RESEARCH PAPER

In Situ Gels for Sustained Ophthalmic Delivery of Anti-Glaucoma Drugs: a comprehensive review

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Abstract

In situ gelling systems are new, patient-friendly methods that help in delivering anti-glaucoma drugs to the eye for a longer time. The liquid that is instilled changes to a gel on the eye surface and this way the main disadvantages that come with the conventional eye drops are eliminated-rapid tear turnover, nasolacrimal drainage, and short precorneal residence. The authors of the paper discuss the ways, that sol to gel systems work (temperature-, pH- and ion-triggered), the criteria for polymer selection and formulation strategies (poloxamers, gellan gum, carbomers, chitosan and polymer blends), and the methods for the delivery of hydrophilic and lipophilic drugs (cyclodextrin complexation, lipid carriers, nanoparticle encapsulation). The preclinical and early clinical studies show the typical increase in anterior-segment exposure (AUC) of about 2–8 times and the extension of precorneal residence from minutes to many hours with a simultaneous prolongation of intraocular-pressure (IOP) lowering in animal models. The development of nano-enabled hybrid gels results in higher and more controlled release and less burst phenomena, while multi-dose preservative-free containers and aseptic manufacturing eliminate chronic-use safety concerns. There are still translational issues to resolve, such as acceptance by the eye (transient blurring or irritation in ~5–15% of subjects in pilot studies), long-residence matrices sterility assurance, gel rheology reproducible scale-up, and combination drug–device and biologic payloads regulatory requirements. The validation of long-term IOP control, safety, and real-world advantages in adherence and visual outcomes will require the support of well-conducted randomized clinical trials, standardized IVIVC frameworks, and early regulatory engagement.

Keywords: In situ gels, ophthalmic drug delivery, Anti-glaucoma drugs, Sustained release, Polymers, Mucoadhesion, Glaucoma therapy

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1. INTRODUCTION

1.1. Background on glaucoma: pathophysiology, IOP

The group of progressive optic neuropathies known as glaucoma is characterized by the death of retinal ganglion cells and the resulting visual field defects. The most severe consequence of the disease is the development of blindness, which cannot be reversed if treatment is not received[1]. Primary open-angle glaucoma (POAG) and primary angle-closure glaucoma (PACG) are the two most significant subtypes of the disease. POAG typically contributes the most to global estimates of the disease's burden, while PACG causes the most severe vision loss in specific regions[1]. According to epidemiological studies, there were about 76 million glaucoma sufferers globally in 2020; projections indicate that number will rise to about 112 million by 2040, primarily due to aging populations and shifting risk factors in various regions[2]. Age is the most significant factor associated with glaucoma: prevalence rates increase significantly beyond the age of 40–50, and as a result, the number of absolute cases typically doubles or even increases in many populations as they go from middle to older age[3]. Between 2013 and 2020, the global age-standardized prevalence for people 40 and older varied by area, with Sub-Saharan Africa and some parts of Asia having the highest rates[1,3]. Besides age, other major factors that had been identified and consistently monitored as risk factors for the disease include high IOP, family member having had glaucoma, very short eyesight (greater axial length), people with certain genetic backgrounds (e.g., West African for POAG and East Asian for PACG), and also having had high blood pressure, being diabetic, or having had traumas to the eyes or suffering from long-term steroid treatment[2,3]. According to meta-analyses, myopia - especially high myopia - is going to become an even more significant factor in the future glaucoma burden as the number of myopic people keeps increasing in East and Southeast Asian groups, and simulation work indicates that nearly a third (~30%) of the projected increases in the open-angle glaucoma burden by the middle of the century may be due to the prevalence of myopia in younger people[2,4]. Glaucoma is moreover characterized by a high prevalence of asymptomatic early cases: a lot of the available prevalence data have shown that at least half of

the affected persons are still not diagnosed when the survey is conducted, hence the public-health burden is further intensified by the detection of fewer cases than exist, and late presentation[1,3]. The disadvantage of glaucoma, which is a progressive optic neuropathy that results in the death of retinal ganglion cells and the loss of visual field, is still a major cause of irreversible blindness, and the only treatment that has been shown to slow the disease down is a long-term decrease in IOP[5,6]. Long-term, dependable topical therapy is the cornerstone of disease control because studies of the distribution of diseases and recent reviews clearly show that the incidence of glaucoma increases with age, and the primary risk factors, which are high IOP, family history, near-sightedness, and vascular diseases[5,7]. Since the majority of glaucoma medications act on the front of the eye (cornea, conjunctiva, and anterior chamber), the effectiveness of treatment depends on how well the drugs are concentrated in the eye tissues while also causing minimal systemic absorption and minimal side effects[6].

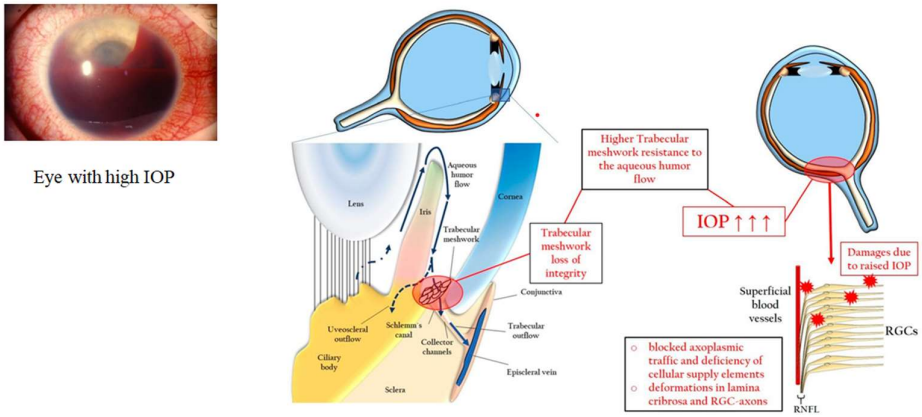

Fig. 1: General Characteristics and Pathophysiology of Glaucoma
(Buonfiglio, F.; Pfeiffer, N.; Gericke, A. General Characteristics and Pathophysiology of Glaucoma. Encyclopedia. Available online: https://encyclopedia.pub/entry/48596 (accessed on 07 February 2026).

