Advances in Ocular Drug Delivery: In-Situ Gels versus Conventional Dosage Forms

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Abstract:
Ocular drug delivery faces unique anatomical, physiological and protective barriers that severely limit drug bioavailability from conventional topical preparations such as eye drops and ointments. In-situ gelling systems - liquid formulations that undergo sol→gel transition upon application to the eye (triggered by temperature, pH, or ions) - have emerged as an attractive strategy to increase precorneal residence time, sustain drug release and improve therapeutic outcomes. This review compares in-situ gels with conventional ocular dosage forms, summarises gelation mechanisms and commonly used polymers (gellan gum, poloxamers, chitosan, alginates, hyaluronic acid), discusses formulation and evaluation methods, highlights recent advances (nanoparticle/niosomes-in-gel hybrids, mucoadhesive and multifunctional systems), reviews clinical/market examples, and outlines current challenges and future directions. Evidence from preclinical and clinical studies indicates that in-situ gels can substantially improve ocular retention and bioavailability compared with conventional eye drops, but regulatory, safety and patient-acceptability issues must be addressed before wider adoption.

Keywords: in-situ gel, ophthalmic delivery, mucoadhesion, gellan gum, poloxamer, conventional eye drops, bioavailability.

How to cite this article: Patil RD, Desai ND, Mane MV, Patil AS, Navale SS, Surwase SV, Wagh SS, Magdum SB. Advances in Ocular Drug Delivery: In-Situ Gels versus Conventional Dosage Forms. Int J Drug Deliv Technol. 2026;16(47s): 1007-1013. DOI: 10.25258/ijddt.16.47s.130

1. INTRODUCTION :

Topical ocular administration (eye drops, suspensions, ointments) is the most common route for treating anterior segment diseases because it is non-invasive and easy for patients. However, only a small fraction (<5–10%) of drug instilled as a conventional aqueous drop penetrates the cornea and reaches intraocular tissues; most is lost by tear turnover, reflex blinking, nasolacrimal drainage and non-productive conjunctival absorption. These limitations necessitate frequent dosing, reduce efficacy and increase systemic exposure via drainage, creating a clear need for improved topical systems that prolong precorneal residence and provide controlled release.[1]

In-situ gel systems were developed to combine the ease of administration of drops with the sustained retention of gels. Administered as a liquid drop, they undergo gelation on the ocular surface in response to

physiological stimuli (temperature, pH, cations), forming a soft gel that resists washout and releases drug over extended periods. Over the past two decades, extensive research and several clinical formulations have validated the concept and expanded polymer options and hybrid designs that incorporate nanoparticles or mucoadhesive moieties. This review examines the comparative advantages, scientific basis, evidence and remaining obstacles for in-situ gels relative to conventional forms. [2]

2 . ANATOMY AND PHYSIOLOGY OF THE EYE RELEVANT TO DRUG DELIVERY [3]

