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THERMORESPONSIVE IN SITU GELS FOR OCULAR DRUG DELIVERY IN GLAUCOMA: FORMULATION STRATEGIES AND RECENT ADVANTAGES

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Abstract:

Glaucoma is a long-term optic nerve disease in which raised intraocular pressure (IOP) damages retinal ganglion cells and, if left untreated, leads to permanent vision loss. Most patients are treated with eye drops, but a single drop is mostly lost within minutes through tear turnover and nasolacrimal drainage. Only a small share of the dose reaches the inner eye, so frequent dosing, side effects and missed doses are common. Thermoresponsive in situ gels offer a practical alternative. They are instilled as a free-flowing liquid at room temperature and set into a gel at the temperature of the ocular surface (about 33–36 °C), which keeps the drug in contact with the cornea for longer. This review explains the sol–gel transition of poloxamer 407 and poloxamer 188 and describes how mucoadhesive polymers such as HPMC, chitosan, xanthan gum and sodium alginate change gelation temperature, gel strength and adhesion. It then covers drug and excipient selection, cold-method preparation, factorial optimization and the loading of liposomes and other nanocarriers. Evaluation methods are summarized, including gelation temperature, rheology, mucoadhesion, in vitro release, ex vivo permeation, irritation testing and rabbit IOP studies. Reported work on latanoprost, timolol, fasudil and metoprolol gels shows longer IOP reduction, slower release and better corneal permeation than conventional drops. Limitations remain in stability, safety, scale-up and clinical evidence, and these are discussed with directions for future work.

Keywords: *Thermoresponsive in situ gel; glaucoma; poloxamer 407; ocular drug delivery; mucoadhesion; liposomes; intraocular pressure; sol–gel transition*

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1.INTRODUCTION:

Glaucoma is a group of optic neuropathic disease which is mainly caused due to damage in retinal ganglion cells dies. When glaucoma happens the pressure inside the eye increase at the point that the optic nerve were damaged , the optic nerve that carries visual information from eyes to the brain, the pressure in the eyes which destroy the optic nerve & ultimately this leads to vision loss. If glaucoma is not getting treatment & lower pressure the and prevent for the damage eventually can cause permanent blindness. [3,4,6]

As per WHO report every 5 seconds in the world goes blind and every minute child loss their sight.Around 76 million people were loss their vision thought the glaucoma disease to have it in 2020, and the ratio is to reach about 112 million by 2040.[1,2] In the last decade extensive research as we dine yet preclinical and clinical level for the development of therapeutic ocular diseases including glaucoma to deliver these therapeutic various drug delivery systems like such as eye drops, solutions, gels, contact lens for the effective ocular drug delivery.[13,14] At present time the primary method of treating glaucoma is to reduced intraocular pressure and overdue or inhibit the process medical management using eye drops applied directly to nerve system is the primary treatment approach.[3,5,15]

Ophthalmic drug delivery is an extremely difficult & highly challenge processes to transfer the drug through the anatomical and physiological barriers like coronel layer, blood aqueous barrier, blood retinal barriers [11,12] the landscape of ophthalmic drug delivery is a tough process and rapidly evolving. Researcher have increasingly switched in situ gelling system is a smart way upgrade topical treatment.[18,19,20] Resent developments in ocular drug delivery is in situ gelling system and nano technology-based drug delivery system.In this, we look at the physical and body-related challenges that make it hard to deliver medicine effectively to the eye. We also talk about the problem with old ways of making medicines and other methods of delivering medicines

The in-situ gelling system is superior because it can be administered as a liquid to the eye, they go into the eye as just like a normal eyedrop, making it easy and not painful process, and it ensures the right amount of medicine reaches the eye to the eye to cure the glaucoma. When the in-situ formulation turns into a gel inside the eye's Cul de sac, it solves the problems of eye drops like quick drainage through the nose and limited time the drops stay on the eye's surface.[10,20] These clever gels can be change in temperature, PH & Ions[21,22] because body heat is constant reliable, trigger, the formula does not need to on unusual pH levels or special ion balance. This review focuses specifically focus on thermoresponsive in situ gels for the, management of the glaucoma disease.

This situ gels undergoes in situ gel to solutions transition which result change temperature incoherence of salt or media PH change where the in-situ gels which have less viscosity which causes the low therapeutic effect one way to make up for the low viscosity of these gels is to mix with then liposomes to improve therapeutic effect[53,55] and these addition to frequent installation of the drug overcome the problem of the low therapeutic effect of the drug.

Several drug classes lower IOP, and many of them run into the same delivery problem. Latanoprost, a prostaglandin analogue, is one of the best examples. It is a prodrug. After it crosses the cornea, esterases convert it to the active acid, which increases outflow of aqueous humour through the uveoscleral pathway.[7] Despite its long duration of action, less than 7% of an instilled dose is thought to reach its site of action.[46] Repeated dosing exposes the eye to preservatives, which can cause irritation, burning and dryness.[8] Latanoprost is also unstable in aqueous solution when warm, so it has to be kept at 2–8 °C.[46]

Beta-blockers such as timolol have a different problem. At physiological pH, about 98% of timolol is protonated and poorly lipophilic, and under 5% reaches the inner eye.[17]What drains away can be absorbed through the nose and cause systemic side effects.[17,42] Other glaucoma drugs, including betaxolol, brinzolamide and dorzolamide, have been studied with nanoparticles or liposomes to improve retention and penetration.[53,55]