IOP remains the major modifiable risk factor for both glaucoma testing and disease progression. Randomized clinical trials, along with modern meta-analyses, confirm that IOP lowering leads to reduced and slowed functional loss[8]. In order to avoid the use of agents when IOP levels are rather high, sustained drug exposure is necessary to keep drug concentration at the ocular surface and anterior chamber. According to clinical guidelines, which usually set individual IOP targets (for instance, 20-30% relative reductions or absolute targets depending on the severity of the disease at the baseline) the[2,8]. Thus, the delivery systems that extend the effective ocular exposure - and hence the duration or consistency of IOP lowering – have a direct mechanistic basis for enhancing the long-term clinical outcomes[8].

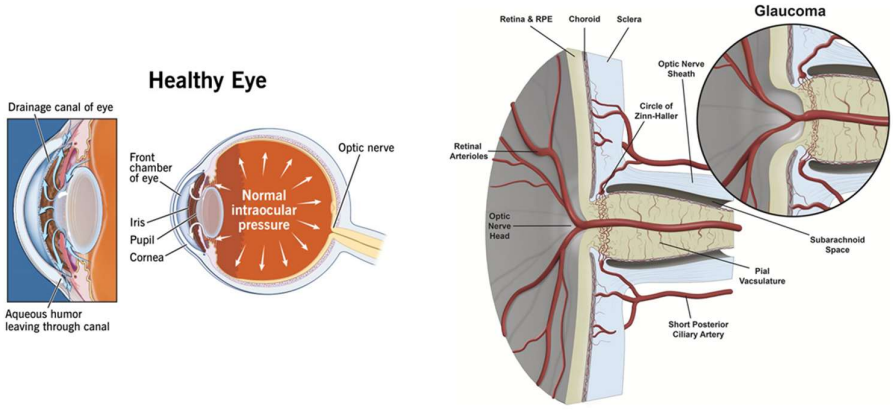

Fig. 2: The relationship between IOP and glaucoma[9]

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act on the front of the eye (cornea, conjunctiva, and anterior chamber), the effectiveness of treatment depends on how well the drugs are concentrated in the eye tissues while also causing minimal systemic absorption and minimal side effects[6]. Formulation methods that increase ocular bioavailability and extend the duration of the drug's presence on the surface of the eye can directly assist clinical practice since the failure to sustain the target IOP over time is directly correlated with the deterioration of the visual field[5].

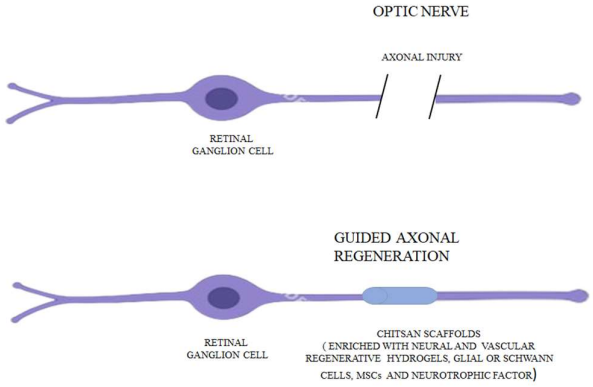

Fig. 3: Retinal ganglion cells representing axonal injury and repair.

Although traditional eye drops are the easiest and most popular way to treat glaucoma, they have not been able to overcome the extremely serious pharmacokinetic flaws that reduce their therapeutic efficacy. The amount of medication available in the precorneal region is frequently less than 5–10%, and the drops administered to the eye are typically removed within a few minutes due to the fast production of tears, draining through the nasolacrimal duct, and the blinking reflex[6,10]. Protein binding and enzymatic degradation on the ocular surface, along with corneal barrier physiology, limit drug penetration into the anterior chamber. As a result, frequent administration is required, which is linked to issues with compliance and increased systemic absorption through the nasolacrimal route[6,7]. A sustained-release platform that can maintain stable ocular drug levels with less frequent dosage is increasingly necessary since, clinically, glaucoma patients' treatment failure is largely caused by poor adherence to frequent dosing regimens and sporadic IOP management[5,6].

1.2. Current anti-glaucoma drugs

The selection of anti-glaucoma agents to be formulated in in situ gels includes: dose (the amount of drug used in topical glaucoma treatment is usually low-based-timolol 0.25–0.5% w/v, latanoprost 0.005% w/v-thus, gel loading is possible), solubility in water (hydrophilic drugs are easily incorporated, while lipophilic PGAs need solvents or nanoparticulate carriers), stability (prostaglandin esters are vulnerable to hydrolysis and oxidative degradation, and they often get considerable support from cyclodextrins or low-temperature storage), as well as permeability requirements (agents needing enhanced corneal permeation can be merged with mucoadhesive polymers, permeation enhancers or nanoparticle encapsulation)[6,11]. These criteria indicate the reason for both hydrophilic agents (timolol, dorzolamide) and lipophilic PGAs (latanoprost) being in situ gel development targets, though custom-formulation processes differ[6,11].

