and prevents lipophilic medications from diffusing [6]. Inside the eye, the conjunctiva is a thin, translucent, and delicate epithelial barrier that covers the anterior and one-third of the eyeball and channels inward toward the eyelids. The upper layer, epithelial cells, and their innate substantia propria make up the conjunctiva. With significant electrolyte, fluid, and mucus secretion, the conjunctiva helps form the tear film, which keeps microorganisms out and lubricates the eye cavity. Compared to the cornea, the conjunctiva has a higher surface area and is more drug-permeable. However, the lymphatic and blood capillaries that are pulled into the systemic circulation cause the substantial drug loss. Because of the conjunctival blood cells, capillaries, and tight junctions, which cause excessive drug loss in the systemic circulation and poor ocular drug bioavailability, conjunctival medication absorption is thought to be pointless [6].

### 2.2. Aqueous Humor

The rear and anterior regions of the eye are filled with this clear, translucent, nonvascular fluid. It transports waste products from nonvascular tissue to the cornea, supplies vital nutrients such sodium, chloride ions, and ascorbate salt, and regulates Schlemm's canal and corneal shape to maintain intraocular pressure. Schlemm's canal is a circular groove that receives aqueous humor from the anterior chamber and delivers it into the bloodstream through the anterior ciliary veins. In humans, the turnover rate of aqueous humor production ranges from 1% to 1.5% of the anterior chamber volume each minute. Aqueous humor forms at a rate of around 2.5 μL/min [7].

### 2.3. Pupil, Iris, and Ciliary Muscle and Vitreous Humor

The middle of the black portion of the eye is where light enters the chamber. Through an important phenomena known as the light reflex, the pupillary reflex modifies pupil size and shape. The iris is a round, muscular, contractile structure that faces the lens before returning to the cornea. The iris's diaphragm varies in size to regulate the quantity of incident light that enters the eye and to align the pupil size. It is a colorful area of the eye that ranges in color from blue to gray and provides various visual qualities. The ciliary muscle, which controls the passage of aqueous humor

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into Schlemm's canal and eyeshot to objects at suitable distances, is located in the central layer of the eye. The ciliary muscle's contraction or relaxation allows the eye to focus on nearby or far-off objects. Vitreous fluid makes up about 80% of the volume in each human eye. It is located in the chamber that returns to the lens of the eye and appears physically as a transparent substance that looks like jelly [8]. The components of each eye part are shown in detail schematically below (Figure 1).

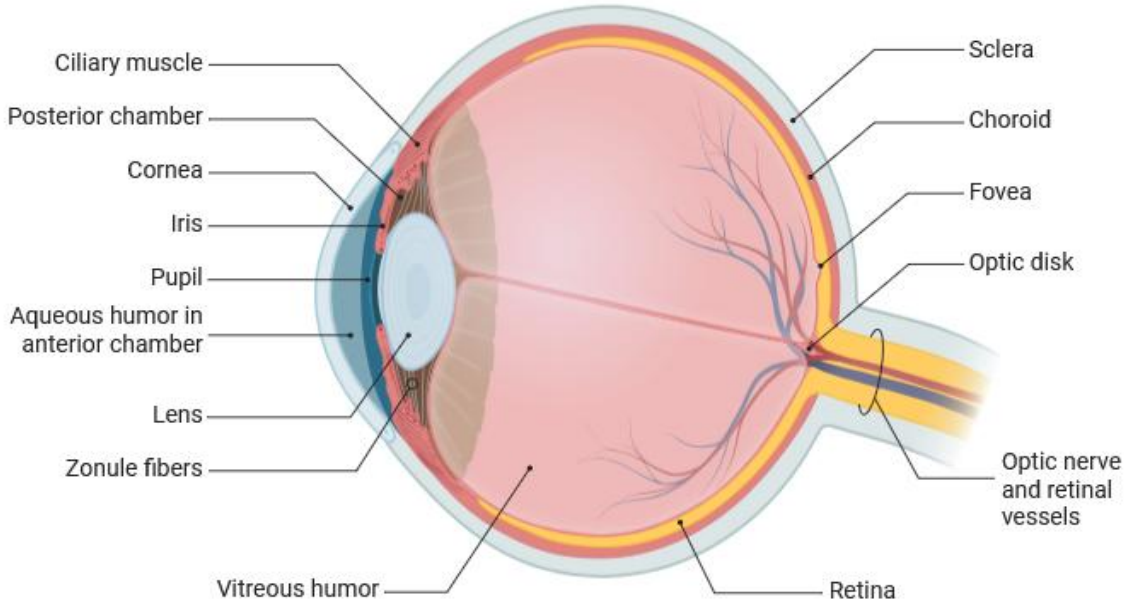


Figure 1. Anatomy of Eye anterior, Created using https://www.biorender.com/

2.4. The Retina, Macula, Choroid, and Optic Nerve

The retina is located on the back of the eye. It is made up of photosensitive rod and cone cells as well as glial, neuronal, vascular, and nerve fibers that transmit light via nerve impulses and go to the brain via the optic nerve. Numerous photoreceptor cells that convert light into nerve signals are found in the macula, which is situated in the middle of the retina.

The macula contains about 200 million neurons and a variety of ganglion cells in its noval structure, a pigmented area close to the center of the retina. The pigment absorbs light and uses the optic nerve to send the light signal to the brain. The brain receives signals from the eye through the optic nerve. The brain then processes the picture data for the central nervous system. Choroids, a thin layer of tissue between the sclera and retina, have blood arteries that provide the eye with nutrition and oxygen while limiting the delivery of medications into the posterior chamber. An optic disk is the front portion of the optic nerve [8].

2.5. Accessory Parts in Eye

The eyebrows, eyelids, lashes, and lacrimal apparatus are some of the components of the eye that shield it from harm. The anterior portion of the eyeball is shielded from dust, pollen, and other

objects by the eyebrow. The delicate cornea and eye front are shielded by the several tissue layers that make up the eyelids and conjunctiva. The lachrymal glands release the tear fluid, which includes water, mineral salts, lysozyme, antibodies, and antibacterial enzymes, when eye drops are applied to the lower conjunctival sac. Upon instillation, the surplus eye drops instantly flow into the gastrointestinal tract through the nasolacrimal system. This could be due to either reflex tearing or the drug dose exceeding the volume of lachrymal fluid. The nasolacrimal drainage system allows the extra volume to enter the digestive system [9-10].

## III. BARRIERS IN OCULAR DRUG DELIVERY

The existence of several obstacles is the main cause of the difficulty in achieving appropriate therapeutic dosages within the eye. Before a dose form reaches its site of action, it must overcome a number of challenges, whether it is applied topically or systemically. Ocular bioavailability from topically applied medication is therefore often just 1%–7% of the applied dose. These obstacles fall into two general categories: physiological and anatomical.

### 3.1 Anatomical barriers

The cornea or the non-corneal pathway are the two ways that a dose form might enter the body when applied topically. Bowman's membrane, endothelium, stroma, descemet's membrane, and epithelium make up the five main portions of the cornea, which is an extremely tight stratified structure. The epithelium serves as the main barrier among them. High paracellular resistance of 12–16 kΩ.cm is produced by these 5–6 layers of columnar epithelial cells with extremely tight connections [11]. It serves as a significant obstacle to the transfer of hydrophilic drugs across intercellular gaps. However, the stroma, which is made up of several layers of hexagonally organized collagen fibers with aqueous pores or channels, functions as a major barrier for lipophilic medications while facilitating the easy passage of hydrophilic pharmaceuticals. Therefore, a medication must have the proper ratio of hydrophilicity to lipophilicity in order to have the best bioavailability. The remaining layers are not very effective barriers and are leaky.

The non-corneal pathway moves via the conjunctiva and sclera, avoiding the cornea. This pathway is crucial, particularly for big, hydrophilic molecules including proteins, peptides, and siRNA [12]. Because the conjunctiva expresses less tight junction proteins than the corneal epithelium, it is more permeable than the cornea, particularly for hydrophilic molecules. Due to the limbal area's high vascularity, a significant portion of the absorbed dose is removed by the blood vessels, making this route unsuitable for drug delivery [13]. The vitreous receives very little of the dosage.

### 3.2 Physiological barriers

The tear film serves as the eye's main defense. Precorneal variables such solution drainage, tear dilution, tear turnover, and enhanced lacrimation further decrease the bioavailability of topically applied medications [14]. The lacrimal fluid is an isotonic aqueous solution that contains a combination of lipids and proteins, including lysozyme. Lacrimation is much increased after topical application, which causes the dose to be diluted. Drug absorption is then reduced as a result

of the decreased drug concentration. Lacrimation and nasolacrimal drainage and spillage facilitate quick removal from the precorneal region, which further shortens the period that drug molecules are in touch with tissue. Consequently, the precise time for absorption is shortened, resulting in decreased bioavailability. The turnover rate is 16% per minute, and the typical tear volume is 7-9 μL [15]. To avoid severe precorneal loss, medications used as eye drops must be isotonic and non-irritating.