Thermoresponsive gels have shown real benefits for these drugs in preclinical work. A Pluronic F-127 and HPMC gel of latanoprost lowered IOP in rabbits for about 8–9 hours, against about 3 hours for a marketed drop, and the area under the effect curve was roughly 2.9 times higher.[46]The same gel was more stable than the commercial drop. The time for 10% loss was about 17 months at 4 °C, versus about 3 months for the drop.[46] For timolol, a Pluronic F-127 and chitosan gel increased corneal permeation and delayed clearance from the eye surface.[42,44,48] Gamma scintigraphy showed no radioactivity in the kidney or bladder after two hours, unlike the plain solution . used a different approach, a thermosensitive chitosan, gelatin and glycerophosphate hydrogel that was injected under the conjunctiva. In rabbits it released latanoprost steadily without a burst, and IOP stayed in the normal range for 31 days.[45]

Gels do not solve everything. A gel strong enough to resist drainage can release drug slowly, and

higher polymer content slowed release in several of the studies above.[46,47] Viscosity must also be controlled, because a thick gel can be uncomfortable on the eye.[20,35] Gels from a single polymer have limited strength and bioadhesion, which is why most current designs combine more than one polymer. Nanocarriers add a further layer of options. Liposomes, nanoparticles and lipid carriers can be loaded into gels to temper burst release and extend retention. Their drawbacks are scale-up, reproducibility and long-term safety, and nanoparticles may block the punctum if given repeatedly.[55]

Against this background, the present review looks at thermoresponsive in situ gels for glaucoma. It starts with the fundamentals of the sol-gel transition, then covers the polymers most often used, namely poloxamers, HPMC and other mucoadhesive agents. It then goes through formulation and evaluation methods and the drug-delivery results reported so far, and ends with current limitations and the direction of future work

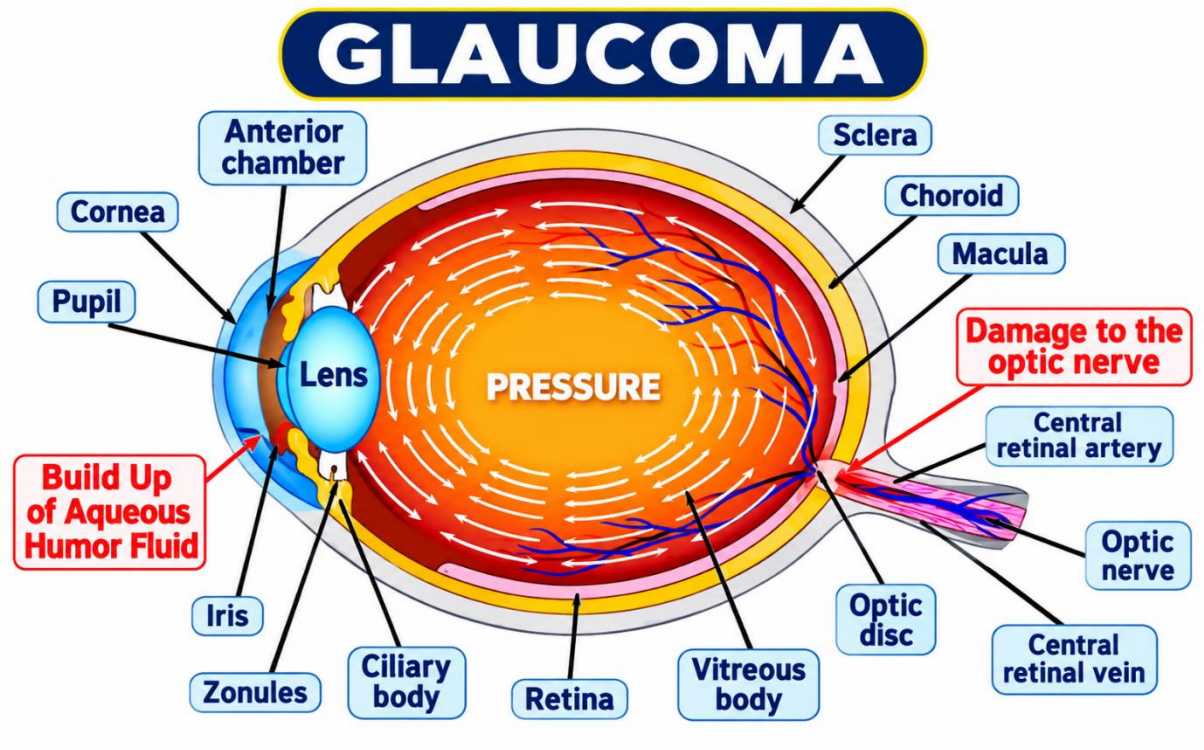

Figure1:Cross-section of an eye affected by glaucoma.Fluid showing fluid build-up in the anterior chamber and the raised pressure that harms the optic nerve at the disc

2.Ocular Drug Delivery Challenges in Glaucoma

Glaucoma is a chronic disease, so treatment means keep the drug at beneficial level in the eye for years. that is hard to do with topical therapy. Most anti glaucoma agents are given as drops several times a day, and each dose reaches the target tissue only in small amounts the drugs own chemistry adds to the problem. At physiological level timolol exist almost entirely in its ionized form, so it dissolves poorly in lipid & under 5% of each instilled drug reaches the interior of the eye.[17] Prostaglandin analogs are carboxylic acids with weak corneal permeability. There are made as easter prodrug, such as latanoprost, which corneal esterases convert to active acid.[7] Even so, irritation remain a concern.[8] Low delivery efficiency means frequent dose and a greater chance of missed doses. Continue dosing also exposes patient systemic side effect, so improving delivery is as much a matter of adherences and safety as of potency