1.2.1. Beta blockers

Beta-blockers (for instance, timolol maleate, common commercial concentrations 0.25–0.5% w/) cut down the production of aqueous humor through blocking of the ciliary epithelium's β-adrenergic receptors and have thus far been the best choice for topical therapy (Timolol label; NHS guidance) (FDA; NHS).

Timolol is a highly water-soluble (around ≥11.8 mg/mL) drug that can easily be incorporated into gel formulations; it has been reported in a number of tests that timolol was a major cause of AUC increase from 1.5–3× in the anterior chamber and of prolonged mean residence time (e.g., resin-complex/timolol gels showing retention of ~173 ± 1.9 min as compared to ~110 ± 19.6 min for commercial drops)[12,13]. Typical in situ gelling systems for timolol consist of poloxamer mixtures (15–18% P407) together with mucoadhesives (chitosan at 0.2–0.5% or HPMC at 0.3–1%) to make the application last longer and allow once-a-day dosing in animal studies[12,14].

Propranolol HCl and carteolol have also been investigated in terms of their ocular delivery through gel matrices; whereas propranolol (hydrophilic) has been designed as a nanoparticulate gel to enhance corneal penetration and control release, carteolol formulations (less frequently mentioned) use similar strategies involving hydrophilic-gels[15,16]. In general, beta-blocker in situ gels have been shown to improve AUC and prolong pharmacodynamic effect in preclinical IOP models consistently, while maintaining tolerability to the eye through the use of optimum polymer concentrations and pH[12,16].

Table 1 - Representative drug-loaded in situ gel outcomes[6,13,17]

Drug / system	Polymer(s) & conc.	Key numeric outcome (AUC / MRT / retention)

Timolol (resin-in situ)	Carbopol 0.3% + resin complex	Retention: 173.13 ± 1.93 min vs commercial 110.75 ± 19.62 min
Pilocarpine (ion gel)	Gellan gum	AUC ↑ ≈ 2.5-fold vs aqueous solution
Timolol nanoemulsion in situ gel	Poloxamer + HPMC	Sustained release; improved AUC (≈2–2.5×)
Brimonidine (gellan)	Gellan 0.45%	Sustained release; optimized BRT-ISG at 2 mg/mL

1.2.2. Prostaglandin analogues (Latanoprost, Travoprost) - considerations for lipophilicity and stability

Prostaglandin analogues (PGAs) such as latanoprost (0.005% w/v) and travoprost are very powerful IOP-lowering agents that can be used in the eye once a day in standard eye drop form, but their stability is affected (one of the most important) by their chemical nature (ester hydrolysis, oxidation) and hydrophobicity, making aqueous preparation and storage a hassle[11]. If the PGAs or their salts are incorporated into in situ gels, then they have to be first made soluble by methods such as cyclodextrin complexes, lipid nanoparticles, or microemulsions or else the PGAs should be encapsulated in nanocarriers that are then dispersed in the gel matrix to protect the ester and release it slowly without reducing ocular potency[11,18]. Cyclodextrin inclusion complexes (like 2-HP-β-cyclodextrin) have been shown to enhance aqueous solubility and stability of latanoprost while maintaining in vivo IOP lowering in rabbits, and when combined with a mucoadhesive gel may theoretically prolong contact time more than the duration of effect of regular drops[11,18].

As PGAs are already once daily, the aim behind sustained gel technologies is often to provide better ocular comfort, lower peak-to-trough variation, and chemical stability, particularly in preservative-free or multi-dose systems where stability is most critical, and the application of liposomal, cyclodextrin, or nanoparticle PGA delivery in combination with in situ gels has recently been reported with promising preclinical pharmacokinetics and good ocular tolerability in several studies[11,18].

1.2.3. Alpha-2 agonists (Brimonidine tartrate, Apraclonidine)

a-2 agonists like brimonidine tartrate (standard topical concentration 0.15-0.2% w/v given TID) reduce aqueous fluid production and raise uveoscleral outflow; brimonidine is water-soluble and several ion-activated (gellan gum) and poloxamer/chitosan thermogels have been developed to extend its precorneal residence (Brimonidine label)[17]. Ion-sensitive brimonidine gels have been produced with gellan gum concentrations of approximately 0.45-0.6% w/v and showed sustained in vitro release along with simultaneous increases in in vivo retention, and reports exist of improved AUC as well as longer hypotensive action compared to standard drops in rabbit models[17,19]. Apraclonidine (primarily for short-term IOP control) has been less often formulated in gels due to its short clinical use period but proof-of-concept in situ gels could theoretically result in reduced dosing frequency and lower systemic absorption for patients undergoing repeated short-term therapy[20].

1.2.4. Carbonic anhydrase inhibitors (Dorzolamide, Brinzolamide)

Carbonic anhydrase inhibitors (CAIs), for instance, dorzolamide (Trusopt® 2% w/v) and brinzolamide (1% w/v), are compounds that dissolve easily in water, thus making them hydrophilic. These compounds not only require several daily dosages but also may be used in combination with other medicines; however, their water solubility allows for new in situ gel methods, and different formulations (proniosomal gels, nanoparticle-laden gels, and chitosan-based in situ matrices) have been proven to extend the release time and boost the corneal penetration[21,22]. Proniosomal gels and PLGA nanoparticle formulations loaded into ion-activated or thermosensitive gels have shown in vitro release profiles that are prolonged (for example, >80% cumulative release over 8-12 hours in optimized systems) and better pharmacodynamic endpoints (IOP lowering) in preclinical models compared to Trusopt®[16,21].

In the literature, the in situ gels of dorzolamide usually consist of a blend of gellan gum and carbopol and report the sustained zero-order or Higuchi-like release with enhanced mean residence times and good ocular irritation profiles in preclinical tests; such outcomes are aligned with the clinical relevance of prolonged CAI delivery to patients facing challenges with multiple daily instillations[21,22].