3.3 Pharmacokinetic barriers

The following procedures are indicated by the numbers:[16]

1. Transcorneal penetration into the anterior chamber from the lachrymal fluid,
2. Noncorneal drug penetration into the anterior uvea through the conjunctiva and sclera,
3. Drug delivery enters the anterior chamber from the bloodstream via the blood-aqueous barrier,
4. Drug removal from the anterior chamber through the aqueous humor turnover to Sclemm's canal and the trabecular meshwork,
5. Drug removal through the blood-aqueous barrier from the aqueous humor into the systemic circulation,
6. Drug delivery via the blood-retina barrier to the posterior eye,
7. Intravitreal drug delivery,
8. Drug removal from the vitreous across the blood-retina barrier via the posterior pathway, and
9. The anterior pathway of drug removal from the vitreous to the posterior chamber.

## IV. IN-SITU GELLING OCULAR SYSTEMS

Increasing the viscosity of the implanted solution by adding water-soluble polymers is a conventional method of addressing the issue of extending the drug's contact time. The patient population is very receptive to liquid dose forms, such as eye drops. The best delivery system is made up of phase transition polymers that are injected in a liquid state and change to a gel phase once they reach the cul-de-sac of the eye. This allows for sustained medication release and prolonged contact with the cornea of the eye. Improved local bioavailability, lower dose concentrations and frequency, and better patient acceptability might all be attained if a medication's precorneal residence duration could be extended from a few minutes to several hours. These characteristics should be provided by the idea of in-situ gel production.

Longer precorneal residence duration, increased ocular bioavailability, and increased patient acceptability are the goals of ocular drug delivery systems built on the idea of in-situ gel formation. In terms of tissue compatibility, gellan gum, an anionic exocellular polysaccharide derived from microorganisms, and sodium alginate, which has a high glucuronic acid content, are both highly biocompatible and exhibit the distinctive feature of cation-induced gelation.

Conventional liquid ophthalmic formulations (eye drops) exhibit limited bioavailability due to systemic drug absorption, enzymatic metabolism, naso-lachrymal drainage, spillage by overflow, and drug dilution by tear turnover [17].

4.1 Principle of In-situ Gel

A gelling agent that can create a stable sol/suspension system to hold the dispersed medication and additional excipients is used in the formulation of an in-situ gel system. This sol/suspension solution will gel in the stomach environment as a result of ionic complexation brought on by a pH shift. The formulation used is a sodium alginate or gellan gum solution with calcium chloride and sodium citrate, which complexes the free calcium ions and releases them only in the stomach's acidic environment. As a gelling ingredient, sodium alginate or gellan gum can create textures in the finished product that range from fluid gels to rigid, brittle, non-elastic gels [18]. When free calcium ions become trapped in sodium alginate or gellan gum polymeric chains, the polymer chains crosslink to produce a matrix structure. Double helical junction zones are created during this gelation process, and then double helical segments re-aggregate to form a three-dimensional network through complexation with cations and hydrogen bonding with water [19].

4.2 Advantages

Compared to an already-formed gel, the ability to inject precise and repeatable medication quantities is the main advantage of the in- situ gel. Additional benefits of in-situ forming gel consist of:

- The fewest possible systemic and local adverse effect
- The simplicity of use
- A low dosage is necessary for therapy.
- Enhanced bioavailability
- A decrease in the frequency of drug administration
- It can also be given to unconscious people.
- Enhanced patient comfort and compliance
- increased residence time [20]

4.3 Limitations of Single Stimuli-Responsive Systems

Despite showing great promise for ocular drug administration, single stimuli-responsive in-situ hydrogels (temperature-, pH-, or ion-triggered systems) have a number of drawbacks that could compromise their clinical efficacy. Dual- and multi-stimuli-responsive systems have been developed as a result of these limitations.

4.3.1 Dependence on a Single Physiological Trigger

The gelation of single-responsive hydrogels is triggered by a single environmental stimulus. However, due to the complexity and dynamic nature of ocular physiological parameters, gel formation and drug release may not always be adequately controlled by a single trigger. As a result, the system might not function at its best under different physiological circumstances [21].

4.3.2 Risk of Premature Drug Leakage

Nasolacrimal drainage may remove some of the formulation before gel formation if the quick sol-to-gel transition does not happen right away after instillation. Drug retention and bioavailability may suffer as a result [22].

4.3.3. Need for Higher Polymer Concentrations

To obtain sufficient viscosity and gel strength, single-responsive systems frequently need comparatively high concentrations of gelling polymers. Increased polymer content may result in irritation, impaired vision, ocular discomfort, or decreased patient compliance [23].

4.3.4. Limited Control over Drug Release

It is challenging to precisely modulate gel shape and drug release kinetics since gel formation is controlled by a single stimulus. When compared to dual- or multi-responsive formulations, this could result in less than ideal sustained-release performance [24].

## V. SMART OCULAR DELIVERY USING STIMULI-RESPONSIVE IN-SITU GEL PLATFORM

5.1 Thermo-Responsive Thermo-Responsive In-situ Gelling Systems

The most studied stimuli-responsive in-situ gelling systems are thermoresponsive ocular gelling systems. Because of the increased hydrophobicity, this polymeric system experiences a phase transition (solution → gel) in response to temperature changes [25]. To avoid storing the ophthalmic in-situ gel in the refrigerator, where the low temperature could irritate the eyes, it is advised that an ideal thermosensitive in situ gel undergo sol-gel transition upon contact with the eye physiological temperature [6]. Numerous thermo-responsive in-situ techniques have been used to treat a variety of eye conditions, including viral infections, bacterial infections, fungal infections, and glaucoma. The most widely used polymers can be broadly divided into two categories: synthetic polymers (such as poloxamers and poly(N-isopropylacrylamide) or PNIPAAM) and natural polymers (such as cellulose derivatives).

5.2 pH-Responsive In-situ Gelling Systems

The external pH environment is another kind of stimuli-responsive strategy. These polymers are typically polyelectrolytes with repeating units containing basic or acidic groups. When the pH of the surrounding environment rises, weak acidic group polymers (polyacids) exhibit swelling qualities, while weak basic group polymers (polybases) do the same. These polymers' protonation causes electrostatic repulsion and the formation of a network-like matrix, which results in an appearance of swelling and size expansion [8]. These polymers are anticipated to gel when they come into contact with the neutral pH of the ocular surface in the formulation of ocular medication delivery.

5.3 Ion-Responsive In-situ Gelling Systems

The sol–gel transition of ion-responsive in-situ ocular gelling systems, often referred to as ion-activated or ion-sensitive systems, is caused by cross-linking with monovalent (Na+) or polyvalent (Ca2+ and Mg2+) cations in the lachrymal fluids [26-27].

## VI.RECENT RESEARCH ON APPLICATION OF MULTI-STIMULI-RESPONSIVE IN-SITU GELLING SYSTEMS

As was previously mentioned, an excellent option for active medication delivery to the administration sites is in situ gel formulation. Having stated that, the body's physiological state, which includes the ocular location, is extremely complex. As a result, in some situations, single-stimuli-responsive in-situ gel formulations might not produce the intended results in drug delivery. The shortcomings of single-stimuli-responsive in-situ gel formulations were addressed by more recent inventions, such as multi-stimuli-responsive in-situ gel formulations, which optimize additional parameters in a more thorough manner. The creation of multi-stimuli-responsive in-situ gel formulations for the treatment of glaucoma, bacterial, fungal, and viral ocular infections, allergic conjunctivitis, and capsaicin-induced eye irritation is the primary focus of this section.

## VII. DUAL STIMULI-RESPONSIVE IN-SITU GELLING SYSTEMS

7.1 Concept and Design Principles of Dual Stmuli-Responsive In-Situ Hydrogels

Advanced smart biomaterials called dual stimuli-responsive in-situ hydrogels are made to change from a sol to a gel in response to two different physiological or environmental events. Dual-responsive hydrogels use two complementing stimuli to achieve more precise control over gelation behavior, drug release kinetics, and ocular residency length, in contrast to single stimulus-responsive systems that rely on a single trigger, such as temperature, pH, or ionic strength. Improved therapeutic efficacy is made possible by this dual responsiveness, which has become a viable method for getting around the drawbacks of traditional ocular drug delivery methods, such as quick precorneal drug loss and low bioavailability [28-29].