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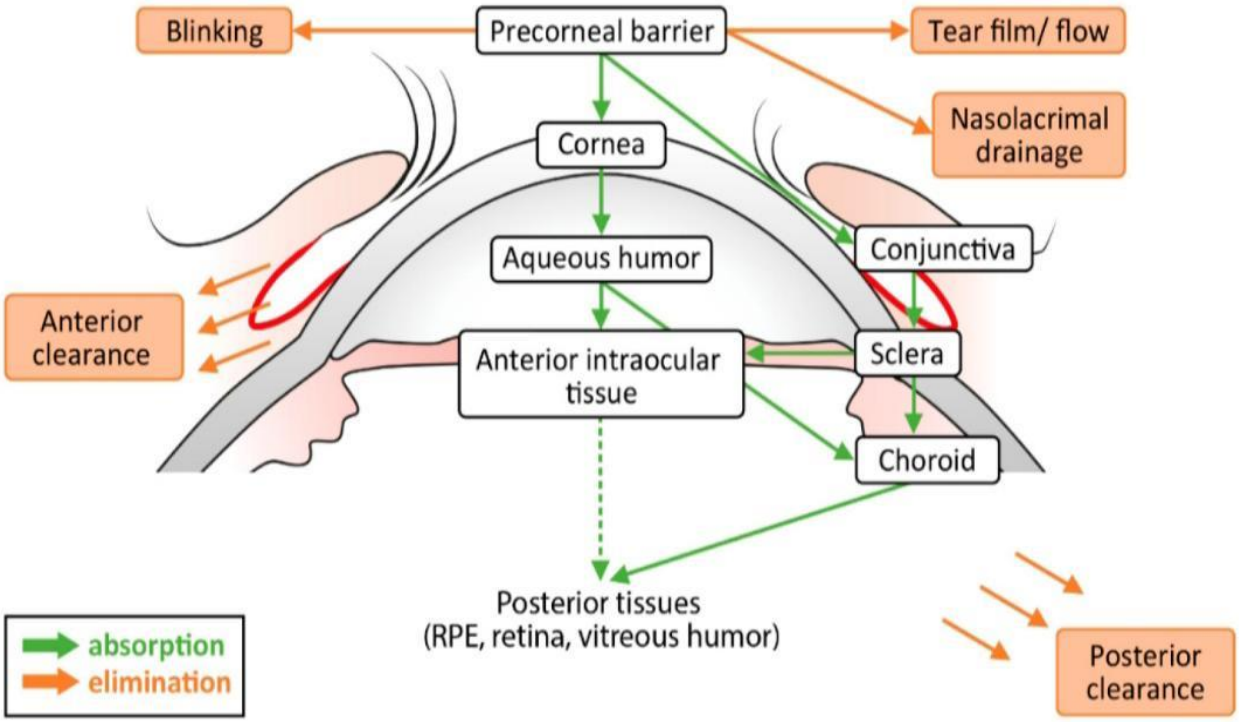

Figure 2: Ways a drug is absorbed show as green arrows and elimination show as orange arrows after it is dropped into the eye. Blinking, tears and drainage through the nasolacrimal duct wash much of the drug away from the front of the eye. What stays on the surface can pass through the cornea, conjunctiva and sclera into the aqueous humour and on to the front and back tissues of the eye.[11,12,13]

2.1Ocular Barriers to Drug Delivery

A drug must pass several defences before it reaches the tissue it is meant to treat. The first is the tear film. The tear film is roughly replaces every five min, and irritation can result trigger reflex tearing that pushes lacrimal flow far above its base line.[9,10]The drug is diluted and flushed away as result.This dilutes the drug and washes it away. The mucin layer adds a second obstacle.It is negatively charged because of its sialic acid content, and it traps foreign material.[25]

The cornea is the main route for topical drugs and works as a selective filter. Its epithelium and endothelium are lipid-rich and hold back polar, water-soluble molecules, while the water-rich stroma resists lipophilic ones[12,13].A drug therefore has to cross both fatty and aqueous layers in turn. Tight junctions between epithelial cells restrict passage further. The conjunctiva offers another entry route, but its blood and lymphatic vessels carry part of the dose into the systemic circulation.Some drug also drains through the nasolacrimal duct and is absorbed through the nasal mucosa.[9,11]

Elimination continues inside the eye. Aqueous humour turnover and uveal blood flow remove drug from the anterior segment. Melanin binding in the iris and ciliary body can hold some drugs for longer. Efflux proteins and metabolic enzymes in ocular tissues lower the effective concentration still more. At the back of the eye, the sclera, the choroid and the blood–retinal barrier keep most drug from reaching the retina.

2.2Limitations of Conventional Eye Drops

Attempts to fix these problems bring their own difficulties. Ointments stay longer on the surface, but they blur vision and reduce compliance.Viscosity-enhancing polymers can alter the refractive index or make accurate dosing harder. Many drugs are lipophilic or high in molecular weight, so solubilizing them in water needs oils or surfactants, which can disturb vision and reduce tolerability. Permeation enhancers such as benzalkonium chloride can accumulate in the cornea and cause toxicity.[8]Eye drops also work poorly for posterior-segment disease, even at high dosing frequency.[13]These limits explain the interest in mucoadhesive, in situ gelling and nanocarrier systems for glaucoma.[20,55]

3. Fundamentals of Thermoresponsive in Situ Gels

They are applied as a liquid, so the dose is accurate and reproducible, and they thicken into a gel once inside the cul-de-sac, which lengthens contact with the cornea.[18,19,20] The change from sol to gel can be triggered by the body's own conditions. Common triggers are a rise in temperature (poloxamer 407), a shift in pH (cellulose acetate

phthalate), or the presence of cations in tears (deacetylated gellan gum, alginate).[18,22,23,24] Some formulations combine two triggers, such as Pluronic F-127 with chitosan, which responds to both temperature and PH.[42] Thermoresponsive gels are the most studied of these, and the polymers behind them are mainly the Pluronic/poloxamer family, including P407 and P188. For ocular use, a good thermoresponsive gel must meet several conditions. It should stay a clear liquid at room temperature, gel close to the from33-36 °C range of the ocular surface, keep a pH near that of tears, cause no irritation, and cling to the mucus layer long enough to matter. Poloxamer 407 alone does not meet all of these well. It needs a high concentration to gel at body temperature, it is weakly mucoadhesive, and high levels have been linked to a risk of raised blood lipids.[30]This is why most current work blends it with poloxamer 188 or with mucoadhesive polymers such as HPMC, alginate or xanthan gum.[36,40,41] The two subsections that follow explain how the temperature trigger is controlled and what happens at the molecular level when the gel forms.

