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Smart Ocular Drug Delivery for Chronic Glaucoma Management: The Pharmaceutical Formulation Perspective

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ABSTRACT

Glaucoma stands as a leading global cause of irreversible blindness, traditionally managed through lifelong, topical intraocular pressure (IOP)-lowering drops. However, conventional eye drops suffer from poor ocular bioavailability (<5%), driven by physiological barriers such as reflex tearing, blinking, and nasolacrimal drainage. This rapid precorneal loss necessitates frequent dosing, culminating in poor patient adherence, fluctuating IOP, and accelerated visual field loss. Objective of this review evaluates modern ophthalmic drug delivery systems, specifically focusing on thermosensitive *in situ* gelling systems designed to prolong precorneal retention, simplify dosing regimens, and maximize therapeutic outcomes in glaucoma management. Methods of comprehensive synthesis of glaucoma pathophysiology, aqueous humour dynamics, and conventional therapeutic constraints was performed. The review examines various stimuli-responsive polymers—categorized by temperature, pH, and ion activation triggers—highlighting the physical mechanisms governing their phase transitions. Special emphasis is placed on synthetic polyether copolymers like Poloxamer 407, analyzing their reverse thermal gelation behaviors, micellar assembly mechanisms, and compounding strategies involving secondary mucoadhesive polymers. Furthermore, modern optimization frameworks utilizing statistical Design of Experiments (DoE) and Quality by Design (QbD) principles are evaluated. Results of *In situ* gelling systems effectively bypass the constraints of traditional eye drops by instilling easily as a liquid and immediately setting into a solid gel upon contact with the ocular surface temperature (~32–35 °C). While solitary Poloxamer 407 vehicles exhibit poor mucoadhesion and rapid dilution under tear flow, combining them with secondary bioadhesive polymers (e.g., Carbopol, HPMC, or chitosan) strengthens the physical matrix, extends transcorneal drug release, and limits systemic absorption. The application of Box-Behnken or central composite response surface designs successfully establishes a predictable "design space" that ensures optimal gelation boundaries, critical quality attributes, and reliable verification protocols. In Conclusion the thermosensitive *in situ* gels serve as a robust, non-invasive, and clinically viable compromise between conventional drops and complex intraocular implants. By lowering application frequency and stabilizing long-term IOP control, these systems present an accessible strategy to enhance elderly patient adherence and reduce global blindness rates.

Keywords: Glaucoma; Thermosensitive *in situ* gel; Poloxamer 407; Ocular drug delivery; Design of Experiments (DoE); Mucoadhesion.

INTRODUCTION

Overview of Glaucoma

Glaucoma is a heterogeneous group of chronic, progressive optic neuropathies characterised by degeneration of retinal ganglion cells and their axons, structural remodelling of the optic nerve head, and a corresponding loss of the visual field [1,2]. Because the damage is usually painless and begins in the peripheral field, many patients remain unaware of the disease until a substantial proportion of ganglion cells has already been lost. Elevated intraocular pressure (IOP) is the most important modifiable risk factor, although glaucomatous damage can also occur at statistically normal pressures [3]. The condition is therefore best understood as a multifactorial neurodegenerative disease in which pressure-dependent and pressure-independent mechanisms act together to injure the optic nerve [4]. Early recognition, regular monitoring and sustained therapy are therefore essential to preserve sight over the remaining lifetime of the patient.

Glaucoma is one of the leading causes of irreversible blindness worldwide, second only to cataract as a cause of blindness in global estimates [5]. Since vision lost to glaucoma cannot be restored, the therapeutic aim is to slow progression and preserve functional vision for the patient's lifetime. Lowering IOP is the only intervention proven in large, randomised trials to delay the onset and progression of the disease, and it remains the cornerstone of management [6,7]. Topical ocular hypotensive eye drops are the first-line treatment in most patients, which makes the performance of the topical dosage form a decisive factor in long-

term outcomes [8]. This work addresses that performance through a thermosensitive in situ gelling system.

Anatomy and Physiology of the Eye Relevant to Glaucoma

Aqueous Humour Dynamics

Aqueous humour is a clear, low-protein fluid secreted by the non-pigmented epithelium of the ciliary processes into the posterior chamber at a rate of roughly 2 to 3 microlitres per minute [9,10]. It is produced by active secretion, diffusion and ultrafiltration, then flows through the pupil into the anterior chamber. Besides maintaining the shape and pressure of the globe, aqueous humour supplies oxygen, glucose and amino acids to the avascular lens and cornea and carries away metabolic waste. Any imbalance between its formation and drainage changes the intraocular pressure, so the rate of production and the resistance to outflow are the two physiological targets of every currently used antiglaucoma drug [10].

Aqueous humour leaves the eye by two routes. In the conventional pathway, fluid passes through the trabecular meshwork into Schlemm's canal, then into collector channels and episcleral veins, and this route carries the majority of outflow in adults [11]. In the unconventional (uveoscleral) pathway, fluid percolates through the ciliary muscle into the suprachoroidal space, and its contribution varies with age [9]. Most of the resistance to conventional outflow is believed to reside in the juxtacanalicular tissue and the inner wall of Schlemm's canal [11]. The relative contribution of each route differs between individuals, and several drug classes act mainly on one of them, for example prostaglandin analogues that enhance uveoscleral drainage [12].