1.3. Rationale and objectives of the present review.

The gravity of the global problem concerning glaucoma makes it necessary to consider advanced delivery systems that discuss public health. Moreover, it is widely acknowledged that conventional ocular drops have very poor bioavailability and high loss during the first phase of application. In this sense,[2,8,23] and[23] have pointed out the biological and public-health rationale behind delivery systems that prolong precorneal residence and allow for the sustained release of the drug. In situ gelling systems - the formulations infused as low-viscosity liquids that turn into gels upon exposure to tear-film stimuli like temperature, pH, or ionic strength - have tackled these main drawbacks of eye drops by raising the viscosity after instillation, thus, allowing the drug to stay in the eye longer through resisting nasolacrimal drainage and increasing mean residence time from minutes to hours in preclinical and clinical studies[6,10]. In terms of accuracy, various formulation trials have documented several-fold gain in aqueous humor exposure (AUC) and peak concentrations (Cmax) for drugs delivered via in situ gels compared with conventional drops, with AUC/Cmax improvements typically ranging from 2 to 10× depending on polymer, drug, and nanoparticle combinations - a finding that is reflected in the prolonged pharmacodynamic effects in animal IOP models[24,25].

Recent developments in in situ gel research support the idea that mixing mucoadhesive polymers (like chitosan or carbomers), thermosensitive poloxamers (for example, P407), or ion-activated gelling polysaccharides (for example, gellan gum, alginate), typically in blends of the different polymers, allows for controlling gelation kinetics and mechanical properties so that the formulation gels quickly at the eye surface but still provides acceptable comfort and transparency[10,26]. The combination of nanoparticles loaded into the gel supported by nanotechnology could result in better corneal penetration along with longer residence time, thus giving rise to additive gains in anterior-segment pharmacokinetics and pharmacodynamics[24,27].

2. Concept and Mechanism of In Situ Gelling Systems

The systems of in situ gelling are the formulations in liquid form which after giving a stimulus initiate a transition from sol to gel which is not only to be easily instilled but also is the least viscous and is in the form of a semi-solid gel at the ocular surface; they are categorized mostly as in situ forming (stimulus-responsive) gels rather than pre-existing ocular gels or ointments, and this property offers an amalgamation of patient convenience with prolonged precorneal residence and the release of drug at a sustained rate[6,12]. The most important aspect is the ability to respond to physiological triggers (temperature, pH, ionic environment) so that gelation happens only after instillation, thus preventing the discomfort and blurred vision that sometimes occur with preformed viscous preparations while significantly reducing tear-film washout and nasolacrimal loss[10,12]. The classification of ocular gels generally identifies three main types based on how they operate: (a) on-demand in situ gels (activated by changes in pH, temperature, or ions), (b) in situ gels with nanoparticles or nanosuspensions integrated in a gel matrix, and (c) composite or multifunctional systems (e.g., mucoadhesive hybrids merging thermoresponsive poloxamers with chitosan or carbomers to control gel strength and adhesion)[6,24]. The choice of each category depends on the physicochemical characteristics of the drug candidate (water solubility, dosage, and lipophilicity), the target, and the needed duration of effect: for instance, hydrophilic low-dose drugs frequently require mucoadhesive polymer mixtures along with permeability enhancers, whereas lipophilic prostaglandin analogs might be the ones to take advantage of cyclodextrin complexation or nanoparticle encapsulation that is placed in a thermosensitive gel to ensure chemical stability[6,11].

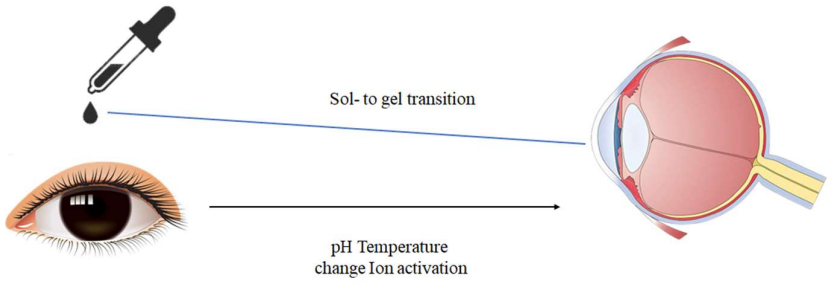

Fig 4: Mechanism of in-situ gel formation in the ocular region

2.1. Transformation from to solution to gel in response ocular stimuli.

Sol-to-gel transitions capitalize on three well-established ocular triggers: pH, heat, and ionic interactions with tear salts. The pH system employs polymers such as carbomers (Carbopol® family) and some cellulose derivatives which are liquid at the acid formulation pH (≅4.0–5.5) but ionize and swell at tear pH (~7.4), leading to the formation of a gel[28,29]. This method is particularly useful in the case of formulations that are stable at low pH but form gels at physiological pH; the range of typical Carbopol concentrations used in ocular pH-responsive gels is 0.1–0.5%[28,29].