3.1 Temperature-induced sol–gel transition

A thermoresponsive in situ gel is dropped into the eye as a free-flowing liquid and turns into a gel once it warms to the temperature of the ocular surface. That surface sits at roughly 33.5–35.5°C, with an average near 34.5°C.[34] So, the formulation has to be liquid at room temperature, which allows an accurate dose and easy instillation, and it must gel within a narrow window above that. If gelation happens below this range, the product thickens during manufacture, storage and handling. If it happens above, the product stays liquid in the eye and is lost through lacrimal drainage.[10,33] Poloxamer 407 (Pluronic F-127) is the most widely used polymer for this purpose, but used alone it has a practical problem. and below that its gelation temperature climbs out of the useful range. Formulators therefore adjust the transition by blending polymers. Combining poloxamer 407 with poloxamer 188 at 15/15% brought gelation down to about 36°C.[60] while poloxamer 407 alone gelled at 19–26°Cand25% poloxamer 188 alone stayed above 50 °C.[60] In a factorial design, whereas adding poloxamer 188 raised it.[46]

Mucoadhesive polymers also shift the transition. HPMC, xanthan gum and sodium alginate all lowered gelation temperature as their concentration rose. In a poloxamer 407 system, 0.5% HPMC K4M pulled the gelation temperature of a 20% gel from 36.1 °C to 32.8 °C and cut gelling time to about 11 seconds. The change shows up clearly in viscosity. One metoprolol gel went from 573–815 cP at 25°C to roughly 17000 to 225000 cP at 34°C . The usual lab method is tube inversion, where the gel point is the temperature at which the meniscus stops moving.[12] A sudden rise in viscosity is also used as an end point. One practical caution is that tear fluid dilutes the gel on instillation. In one study, lowering poloxamer from 20% to 17.5% pushed gelation above 45°C, so tests are often run after dilution with simulated tear fluid. Temperature is not the only trigger that can be used.A 9% Pluronic F-127 and 0.25% chitosan system gelled above 35°C and at pH 6.9–7.0, and the same system was sterilized by autoclaving, converting back to liquid on cooling.[59]

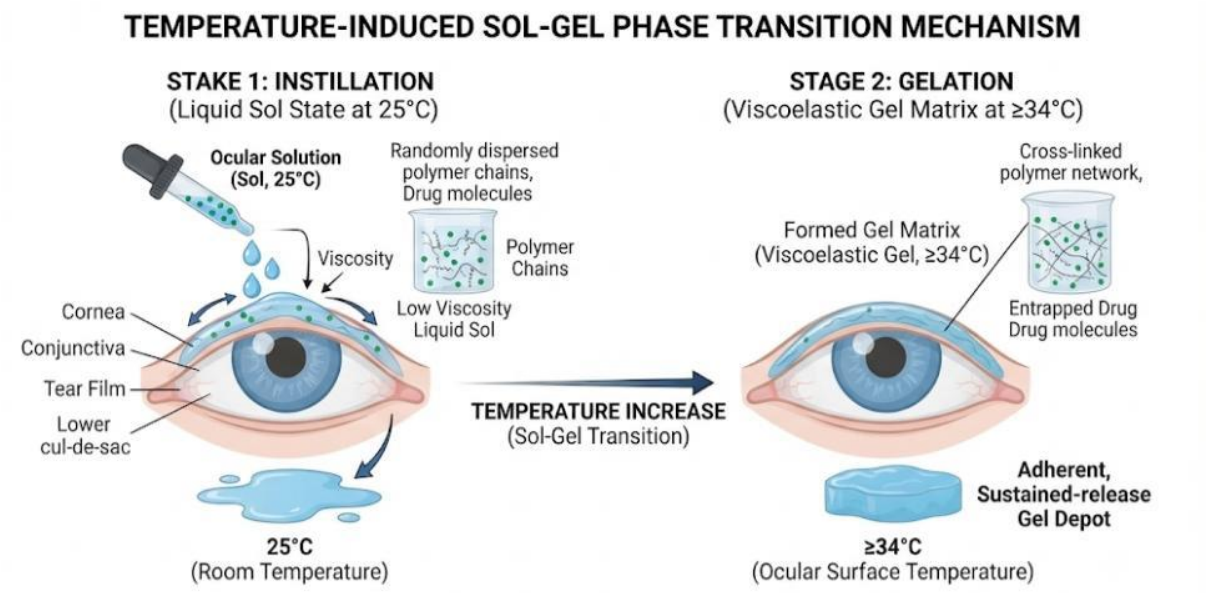

Figure 3:Schematic illustration of temperature-induced sol–gel transition of a thermoresponsive in situ gel on the ocular surface.

3.2 Mechanism of gel formation

Poloxamers are triblock copolymers with a central hydrophobic polypropylene oxide (PPO) block flanked by two hydrophilic polyethylene oxide (PEO) blocks. The PEO:PPO ratio is about 7:3 in poloxamer 407 and 8:2 in poloxamer 188[27,28,30] At low temperature, water surrounds both blocks and the chains stay dissolved as a clear, low-viscosity solution. When the temperature rises, the PPO blocks lose their water and become hydrophobic. To limit contact with water, the chains assemble into micelles, with a PPO core and a hydrated PEO shell, once the critical micellization temperature is crossed.[28,29]As heating continues, or as concentration increases, the micelles multiply and crowd together until they touch and can no longer move freely. At this point the solution behaves as a gel.[36,41]Some authors also propose that the micelles pack into an ordered cubic crystalline arrangement and that hydrogen bonding between chains reinforces the network. Because all this depends on weak physical interactions and not chemical bonds, the process reverses on cooling.[30] Additives work through the same chain interactions. HPMC and similar polymers are thought to bind to the PEO segments through hydrogen bonds, which encourages dehydration and tighter entanglement. This raises viscosity and moves gelation to a lower temperature. Alginate adds a second effect, since calcium ions in tears can help build a stronger network. Poloxamer 188 works the other way.[41] Its higher PEO content makes it more hydrophilic, so it delays micellization and raises the gelation temperature.[30,31]