Intraocular Pressure and the Optic Nerve Head

Intraocular pressure is determined by the rate of aqueous formation, the resistance to outflow and the episcleral venous pressure. The statistical normal range of about 10 to 21 mmHg is a population descriptor rather than a threshold of safety, because many individuals develop glaucomatous damage within this range while many with higher pressures never do [13]. The lamina cribrosa at the optic nerve head is considered the principal site of injury, since mechanical strain at this point may compress axons, disturb axonal transport and compromise local blood supply [1,14]. Consequently, the amount of IOP reduction needed is individual, and therapy is chosen to reach a target pressure at which progression is expected to stop.

Epidemiology and Global Burden

A systematic review and meta-analysis estimated the global prevalence of glaucoma in people aged 40 to 80 years at 3.54%, equal to about 64.3 million people in 2013, with projections of 76.0 million in 2020 and 111.8 million in 2040 [15]. Primary open-angle glaucoma is most prevalent in populations of African descent, whereas primary angle-closure glaucoma is more common in Asian populations, and Asia carries the largest absolute number of cases **15**. An earlier analysis had projected that bilateral blindness from glaucoma would rise from 8.4 million people in 2010 to 11.1 million in 2020 [16]. Prevalence rises steeply with age in all populations, and the burden is expected to grow in parallel with the ageing of the global population, particularly in Asia and Africa [15].

The burden of glaucoma is expected to increase with population ageing and rising life expectancy, because age is among the strongest risk factors for the disease [15]. A large fraction of affected people remains undiagnosed, particularly in low- and middle-income settings where screening is limited, and presentation is frequently late [17]. Advanced disease impairs mobility, driving, reading and independence, and it increases the risk of falls and depression, so the personal and economic costs are considerable. These facts emphasise the need for treatments that are effective, affordable and easy for patients to use over many years. Consequently, health systems must plan for long-term, repeated treatment of large numbers of patients, which favours therapies that are inexpensive, simple to administer and tolerated for many years [4].

Pathophysiology of Glaucoma

Two broad theories explain how elevated pressure damages the optic nerve. The mechanical theory holds that raised IOP deforms the lamina cribrosa and compresses or shears the passing axons, blocking retrograde transport of neurotrophic factors needed for ganglion cell survival [1]. The vascular theory proposes that reduced ocular perfusion pressure, vascular dysregulation and ischaemia contribute to damage, which may explain progression in patients with normal-tension glaucoma [14]. Evidence from clinical trials supports a central role for pressure, as lowering IOP delayed the onset and progression of glaucomatous damage [6,7]. In practice both mechanisms probably operate in the same patient to different degrees. Neither theory alone accounts for all clinical observations, and current opinion treats glaucoma as a multifactorial disease [4].

At the cellular level, retinal ganglion cell death in glaucoma is largely apoptotic and involves several interacting processes, including glutamate excitotoxicity, oxidative stress, mitochondrial dysfunction, neurotrophin deprivation and activation of astrocytes and microglia [18]. In the anterior segment, loss of trabecular meshwork cells and accumulation of extracellular matrix raise outflow resistance and sustain the elevation of pressure [11]. Understanding these mechanisms has encouraged research into neuroprotection, but lowering IOP remains the only approach with a proven benefit, and therefore the ocular hypotensive drug and its delivery system are the focus of formulation research. Disease in the anterior segment and in the retina thus forms a continuum, and effective therapy must act early and consistently to prevent irreversible neuronal loss [1].

Classification of Glaucoma

Glaucoma is classified by the configuration of the anterior chamber angle and by the underlying cause. Open-angle forms are distinguished from angle-closure forms by gonioscopic examination, and each may be primary, when no other ocular or systemic cause is identified, or secondary, when another condition raises the pressure [19,20]. Developmental or congenital forms arise from abnormal angle formation. This classification guides treatment, because open-angle disease is generally managed first with topical drugs, whereas angle-closure disease often requires laser iridotomy or lens extraction to relieve the anatomical obstruction. Table 1 summarises the main types and their features. Secondary glaucomas may follow corticosteroid use, inflammation, trauma, pseudoexfoliation or new vessel growth, and recognition of the cause is essential for correct management [20].

Risk Factors and Clinical Diagnosis

Established risk factors for open-angle glaucoma include higher IOP, older age, a family history of glaucoma, African ancestry, myopia, thinner central corneal thickness and larger cup-to-disc ratio [6,21]. Some of these, such as corneal thickness and optic disc appearance, were identified as independent predictors of conversion from ocular hypertension to glaucoma in the Ocular Hypertension Treatment Study [6]. Low ocular perfusion pressure, diabetes and systemic hypotension have also been associated with disease in some populations, although the evidence is less consistent [4,21]. Recognition of these factors allows clinicians to identify people who merit closer monitoring and earlier treatment. Because several of these factors are not modifiable, control of IOP remains the practical focus of treatment for most patients [6].

Diagnosis rests on a combination of examinations because no single test is sufficient. These include measurement of IOP by Goldmann applanation tonometry, gonioscopy to assess the angle, dilated examination of the optic nerve head, standard automated perimetry for functional loss and optical coherence tomography for the retinal nerve fibre layer [17,22]. Structural changes frequently precede detectable visual field loss. Follow-up examinations are scheduled according to the stage of disease and the target pressure, and the rate of progression is used to decide whether therapy needs to be intensified. Glaucoma is diagnosed and staged by combining these findings, and a single normal measurement does not exclude disease, since IOP fluctuates during the day and can be normal in patients with established damage [13,17].