Adding two stimuli-sensitive polymers or functional groups to a single formulation is the fundamental idea behind dual stimuli-responsive hydrogels. When exposed to physiological ocular conditions, the formulation quickly gels after being injected into the eye as a liquid. In comparison to single-responsive systems, the simultaneous or sequential reaction to several stimuli improves gel formation and retention [30]. Hydrogels that take advantage of the physiological properties of the ocular surface, such as tear fluid pH, ionic composition, and ocular surface temperature, include temperature–pH responsive, temperature–ion responsive, and pH–ion responsive hydrogels [31].

The choice of suitable stimuli that match the visual environment is one of the main design ideas. While pH-responsive polymers like carbopol swell and form gel structures at the physiological tear fluid pH of roughly 7.4, thermoresponsive polymers like poloxamer 407 undergo reversible gelation at ocular surface temperatures (about 34–35°C) [32]. Similar to this, when mono- and

divalent cations found in tear fluid are present, ion-sensitive polymers such sodium alginate and gellan gum undergo ionic cross-linking, which improves gel formation and prolongs retention on the ocular surface [33].

Another important factor to take into account while designing dual-responsive systems is polymer compatibility. In order to produce desired physicochemical qualities without generating instability, precipitation, or phase separation, the chosen polymers should work in concert. While preserving patient comfort, suitable polymer combinations can improve gel strength, viscosity, mucoadhesion, and transparency. For instance, poloxamer–alginate systems use temperature-dependent viscosity increase in addition to ion-induced gelation, whereas poloxamer–carbopol systems combine thermogelation with pH-triggered swelling [29,34].

For ocular use to be successful, gelation characteristics must be optimized. When the formulation comes into contact with the ocular surface, it should quickly turn into a gel while being sufficiently fluid to allow for precise instillation. Additionally, the final gel network should have sufficient mechanical strength to endure blinking and tear drainage while enabling regulated and prolonged medication delivery. These characteristics are greatly influenced by variables such polymer content, molecular weight, cross-linking density, and rheological behavior, which calls for careful optimization [35].

Because improved interaction with the mucin layer can greatly extend precorneal residency time, mucoadhesion is another crucial design criteria. By fostering close contact between the formulation and ocular tissues, the use of bioadhesive polymers reduces medication elimination brought on by nasolacrimal drainage and tear turnover. Thus, increased ocular bioavailability and extended therapeutic effect are facilitated by better mucoadhesion [36].

Throughout the formulation development process, biocompatibility and optical clarity must be preserved. All polymers and excipients used in ophthalmic formulations should be physiologically compatible, non-toxic, and non-irritating because they are applied directly to extremely sensitive ocular tissues. In order to prevent visual disruptions and guarantee patient satisfaction, the hydrogel should also stay transparent following gelation [37].

Dual-responsive systems now provide more design options thanks to recent developments in hydrogel engineering. The creation of multifunctional hybrid delivery systems that can improve drug stability, increase corneal penetration, and provide prolonged drug release has been made possible by the inclusion of nanoparticles, liposomes, micelles, and other nanocarriers within hydrogel matrices. These dual-responsive hydrogels enabled by nanotechnology offer a viable path for the development of next-generation ocular medication delivery systems [38].

In order to accomplish quick gelation, extended ocular retention, regulated drug release, and enhanced patient compliance, dual stimuli-responsive in-situ hydrogels are often designed by carefully combining complimentary stimuli-responsive polymers. These ideas serve as the basis for the creation of sophisticated ophthalmic medication delivery systems that can overcome the main drawbacks of traditional eye drop formulations [28,35].

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7.2 Types of Dual Stimuli Systems

7.2.1 pH and temperature-Responsive In-situ Gels

Mono-responsive in-situ gels outperform dual-responsive ones. For instance, in addition to enhanced biological adhesion, mechanical strength, and greater control over drug release, pH and temperature-sensitive gels would be better able to adjust to the physiological complexity [39].

The four stages listed below form the basis for drug release from these matrices:

(a) drug migration and disintegration into adjacent polymers or pores,

(b) drug diffusion due to a gradient in concentration,

(c) drug diffusion to bodily fluids or surrounding media and (d) drug desorption from polymer exteriors [39].

First-order drug release from PF127/TMC/PEG-HA hydrogel, which is made up of pluronic F-127, trimethyl chitosan, and pegylated hyaluronic acid, has demonstrated the advantage of this combination over PF127 alone because TMC and PEG-HA increase contacts between pluronic micelles [40]. Temperature sensitivity was shown by the DOX-loaded CS/HA/GP hydrogel, which changed to a gel form at 37 °C. It has also been demonstrated to release DOX in a pH-dependent manner [41].

Huperzine administered intranasally When exposed to nasal temperature and pH, a loaded TPISG microemulsion (based on 20.80% pluronic F127, 2.8% pluronic F-68, and 0.88% chitosan; creating hup A-M-TPISG) created a mucoadhesive gel that may aid huperzine When compared to parenteral injection, A is delivered through olfactory neurons and avoids the blood-brain barrier (BBB), resulting in a somewhat greater AUCBrain/AUCPlasma [42].

7.2.2 Light and Glucose- Responsive In-situ Gels

In order to overcome unique reactions to conventional medicines, light and glucose responsiveness have been combined in cancer treatment. By combining glucose oxidase (GOx) and gallic acid-ferrous (GA-Fe), which function as glucose and NIR sensitive agents, one of these systems has been proposed. A gel forms at the injection site as a result of GA-Fe's facilitation of temperature rise and enhancement of both parts' catalytic activity upon NIR irradiation. Additionally, the GOx component effectively destroys breast cancer by continually producing hydroxyl radicals and depleting glucose [43].

7.2.3 Dual Light- Responsive In-situ Gels

Various light irradiation causes various reactions in dual light-responsive gels. Dual light responsiveness has been described for the ZPTA-G/HMA platform, which consists of polydopamine-modified zinc oxide (ZP) acting as a photocatalytic material, tannic acid (TA) acting as an anchor moiety, and gelatin-methacrylate hyaluronic acid gel (G/HMA) acting as the scaffold. This mixture has antibacterial properties and can cross-link to the oral mucosa when exposed to green light with a wavelength of 520 nm. However, tannic acid release, zinc oxide photothermal treatment, and the anti-inflammatory action are mediated by NIR irradiation at 808 nm [44].

7.2.4 Temperature and Glucose- Responsive In-situ Gels

Phenylboronic acid (PBA)-based glucose-responsive gels are difficult to inject because they are made of covalent links between PBA and cis-diol groups. On the other hand, temperature-sensitive gels are easy to inject and simply undergo phase change at various temperatures. Therefore, the solution can be administered at room temperature and converted to a gel state at body temperature by incorporating temperature-responsive properties into glucose-triggered gels. This approach has been used in insulin-dispersed alginate-g-P (NIPAM-co-AAPBA) [45]. The gel turns into a solution and releases insulin when the glucose concentration is high, but only a tiny amount of insulin is produced when the glucose level is normal, according to an in vitro examination of this formula. [45].

7.2.5 pH and Glucose- Responsive In-situ Gels

Due to the existence of imine and phenylboronate linkages, DOX-loaded CSPBA/oxidized dextran hydrogel made of modified chitosan with phenylboronic acid and oxidized dextran has demonstrated dual responsiveness to pH and glucose. Because it contains imine and phenylboronate linkages, CSPBA/oxidized dextran quickly changes into a gel state and encapsulates DOX when the pH is raised from an acidic to a physiological level (7.4). Additionally, it was shown that a decrease in pH or an increase in glucose concentration could hasten the release of drug molecules, primarily through diffusion from a swollen matrix [46].

7.2.6 Light and Tempeature- Responsive In-situ Gels

By using the process of light absorption and subsequent temperature raising to cause targeted damage to tumor cells, photothermal therapy has become a promising cancer treatment approach. Using 808 nm NIR irradiation, it was demonstrated that incorporating graphene oxide (GO) or its reduced form (r-GO) into a thermogel made by physically mixing heated agarose and chitosan (thermogel-GO and thermogel-rGO) might induce photothermal therapy against breast cancer cells. This gel demonstrated an antibacterial activity against both gram-positive and gram-negative bacteria due to the presence of chitosan, which was strengthened by NIR irradiation. Because of the increased chitosan dissolution brought on by higher temperatures, the thermogel-rGO antibacterial activity against S. aureus increased by around 12% under NIR irradiation with 1.7 W/cm2 intensity for 10 minutes. Additionally, cell viability was reduced to 34% when doxorubicin: ibuprofen (DOX: IBU) was added to the thermogel-rGO in a 1:5 M ratio [47].