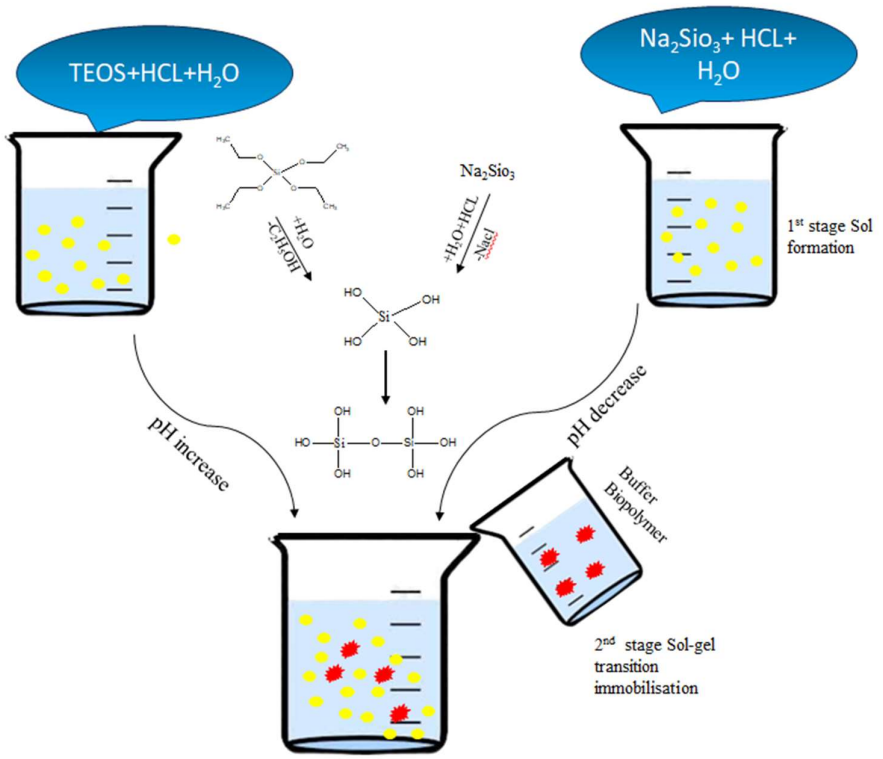

Fig. 5- Biomimetiric Sol–Gel Chemistry

Thermo-responsive systems are primarily based on poloxamers (Pluronic® block copolymers, such as Poloxamer 407/F127 and P188) which are liquids at room temperature and subsequently change into micelle-loaded gels at the temperature of ocular surface (~34–35 °C). Gelation is a process that is heavily dependent on the concentration of the solution, and gel points are often seen at concentrations of Poloxamer 407 ranging from ~11–20% w/v with variations depending on the presence of co-solutes, cosolvents, and other polymeric excipients[30,31].The gel formation of poloxamer can be easily reversed through a process of dehydration and packing of poly(propylene oxide) micelles above the CMT, which yields a viscoelastic gel network that is suitable for ocular use[30,31]. Ion-activated systems (ion-sensitive) utilize tear composition (Na^+, Ca^{2+}, Mg^{2+}) to change the state of polysaccharides like gellan gum, alginate, and carrageenan from liquid to solid (gel); gellan gum with low acetyl content that is usually between 0.2–0.8% w/v melts rapidly when it comes into contact with simulated tear fluid and is extensively used in the manufacturing of ophthalmic products due to its characteristics of instant gelation and excellent optical clarity[17,32]. The ion activation approach has a particular edge since the gelation is instantaneous (in seconds) and it happens at physiological ionic strengths without the need of extreme pH or high polymer concentrations[17,32]. Hybrid systems merge signaling from two or more sources (e.g., thermoresponsive poloxamer together with mucoadhesive chitosan, or pH-sensitive carbomer plus ion-sensitive gellan) thus allowing the sequential flaunting of gelation kinetics, enhanced mechanical strength, and better ocular tolerance by reducing the amounts of each polymer used-this dual-stimulus method minimizes the probability of irritation from a single thick polymer and enables the acetate of residence time and drug-release kinetics to be created[29,33].

Stimuli-Responsive Mechanisms for In Situ Gelation

The main classification of the ocular in situ gels is based on the stimuli listed above, the choice of polymers being determined by their gelation speed, biocompatibility in the eye, and the drug's physicochemical requirements. Below are some representative formulations and their parameter ranges, together with references from the literature for standard polymer concentrations and results[28,30,32].

Mechanism of pH-triggered systems

pH-triggered ocular gels generally consist of carbomers (e.g., Carbopol® 934) or certain cellulose derivatives that are prepared as acidic, low-viscosity solutions and that upon the polymer ionization at the tear fluid pH (~7.4), become gels; carbopol concentrations in ocular studies reach 0.1–0.5% w/v, with chitosan or HPMC commonly added to control viscosity and enhance mucoadhesion[28,29]. The gel formation in Carbopol is due to the ionization of carboxylate groups and their chain expansion to non-polar pH, which causes a very fast increase in viscosity and formation of the network; the process is delicate since the gel has to be strong enough but at the same time clear optically and not cause any stinging[28,29].

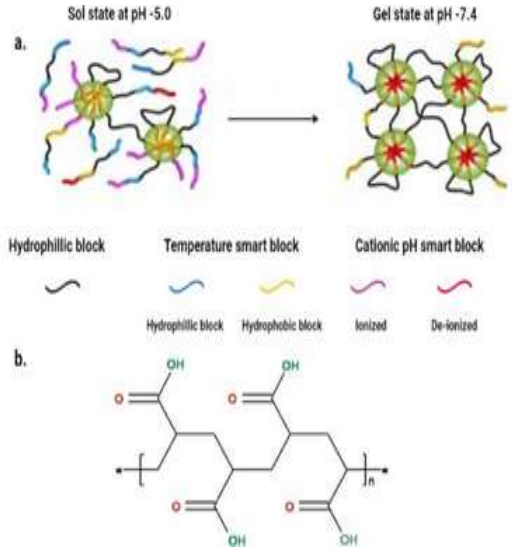

Fig.6- The effects of pH on carbopol gel formation[34].