Table 1. Classification and main features of glaucoma

Type	Key feature	Usual first-line approach
Primary open-angle (POAG)	Open angle; raised IOP due to increased trabecular outflow resistance; slow, painless progression	Topical IOP-lowering drugs; laser trabeculoplasty
Normal-tension glaucoma	Glaucomatous optic neuropathy with IOP in the statistically normal range	IOP reduction to individual target; review of vascular risk
Primary angle-closure (PACG)	Narrow or closed angle with iridotrabecular contact; may be acute or chronic	Laser peripheral iridotomy; lens extraction; drugs
Secondary glaucoma	Raised IOP due to another cause (steroids, uveitis, trauma, pseudoexfoliation, neovascularisation)	Treat the cause; drugs, laser or surgery
Developmental / congenital	Abnormal development of the anterior chamber angle, presenting in infancy or childhood	Primarily surgical (goniotomy, trabeculotomy)

Table 2. Major classes of topical antiglaucoma drugs

Drug class	Examples	Mechanism	Typical IOP reduction	Common adverse effects
Prostaglandin analogues	Latanoprost, travoprost, bimatoprost	Increase uveoscleral outflow	25-33%	Conjunctival hyperaemia, iris pigmentation, eyelash growth
Beta-blockers	Timolol, betaxolol	Reduce aqueous production	20-25%	Bradycardia, bronchospasm, fatigue
Alpha-2 agonists	Brimonidine, apraclonidine	Reduce production; increase uveoscleral outflow	20-25%	Allergic conjunctivitis, dry mouth, drowsiness
Carbonic anhydrase inhibitors	Dorzolamide, brinzolamide	Reduce aqueous production	15-20%	Stinging, bitter taste, allergy
Cholinergic agonists	Pilocarpine	Increase trabecular outflow via ciliary muscle contraction	About 20%	Miosis, brow ache, blurred vision

Current Management of Glaucoma

Pharmacotherapy

Medical therapy lowers IOP either by reducing aqueous humour production, by increasing outflow, or by both. The main classes are prostaglandin analogues, beta-adrenergic blockers, alpha-2 adrenergic agonists, carbonic anhydrase inhibitors, cholinergic agonists and, more recently, rho-kinase inhibitors [12]. Prostaglandin analogues are usually preferred as initial therapy because they give the largest pressure reduction with once-daily dosing, while beta-blockers, alpha-agonists and carbonic anhydrase inhibitors are used as alternatives or adjuncts [8]. When monotherapy does not achieve the target pressure, fixed-dose combinations are used to reduce the number of drops and bottle preservative exposure. Table 2 lists these classes, with their mechanisms and common adverse effects. The choice among these agents depends on efficacy, systemic safety, comorbidities, cost and the likelihood that the patient will use the drug regularly [8].

Timolol maleate, a non-selective beta-blocker, remains a reference drug against which newer agents are compared, but systemic absorption through the nasolacrimal duct and nasal mucosa may produce bradycardia, bronchospasm and fatigue in susceptible patients [24]. Brimonidine, a selective alpha-2 agonist, lowers IOP by decreasing aqueous production and increasing uveoscleral outflow, and it is commonly given two to three times daily [25]. Prostaglandin analogues may cause hyperaemia, periocular pigmentation and eyelash changes [23]. These examples illustrate that even well-established drugs depend on formulation and dosing frequency to balance efficacy and tolerability. The pharmacokinetic aspects of each drug, including corneal permeability and nasolacrimal drainage, therefore influence how much reaches the target tissue and how much is absorbed systemically, which supports the development of vehicles that retain the drug on the eye [26].

Laser and Surgical Treatment

When medication is insufficient, poorly tolerated or not taken as prescribed, laser or surgical options are used. Selective laser trabeculoplasty enhances trabecular outflow and can serve as initial or adjunctive therapy, laser peripheral iridotomy treats pupillary block in angle-closure disease, and trabeculectomy or tube shunts create alternative drainage routes in advanced disease [20,22]. Minimally invasive glaucoma surgeries have expanded the choices for mild to moderate disease. These procedures carry risks such as infection, hypotony and scarring, and the effect may decline with time, so most patients still depend on lifelong medical therapy for at least part of their treatment [8]. Such procedures are usually offered according to disease stage, target pressure and patient preference [22].

Limitations of Conventional Topical Therapy

Ocular Barriers and Precorneal Loss

Eye drops are the most widely used ophthalmic dosage form, accounting for the large majority of marketed ophthalmic products, yet only a small fraction of the instilled dose, often less than five percent, reaches the intraocular tissues [27]. A drop of 25 to 50 microlitres exceeds the capacity of the conjunctival sac, which holds approximately 7 to 10 microlitres, so much of the dose spills over or is drained within seconds [28]. Reflex tearing, blinking and drainage through the nasolacrimal duct further shorten the precorneal residence time to a few minutes, and absorbed drug can reach the systemic circulation through the nasal mucosa [26]. This low ocular bioavailability means that large doses must be instilled to achieve a modest intraocular concentration [26].