7.2.7 pH and Light- Responsive In-situ Gels

One study used cross-linked carboxymethyl chitosan (CMCS), 2-formylphenylboronic acid (2-FPBA), and epigallocatechin (EGCG) to treat diabetic ulcers by combining pH and light sensitivity. As a multifunctional treatment, the CMCS/2-FBPA/EGCG (CFE) wound dressing hydrogel produced EGCG in response to pH and 808 nm NIR radiation, exhibiting angiogenic and anti-inflammatory effects due to its composition as well as antibacterial activity due to NIR. Spraying natural organic acid might then separate this compound, preventing further damage [48].

Polydopamine-Fe(III)-doxorubicin (PFD) nanoparticles and sodium alginate-graft-dopamine (SD) were synthesized for a study on skin regeneration in melanoma. The resultant doxorubicin-loaded SD/PFD gel demonstrated a synergistic effect in which PFD nanoparticles transformed NIR light into thermal energy. Doxorubicin separated from the SD/PFD gel due to protonation. As a result, doxorubicin was released more readily. Furthermore, the PFD nanoparticles showed catalase-like activity, reducing tumor hypoxia by turning hydrogen peroxide into oxygen [49].

7.2.8 Light and ROS- Responsive In-situ Gels

In addition to producing ROS, photodynamic treatment has the ability to cleave ROS-sensitive linkers, which can further mediate desired hydrogel breakdown and drug release. Adipic dihydrazide-modified hyaluronic acid (HA-ADH) and protoporphyrin IX were conjugated to create a chemo-photo-dynamic cancer treatment. This was followed by covalent coupling with functionalized thioketal (TK-CHO), which is made up of a ROS-triggered TK linker. Under NIR irradiation, this conjugate, known as HA-ADH-PpIX, produced ROS, cleaved the ROS-sensitive linker, and released loaded-DOX. Additionally, it was noted that HA-ADH-PpIX could offer selective therapeutic delivery to targeted areas on demand in addition to extending PpIX delivery [50].

7.2.9. Tempeature and Ion- Responsive In-situ Gels

A dual-responsive system was created by taking into account the ion-sensitivity of Gelrite® and the temperature-responsiveness of pluronic. Gelrite® solution was added to the F-68/F-127 solution to confirm this. The vagina was filled with an optimal formula that contained F-127 18%, F-68 5%, Gelrite® 0.3%, and lidocaine 2%. At vaginal temperature (28 °C), the formulation produced a gel. Prior to IUD implantation, the gel formation maintained the lidocaine release to lessen discomfort [51].

7.2.10 Light and Redox- Responsive In-situ Gels

An injectable CAM-established hydrogel with a reasonable gelation time after injection into the tumor sites was created by functionalizing cartilage acellular matrix (CAM) with norbornene and then combining the resulting CAM-Nb with di-selenide-di-polyethylene glycol-di-tetrazine (DSe-DPEG-DTz) cross-linker. When indocyanine green (ICG) was added to the gels, the solid in-situ gel maintained doxorubicin release under a decreasing state, which was increased by NIR irradiation. Additionally, it might completely eradicate tumors by preventing HT-29 cell metabolic activity after GSH or UV irradiation, such as free doxorubicin with targeted and delayed delivery [52].

## VIII. MECHANISM OF DUAL RESPONSIVENESS

Dual stimuli-responsive in-situ hydrogels work because they can change physicochemically in response to two different physiological stimuli. Dual-responsive hydrogels improve therapeutic effectiveness and bioavailability by providing more control over gelation behaviour, swelling

properties, drug release kinetics, and ocular retention as compared to single-responsive systems [53-54]. These systems are specifically made to stay in a low-viscosity solution state while being administered and then change into a gel when exposed to the physiological circumstances of the eyes.

Temperature-pH responsive hydrogels are the most studied dual-responsive technology for ocular medication delivery. When exposed to ocular surface temperatures of roughly 34–35°C, thermosensitive polymers like poloxamer 407 in these formulations undergo a reversible sol-to-gel transition. Polymer chains stay hydrated and readily distributed in solution at lower temperatures. Dehydration of hydrophobic polypropylene oxide segments encourages the creation of micelles and the subsequent development of gel networks as the temperature rises [55]. Concurrently, ionizable carboxyl groups in pH-responsive polymers like carbopol undergo ionization at physiological tear fluid pH (~7.4), which causes electrostatic repulsion between polymer chains and gel network expansion. Gel strength, viscosity, and ocular retention are further improved by this pH-induced swelling [56,29]. As a result, thermogelation and pH-responsive swelling work together to create a hydrogel matrix that is stronger and more stable than either process alone.

The mechanism by which temperature-ion responsive hydrogels function is distinct but complementary. While ion-sensitive polymers like sodium alginate and gellan gum undergo ionic cross-linking in the presence of mono- and divalent cations found naturally in tear fluid, such as sodium, calcium, and magnesium ions, thermoresponsive polymers aid in the formation of gel at physiological temperature [58]. A three-dimensional cross-linked network that improves mechanical stability and extends residence time on the ocular surface is created as a result of the interaction between polymer chains and tear fluid ions. This synergistic reaction promotes extended drug release and increases resistance to nasolacrimal drainage and tear dilution [59].

Ionic cross-linking and polymer ionization occur simultaneously in pH-ion sensitive systems, leading to gel formation. While tear fluid ions reinforce the polymer network through intermolecular ionic interactions, changes in physiological pH cause pH-sensitive polymers to inflate. When compared to single-responsive formulations, the combination of these processes enhances gel integrity and offers more control over drug release behaviour [60].

The performance of dual-responsive hydrogels is significantly influenced by swelling behaviour. Water molecules enter the polymer network after being exposed to physiological stimuli, which causes the hydrogel matrix to expand. Cross-linking density, environmental factors, and polymer makeup all affect how much swelling occurs. While excessive cross-linking may limit drug mobility and extend release duration, increased swelling allows drug molecules to diffuse through water channels inside the gel matrix [54,61]. Therefore, attaining the intended therapeutic results requires careful tuning of swelling features.

Diffusion-controlled and polymer relaxation-controlled processes are typically combined to release drugs from dual stimuli-responsive hydrogels. Drug molecules that are close to the hydrogel surface may first be quickly released into the tear fluid. Diffusion from the inflated polymer matrix and slow relaxation or degradation of the gel network then result in sustained

release [9]. Dual-responsive mechanisms provide more accurate control of these processes, resulting in extended and consistent drug release profiles that improve ocular bioavailability and lower the frequency of dosage [62].

Multifunctional systems that can react to additional stimuli including enzymes, redox conditions, inflammation-associated biomarkers, and external triggers have been made possible by recent advancements in hydrogel engineering. These cutting-edge technologies may be the next generation of intelligent ocular drug delivery platforms since they can further modify drug release behaviour in accordance with disease-specific microenvironments [63].

In general, two separate stimuli-responsive pathways work in concert to control gel formation, swelling, mucoadhesion, and medication release as part of the dual responsiveness process. When compared to traditional ophthalmic formulations and single-responsive hydrogel systems, the synergistic action of these mechanisms greatly improves ocular retention, prolonged drug administration, and therapeutic efficacy [53-54].