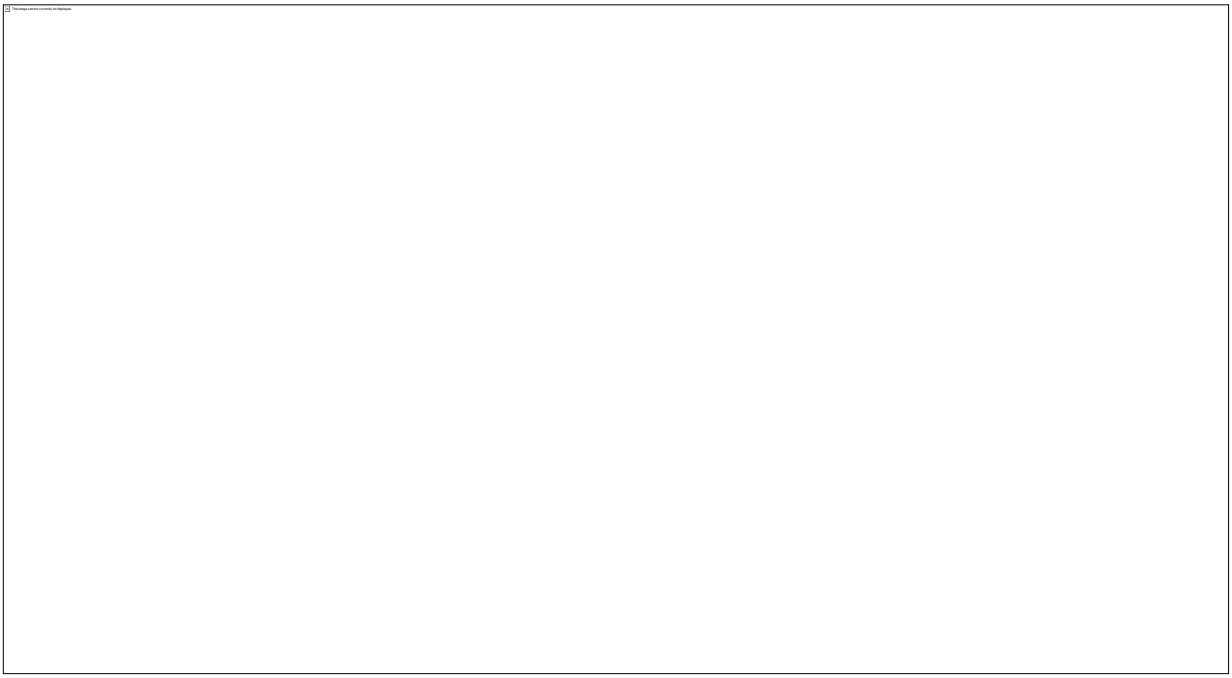

Fig. no. 1 – Anatomy of eye.

The eye is a highly specialized organ with complex physiological structures that pose significant challenges to drug delivery. Understanding these barriers is essential for designing successful ocular formulations.

2.1 External Ocular Barriers :

2.1.1 Tear Film

The tear film is a trilaminar structure comprising:

Lipid layer (outer) , Aqueous layer , Mucin layer

Its rapid turnover (1–3 µL/min) and reflex tearing lead to dilution and elimination of instilled drugs.

2.1.2 Corneal Barrier

The cornea comprises five layers:

Epithelium (major barrier) , Bowman's membrane , Stroma , Descemet's membrane , Endothelium

The epithelium restricts hydrophilic drug penetration, whereas the stroma limits lipophilic drugs.

2.1.3 Conjunctiva

Contains numerous blood vessels and lymphatics, contributing to systemic absorption and drug loss.

2.2 Internal Ocular Barriers :

2.2.1 Blood-Aqueous Barrier (BAB)

Prevents entry of circulating drugs into the anterior chamber.

2.2.2 Blood–Retinal Barrier (BRB)

Restricts transport to the posterior segment.

2.2.3 Vitreous Humor

Dense gel-like matrix limiting diffusion of large molecules.

3 . OPHTHALMIC DOSAGE FORMS - OVERVIEW AND LIMITATIONS :[4,5,6]

3.1 Eye drops (solutions and suspensions)

Aqueous eye drops are the dominant topical form. They are simple to manufacture, dose and use, but they suffer from extremely low ocular bioavailability because the cul-de-sac holds a small volume (~7–30 µL) and typical drop sizes (20–50 µL) immediately overflow reflex blinking and tear turnover (0.5–2 µL/min baseline) remove much of the instilled drug; only drugs that are sufficiently lipophilic and small can penetrate the corneal epithelium effectively. Suspensions can extend contact time slightly but may cause blurring and dose variability.

3.2 Ointments and gels (preformed)

Ointments and viscous gels increase residence time but impair vision and are poorly accepted for daytime use. They are useful at night (e.g., lubricants) but lead to blurred vision and dosing inconvenience. Preformed gels also may require special manufacturing and sterilisation considerations.