Drug that remains on the ocular surface must still cross the cornea, a three-layered barrier made up of a lipophilic epithelium with tight junctions, a hydrophilic stroma and an endothelium. A molecule therefore needs balanced lipophilicity and hydrophilicity for effective permeation [29]. The conjunctiva and sclera offer an alternative, non-corneal route, but absorption there is largely lost to the conjunctival blood and lymphatic flow [29]. The combined effect of precorneal loss and these static barriers is a short duration of action, large peaks

and troughs in drug concentration, and the need for frequent administration, which is the main pharmaceutical problem to be overcome. Hence, drug candidates and vehicles for the anterior segment are designed around both transcorneal and conjunctival absorption [27].

Patient Adherence and Dosing Problems

Glaucoma therapy must be continued for life, usually without symptoms that reward adherence, and this is difficult for many patients. Barriers include forgetfulness, complex regimens with several bottles, difficulty instilling drops, adverse effects, cost and limited understanding of the disease [30,31]. In one cross-sectional survey, forgetting to instil the medication was among the most frequently reported barriers [31]. Poor adherence produces fluctuating IOP and is associated with faster visual field loss, which may be wrongly interpreted as treatment failure and lead to unnecessary changes of drug or surgery. Reducing the dosing frequency is therefore one of the most direct ways of improving real-world outcomes. Simplified regimens are expected to ease some of these barriers, which guides the design of sustained-release formulations [30].

Long-term use of multi-dose preparations also exposes the ocular surface to preservatives, such as benzalkonium chloride, which can disrupt the tear film and damage the epithelium, causing discomfort and ocular surface disease that in turn reduce adherence [32]. Therefore, an ideal glaucoma formulation should prolong the contact time of the drug, give a controlled release that reduces the dosing frequency, remain comfortable and cause little blurring of vision. These requirements have encouraged work on delivery systems that extend residence time without sacrificing patient acceptability [33]. Benzalkonium chloride toxicity has prompted interest in preservative-free or low-preservative systems, and a gel that provides prolonged action with fewer instillations would reduce the cumulative amount of preservative to which the eye is exposed [32].

Novel Approaches to Ocular Drug Delivery

Many strategies have been explored to increase the residence time and the corneal penetration of ophthalmic drugs. Simple approaches include viscosity enhancers, mucoadhesive polymers, suspensions and ointments, whereas more advanced systems include inserts, liposomes, nanoparticles, nanoemulsions, medicated contact lenses and implants [34]. Penetration enhancers and bioadhesive polymers are further options that improve drug contact with the corneal surface [35]. In glaucoma specifically, sustained-release approaches are of particular interest because the therapeutic goal is a steady, lasting reduction of pressure rather than a brief peak effect [33]. Each approach is selected according to the physicochemical properties of the drug, the target tissue and the acceptable complexity of the product, and the anterior segment is more accessible to topical vehicles than the posterior segment [27].

Each of these approaches has trade-offs. Ointments blur vision, and ocular inserts may cause foreign-body sensation and are often unwelcome to patients, while nanocarriers can face problems of stability, sterilisation, scale-up and regulatory approval, and implants require an invasive procedure [33,35]. In situ gelling systems offer a pragmatic compromise. They are instilled as easily as a conventional drop yet convert to a gel on the ocular surface, which prolongs retention and drug release, and they are generally simple and economical to manufacture [36]. For the anterior-segment disease of glaucoma, an approach that is easy to apply, inexpensive and acceptable to elderly patients, who may have limited dexterity, is more likely to be adopted in routine practice than a complex device [34].

In Situ Gelling Systems

Concept and Advantages

In situ gelling systems are polymer solutions that are administered as liquids and undergo a sol-to-gel transition at the site of application in response to a physiological stimulus, such as the temperature, pH or ionic composition of the tear fluid [36,37]. The idea was applied to ophthalmic use in the early 1980s with a poloxamer 407 vehicle for pilocarpine, which prolonged miotic activity in rabbits [38]. A few years later, an ion-activated

gellan gum vehicle increased the ocular bioavailability of timolol and permitted less frequent administration [39]. These early reports established in situ gelation as a practical approach for topical ocular drugs. Several in situ gelling products have subsequently reached the market, confirming the clinical feasibility of the concept [36].

Compared with preformed gels, in situ gels allow accurate and reproducible dosing, because the formulation is delivered as a drop, and they avoid the blurred vision and sticky eyelids often associated with ointments and viscous gels [36]. Compared with simple solutions, they extend precorneal retention and so may increase bioavailability, reduce dosing frequency and limit systemic exposure [37]. Because

the formulation is a liquid, it can be filled and sterilised with conventional equipment, and the main components are polymers with long safety records. Together these features favour better patient comfort and adherence in chronic conditions such as glaucoma. Additionally, since the gel forms only after instillation, the product can be formulated at low viscosity, which facilitates drop formation, filtration and accurate delivery from the dropper bottle [36].