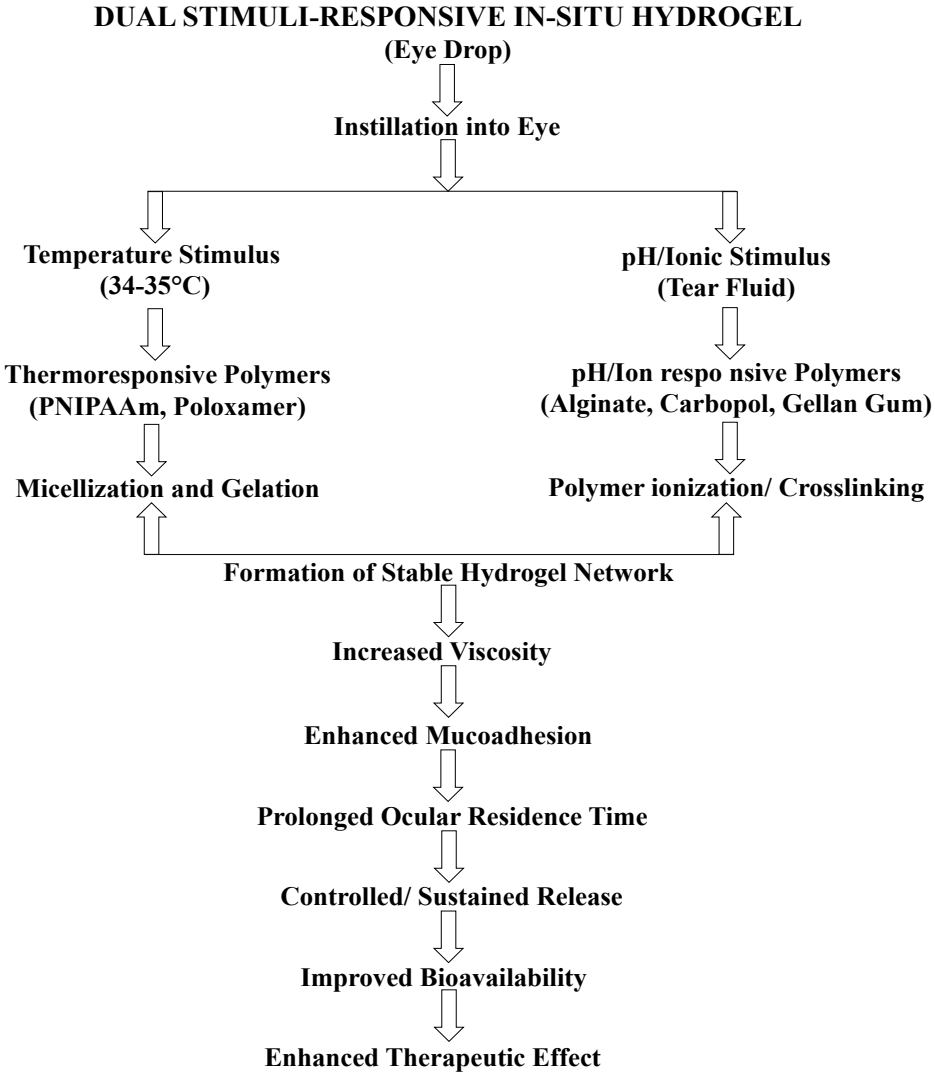


Figure 2. Mechanism of Dual Stimuli-Responsiveness in Ocular In-situ Hydrogels

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## IX. ADVANTAGES OF DUAL STIMULI-RESPONSIVE SYSTEMS OVER SINGLE STIMULUS-RESPONSIVE SYSTEMS

By concurrently using two physiological triggers, such as pH, temperature, ionic strength, or enzymes, dual stimuli-responsive in-situ hydrogels provide a number of advantages over traditional single stimulus-responsive systems. In ocular drug delivery systems, the combination of several stimuli improves formulation performance and therapeutic efficacy by giving more control over the sol-to-gel transition process.

### 9.1 Better Gelation Control

The improved gelation control of dual stimuli-responsive hydrogels is one of their main benefits. Variations in physiological circumstances can cause premature gelation or inadequate gel formation in single stimulus-responsive systems. Dual-responsive systems, on the other hand, produce more consistent and repeatable gel formation as they need two distinct stimuli to fully gel. By reducing formulation instability during injection and guaranteeing quick gelation upon contact with the ocular surface, this dual-trigger mechanism enhances patient compliance and therapeutic efficacy [64].

### 9.2 Enhanced Ocular Retention

Hydrogels that respond to two stimuli have better precorneal retention than formulations that respond to one stimulus. The formulation's viscosity and mucoadhesive qualities are increased by the stronger and more stable gel network created by the combined action of two physiological triggers. As a result, the hydrogel prolongs the drug's residence duration on the ocular surface by resisting lacrimal drainage and blinking-induced removal. While lowering the frequency of delivery, increased retention improves medication absorption and bioavailability [65-66].

### 9.3 Improved Sustained Drug Release

Compared to single stimulus-responsive hydrogels, the denser polymeric network produced by dual-responsive systems offers more effective control over drug dispersion. The hydrogel's synergistic reaction to environmental changes can modulate drug release, leading to controlled and extended-release profiles. Sustained drug administration improves treatment outcomes by lowering variations in ocular medication levels and maintaining therapeutic drug concentrations for longer periods of time [67-68].

### 9.4 Reduced Burst Release

A frequent drawback of many traditional ocular formulations and certain single stimulus-responsive hydrogels is burst release. Due to the tighter and more ordered three-dimensional polymer network that prevents rapid drug diffusion right after delivery, dual stimuli-responsive hydrogels can greatly lessen the initial burst effect. The formulation's safety and effectiveness are improved by the regulated gelation process and increased cross-linking density, which encourage progressive drug release and reduce the possibility of dose dumping [66,68].

## X. POLYMERS USED IN DUAL STIMULI-RESPONSIVE OCULAR HYDROGELS

The selection and combination of appropriate polymers that can react to physiological ocular circumstances are critical to the effective development of dual stimuli-responsive in-situ hydrogels. These polymers aid in controlled medication release, mucoadhesion, gel formation, and drug encapsulation. Because of their biocompatibility, responsiveness, and capacity to extend ocular residency length, both natural and synthetic polymers have been thoroughly studied. These polymers work in concert to create sophisticated hydrogel systems that react to various environmental cues while preserving patient comfort and therapeutic effectiveness [31,53].

### 10.1 Natural Polymers

#### 10.1.1 Sodium Alginate

A naturally occurring anionic polysaccharide, sodium alginate is obtained from brown seaweed. Because of its ion-sensitive gelation characteristics, it is frequently employed in ocular medication administration. Alginate experiences ionic cross-linking and creates a three-dimensional gel network when divalent cations, like the calcium ions found in tear fluid, are present. It is especially helpful in ion-responsive and temperature-ion responsive hydrogel systems because of its characteristic. Additionally, sodium alginate has outstanding mucoadhesive, biocompatible, and biodegradable qualities that support sustained drug release and extended ocular retention [69,58].

#### 10.1.2 Chitosan

Chitosan is a cationic polysaccharide that is produced by deacetylating chitin. Its mucoadhesive and permeation-enhancing qualities are widely recognized. Chitosan's positively charged amino groups interact with the negatively charged mucins on the surface of the eye to extend residence time and enhance drug absorption. Dual-responsive hydrogels often include chitosan to improve ocular permeability, bioadhesion, and gel strength. It is also a good polymer for ophthalmic applications due to its biocompatibility and biodegradability [33,29].

#### 10.1.3 Hyaluronic Acid

A naturally occurring glycosaminoglycan, hyaluronic acid is present in tear fluid and ocular tissues. It has outstanding biocompatibility, hydration capacity, and viscoelasticity. Hyaluronic acid is frequently employed to enhance patient comfort and ocular surface hydration because of its potent water-retaining capacity and lubricating qualities. It reduces eye irritation while increasing viscosity, mucoadhesion, and extended drug retention when paired with stimuli-responsive polymers [70].

### 10.2 Synthetic Polymers

#### 10.2.1 Poloxamer 407

One of the most popular thermoresponsive polymers for ocular medication administration is poloxamer 407. Polyethylene oxide (PEO) and polypropylene oxide (PPO) segments make up this

triblock copolymer. Poloxamer solutions stay fluid at low temperatures, but dehydration of PPO segments causes micellization and gel formation when exposed to physiological temperature. Poloxamer 407 is commonly used with pH-responsive or ion-responsive polymers to create dual stimuli-responsive ocular hydrogels because of its reversible thermogelation characteristic [32].

10.2.2 Carbopol 934

Cross-linked polyacrylic acid polymer Carbopol 934 is frequently used as a mucoadhesive and pH-responsive substance. Carbopol stays compact at acidic pH levels, but at physiological tear pH, ionization of carboxyl groups results in polymer swelling and gel network expansion. To improve gelation, viscosity, and ocular retention in dual-responsive systems, carbopol is frequently used with thermosensitive polymers like poloxamer 407 [56].

10.2.3 Hydroxypropyl Methylcellulose (HPMC)

HPMC is a semi-synthetic cellulose derivative that is frequently used in ophthalmic formulations as a stabilizer and viscosity enhancer. HPMC is commonly added to dual-responsive hydrogels to enhance gel consistency, lower the critical gelation concentration of thermoresponsive polymers, and control drug release even though it is not intrinsically stimuli-responsive. Patient comfort and ocular residence time are enhanced by its superior biocompatibility and film-forming qualities [37].

10.2.4 Poly(N-isopropylacrylamide) (PNIPAAm)

A synthetic thermoresponsive polymer with a lower critical solution temperature (LCST) around physiological temperature is called PNIPAAm. The polymer experiences a fast phase transition and gel formation above the LCST, while it stays hydrated and soluble below. PNIPAAm has garnered significant interest in the creation of sophisticated temperature-sensitive ocular hydrogel systems due to its acute temperature responsiveness. However, its clinical use has been restricted due to worries about biodegradability and long-term safety [71].