3.3 Ocular inserts and implants

Solid or semisolid inserts (e.g., Ocuserts historically) and intravitreal implants provide long-term release but are often intrusive, require insertion/ removal, can be uncomfortable, and carry risks of dislocation and local irritation. Inserts and implants are useful for chronic conditions when compliance is an issue but are less convenient than topical drops.

3.4 Major clinical consequences of limitations

Because of the above, topical therapy typically requires frequent dosing, reducing patient adherence; systemic absorption via nasolacrimal drainage can increase side effects; and therapeutic concentrations in target tissues are hard to maintain. These issues drive the search for advanced topical systems that improve retention and provide sustained release.

4. IN-SITU GELS: DEFINITIONS, MECHANISMS AND COMMON POLYMERS :[7,8]

4.1 Definition

In-situ gelling systems are instilled as low-viscosity liquids that transition to a gel state upon exposure to ocular physiological stimuli. The main triggering mechanisms are:

4.2 Table no. 1 - Polymers used in In- situ gel system and their properties :

Polymers	Types of stimulus	Chemical Nature	Mechanism of Gelation	Key Properties	Advantages in ocular drug delivery	Limitations
Poloxamer 407 (Pluronic F127)	Temperature sensitive	Synthetic triblock copolymer (PEO-PPO-PEO)	Micellization and packing at ocular temperature	Thermoreversible , Clear Gel , Pseudoplastic	Easy administration , good clarity , sustained drug release	Requires high concentration , weak mechanical strength .
Poloxamer 188 (pluronic F68)	Temperature sensitive	Synthetic copolymer	Miceller aggregation	Low toxicity , Enhance solubility	Improves gelation of poloxomer 407	Low gel strength alone
Carbapol (carbomer 934/940)	pH sensitive	Synthetic polyacrylic acid	Ionization and swelling at pH >5.5	High viscosity , strong mucoadhesion	Prolonged residence time , good gel strength	May cause irritation at acidic pH
Polyacrylic acid	pH sensitive	Synthetic polymer	pH dependent swelling	High swelling capacity	Enhanced bioavailability	Sensitive to ionic strength
HPMC	Viscocity enhancer	Semi synthetic cellulose derivative	Chain entanglement	Hydrophilic , biocompatible .	Improves viscosity and comfort	Weak gelation alone
Gellan gum	Ion activated	Natural polysaccharide .	Gelation in presence of ca^{2+} , Na^{+} ions .	Transparent gel , high elasticity .	Low polymer concentration required , good retention .	Sensitive to tear electrolyte levels
Sodium alginate	Ion activated	Natural polysaccharide .	Cross linked with divalent ions .	Biodegradable , biocompatible	Mild gelation . sustained release .	Variable gel strength
Chitosan	pH sensitive / ion sensitive .	Natural polysaccharide.	Protonation of amino groups	Mucoadhesive , biodegradable.	Enhance corneal permeation	Solubility issues at neutral pH
Xanthan	Ion	Natural	Polymer	High viscosity ,	Improves	High

gum	activated	polysaccharide.	chain interaction	stable .	retention time	viscosity may cause discomfort
Pectin	Ion activated	Natural polysaccharide.	Calcium induced gelation .	Non toxic , bioadhesive .	Gentle gelation	Weak mechanical strength
Hyluronic acid	Hydration responsive	Natural glycosaminoglycan .	Water absorption and swelling	Viscoelastic , lubricating .	Ideal for dry eye therapy	Rapid degradation
Eudragit L-100	pH sensitive	Synthetic methacylate polymer.	Disso. At pH>6.	Film forming .	Controlled drug release	Limited ocular use

5. FORMULATION STRATEGIES AND EVALUATION METHODS :[9,10,11]

5.1 Design considerations

Key formulation objectives are: easy instillation (low viscosity at room temperature), rapid gelation on the eye, appropriate gel strength (resist shear from blinking but be comfortable), sustained yet therapeutically relevant drug release, sterility and ocular tolerability. Selection of polymer type and concentration, pH, osmolality, tonicity agents and preservatives (or preservative-free strategies) is critical. For drug molecules with poor aqueous solubility, solubilisation strategies (cyclodextrins, cosolvents, nanoparticles/niosomes embedded in the gel) are commonly used.