Mechanisms of Gelation

Three principal triggers are used for ocular in situ gels. Temperature-induced systems gel when warmed from room temperature to the ocular surface temperature, pH-triggered systems gel when the acidic polymer solution meets the near-neutral tear fluid, and ion-activated systems gel through cross-linking with cations such as sodium, calcium and magnesium in the tears [36,37]. Combined systems use two triggers to obtain a stronger gel with lower polymer content. The classification of these systems and the features of each mechanism are compared in Table 3. The choice between triggers depends on the drug, the tolerance of the eye and the strength of gel needed, and temperature has the advantage that the stimulus is constant and does not depend on the tear composition [37,40].

pH-triggered systems based on Carbopol must be formulated at an acidic pH, which may irritate the eye and can be limited by the buffering capacity of tear fluid, so the amount of gelation produced in the eye is often modest [41]. Ion-activated systems such as gellan gum and alginate respond to the cations present in tears, but their gelation can vary with the volume and composition of the tear fluid among individuals [39]. Combinations, for instance alginate with hydroxypropyl methylcellulose or Carbopol with a poloxamer, are frequently used to strengthen the gel and prolong release [42,43]. In practice, the polymer concentration needed for sufficient gel strength must be balanced against viscosity before gelation and against ocular comfort [42].

Thermosensitive In-Situ Gels

Principle of Thermogelation

Thermosensitive in situ gels are liquid at storage or room temperature and turn into a gel at the temperature of the ocular surface. An ideal ophthalmic system should have a gelation temperature above ambient temperature, to remain a liquid during storage and handling, and below the surface temperature of the eye, so that it gels quickly after instillation. A range of about 25 to 34 degrees Celsius has been suggested for this purpose [44]. Because the trigger is the body's own temperature, no change of pH or addition of ions is needed, and the transition is reversible and independent of the volume or composition of tear fluid [40].

Thermogelation is usually driven by a change in the balance of hydrophilic and hydrophobic interactions as the temperature rises. Hydration of the polymer chains falls, hydrophobic segments associate, and physical cross-links form between chains or micelles, yielding a three-dimensional network that traps water [40,45]. The process needs no chemical cross-linker, organic solvent or initiator, which is an important safety advantage for ocular products. A conceptual illustration of the viscosity change with temperature and of the micellar arrangement in the sol and gel states. Additives, ionic strength and the presence of drug can shift the transition temperature, so each formulation

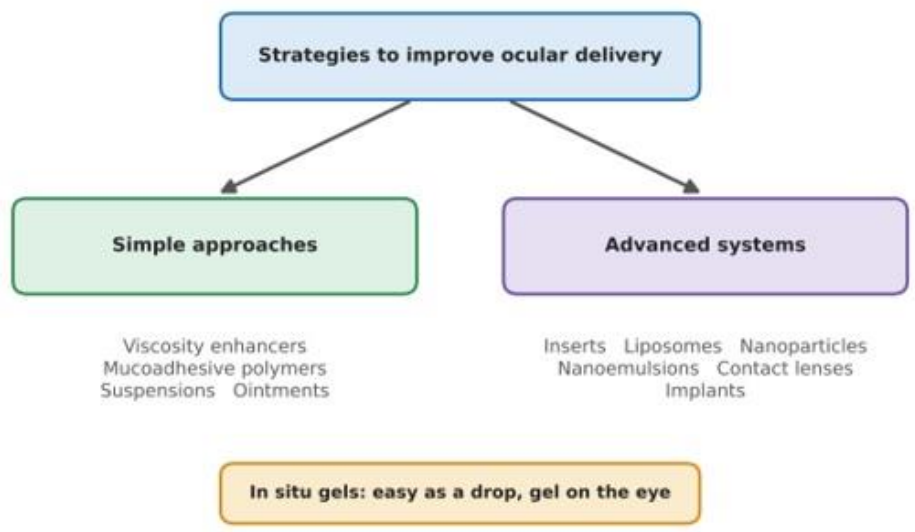


Figure 1. Strategies used to improve ocular drug residence time and corneal penetration.

Table 3. Comparison of gelation mechanisms for ocular in situ gels

Trigger	Representative polymers	Gelation condition	Main advantages / limitations
Temperature	Poloxamer 407, PNIPAAm, xyloglucan, chitosan-glycerophosphate	Warming to about 32-35 °C at the eye surface	Reversible, no pH or ionic dependence; may need high polymer content or gel-strengthening additives
pH	Carbopol, cellulose acetate phthalate	Rise from acidic pH to about 7.4	Simple to formulate; acidic vehicle may irritate; limited by tear buffering
Ions	Gellan gum, alginate	Cross-linking with Na^+, Ca^{2+}, Mg^{2+} in tears	Low polymer levels required; gelation depends on tear volume and composition
Combined	Poloxamer + Carbopol, poloxamer + chitosan, alginate + HPMC	Two triggers act together	Stronger gel and longer retention; more complex formulation and optimisation

needs experimental determination of its own gelation temperature rather than reliance on values quoted for the polymer alone [44].

Thermosensitive Polymers

Several polymers display sol-gel transitions in the physiological range. Poloxamers (Pluronics) are the most widely investigated for ophthalmic use. Others include poly(N-isopropylacrylamide) (PNIPAAm) and its copolymers, xyloglucan, which gels once partially degalactosylated, chitosan with glycerophosphate, cellulose ethers such as methylcellulose and hydroxypropyl methylcellulose, and triblock polyesters such as PLGA-PEG-PLGA [40,46,47]. Their gelation temperatures, advantages and limitations are summarised in Table 4. The choice of polymer depends on the gelation temperature required, biocompatibility, gel strength, mucoadhesion and regulatory acceptability. Natural polymers tend to be better tolerated and mucoadhesive, whereas synthetic polymers offer greater reproducibility and tunability of the transition temperature; the formulation scientist must weigh these properties against cost, availability and the stage of regulatory acceptance of the material [40,45].