4. Polymers Used in Thermoresponsive Ocular Gels

A thermoresponsive ocular gel depends on two things: a polymer that turns from liquid to gel at about the temperature of the eye surface, and a second component that makes the gel stick around and hold together. In practice no single polymer does both well. Most reported systems therefore pair a thermogelling block copolymer, usually a poloxamer, with a cellulose ether or another mucoadhesive polymer. The sections below cover the polymers that appear most often in the formulation studies reviewed here.[30,35]

4.1 Poloxamer 407 and Poloxamer 188

Poloxamers are triblock copolymers with a central polyoxypropylene (PPO) block between two polyoxyethylene (PEO) blocks. The two grades used most in ocular work are Poloxamer 407 (Pluronic F-127) and Poloxamer 188 (Pluronic F-68).[26,27,28]The PEO:PPO ratio is about 7:3 in P407 and 8:2 in P188.[27,28] The hydrophobic PPO segment pushes the gelation temperature down, while the hydrophilic PEO segment pushes it up, so even small changes in the ratio shift the sol-gel point.[27,30]

Gelation comes from temperature-driven micelle formation. As the solution warms, the PPO blocks lose their water and the chains aggregate into micelles with a dehydrated PPO core and a hydrated PEO shell. With further heating the micelles pack together and become entangled, and the solution stops flowing. Gupta et al. described the same sequence for Pluronic F-127: gradual desolvation of the polymer, more micellar aggregation, and entanglement of the network.[42] A practical advantage is that the process is reversible. In their timolol formulation, a gel produced by heat during autoclaving went back to liquid on cooling, so the preparation could be terminally sterilised.[42] Blending the two grades solves this. In the moxifloxacin work, 15% P407 with 15% P188 gelled at 36 ± 0.5 °C,[60] and 15% with 18% gelled at 30 ± 0.5 °C. Increasing P407 meant less P188 was needed to land at the target temperature. The latanoprost study found the same trend in a factorial design. Higher P407 lowered the sol-gel temperature ($P < 0.0037$).[46]while adding P188 raised it ($P < 0.0003$). The highest value, 63 °C, was recorded in a formulation containing 2.5% P188.[46]

Concentration affects mechanics and drug release as well as gelation. Higher P407 increased gel hardness and the consistency index, whereas P188 reduced hardness.[46] Denser gels slowed release. In the latanoprost study, the formulations with more polymer released least, around 67–75% over the test period, against about 91–95% for the leaner ones.[46] This is the usual trade-off: a stronger gel resists drainage but releases the drug more slowly.[35,37]

Poloxamers have two weaknesses. First, a gel made from poloxamer alone is mechanically weak and gives little bioadhesion.[35,40] pointed out that earlier work had focused almost entirely on adjusting the gelation temperature, with little attention to gel strength and bioadhesive force. Second, high concentrations raise handling issues. noted that a poloxamer solution stored in a refrigerator for easy instillation could irritate the eye because of its low temperature.[35]Both problems are the reason poloxamers are normally combined with mucoadhesive polymers, as discussed next.[38,39]

On the positive side, poloxamers are generally regarded as well tolerated. reported good thermal gelling and low irritation for Pluronic F-127 and saw no redness, chemosis or discharge in rabbits with their F127-based gel . The latter authors also suggested that P127 may help permeation by reducing the stickiness and elasticity of the mucus

layer. In their stability work, latanoprost kept better in the gel than in a marketed drop at 4 °C and 25 °C.[39]

4.2 Hydroxypropyl Methylcellulose and Mucoadhesive Polymers

Mucoadhesive polymers are added to thermogelling systems to improve gel strength and to keep the formulation in contact with the ocular surface. The ocular surface is coated with mucin, which carries a negative charge at physiological pH because of its sialic acid residues.[25]Polymers that can interact with this layer, by electrostatic attraction, hydrogen bonding or chain interpenetration, lengthen precorneal retention.[16,25] HPMC. Hydroxypropyl methylcellulose is a non-ionic cellulose ether and one of the most common additives in ophthalmic preparations.[25,41]Because it carries no ionised groups, it does not bind to the sialic acid of mucin in the way that cationic polymers do. Its effect on retention is thought to come mainly from higher viscosity rather than from specific interaction with mucus.[25]HPMC has also been used inside the gel as a drug-retaining matrix. Silva et al. suspended chitosan nanoparticles in an HPMC gel and found slower ceftazidime release than from the nanoparticles alone.[55]

In poloxamer systems, HPMC does more than thicken the vehicle, and the grade matters.Compared HPMC E5 and E50 at 0.25–1%. Moving from E5 to E50 significantly lowered the sol-gel temperature ($P < 0.0004$),[46] probably because the polymer promotes dehydration of the PPO core and encourages micellisation. HPMC concentration had no significant effect on that temperature. On mucoadhesion, only the grade was significant, with E50 giving clearly higher adhesion than E5. Gel hardness was unaffected by either grade or concentration, while consistency rose with both. The formulation chosen as optimal, 18% P127 with 1% HPMC E5 and no P188, gelled at 34.3 °C and gave a flux of 11.4 µg/cm²/h across cow cornea.[46] In rabbits it raised AUC about 2.9-fold over a marketed latanoprost drop and extended the IOP reduction to roughly 8–9 h, against about 3 h for the drop.[46]