5.2 Evaluation (in vitro and in vivo)

Typical tests include: rheological profiling (viscosity vs temperature or pH or ion concentration), gelation time and gel strength, in-vitro release (dialysis or Franz cell), ex vivo mucoadhesion, simulated precorneal retention (washout tests), ocular irritation tests (HET-CAM, Draize in animals), and pharmacokinetic/pharmacodynamic (PK/PD) studies in animal models or clinical trials. Sterility, stability and microbial challenge tests complete the dossier for regulatory submission.

6. EVIDENCE: HOW DO IN-SITU GELS COMPARE WITH CONVENTIONAL FORMS?[12]

6.1 Preclinical and clinical pharmacokinetics

Multiple preclinical studies show that in-situ gels significantly increase precorneal residence time and ocular tissue exposure relative to conventional eye drops. For example, ion-activated gellan formulations and thermoresponsive poloxamer systems have demonstrated prolonged drug retention and sustained release in rabbit models, leading to higher aqueous humor concentrations over time. Clinical comparisons also exist: formulations such as gel-forming timolol (marketed as TIMOPTIC-XE®) achieved greater intraocular pressure (IOP) lowering with reduced dosing frequency compared with conventional timolol 0.5% solutions.

6.2 Patient acceptability and compliance

By reducing dosing frequency (sustained release), in-situ gels can improve adherence. However, potential disadvantages include transient blurring (depending on gel clarity and viscosity), sensation of foreign body in some patients, and formulation sterility/preservative tolerance issues. Many modern formulations are designed to be transparent and minimally vision-affecting; ion-activated systems like gellan often form relatively clear gels.

6.3 Safety and tolerability

Poloxamers, gellan and hyaluronic acid typically show favorable ocular tolerability in published studies; chitosan derivatives require attention to degree of deacetylation and molecular weight for tolerability. Long-term irritation data are limited for many novel polymer blends and combination systems, necessitating further safety studies.

7. RECENT ADVANCES (2018–2025): HYBRID SYSTEMS AND NOVEL APPROACHES :[13,14,15,16]

7.1 Nanoparticles / niosomes / liposomes embedded in in-situ gels

Combining particulate carriers (e.g., nanoparticles, liposomes, niosomes) with in-situ gels can provide dual control: nanoparticle-mediated sustained release or targeted delivery plus gel-mediated extended retention. Reports of niosomal in situ gels and polymeric nanoparticles loaded into gellan/ poloxamer matrices demonstrate enhanced corneal penetration and prolonged therapeutic effect versus particles or gels alone. Such hybrid systems are an active area of research.

7.2 Mucoadhesive and bioactive polymers

Incorporation of mucoadhesive polymers (chitosan, hyaluronic acid) increases adhesive interactions with the mucous layer, boosting residence time and sometimes enhancing permeation. Recent studies also explore bioactive polymers (e.g., poloxamer blends with hyaluronic acid) that may aid ocular surface healing while delivering drugs.

7.3 Stimuli-responsive multi-modal gels

Beyond single triggers, multi-responsive gels (temperature + ion, or pH + ion) give more robust gelation under variable ocular conditions. Researchers have engineered formulations that respond faster and maintain gel integrity under blinking shear and tear dilution.

7.4 Advanced actives: biologics and gene therapy delivery

There is growing preclinical interest in using gel matrices to deliver biologics (peptides, proteins) or nucleic acid therapeutics to the ocular surface; gels may protect labile molecules and prolong contact time to allow local uptake. This field is nascent, with formulation stability and sterility being key hurdles.

8 . COMPARATIVE STUDY :[17]

Table no. 2 : comparative table ocular conventional dosage forms vs *In-situ* gels .