Table 4. Thermosensitive polymers investigated for ocular in situ gels

Polymer	Gelation behaviour	Advantages	Limitations
Poloxamer 407	Gels at about 20-30% w/v near body temperature; depends on concentration and additives	Good solubilising ability; low toxicity; reversible; commercially available	High concentration needed; weak, rapidly eroding gel; no mucoadhesion
PNIPAAm and copolymers	Lower critical solution temperature of about 32 °C	Sharp transition; tunable by copolymerisation	Non-biodegradable; residual monomer toxicity concerns
Xyloglucan	Gels at 35-40 °C after partial galactose removal	Natural, biocompatible, mucoadhesive	Requires enzymatic modification; batch variability
Chitosan-glycerophosphate	Gels near 37 °C when neutralised	Biodegradable, mucoadhesive, antimicrobial	Neutral pH needed; slow gelation; stability issues

PNIPAAm has a lower critical solution temperature of about 32 degrees Celsius, which is close to the ocular surface temperature, and it has been investigated as a temperature-responsive vehicle for glaucoma drops [45,48]. Its use in ophthalmic products has been limited by its non-biodegradable nature and by the toxicity concerns that accompany residual monomer. Natural polymers such as xyloglucan and chitosan are biocompatible and mucoadhesive, but they can vary between batches and need careful control of modification or neutralisation [46,47]. These limitations explain why poloxamer-based systems are still the most commonly chosen platform for thermosensitive ocular gels. For these reasons, synthetic polyether copolymers with a long pharmaceutical history usually provide the most practical balance of properties for an ocular product [49].

Poloxamer 407 (Pluronic F-127)

Poloxamer 407 is a synthetic triblock copolymer of polyoxyethylene (PEO) and polyoxypropylene (PPO) arranged as PEO-PPO-PEO, with an average molecular weight of about 12,600 Da and roughly 70% PEO content [49]. The hydrophilic PEO blocks and the hydrophobic PPO block give it amphiphilic character and surface-active properties. It is listed in pharmacopoeias and the Handbook of Pharmaceutical Excipients, shows low toxicity and is used in oral, topical and ophthalmic preparations [50]. The combination of safety, solubilising capacity and reverse thermal gelation accounts for its prominence among thermosensitive vehicles. Poloxamer 407 is also compatible with many ophthalmic drugs and excipients and can solubilise poorly soluble drugs within its micelles, which broadens the range of molecules that can be formulated [49,51].

Aqueous solutions of poloxamer 407 at concentrations of about 20 to 30% w/v exhibit reverse thermal gelation. At low temperature the copolymer is dissolved as unimers, but as the temperature rises the PPO blocks dehydrate and the molecules self-assemble into spherical micelles, which at higher temperature pack into an ordered cubic lattice that behaves as a gel [49,51]. The gelation temperature falls with an increase in polymer concentration and is changed by additives such as salts, other polymers and drugs, which makes it possible to tune the system to the ocular temperature [51,52]. This reversibility is useful in manufacture, as the solution can be prepared and sterile-filtered in the cold state and then returned to room temperature without loss of properties [51].The use of poloxamer 407 alone has limitations. Concentrations of 20% w/v or more are often needed to gel at physiological temperature, yet such gels are mechanically weak, erode quickly in the presence of tear fluid, may feel viscous on instillation and do not adhere to mucin [44,52]. To overcome these problems, poloxamer 407 is usually blended with a second polymer, such as Carbopol, chitosan, gellan gum or hydroxypropyl methylcellulose, to lower the gelation temperature, strengthen the gel and add mucoadhesion [43,53,54]. Such blends increase the number of formulation

variables and make systematic optimisation necessary. Optimisation of the type and level of the second polymer is therefore a key part of formulation development [53].

Mucoadhesive and Viscosity-Enhancing Polymers

Mucoadhesive polymers adhere to the mucin layer covering the cornea and conjunctiva through hydrogen bonding, electrostatic interaction and interpenetration of polymer chains, which prolongs precorneal residence time [55]. Hydroxypropyl methylcellulose (HPMC), Carbopol, chitosan, hyaluronic acid and sodium alginate are the most common choices. In ophthalmic gels they act in two ways: they increase gel strength and viscosity, and they hold the formulation at the ocular surface. A poloxamer-chitosan gel showed prolonged retention in the eye [53], and Carbopol-Pluronic mixtures formed phase-change solutions with extended drug release [43]. The type and concentration of the mucoadhesive polymer must be selected carefully, since excessive viscosity may cause discomfort and blurred vision whereas insufficient amounts fail to prolong retention [54,55].

Formulation and Evaluation Considerations

The critical quality attributes of a thermosensitive ocular gel include clarity, pH, osmolality, gelation temperature and time, viscosity of the sol and gel states, gel strength, mucoadhesion, drug content and in vitro release [36,37]. The pH should be close to that of tear fluid and the osmolality near isotonic to avoid irritation. Rheological measurement as a function of temperature is used to determine the gelation temperature and to verify that the formulation remains fluid at storage temperature but gels at the eye surface [52]. Sterility, preservative efficacy and physical and chemical stability complete the pharmaceutical evaluation. Transparency is particularly important because a cloudy gel would obscure vision, and dropability should be confirmed for the sol at room temperature [36].