Xanthan gum and sodium alginate.Added these two to a P407/P188 (15/15) base at 0.3–0.7%. In both cases the gelation temperature fell as polymer concentration rose, and gel strength and bioadhesion rose.The authors explained the lower gelation temperature by the polymers binding the PEO chains, which promotes dehydration and entanglement of neighbouring molecules. At matched concentrations, alginate gave stronger gels and higher bioadhesive force than xanthan gum. Bioadhesion values ranged from about 2,474 to 4,130 dyne/cm² across the series.Drug release was slower with alginate, which the authors linked to its ionotropic gelation with calcium in the tear fluid.[42]At low pH its amino groups are protonated, which allows electrostatic attachment to mucin.[25,40]. coTranscorneal permeation after 4 h was about 63% from the gel against about 42% from plain drug solution, and gamma scintigraphy in rabbits showed slower clearance and no activity in the kidney or bladder at 2 h, unlike the solution. Other workers have reported that poloxamer–chitosan gels gain mechanical strength and mucoadhesion compared with poloxamer alone.[41]

5. Formulation Strategies

The development of thermoresponsive in situ gels for ocular drug delivery requires careful selection of polymers, drug substances, and other formulation ingredients to achieve suitable performance after administration. These formulations are designed to remain in a liquid state at room temperature and undergo gel formation when exposed to the temperature of the ocular surface. This change helps the formulation remain in contact with the eye for a longer period and may improve drug availability compared with conventional eye drops.[20,35]

5.1 Selection of Drug and Excipients

In Glaucoma the Drug choice usually starts with the clinical problem.the candidates range from established agents such as timolol maleate and latanoprost to repurposed or newer molecules such as metoprolol and the Rho-kinase inhibitor fasudil. Their physicochemical profiles differ, and so do the formulation problems they raise. Highly hydrophilic drugs like fasudil (log P 0.16) permeate the cornea poorly,[49,50]whereas latanoprost is a heat-labile prodrug whose ester hydrolyses in aqueous solution.[46]Because of this, the dose, solubility and stability of the drug have to be known before any vehicle is chosen.Excipient selection follows from the gelation target. Poloxamer 407 is the usual backbone, since it is thermoreversible and forms clear gels.[30,35]Used alone, however, it needs high concentrations, and the gel it forms adheres poorly to mucus. Co-polymers are therefore added to adjust the transition temperature. Poloxamer 188 raises it, as seen in the 15/15 P407/P188 blend that gelled near 36 °C. Cellulose derivatives, xanthan gum and sodium alginate lower the transition temperature and improve bioadhesion. HPMC grade matters: E50 lowered the gelation temperature more than E5 in the latanoprost study.[46]Chitosan serves a different purpose, acting as a mucoadhesive and permeation enhancer, and it also contributes pH-triggered gelation when combined with Pluronic F-127.[42]Isotonicity agents, preservatives and buffers are then adjusted so that pH stays within the tolerated range of roughly 6–7.4.[16,25]

5.2 Preparation and Optimization of Formulations

Most poloxamer systems are made by the cold method.[31,35] The polymers are dispersed in water at 4–8 °C and left in the refrigerator overnight to hydrate fully, and the drug or the nanocarrier dispersion is added once a clear solution forms. Where HPMC is used, it is generally dissolved first, so that the poloxamer can then be added without lumps.[47]

Optimization is largely a matter of balancing competing responses.The sol-gel temperature should fall close to the temperature of the ocular surface, about 33–36 °C.[34] The solution must stay fluid at room temperature,yet thicken within seconds on contact with the eye. Beyond gelation temperature, the key readouts are gel strength,viscosity, mucoadhesion, drug release and corneal permeation. Factorial designs make this tractable. In one example, poloxamer and HPMC levels were varied together, and the effects on transition temperature, gel strength and adhesion were modelled.[46]Other studies screened poloxamer at 17.5–25% with and without HPMC and chose about 20% as the best compromise.[47,50]The pattern is consistent: more polymer gives faster gelation and higher viscosity, but slower drug release. Stability must also be confirmed, and autoclaving, storage temperature and sterility testing are routinely included.[42]

5.3 Incorporation of Antiglaucoma Drugs and Nanocarriers

Free drug can be dissolved directly in the gel, but nanocarriers offer more control. Liposomes are the most common choice.They can improve corneal transport, yet in dispersion they are too fluid to stay on the eye, and dispersing them in a thermosensitive gel addresses that weakness.[49,53]Coating them with chitosan adds positive charge, which promotes interaction with negatively charged mucin.[49,54] Metoprolol-loaded chitosan-coated deformable liposomes in a poloxamer/HPMC gel raised transcorneal permeation 4.4-fold over the plain drug gel and gave a longer-lasting fall in intraocular pressure.[49]For hydrophilic drugs, a drug–phospholipid complex can raise entrapment before liposome formation.[50]

Incorporation does change the systemVesicle size and zeta potential may shift in the gel, and in some cases viscosity rises slightly.Release can also behave unexpectedly, since gelation inside a dialysis bag may dilute the polymer. Entrapment, particle size and release should therefore be measured both before and after the gel is formed.[49,50]Other carriers have also been loaded into in situ gels, including solid lipid nanoparticles, nanostructured lipid carriers and nanoemulsions.[51,55]Hence, the carrier and the gel should be developed together.