Parameters	**Conventional eye drops .**	**Oinments**	**Suspensions**	***In situ* Gels**
viscosity	low	high	Moderate	Low before instillation , high after gelation .
Drug bioavailability	low	moderate	Variable	high
Dosing frequency	high	low	Moderate	low
Initial burst release	high	low	Moderate	controlled
Patient compliance	low	moderate	Moderate	high
Manufacturing complexity	low	low	Moderate	high
Stability	good	good	Good	variable

9. REGULATORY & COMMERCIAL LANDSCAPE :

9.1 Marketed examples :

One of the earliest commercial successes demonstrating the clinical value of ion-activated in-situ gels was timolol maleate in a gel-forming formulation (TIMOPTIC-XE®), which showed improved IOP control and allowed less frequent dosing compared with conventional timolol solutions. This example validated the concept for glaucoma therapy and inspired further product development.

9.2 Regulatory considerations :

From a regulatory standpoint, in-situ gels are assessed like other ophthalmic liquids/gels: sterility, preservative safety (or justification for preservative-free design), ocular irritation, biocompatibility, and PK/PD efficacy must be demonstrated. When combining with particulate carriers (nanoparticles) or biologics, additional safety and CMC (chemistry, manufacturing and controls) data are required. Stability of the sol form and control of gelation properties are critical for consistent performance.

10. CHALLENGES, LIMITATIONS AND KNOWLEDGE GAPS :[18]

10.1 Blurring and visual quality :

Although many in-situ gels aim to be optically clear, some patients experience transient blurring or foreign-body sensation that can affect daytime use. Formulators must carefully tune gel clarity and rheology to minimize these effects while preserving sustained release.

10.2 Sterility and preservative use :[19]

Preservative-free unit-dose formats are often preferred, but increase packaging complexity and cost. Preservatives (e.g., benzalkonium chloride) can damage the ocular surface with chronic use; many modern in-situ gel studies therefore test preservative-free formulations or safer alternatives.

10.3 Scalability and manufacturing reproducibility :

Precise control of polymer molecular weight, concentration, and solution rheology is required to ensure reproducible gelation and dosing characteristics across batches. Scale-up and long-term stability of the sol can pose manufacturing challenges.

10.4 Long-term safety data :

While short-term animal and clinical studies are encouraging, long-term safety (chronic use) data for many novel polymers or composites (especially those

combined with nanoparticles or bioactives) remain limited. This is especially important for chronic conditions like glaucoma where treatment is lifelong.

11. FUTURE PERSPECTIVES AND RESEARCH DIRECTIONS :[20,21,22,23]

1. Hybrid systems will expand: Embedding nanoparticles/niosomes/vesicles in in-situ gels to combine targeted delivery and residence time extension is likely to grow, with particular interest in poorly soluble drugs and biologics.
2. Mucoadhesive, healing-promoting polymers: Polymers that both adhere to mucosa and promote ocular surface repair (e.g., hyaluronic acid blends) will be attractive for treating dry eye and surface disease while delivering drugs.
3. Smart, multi-responsive gels: Formulations that respond to combinations of stimuli (temperature, ions, pH, enzymatic activity) can provide more reliable gelation and tailored release under variable pathological tear conditions.
4. Regulatory science and real-world adherence studies: Longer and larger clinical trials evaluating real-world adherence, patient preference, and long-term safety will be pivotal to wider commercial uptake.

12. CONCLUSION :

In-situ gelling ophthalmic systems offer a compelling middle ground between the simplicity of eye drops and the sustained performance of inserts/implants. By converting to a gel on the ocular surface, these systems increase precorneal residence, sustain drug release, reduce dosing frequency and can improve efficacy and adherence. Ion-activated (gellan), thermoresponsive (poloxamer) and mucoadhesive (chitosan, hyaluronic acid) systems are the most studied and have shown promising preclinical and clinical results; TIMOPTIC-XE® remains an instructive clinical example. Recent developments - notably particulate carriers embedded within gels and multifunctional polymer blends - have further expanded possibilities. Remaining challenges include ensuring optical clarity, long-term safety, preservative strategies, and scalable manufacturing. Continued translational research and well-designed clinical studies will determine the ultimate role of in-situ gels in routine ophthalmic practice.

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