## XI. ROLES POLYMER COMBINATIONS

11.1 Gelation

Achieving quick and effective gelation under physiological ocular circumstances is the main goal of mixing various polymers. While carbopol, sodium alginate, and gellan gum contribute to pH-responsive or ion-sensitive gel formation, thermoresponsive polymers like poloxamer 407 give temperature-triggered gelation. Compared to hydrogel networks created by individual polymers alone, the synergistic interaction between these polymers produces stronger and more stable networks [53,56].

11.2 Mucoadhesion

Mucoadhesion is essential for prolonging ocular residence time and decreasing precorneal medication loss. Through hydrogen bonding, electrostatic interactions, and polymer chain

entanglement, polymers such sodium alginate, chitosan, carbopol, and hyaluronic acid interact with the mucin layer of the ocular surface. These interactions enhance formulation retention, which raises the bioavailability of the medicine [33,36].

11.3 Drug Release Modulation

By changing gel structure, swelling properties, and cross-linking density, polymer combinations have a major impact on drug release behavior. While bioadhesive and ion-sensitive polymers govern matrix swelling and drug transport channels, thermoresponsive polymers control gel formation. Dual-responsive hydrogel systems can therefore improve treatment outcomes and patient compliance by minimizing burst release, reducing dose frequency, and providing prolonged and regulated drug release [31,60].

In general, dual stimuli-responsive ocular hydrogels are based on the deliberate blending of synthetic and natural polymers. These polymer systems offer great promise for enhancing the effectiveness of ocular drug delivery and getting around the drawbacks of traditional ophthalmic formulations by combining complementary functions like thermogelation, pH responsiveness, ion sensitivity, mucoadhesion, and controlled drug release.

## XII. DRUG INCORPORATION METHODS

Because it directly affects drug loading capacity, formulation stability, release behavior, and therapeutic efficacy, effective drug incorporation is essential to the creation of dual stimuli-responsive in-situ hydrogels. The physicochemical characteristics of the drug, the composition of the polymer, and the desired release profile all influence the drug inclusion technique. To effectively load therapeutic molecules into ocular hydrogel systems while preserving drug stability and responsiveness to physiological stimuli, a variety of techniques have been used [66,35].

Direct drug dissolution is the most straightforward and widely used technique, where the medication is dissolved or evenly distributed throughout the polymeric solution prior to gel formation. After the medication is administered, physiological cues like temperature, pH, or ionic strength create a three-dimensional hydrogel network that traps the drug. This approach is easy to formulate and requires little processing, making it especially appropriate for water-soluble medications. However, because of their quick diffusion from the wet polymer matrix, hydrophilic medications added by direct loading may show an initial burst release [61,65].

Drug suspension or dispersion methods are frequently used for medications that are poorly soluble in water. This method involves evenly distributing micronized medication particles throughout the polymeric solution prior to gelation. The medicine can then gradually dissolve and diffuse into the surrounding tear fluid thanks to the hydrogel matrix's role as a reservoir. This approach can increase drug retention and extend the length of release; however, maintaining physical stability and attaining uniform particle distribution continue to be significant formulation issues [58].

The integration of drug-loaded nanoparticles into hydrogel matrices to create hybrid "nano-in-gel" systems has been the focus of recent developments in ocular drug delivery. Dual-responsive

hydrogels can incorporate nanoparticles, polymeric nanocarriers, nanomicelles, liposomes, niosomes, and solid lipid nanoparticles to improve corneal penetration, preserve labile molecules from degradation, and increase drug encapsulation efficiency. A dual-controlled delivery mechanism is provided by the hydrogel's extended precorneal retention after administration and the nanocarriers' control over drug release [38,72].

Molecular entrapment within the polymer network is another potential strategy. Drug molecules are physically confined within the cross-linked polymer matrix during hydrogel formation by electrostatic, hydrophobic, or hydrogen bonding interactions. Cross-linking density, drug–polymer compatibility, and polymer composition all affect the extent of drug entrapment. This approach is very useful for limiting early medication leakage and attaining sustained release [30].

Encapsulation in carrier systems before hydrogel inclusion is commonly used for sensitive medicinal agents like proteins, peptides, growth factors, and nucleic acids. Microspheres, liposomal systems, and biodegradable nanoparticles can offer an extra line of defense against environmental stress and enzymatic deterioration. By adding these carrier systems to dual-responsive hydrogels, stability is further improved and long-term controlled release of biologics is made possible [73].

A number of formulation factors, including as polymer concentration, cross-linking density, molecular weight, drug solubility, and drug–polymer interactions, affect drug loading efficiency in dual-responsive hydrogels. By creating denser networks, higher polymer concentrations often increase drug entrapment; nevertheless, an excessive polymer content may decrease drug diffusion and have a detrimental impact on syringeability and patient comfort. To balance loading capacity, gelation behaviour, and release performance, formulation parameters must be carefully optimized [74].

Overall, the therapeutic efficacy of dual stimuli-responsive ocular hydrogels is largely dependent on drug inclusion techniques. While sophisticated nano-enabled methods have emerged as potential solutions for enhancing drug stability, bioavailability, and sustained release, conventional drug dissolving techniques are still often employed for small-molecule medicines. The physicochemical properties of the medication and the intended therapeutic goals should be taken into consideration when choosing a loading method [66,38].

## XIII. FACTORS AFFECTING DRUG RELEASE FROM DUAL STIMULI-RESPONSIVE HYDROGELS

A number of formulation- and environmental variables affect drug release from dual stimuli-responsive hydrogels. These variables eventually impact treatment efficacy by determining the rate, extent, and mechanism of drug diffusion from the polymeric matrix. Designing hydrogels that can transport drugs to the eyes in a continuous and controlled manner requires an understanding of these factors.

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13.1 Polymer Composition and Concentration

Drug release behaviour is greatly influenced by the kind and concentration of polymers employed in hydrogel composition. Increasing polymer concentration typically results in the creation of a denser gel network with smaller pores, which prolongs release and decreases drug diffusion. Additionally, gel strength, swelling behaviour, and release kinetics can be altered by combining polymers with various response properties. For instance, formulations that combine pH-responsive polymers like carbopol with thermoresponsive polymers like poloxamer show improved control over drug release because of synergistic gel formation [56].

13.2 Cross-Linking Density

A key factor in determining the structural characteristics of hydrogels is cross-linking density. By decreasing mesh size and raising diffusion resistance, a heavily cross-linked network limits the mobility of drug molecules. Drug release consequently becomes more gradual and prolonged. On the other hand, hydrogels with less cross-linking density have bigger holes that speed up drug transport and could cause burst release [66,68].

13.3 Swelling Behaviour

Drug release is directly impacted by hydrogel swelling, which controls polymer relaxation and water absorption. Drug molecules can permeate through the wet polymer matrix when hydrogels are exposed to physiological circumstances because they absorb tear fluid and swell. Temperature, ionic strength, pH of the surrounding environment, and polymer composition all affect how much swelling occurs. While minimal edema may delay release, greater swelling typically promotes drug diffusion [67,75].

13.4 Physiochemical Properties of the Drug

Release kinetics are greatly influenced by drug-related variables as molecular weight, solubility, partition coefficient, and drug-polymer interactions. Compared to big or poorly soluble chemicals, small and highly water-soluble molecules diffuse through hydrogel networks more quickly. Strong contacts between the drug and polymer chains may also delay drug diffusion and increase the time of release [76].

13.5 Environmental Stimuli

Environmental triggers including pH, temperature, ionic strength, or enzymatic activity control the responsiveness of dual stimuli-sensitive hydrogels. Drug release can be impacted by changes in various physiological circumstances, which can also change polymer conformation, swelling behaviour, and gel structure. When it comes to ocular drug delivery, concurrent exposure to the pH of tear fluid and the temperature of the ocular surface frequently causes gel formation and regulates the drug's subsequent release [77].

13.6 Hydrogel Degradation and Erosion

Drug release can also happen when the hydrogel matrix erodes or degrades. The structural disintegration and release of confined drug molecules result from the slow hydrolysis or enzymatic degradation of biodegradable polymers. Environmental factors, cross-linking properties, and polymer chemistry all affect the rate of breakdown. Controlled-degradation hydrogels can minimize the requirement for frequent administration while offering extended drug release [31,78].

13.7 Initial Drug Loading

Release kinetics may be affected by the quantity of medication added to the hydrogel. A greater concentration gradient between the hydrogel and the surrounding media is often produced by higher drug loading, which speeds up diffusion. On the other hand, an unwanted initial burst release or drug crystallization could result from excessive drug loading. Therefore, in order to obtain regulated and sustained release characteristics, drug loading optimization is required [67,76].