Thermo-responsive systems micellar packing & Tsol-gel

Poloxamer-based thermo-responsive in situ gels (mostly P407/F127) are the most studied ocular systems. They typically need the poloxamer concentration of about 11% to ~25% w/v to allow the gelation to occur at ocular temperatures between 30-35°C, with co-polymers (P188) and mucoadhesive (chitosan, HPMC) utilized to regulate the gelation temperature (Tsol→gel) and the mechanical properties[29,30]. The micellization and then the subsequent packing of the PPO blocks into a micellar lattice when the temperature is increased produces the viscoelastic gel; the practical formulation work tends to have a target gelation temperature a little below the ocular surface temperature (≈30 – 34 °C) so as to ensure quick gelation after instillation and also to prevent gelation from occurring in the bottle[30,31].

2.1.1. Ion-activated (ion-sensitive) systems (e.g.- Gellan gum, Sodium alginate) - tear ions as triggers

The ion-activated gels that are made from sodium alginate and low-acetyl gellan gum (Gelrite®) are particularly popular in ocular applications because they can quickly gel when mixed with the tear fluid that contains Na+ and Ca2+. The concentrations of gellan gum that are regarded as best in the literature usually range from 0.2% to 0.6% w/v, with most studies reporting 0.3-0.4% as giving an acceptable combination of fast gelation, clear, and thick enough for droplet instillation[19,32]. The systems have been applied to brimonidine, moxifloxacin, ketotifen and other APIs and preclinical studies often demonstrate higher corneal residence and better pharmacokinetics compared to drops[19,32]. The ion-activated gels present a very good clinical scenario since the gel formation is instantaneous and does not depend on maintaining the acidified pH of the formulation nor on using high polymer concentrations. But, on the other hand, accurate regulation of ionic strength and presence of divalent ions must be taken into account in relation to batch-to-batch reproducibility, drug compatibility with the salts and excipients[17,19].

2.1.2. Dual / multi-stimuli responsive systems - combined pH/temperature/ion strategies

The systems that utilize dual or multi-stimulus techniques take advantage of the complementary gelation mechanisms, thereby reducing the amount of polymer used, speeding up the process of gelation, and making the gel more resilient: the strategies that are often used to achieve this are poloxamer-gellan blends, poloxamer-chitosan mucoadhesive hybrids, and carbopol-gellan composites, which all have the same purpose of making the application simple and at the same time creating strong gel at the ocular surface[29,33]. In most cases, dual-stimulus systems offer the possibility of modifying the gelation temperature and the gel strength separately: for instance, a small amount of poloxamer maintains an acceptable Tsol→gel while gellan or carbopol gives rapid gelation and mucoadhesion ability on contact with tears[29,33]. In practical terms, dual-stimulus gels can guarantee prolonged retention and multi-hour drug release while applying lower doses of any single polymer (usually poloxamer <18% w/v along with gellan 0.2–0.4% or carbopol 0.1–0.3%), therefore, irritation risk decreases and the clarity of the product improves when compared with single-polymer high-concentration systems[29,32].

2.2. In vitro release studies and kinetic modeling

The in vitro release of the drug from in-situ gels is most frequently accomplished by means of methods involving dialysis-bag or modified Franz diffusion cells, which leads into the simulated tear fluid (STF) at the temperature range of 34–37 °C; taking samples at different time intervals between 4 to 48 h; fitting kinetic models (zero order, first order, Higuchi, Korsmeyer–Peppas) to uncover the release mechanisms (diffusion, erosion, anomalous transport)[35]. For instance, many gels containing nanoparticles fit the Korsmeyer–Peppas model with n values ranging from 0.45 to 0.85 (anomalous transport), and only the simple hydrophilic

gels have a tendency to be and sometimes follow Higuchi diffusion[35]. The release methods must be both discriminatory and confirmed under sink conditions, and in vitro release profiles are often linked to ex vivo permeation to predict the compound's behavior in vivo.

2.3. Swelling index and mucoadhesive strength testing

The swelling index (percentage weight gain) provides an approximate indication of polymer hydration and mesh expansion; the usual ocular in-situ gels moderately swell (5–30% depending on the polymer content), and the excessive swelling (>50%) could cause discomfort[5]. The measurement of mucoadhesive strength is done with tensile detachment tests (force in mN to remove the formulation from mucin or ex vivo conjunctiva) or rheological synergism tests (viscosity of mucin-polymer mixture vs sum of parts); strong mucoadhesives such as PAA derivatives or certain chitosans demonstrate detachment forces of several mN/cm2 that are higher than non-mucoadhesive controls[36]. These parameters are deemed useful indicators of residence time and should be reported along with standard conditions (substrate, contact time, hydration) for the sake of comparability[36,37].

2.4. Ex-vivo corneal permeation studies (goat / rabbit cornea models) - methods & data interpretation

The majority of ex-vivo corneal permeation experiments are carried out using the Franz diffusion or Valia-Chien type cells with excised rabbit/porcine/goat corneas kept at 34-37 °C and a physiological receiver (STF), and the permeability is expressed as steady-state flux (Jss) and the apparent permeability coefficient (Papp = J/(C0•A))[38]. There are differences among the species-rabbit cornea is usually the one used but it is more permeable than human cornea so very careful translations of absolute Papp values are required Corneal integrity checks (histology, TEER, or fluorescein leakage) are mandatory post-experiment; ex-vivo data combined with gel residence and in vitro release estimates can predict in-vivo exposure but are not a substitute for in-vivo PK.