The release of the drug from the gel is studied in vitro using a diffusion cell fitted with a membrane and a simulated tear fluid, and the data are fitted to kinetic models to understand the release mechanism. Ocular tolerance is then assessed using irritation tests, with the rabbit-based Draize test being the classical in vivo reference, although alternative methods are increasingly preferred [56]. Finally, in vivo studies in a suitable animal model measure pressure reduction and its duration and compare the gel with a marketed solution to show that the new system gives a more sustained effect [57]. The comparison of release from the gel with that from a plain drug solution is the basic test of sustained-release behaviour [36].

Formulation Optimisation Using Experimental Design

Conventional formulation development varies one factor at a time, which is inefficient and cannot reveal interactions between the components. For polymer blends such as poloxamer with a mucoadhesive polymer, interactions are significant, because one polymer may change the gelation temperature of the other. The Quality by Design approach, described in the International Council for Harmonisation guideline Q8(R2), encourages systematic identification of critical material attributes and critical process parameters and their relationship to the critical quality attributes [58,59]. Statistical design of experiments is the main tool for this approach [60]. The method also reduces the number of experiments needed, which is important when the formulation uses expensive drugs and when each batch must be characterised for several attributes [60].

Factorial, central composite and Box-Behnken designs allow a limited number of experimental runs to be used to estimate the main effects, interactions and curvature of the factors, for example the concentrations of poloxamer 407 and a mucoadhesive polymer [61,62]. Response surface methodology fits polynomial equations that relate these independent variables to dependent responses such as gelation temperature, gel viscosity, mucoadhesive strength and percentage of drug released [60]. The significance of each term is judged by analysis of variance, and the contour

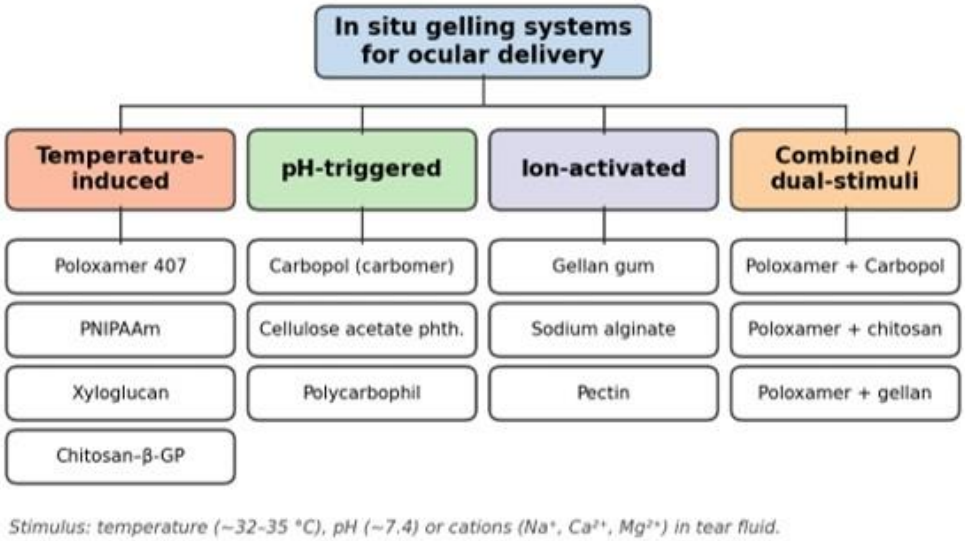


Figure 2. Concept of an in-situ gelling system: a liquid instilled as a drop gels on the ocular surface in response to a physiological stimulus.

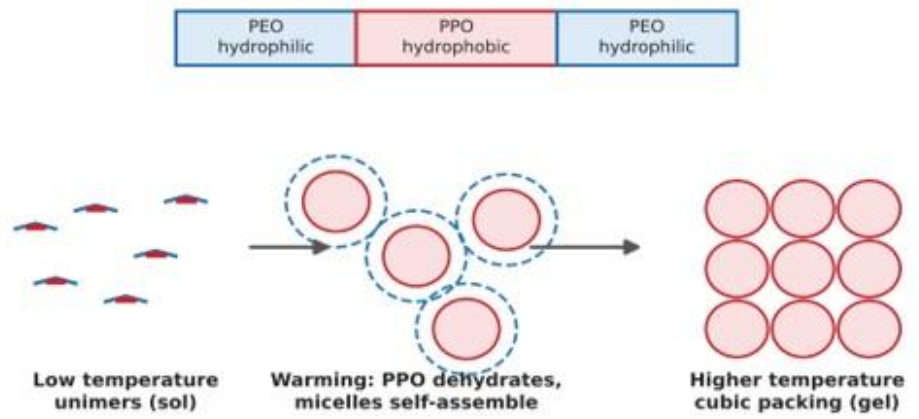


Figure 3. Structure of poloxamer 407 and its temperature-driven sol-gel transition from unimers to micelles to a packed cubic gel (schematic).