## XIV.RECENT ADVANCES IN DUAL-STIMULI RESPONSIVE IN-SITU HYDROGELS FOR OCULAR DRUG DELIVERY

The creation of dual stimuli-responsive in-situ hydrogels for ocular medication administration has been the subject of extensive research in recent years. These systems provide better gelation characteristics than single stimulus-responsive formulations because they undergo a sol-to-gel transition in response to two physiological triggers, usually temperature, pH, or ionic strength. Precorneal retention is improved, drug release is prolonged, ocular bioavailability is increased, and dose frequency is decreased because to the synergistic effect. Their use in treating a number of ocular conditions, such as allergic conjunctivitis, glaucoma, dry eye syndrome, bacterial infections, and corneal inflammation, has been the subject of recent research [31,75].

14.1 Allergic conjunctivitis

One of the most prevalent ocular hypersensitivity conditions still requiring frequent topical antihistamine medication is allergic conjunctivitis. Dual-responsive hydrogels containing antiallergic medications including olopatadine hydrochloride, ketotifen fumarate, and epinastine hydrochloride have been the subject of recent developments. Formulations that combine pH-sensitive polymers like carbopol 934 with thermosensitive polymers like poloxamer 407 have shown sustained drug release, extended ocular residence time, and quick gel formation upon instillation. By eliminating the need for numerous daily doses while preserving therapeutic drug concentrations on the ocular surface, these methods greatly increase patient compliance [79].

14.2 Glaucoma

Long-term intraocular pressure (IOP) reduction is necessary for glaucoma treatment, however traditional eye drops have limited ocular absorption. Dual stimuli-responsive hydrogels have shown promise as delivery systems for antiglaucoma medications such latanoprost, brimonidine

tartrate, timolol maleate, and dorzolamide hydrochloride. In comparison to traditional ophthalmic solutions, recent formulations based on pH- and temperature-responsive polymer combinations have demonstrated increased corneal contact duration, sustained drug release over several hours, and improved IOP-lowering performance. Drug penetration and therapeutic efficacy have been further enhanced by the addition of nanoparticles to dual-responsive hydrogels [4,80].

### 14.3 Dry Eye Syndrome

The symptoms of dry eye syndrome include irritation of the ocular surface and instability of the tear film. Dual-responsive hydrogels have been investigated recently for the delivery of lubricants, anti-inflammatory drugs, and tear replacements. Poloxamer, gellan gum, and hyaluronic acid-based thermosensitive and ion-sensitive systems have been shown to prolong ocular surface hydration and improve therapeutic drug retention. By offering constant lubrication and prolonged medication release, these formulations lessen tear deficiency symptoms and enhance eye comfort [81].

### 14.4 Bacterial Infections

Although topical antibiotics are frequently used to treat conjunctivitis and bacterial keratitis, their efficacy is limited by the quick turnover of tears. Antibiotics like moxifloxacin, ciprofloxacin, gatifloxacin, and ofloxacin incorporated into dual stimuli-responsive hydrogels have demonstrated great potential in getting over these restrictions. Hydrogels that are sensitive to pH and temperature have been shown in recent research to extend the duration of drug residence, preserve effective antimicrobial concentrations at the site of infection, and lower the frequency of dosing. Additionally, when compared to traditional formulations, nanoparticle-loaded dual-responsive systems have demonstrated greater corneal penetration and increased antibacterial efficacy [64].

### 14.5 Corneal Inflammation

When infection, trauma, surgery, or immune-mediated illnesses cause corneal inflammation, corticosteroids or non-steroidal anti-inflammatory medicines must be administered for an extended period of time. Recently, the delivery of dexamethasone, prednisolone acetate, fluorometholone, and diclofenac sodium has been studied using dual stimuli-responsive hydrogels. These formulations minimize systemic absorption and dosage frequency while delivering anti-inflammatory drugs in a controlled and sustained manner. By ensuring quick gelation upon administration and extended retention on the corneal surface, the combination responsiveness to physiological stimuli improves therapeutic efficacy and lessens ocular discomfort [75,78].

Dual stimuli-responsive in-situ hydrogels are a very promising approach for ocular medication administration, according to recent developments. Compared to traditional ophthalmic formulations and single stimulus-responsive systems, their capacity to react to several physiological triggers allows for fine control of gelation behavior and drug release kinetics (31,75].

## XV. CHALLENGES AND LIMITATIONS

Dual stimuli-responsive i- situ hydrogels show great promise for ocular drug delivery, but there are still a number of obstacles to overcome in terms of formulation development, biological performance, manufacturing, and regulatory approval. For these cutting-edge drug delivery systems to be successfully translated into clinical settings and commercialized, these constraints must be addressed.

### 15.1 Formulation Challenges

#### 15.1.1 Polymer Compatibility

Combining two or more polymers with distinct physicochemical characteristics and responsiveness mechanisms is frequently necessary for the creation of dual stimuli-responsive hydrogels. Because unwanted interactions between polymers can impact gelation behavior, viscosity, transparency, drug loading efficiency, and mechanical strength, achieving good polymer compatibility is a major challenge. Phase separation, instability during storage, and uneven medication release profiles can also result from incompatible polymer combinations. Therefore, to guarantee formulation stability and reproducibility, thorough selection and optimization of polymer blends are required [67,31].

#### 15.1.2 Drug Stability

Another crucial issue is preserving medication stability inside the hydrogel matrix. The chemical stability of integrated medications may be impacted by environmental factors as pH shifts, temperature variations, and ionic interactions. During formulation production and storage, some medications may experience hydrolysis, oxidation, or deterioration. Moreover, drug release behaviour can be changed by interactions between drug molecules and polymer chains, which may lower therapeutic efficacy. Therefore, during formulation development, comprehensive compatibility and stability investigations are necessary [76].

### 15.2 Biological Challenges

#### 15.2.2 Ocular Irritation

When designing ophthalmic hydrogels, ocular tolerance is a key consideration. Even though biocompatible polymers are typically used in the formulation of dual stimuli-responsive systems, excessive viscosity, improper pH, high polymer concentrations, or residual impurities may result in ocular pain, irritation, obscured vision, or foreign-body sensation upon injection. Prolonged contact of the hydrogel with the ocular surface may also trigger local inflammatory responses in sensitive patients. Therefore, prior to clinical application, biocompatibility and ocular safety assessments are crucial [4,78].

#### 15.2.3 Variable Tear Fluid Composition

Physiological triggers including pH, temperature, and ionic strength affect how well dual stimuli-responsive hydrogels function. However, each person's tear fluid composition is unique and can

be changed by age, illnesses, environmental conditions, or concurrent drugs. Drug release kinetics, swelling properties, and gelation behaviour can all be impacted by changes in tear pH, osmolarity, and electrolyte concentration. Such interpatient variability is a challenge to the creation of formulations that are universally efficacious and may lead to inconsistent therapeutic outcomes [81].

15.3 Manufacturing Challenges

15.3.1 Sterilization

Ophthalmic products must be sterile. However, conventional sterilization methods such as autoclaving, gamma irradiation, or filtration may adversely affect the physicochemical properties of stimuli-responsive hydrogels. Polymer structure, viscosity, gelation temperature, medication stability, and release characteristics can all be changed by exposure to high temperatures or radiation. Thus, choosing a suitable sterilizing technique that preserves formulation integrity and sterility continues to be a major industrial difficulty [75,68].

15.3.2 Scale-up

While several dual-responsive hydrogels show encouraging results in the lab, it is still challenging to translate these formulations into large-scale production. Batch-to-batch consistency, repeatable gelation characteristics, consistent medication distribution, and long-term stability must all be guaranteed by scale-up procedures. Furthermore, it might be difficult and expensive to maintain exact control over polymer composition and processing conditions. These elements might restrict the commercialization and industrial manufacturing of sophisticated ocular hydrogel systems [31,74].

15.4 Regulatory Challenges

15.4.1 Safety Requirements

Ophthalmic drug delivery systems must be thoroughly evaluated by regulatory bodies to prove their quality, safety, and efficacy. The long-term ocular consequences of dual stimuli-responsive hydrogels may not be completely known due to their intricate polymeric networks. Before obtaining clinical licensure, extensive preclinical research is required, including evaluations of ocular irritation, toxicity, biocompatibility, pharmacokinetics, and biodistribution. These specifications lengthen the development process and raise total expenses [56,82].