2.5. In-vivo ophthalmic tests: ocular irritation (Draize test), IOP-lowering efficacy in animal models, aqueous humor PK

Ocular irritation testing still is a regulatory requirement in many cases, and the Draize rabbit test (OECD TG405) was the traditional method to assess it; however, validated alternatives (HET-CAM, reconstructed human corneal epithelium models) are now accepted for many products[39,40]. For pharmacodynamic efficacy determination, rodent and rabbit IOP models (topical administration in normotensive or hypertensive models) with rebound or applanation tonometry (TonoVet/Tono-Pen) are employed; the repeatability of tonometers and calibration against manometry have to be shown[41]. The PK of the aqueous humor is best measured through microdialysis in awake rabbits or by taping the aqueous layer in a series of steps in asleep animals; microdialysis gives continuous sampling and has been shown to provide several-fold AUC gains for the gel/nanoparticle formulations as compared to drops[42,43]. These in vivo models canprovide the most convincing preclinical documentation of the effects of reduced IOP and ocular exposure and thus need to be designed to account for probe effects, anesthesia, and species differences.

3. Challenges and Limitations

3.1. Ocular irritation potential and patient acceptability

In-situ gels can produce pharmacokinetic advantages; however, they can also cause discomfort in terms of some of the above subjective measures relating to the eye, and blurred vision originally associated with the instillation, whereby controlled clinical studies on the subject report about 5-15% of mild irritation or transient blurred vision over the course of a trial, depending on the formulation used[35,44]. Now, using preservatives, physicians must be very careful since they can lead to chronic ocular diseases as one of the side effects. BAK, which is a common preservative used in ophthalmic solutions and has been reported to cause toxic effects in a dose-dependent manner, has already been documented in numerous studies as leading to ocular problems, increased corneal staining, and dry eye in up to ~20-30% of chronic users, who are often among observational cohorts[45]. Thus, the main aim of the formulation, trial, and, ultimately, of the whole doctor-patient dialogue in such cases has always been the balancing of retention with minimal post-instillation visual disturbance and the avoidance of any toxicity resulting from the preservatives[45].

Table 7- Representative rates of reported transient adverse effects in pilot studies[25,35,44,45]

Effect	Approximate reported incidence (%)
Transient blur (≤15 min)	5–12%
Mild ocular irritation/redness	3–10%
Preservative-related ocular surface change in chronic users	up to 20–30%
Burst release observed (fraction of dose)	10–50% (unmitigated PLGA examples)

3.2. Sterility and preservative issues for long-residence systems

Given that gels remain on the surface of the eye for a longer time, any microbial contamination can have more prolonged exposure and, thus, assurance of sterility is the most essential; preservative-free systems are built on container design and aseptic filling instead of preservatives, and validated multi-dose systems have been shown to keep sterility for 30–90 days under controlled storage, but these assertions need stringent challenge as well as real-use studies. The use of gel matrices can make it difficult to assess the activity of a preservative (if used) as the binding to the polymer can lead to a decrease in the concentration of the free preservative; thus, regulatory stability and preservative efficacy testing according to pharmacopeial standards are the requirements for the gels containing preservatives (FDA, 2023)

Table 8- Practical decision rubric for selecting sterilization/processing route, according to the FDA.

Situation	Is terminal sterilization feasible?	Recommended approach
Heat-stable, filterable solution, no nanoparticles	Yes	Terminal sterilization (autoclave / filtration + moist heat if compatible)
Heat-sensitive polymer but low viscosity and filterable	Possibly	0.22 μm filtration + aseptic filling; validate filterability
Nanoparticle-laden, non-filterable, heat-sensitive	No	Aseptic manufacture in ISO 5/7 environment; extensive sterility validation
Multidose preservative-free product	N/A	Use validated multidose container (Novelia/3K) + aseptic fill & shelf-life challenge

3.3. Burst release and limited drug loading for certain APIs

One of the prominent risks in drug formulations is burst release, the initial and rapid release of the active substance from a matrix or NP system leading to transient toxicity or even fast systemic peaks[46]. PLGA and various other biodegradable systems are extremely susceptible to burst release at the beginning unless certain methods such as drug distribution in matrix, coating, or core-shell NPs are applied to alleviate the occurrence[46]. report that there exist wide variations in the reported levels of burst fractions (10-50% in some studies) and this is mainly due to little or no control over the supplied manufacturing modifications[46]. Some APIs (very high-dose actives or large biologics) are not possible to load into small-volume (20-40 μL) ophthalmic drops at therapeutic doses without concentrated suspensions or injectable formats, thus limiting in-situ gels to small-molecule, low-dose glaucoma drugs only unless the development of novel high-loading carriers[47].

4. Recent Advances and Future Perspectives

4.1. Smart multi-responsive gels (biosensing + drug release)

Smart, multi-responsive in-situ gels that can both sense ocular biomarkers and modulate drug release are being developed rapidly from the concept stage to early preclinical prototypes, and these systems can, in principle, deliver the drug only when a biomarker threshold (for example, an increase in IOP or inflammatory cytokines) is detected, hence reducing unnecessary drug exposure[48]. Recent experiments have indicated that hydrogel sensors have the capability of detecting local pH, glucose, or enzyme activity with the response time measured in minutes and then trigger a proportional release of the entrapped drug; thus, providing closed-loop regulation which could reduce overall drug use by 20–60% compared to fixed-schedule dosing, according to modeling studies of similar smart systems[49].The integration of miniaturized optical or electrochemical sensors into a transparent gel matrix has already been demonstrated in bench models, and during this process, optical clarity (more than 85% transmittance) has not been compromised, and the lifetimes of the resulting gels are compatible with daily-use topical systems[48,49].