6.Pharmaceutical and Biological Evaluation

Pharmaceutical and biological evaluation plays an important role in determining the quality, safety, and performance of thermoresponsive in situ gels intended for ocular drug delivery. These studies help establish whether the formulation can be administered comfortably, form a gel at the required temperature, retain the drug on the ocular surface, and provide an appropriate drug-release profile. In glaucoma treatment, these properties are particularly important because maintaining effective drug levels in the eye may help achieve better control of intraocular pressure.[16,42]

6.1 PH, Clarity, Gelation Temperature and Viscosity

Basic physicochemical checks come first. Clarity is judged by eye against black and white backgrounds, both before and after gelation, because a cloudy vehicle blurs vision and annoys patients. pH is measured with a calibrated meter. Reported values sit between about 5.5 and 7.4, which the eye tolerates without trouble.[16]Osmolarity is also checked, with the timolol formulation falling in the 298–308 mOsmol range.[42]

Gelation temperature is usually found by the tube inversion method, in which the sample is warmed gradually and the point where it stops flowing on tilting is recorded.The target is roughly 33–36 °C. A lower value risks gelling at room temperature, and a higher one lets the liquid drain away.[31,34] Gelling time is a useful companion measure, since the gel must set within seconds. Viscosity is measured at storage and eye temperatures. Good formulations are thin at 25 °C and thick at 34–37 °C, as in the jump from 573–815 cP to more than 16,000 cP reported for the metoprolol gels.[49]

6.2 Mucoadhesion and In Vitro Drug Release

Mucoadhesion is assessed in several ways.Texture analysers measure the detachment force and work of adhesion on excised corneal tissue.[16,25]Balance-based methods measure the force needed to separate two membrane-coated surfaces.Two simpler indirect approaches exist.One tracks the change in zeta potential of mucin particles after mixing with the carrier, and the other measures how far viscosity rises when the formulation meets mucin.A viscosity increase greater than the sum of the separate components indicates real interaction.[25]

In vitro release is normally tested by dialysis in simulated tear fluid at about 35–37 °C, with samples replaced by fresh medium. Data are fitted to zero-order, first-order, Higuchi and Korsmeyer–Peppas models.[56,57]and the exponent n indicates

whether release is Fickian or anomalous.A higher polymer content generally slows release, and nanocarrier gels often remove the early burst seen with plain dispersions.[49,50]Interpretation needs care, because the gel may dilute or partly collapse inside the dialysis bag, which can make release appear faster than expected.[50]

6.3 Ex Vivo Permeation and Ocular Irritation Studies

Ex vivo permeation uses excised cornea from goat, cow or rabbit mounted in Franz-type cells[49,50]Cumulative amount, flux and permeability coefficient are calculated, and corneal hydration is checked afterwards to confirm that the tissue stayed intact. Hydration values of 76–80% were taken as normal.[49] In these studies, chitosan-containing and liposomal gels transported more drug than plain solutions, for example 63% versus 42% of timolol in four hours.[42]

Irritation is first screened with the hen's egg chorioallantoic membrane test (HET-CAM), which scores haemorrhage, lysis and coagulation.[58] Saline and sodium hydroxide serve as negative and positive controls.Results are confirmed in rabbits using a modified Draize scheme that scores redness, chemosis and discharge.[59] Most gels scored as non-irritant or mildly irritant, and transient redness was seen with a cationic chitosan-coated system, which cleared within three hours.[49]

6.4 In Vivo Performance and Stability Studies

In vivo work generally uses rabbits.Pharmacodynamic studies measure the percentage fall in intraocular pressure with a Schiotz tonometer,[45,46]in normotensive animals or in steroid-induced ocular hypertension. Maximum effect, time to maximum, area under the curve and mean residence time are derived from the curve.The technetium-labelled timolol gel stayed on the cornea longer and showed no systemic activity at two hours.[42,43]

Stability testing follows ICH-type conditions at refrigerated, room and eye temperatures.Drug content, particle size, zeta potential and entrapment efficiency are tracked, and sterility is tested after autoclaving. The latanoprost gel kept more than 92% of its drug after 12 months at 4 °C, against 45% for the marketed product.[46]

7. Recent Advances in Thermoresponsive Ocular Gels

Thermoresponsive ocular gels have received considerable attention as an alternative approach to conventional eye drops, particularly for the treatment of glaucoma. Recent research has focused on combining temperature-sensitive polymers with antiglaucoma drugs and advanced drug carriers to improve ocular drug retention and drug absorption. These developments aim to overcome the limitations associated with rapid tear drainage, poor corneal permeability and frequent administration of eye drops.[20,35,55]

One important development is the incorporation of lipid-based nanocarriers into thermosensitive gel systems. This combination provides an opportunity to improve drug loading, regulate drug release and maintain longer contact with the ocular surface. Research involving latanoprost, fasudil and metoprolol has demonstrated the potential of these approaches in experimental glaucoma models.[46,49,50]However, further studies are required to establish their long-term safety and clinical usefulness.

7.1 Antiglaucoma Drug-Loaded In Situ Gels

Several anti glaucoma drugs have been investigated for incorporation into in situ gel formulations to improve their ocular delivery. Latanoprost is one of the important examples studied using a thermosensitive pluronic-based system.[46]Developed a mucoadhesive in situ gel containing latanoprost using poloxamer 407, poloxamer 188 and hydroxypropyl methylcellulose (HPMC).[46]

The optimized formulation showed a sol-to-gel transition temperature of approximately 34.3°C. In the experimental glaucoma model, the formulation produced a longer reduction in intraocular pressure (IOP) than conventional eye drops. Its pressure-lowering effect continued for up to 8 hours, whereas the conventional eye drop showed an effect lasting approximately 3 hours.[46] The formulation also demonstrated improved stability under the investigated storage conditions.

Another area of research involves combining different Anti glaucoma agents within a single in situ gel system. Studies involving timolol maleate and brimonidine have reported prolonged drug release and improved IOP reduction.[60] However, some of these investigations used pH-responsive rather than temperature-responsive systems, so their findings should be considered related developments rather than direct evidence of thermoresponsive formulations.