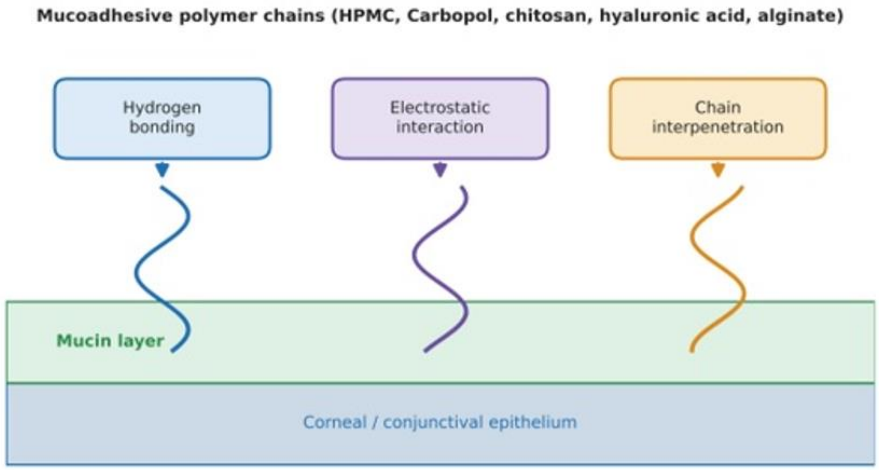


Figure 4. Mechanisms by which mucoadhesive polymers adhere to the mucin layer of the cornea and conjunctiva (schematic).

and three-dimensional response plots show how the factors affect each response. The choice among these designs depends on the number of factors and the nature of the expected response, with Box-Behnken designs being popular for three factors because they require fewer runs than a full three-level factorial design [60,61].

The last step of optimisation is to find the combination of factor levels that satisfies all the desired responses together, for instance a gelation temperature between about 32 and 35 degrees Celsius with adequate gel strength and sustained release over several hours. Numerical optimisation using desirability functions and graphical overlay of the contour plots are commonly employed, and the predicted optimum is verified by preparing and testing a check-point batch [58,60]. This systematic route saves time and materials and gives a defined design space within which the formulation is robust. Finally, the optimised formulation should be reproduced in the laboratory and the observed values compared with the predicted values to confirm the validity of the model and the reliability of the design space [58].

FUTURE PERSPECTIVES

While thermosensitive in situ gelling systems have demonstrated remarkable potential in bridging the gap between conventional eye drops and invasive implants, moving from bench to bedside requires addressing several critical frontiers. The next decade of research and development will likely pivot around four primary areas: Multimodal and Smart Stimuli-Responsive Systems: Future formulations will transition from single-stimulus (temperature) to dual- or multi-stimulus platforms. Combining temperature responsiveness with ion activation (e.g., matching poloxamers with gellan gum or alginates) or pH triggers can create an immediate, resilient gel structure upon contact with tear fluid. This minimizes the transient "spill-over" effect during the brief window before thermogelation is fully complete.

Mitigation of Preservative Toxicity via Auto-Sterilising Systems: Chronic exposure to benzalkonium chloride (BAC) in multi-dose glaucoma bottles induces severe ocular surface disease, driving down patient compliance. Future research must prioritize entirely preservative-free single-dose packaging or novel polymer matrixes with inherent, biocompatible antimicrobial properties (such as modified chitosans). This would eliminate the need for harsh chemical stabilizers while preserving long-term shelf stability.

Combination Therapies and Personalized Medicine via QbD: As glaucoma management frequently relies on polypharmacy (e.g., fixed-dose combinations of prostaglandin analogues and beta-blockers), in situ vehicles must be engineered to simultaneously solubilize and release multiple active ingredients with distinct physicochemical profiles. Utilizing Quality by Design (QbD) and machine-learning-driven Design of Experiments (DoE) will allow automated prediction of customized design spaces tailored to distinct multi-drug ratios, ensuring uniform release rates for each component.

Clinical Translation and Regulatory Standardization: The path to widespread market adoption rests on standardizing automated, non-invasive in vivo testing methods that replace traditional rabbit-based Draize tests. Developing high-throughput in vitro corneal perfusion models that accurately mimic human blink mechanics and tear turnover rates will accelerate regulatory scaling, manufacturing scale-up, and clinical trials—ensuring these affordable, user-friendly gels reach an aging global population.

CONCLUSION

Thermosensitive *in situ* gelling systems represent a paradigm shift in the management of glaucoma, offering a elegant, non-invasive solution to the long-standing challenges of conventional topical therapy. By seamlessly transitioning from a liquid drop to a structured gel at physiological ocular temperatures, these systems effectively overcome rapid precorneal loss, improve bio-availability, and minimize systemic side effects caused by nasolacrimal drainage.

While Poloxamer 407 remains a premier choice for thermogelation due to its safety profile and tunability, its mechanical limitations when used

alone necessitate the integration of secondary mucoadhesive polymers. Blending poloxamers with bioadhesives like Carbopol, HPMC, or chitosan creates a robust network that extends drug release and maximizes retention on the eye surface. Furthermore, implementing modern Quality by Design (QbD) frameworks and statistical Design of Experiments (DoE) ensures that these multi-polymer systems can be precisely optimized, establishing a reliable design space that satisfies strict clinical quality attributes.

Ultimately, bridging advanced polymer science with systematic pharmaceutical optimization yields a delivery vehicle that is simple to manufacture, easy for elderly patients to use, and highly effective at stabilizing intraocular pressure. As the global burden of glaucoma increases with an aging population, transitioning from traditional eye drops to smart *in situ* gels stands as a highly practical strategy to enhance long-term patient adherence, protect visual fields, and reduce preventable blindness worldwide.

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