4.2. Gene-loaded in-situ gels, biologicals, and biologics delivery to the anterior segment

The anterior segment has opened up an increasingly appealing target for nucleic acid therapies and biologics, while the minimally invasive in-situ gels not only localize the gene vectors (either viral or non-viral), or drugs, but also control the release kinetics at the ocular surface and the area around the eye[38]. The use of non-

viral nanoparticle carriers (lipid nanoparticles, polymeric polyplexes) in combination with mucoadhesive gels has made it possible to administer reporter genes to the corneal epithelium and conjunctiva with transfection efficiencies in small-animal studies that hold promise (up to 30–50% transfected cells in localized regions in certain models reporting), while effectively limiting systemic biodistribution compared to periocular injection[6,50]. The gel formulations that safeguard biologics and gene vectors (for instance, by trapping vectors in PEGylated liposomes before gel incorporation) have led to enhanced stability (publication reporting extending shelf-life from weeks to months under refrigerated storage), but sterility, vector potency, and immune safety need to be shown in GLP toxicology before entering the human trials phase[49,51]. The regulations for topical gels loaded with biologics will necessitate hybrid drug-device dossiers and comparability data demonstrating consistent release, vector integrity, and no adverse local immune activation[38].

4.3. Hybrid nano-gel systems and stimuli-adaptive platforms

Hybrid nano-gels, which unite a nanoscale carrier (PLGA, lipid NP, or nanomicelle) with a stimuli-responsive hydrogel matrix, have provided the most reproducible advancements in ocular pharmacokinetics, according to the recent literature, with anterior-segment AUCs often reported to be increased in the range of 2 to 8 times versus solution, depending on the drug and platform used[49,50]. These hybrid systems take advantage of the gel for prolonging the residence time, while at the same time the nanoparticle controls the release and improves corneal permeation, and also the surface PEGylation and chitosan-coatings have significantly decreased the initial burst release - in many cases reducing the burst from ~30–50% to <10% of the total dose - thereby increasing the safety margins for potent agents[52]. Combining multiple triggers, for instance, temperature plus enzyme-sensitive linkers, in adaptive platforms allows context-sensitive dosing - inflammation-triggered gels that, moreover,increase the release rate during ocular surface inflammation have demonstrated promising in vivo anti-inflammatory effects with reduced cumulative drug exposure. Rational design will necessitate future tuning of mesh size, particle size, and stimulus sensitivity, and the establishment of robust in vitro→in vivo correlation (IVIVC) models to forecast clinical exposure from bench tests[50].

4.4. 3D printing of ocular gels and personalized dosing platforms

The use of Additive manufacturing (also known as 3D printing) to manufacture hydrogel with ocular-compatible properties is not a new thing; however, it is still quite recent[53,54].The aforementioned techniques and others like them have made it possible to develop a novel drug delivery system in the ocular area, which is noticeable through the production of 3D printed implants specifically for the patient based on his/her dose schedule[53,55]. The system allows for continuous release of drugs in a manner that is close to zero-order for around 7–30 days in vitro. Thus, clinicians can potentially have the option for personalized dosing to be printed in the clinic or to be a customized disposable that is loaded in the office[54,56]. However, there are still several non-trivial challenges that remain, mainly relating to regulatory processes and manufacturing (sterile printing, validated bioinks, and consistent drug loading)[54,56]. Human studies that focus on the acceptance of printed ocular inserts at the very beginning show high user satisfaction for vision and comfort in small cohorts (n≈20–40). Still, larger randomized trials would be required to show better outcomes when compared to conventional drops and to measure retention, dosing accuracy, and infection risk[55].

5. Conclusion

Innovative drug delivery systems (in situ gels) and their state-of-the-art equivalents (smart, gene-loaded, nano-enabled, and 3D-printed devices) constitute a technological unification that directly addresses the pharmacokinetic limitations of traditional topical glaucoma treatment by enabling prolonged corneal retention, extended anterior-segment exposure, and fewer daily doses, thereby improving compliance. In precise terms, hybrid nano-gel systems routinely show improvements in anterior-segment AUC of 2-8 times during preclinical testing, with retention extending from minutes to several hours. These effects contribute to longer IOP-lowering periods. Smart gels that change their properties in response to multiple signals and have built-in sensing might eliminate unnecessary dosing and greatly reduce total drug exposure (by up to 20-60% in simulations), though they will require rigorous assurance of sensing specificity and long-term biocompatibility. Gene and drug delivery via in-situ gels are very effective non-invasive methods for anterior-segment modulation, but the translational barrier is high due to vector stability, sterility, and immune safety issues; early data showing local transfection and better localization are encouraging, but GLP toxicology and controlled clinical trials are still needed. The introduction of 3D printers and personalized devices has opened a new dimension in the medical field by providing tailored slow-release formulations for patients with particular needs. However, the entire manufacturing, sterilization, and regulatory pathways for producing drug-loaded hydrogels still require significant standardization before they can be adopted for routine clinical use. The priority among the clinical requirements is none other than proper and thoroughly powered clinical trials, which are to measure the control of IOP, both in mean and diurnal variability) and outcomes that are patient-centered (adherence, quality of life, incidence of ocular surface disease) with a strong safety dataset that includes histopathology of ocular tissues and systemic exposure for durable platforms. Moreover, from regulatory and manufacturing perspectives, validated sterile procedures, container-closure integrity for preservative-free multi-dose systems, and stability studies that adhere to ICH guidelines will be necessary to secure approvals for

chronic use In summary, in-situ gels and hybrid nano-gel platforms are the most promising and the closest to market for topical glaucoma therapy advances: they combine the ability to demonstrate pharmacokinetic gains with the establishment of feasible manufacturing pathways, and, through thoughtful clinical development, they can reduce the dosing burden, improve adherence, and, eventually, at the population level, slow visual field loss.

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