15.4.2 Clinical Translation

Relatively few dual stimuli-responsive ocular hydrogels have advanced to clinical trials, despite promising preclinical results. Therapeutic results and formulation efficacy may be impacted by variations between human ocular physiology and animal models. Clinical translation may also be delayed by issues with manufacturing scalability, regulatory approval, patient acceptability, and economic viability. In order to successfully move these systems from laboratory research to

clinical practice, future research should concentrate on creating standardized evaluation procedures and clinically relevant models [31,83].

Overall, even though dual stimuli-responsive in-situ hydrogels have several benefits for ocular drug administration, their widespread clinical use and commercial success will depend on resolving formulation, biological, manufacturing, and regulatory issues.

## XVI. FUTURE PERSPECTIVE

The limitations of traditional ocular medication delivery systems have been shown to be significantly mitigated by dual stimuli-responsive in-situ hydrogels. It is anticipated that further developments in biomaterials science, nanotechnology, artificial intelligence, and precision medicine would further improve their therapeutic effectiveness despite significant gains in formulation design and preclinical evaluation. In order to provide accurate and long-term eye therapy, future research should concentrate on creating intelligent, patient-specific, and therapeutically translatable hydrogel systems.

### 16.1 Advances Smart Hydrogels

It is anticipated that the upcoming generation of ocular hydrogels would have several sensitive components that can respond to intricate physiological and pathological cues. Future smart hydrogels might react to biomarkers like enzymes, oxidative stress, glucose levels, inflammatory mediators, or disease-specific molecular signals in addition to pH, temperature, and ionic strength. By enabling on-demand medication delivery in response to illness progression, these devices may increase therapeutic efficacy while reducing needless drug exposure. It is expected that the development of these sophisticated smart hydrogels would heavily rely on the integration of nanotechnology and multifunctional polymers [31,78].

### 16.2 Personalized Ocular Therapy

A promising strategy for improving treatment results based on unique patient features is personalized medicine. Therapeutic efficacy can be greatly impacted by differences in tear composition, ocular physiology, disease severity, and medication response. Future dual stimuli-responsive hydrogels could be tailored to each patient's needs, enabling personalized control over medication release profiles and gelation behaviour. These customized formulations may enhance therapeutic results and treatment compliance while lowering side effects [84,81].

### 16.3 AI-Assisted Formulation Design

The development of pharmaceutical formulations is increasingly utilizing machine learning and artificial intelligence (AI) technology. Large datasets can be analysed by these computational methods, which can also forecast the best polymer combinations, drug-polymer interactions, gelation properties, and release kinetics. AI-assisted design has the potential to improve formulation performance while drastically cutting formulation development time and expense. Predictive modelling and digital formulation platforms could speed up the creation of dual stimuli-

responsive ocular hydrogels in the future and enable quick optimization of intricate delivery systems [85-86].

16.4 3D-Printed Ocular Hydrogels

The development of personalized hydrogel-based ocular medication delivery devices is made possible by three-dimensional (3D) printing technology. 3D printing is a desirable method for creating drug-loaded hydrogel constructions and patient-specific ocular implants due to its ability to accurately manage geometry, porosity, drug distribution, and mechanical qualities. 3D-printed stimuli-responsive hydrogels may offer highly regulated and prolonged drug administration while improving patient comfort and therapeutic efficacy, according to recent developments in bioprinting and hydrogel engineering [87-88].

16.5 Biomimetic and Bioadhesive Systems

It is anticipated that hydrogel systems in the future would resemble normal ocular tissues in terms of both structure and function. Biocompatibility and therapeutic efficacy may be enhanced by biomimetic hydrogels that mimic the makeup of tear fluid, mucin layers, and extracellular matrix constituents. Additionally, adding bioadhesive polymers like chitosan, hyaluronic acid, and thiolated polymers can improve ocular retention and enable longer drug residency on the surface of the eye. These advancements could lead to decreased dosage frequency and increased medication bioavailability [89-90].

16.6 Gene and Protein Delivery

Biologics, such as proteins, peptides, antibodies, and nucleic acid-based treatments, are becoming more and more important in emerging eye medicines. However, because to their low stability and restricted ocular penetration, these macromolecules continue to be difficult to distribute. A promising foundation for safeguarding delicate biomolecules and permitting their regulated release at specific locations is provided by dual stimuli-responsive hydrogels. In the future, gene-editing tools, siRNA, mRNA, growth factors, and therapeutic proteins may be included into hydrogel matrices to treat chronic inflammatory illnesses, corneal abnormalities, and inherited retinal diseases [91-92].

16.7 Clinical Translation Opportunities

Relatively few dual stimuli-responsive hydrogel formulations have progressed to clinical review, despite the fact that many have shown promising preclinical results. Large-scale production, long-term safety evaluation, regulatory compliance, and clinical validation should be the main focus of future studies. For clinical translation to be successful, standardized characterization techniques, predictive animal models, and strong quality control systems must be developed. The commercialization of these cutting-edge ocular drug delivery devices may be accelerated by cooperation between pharmaceutical scientists, physicians, biomaterial engineers, and regulatory bodies [74].

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In general, the integration of smart biomaterials, customized medicine, artificial intelligence, and sophisticated manufacturing technologies holds the key to the future of dual stimuli-responsive in-situ hydrogels. By offering safer, more efficient, and patient-centered therapeutic solutions for a variety of ocular disorders, these advancements are anticipated to revolutionize ocular drug delivery.

## XVII. CONCLUSION

Compared to single stimulus-responsive systems and traditional eye drops, dual stimuli-responsive in-situ hydrogels are a viable platform for ocular medication delivery. These sophisticated hydrogels offer better gelation control, extended precorneal retention, increased ocular bioavailability, sustained drug release, and decreased dose frequency by reacting to two physiological cues, such as pH, temperature, or ionic strength. Dual-responsive formulations for the treatment of a number of ocular conditions, such as allergic conjunctivitis, glaucoma, dry eye syndrome, bacterial infections, and corneal inflammation, have been successfully developed thanks to recent developments in polymer science and hydrogel engineering.

One significant development in ocular drug administration is the capacity of dual-responsive hydrogels to build stable gel networks under physiological settings. Their greater responsiveness and regulated drug release properties minimize drug loss due to nasolacrimal drainage and rapid tear turnover, while also improving therapeutic efficacy and patient compliance. Additionally, the use of biologics, multifunctional polymers, and nanoparticles has increased their potential for long-term and focused ocular therapy.

Despite these encouraging advancements, a number of obstacles still prevent them from being widely used in clinical settings. Polymer compatibility, drug stability, ocular irritation, tear fluid composition fluctuation, sterilization, large-scale production, and regulatory approval continue to be major challenges. Furthermore, the scarcity of clinical data emphasizes the necessity of additional research to determine patient acceptability, long-term safety, and efficacy.

Future studies are anticipated to concentrate on the creation of sophisticated smart hydrogels that can react to various physiological and pathological stimuli, customized eye treatments, AI-assisted formulation optimization, 3D-printed hydrogel systems, biomimetic and bioadhesive materials, and platforms for the delivery of genes and proteins. Dual stimuli-responsive in-situ hydrogels have the potential to revolutionize ocular drug delivery and aid in the creation of more efficient, patient-friendly, and clinically transferable ophthalmic treatments with further interdisciplinary cooperation and technical advancement.

Conflict of interests

The authors declared no conflict of interests.

Author’s Contribution

Conceptualization: Miss. Khushi Sharma; Literature search and data collection: Miss Khushi Sharma; Writing: Miss. Khushi Sharma; Review and drafting: Miss Khushi Sharma; Supervision: Dr. Subhranshu Panda

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List Of Abbreviation

| | | |
|---|---|---|
| AI | : | Artificial Intelligence |
| BBB | : | Blood-Brain Barrier |
| CMCS | : | Carboxymethyl Chitosan |
| CS | : | Chitosan |
| DOX | : | Doxorubicin |
| EGCG | : | Epigallocatechin Gallate |
| GO | : | Graphene Oxide |
| GOx | : | Glucose Oxide |
| HA | : | Hyaluronic Acid |
| HPMC | : | Hydroxypropyl Methylcellulose |
| IOP | : | Intraocular Pressure |
| LCST | : | Lower Critical Solution Temperature |
| mRNA | : | Messenger Ribonucleic Acid |
| NIR | : | Near-Infrared |
| PEO | : | Polyethylene Oxide |
| PNIPAAm | : | Poly(N-isopropylacrylamide) |
| PPO | : | Polypropylene Oxide |
| ROS | : | Reactive Oxygen Species |
| siRNA | : | Small Interfering Ribonucleic Acid |
| UV | : | Ultraviolet Radiation |

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