Overall, the available studies indicate that incorporating antiglaucoma drugs into in situ gels may improve ocular residence time and extend their therapeutic effect. Nevertheless, the formulation must maintain suitable gelation characteristics, drug stability and ocular tolerability.[46,49,50]

7.2 Liposome- and Nanocarrier-Based Thermosensitive Gels

The combination of nanocarriers with thermosensitive in situ gels represents an important development in ocular drug delivery. Liposomes can accommodate different types of drug molecules within their lipid bilayers or aqueous

compartments. When incorporated into a temperature-sensitive gel, they provide an additional approach for controlling drug release and improving ocular retention.[49,53]
Fasudil-Loaded Liposomal Thermosensitive Gel developed a liposomal thermosensitive gel containing a fasudil-phospholipid complex for glaucoma treatment. Fasudil is a Rho-associated protein kinase (ROCK) inhibitor with potential IOP-lowering activity.[50]However, its high water solubility creates difficulties in achieving sufficient ocular permeation.[50]To address this problem, the researchers prepared a fasudil-phospholipid complex and incorporated it into liposomes. The liposomal formulation was subsequently added to a thermosensitive gel containing poloxamer 407 and HPMC.The optimized liposomes showed a particle size of approximately 132.5 nm and an entrapment efficiency of 78.6%.[50] The final gel formulation contained 20% poloxamer 407 and 0.5% HPMC. Experimental findings showed reduced initial drug release, improved mucoadhesive properties and prolonged corneal permeation.[50]The formulation also produced a greater reduction in IOP in the glaucoma rabbit model compared with the drug solution and liposomal dispersion.Chitosan coating was used to modify the liposomal surface and improve its interaction with the ocular mucosal layer.[49] The resulting formulation showed improved mucoadhesive properties and prolonged drug release.

The optimized chitosan-coated liposomal gel increased ocular permeability approximately 4.4-fold compared with the formulation containing free metoprolol.[49] In the experimental glaucoma model, it also produced a significant reduction in IOP without noticeable ocular irritation under the conditions studied.[49]
These findings suggest that combining deformable liposomes, mucoadhesive polymers and thermosensitive gels may improve the delivery of antiglaucoma drugs. However, the reported results are based on experimental investigations and require further clinical assessment.[49,50]

8. Challenges and Future Perspectives

Despite the promising research findings, the development of thermoresponsive ocular gels still faces several scientific and practical challenges. Although these formulations have demonstrated improvements in drug retention and release, their successful translation into clinical products requires further investigation.[20,55]
Formulation Stability: Maintaining the physical and chemical stability of thermosensitive gels during storage is an important concern.[55] Changes in temperature may influence polymer behaviour, viscosity, gelation temperature and drug stability. Liposomal formulations may also undergo particle aggregation or changes in drug entrapment during storage.[53,55]

Ocular Irritation and Safety: The eye is highly sensitive to changes in pH, osmolality and formulation composition. Excessive polymer concentrations or unsuitable excipients may cause irritation and discomfort.[8]Therefore, long-term ocular safety must be established before these formulations can be considered for routine treatment.

Control of Gelation Temperature: The formulation should remain sufficiently fluid during administration and form a gel after reaching the ocular surface. Small changes in polymer concentration or environmental conditions may influence gelation behaviour. Achieving consistent gel formation is therefore an important formulation challenge.[36,46]

Drug Release and Permeability: Prolonged drug release does not always guarantee sufficient drug absorption into the required ocular tissues. The formulation must provide an appropriate balance between ocular retention, drug release and corneal permeation.[49,50]

Manufacturing and Scale-Up: Preparation of liposomal and nanocarrier-based gels involves several processing steps. Maintaining uniform particle size, drug entrapment and formulation characteristics during large-scale manufacturing may be difficult. Suitable manufacturing procedures and quality-control methods are required to ensure batch-to-batch consistency.[55]

Limited Clinical Evidence: Most of the available research has been conducted using laboratory experiments, isolated ocular tissues and animal models. Although these studies provide useful information, their findings cannot directly establish the safety and effectiveness of the formulations in humans. More extensive clinical investigations are necessary.[55]

Future Perspectives

Future research should focus on developing thermoresponsive gels with improved ocular compatibility, predictable gelation behaviour and better drug-release control. Combining thermosensitive polymers with nanocarriers, such as liposomes and other lipid-based systems, may provide further opportunities to improve ocular drug delivery.[53,55]
The development of formulations containing multiple therapeutic agents may also be worth investigating, particularly for patients who require more than one medication to control intraocular pressure. However, drug compatibility and the

possibility of increased ocular irritation must be carefully evaluated.[60]

Advanced formulation approaches should also be supported by suitable analytical methods, improved manufacturing techniques and long-term stability studies. Greater attention should be given to clinical investigations to determine whether the advantages observed in experimental studies can be reproduced in patients.[55]

Overall, continued research into polymer-based and nanocarrier-assisted ocular delivery systems may help establish more effective approaches for the management of glaucoma.

9. Conclusion:

Thermoresponsive in situ gels have emerged as a promising approach for improving ocular drug delivery, particularly in the management of glaucoma. Their ability to undergo a liquid-to-gel transition at physiological temperature provides an opportunity to increase ocular residence time and control drug release. These properties may help address some of the limitations associated with conventional ophthalmic eye drops.Research involving latanoprost-loaded gels, fasudil-phospholipid liposomes and metoprolol-loaded chitosan-coated deformable liposomes has demonstrated encouraging results in experimental studies. The incorporation of nanocarriers into thermosensitive gels has further improved drug entrapment, mucoadhesion and corneal permeation in the investigated formulations.

However, challenges related to formulation stability, ocular safety, manufacturing and long-term drug delivery still need to be addressed. Most importantly, the available evidence is largely based on preclinical investigations, and further clinical studies are required to establish their therapeutic value in humans.Thermoresponsive ocular gels offer an interesting direction for the development of advanced glaucoma formulations. With continued research and appropriate clinical evaluation, these systems may provide an alternative to conventional eye drops and contribute to improved management of glaucoma.

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