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Insitu Gel Systems: A Novel Drug Delivery Strategy

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Abstract

Conventional liquid and semisolid dosage forms applied to mucosal or periocular surfaces are frequently limited by short residence time, rapid clearance, and poor site specificity, which together reduce bioavailability. In situ gel systems address these limitations by remaining as free-flowing, easily administered solutions that undergo a sol-to-gel phase transition on contact with the physiological environment, triggered by temperature, pH, ionic strength, or specific chemical interactions. Once gelled, the resulting matrix forms a depot at the site of application that prolongs drug residence and supports sustained, controlled release. This property makes the approach particularly valuable for ophthalmic, nasal, oral, vaginal, rectal, and parenteral formulations, where it improves patient compliance by reducing dosing frequency compared with conventional drops, solutions, or injections. This review summarises the principal sol-gel transition mechanisms (thermosensitive, pH-sensitive, ion-activated, and enzyme/redox-responsive systems), the natural and synthetic polymers used to engineer them, and the Quality by Design and Design of Experiments approaches increasingly applied to optimise gelation behaviour and drug release. It further examines regulatory expectations, safety and biocompatibility requirements, manufacturing and scale-up challenges, and the comparative performance of in situ gels against tablets, ointments, and injections. Representative marketed products and preclinical/clinical evidence are discussed by administration route, and emerging directions in nanotechnology-enabled, personalised, and artificial-intelligence-assisted formulation design are outlined. Overall, the availability of a biocompatible, appropriately triggered polymer system remains the central determinant of successful in situ gel development.

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Introduction

The concept of an in situ gel-forming drug delivery system was first proposed in the 1970s (1). In situ gels are formulations administered as low-viscosity solutions that undergo a sol-to-gel phase transition on exposure to physiological stimuli such as body temperature, pH, or ionic strength, converting into a viscoelastic gel after administration. This behaviour makes the systems easy to administer and generally well accepted by patients (1). Conventional dosage forms applied to mucosal and periocular sites often suffer from short residence time, rapid elimination, and limited site specificity. In situ gels address these limitations by forming a gel depot at the site of administration that prolongs residence time and supports controlled drug release (2).

Gelation is the defining feature of these systems and is achieved through a variety of polymer combinations. Cross-linking of polymer chains may occur through chemical (covalent) cross-linking or through physical (non-covalent) cross-linking, depending on the polymer system used. As a prolonged-acting delivery platform, in situ gel technology has attracted growing attention in

pharmaceutical research, including for injectable formulations intended for anti-tumour therapy. In each case, a low-viscosity solution undergoes a phase transition to a viscoelastic gel in response to the physiological environment, driven by changes in polymer conformation or cross-linking density (3, 4).

Beyond the classical mucosal and ocular applications described above, in situ gel technology has more recently been extended to injectable depots for oncology, tuberculosis, and hormonal therapy, reflecting a broader shift toward long-acting parenteral delivery across therapeutic areas (23). This review considers the mechanisms, polymers, formulation strategies, regulatory landscape, and emerging applications of in situ gel systems, with the aim of providing a consolidated reference for their rational design and development.

Advantages

- Improves patient compliance by reducing dosing frequency.
- Is more comfortable to administer than solid inserts or discrete implants.
- Increases bioavailability by extending residence time at the site of application.
- Provides sustained and prolonged drug release.
- Prolongs drug action, reducing the need for repeated dosing.
- Achieves higher local bioavailability at the site of administration (5).

Disadvantages

- Carries a relatively high risk of drug degradation in the solution (pre-gel) state.
- May cause irritation or toxicity arising from the polymers and additives used.
- Drug stability in solution form is generally lower than in the final gelled state.
- Formulation properties are sensitive to processing and storage conditions while the product remains in solution (6).

Method of preparation of in situ gel

In situ gels are commonly prepared by the cold dispersion method or the hot dispersion method, both of which involve dissolving the polymer(s) in a solvent — cold or hot water, respectively — followed by the addition of the drug, preservatives, pH adjusters, and other excipients. In the cold method, polymers are added slowly to cold water while maintaining a low temperature to prevent premature gelation. In the hot method, polymers are dissolved in heated water, after which the remaining ingredients are incorporated before the mixture cools; the final solution is then stirred until homogeneous (7).

Cold dispersion method

- *Preparation of the polymer solution* — Poloxamer 188 and poloxamer 407 are added to cold water with continuous mixing until a clear solution forms.
- *Refrigeration* — The solution is refrigerated overnight to ensure complete dissolution and hydration.
- *Addition of other components* — HPMC, preservatives, and the drug solution are added gently to the poloxamer dispersion with continuous mixing.
- *pH adjustment* — The pH is adjusted using an appropriate agent, such as sodium bicarbonate or sodium hydroxide.
- *Finalisation* — The volume is made up as required, and mixing continues until a homogeneous solution is obtained (7).

Hot dispersion method

- *Preparation of the polymer solution* — Distilled water is heated to the required temperature before polymers such as HPMC and poloxamer 407 are added with continuous stirring to minimise foaming.
- *Combining and cooling* — Once the polymers have dissolved in hot water, the mixture is cooled to room temperature and refrigerated before other ingredients are added.
- *Addition of the drug and other components* — The drug solution, pH adjuster, preservatives, and HPMC are added and mixed thoroughly to form a homogeneous solution (7).
- *Sterilisation and storage* — The final formulation is typically sterilised by autoclaving and stored in amber-coloured bottles under refrigeration (8).

Sol-Gel Transition Mechanisms in In Situ Gels

In response to physiological stimuli, in situ gelling systems undergo a reversible sol-gel transition that allows an injectable or instillable liquid formulation to solidify at the target site for regulated drug release. These systems rely on natural polysaccharides or stimuli-responsive ("smart") synthetic polymers and are frequently combined with solubility-enhancement

strategies, such as solid dispersions, for poorly soluble drugs. The principal triggers, their mechanisms, and their pharmaceutical relevance are described below (9).

1. **Temperature-sensitive transitions (LCST/UCST):** Temperature-responsive polymers shift from hydrophilic to hydrophobic character at either a lower critical solution temperature (LCST) or an upper critical solution temperature (UCST) (3).
2. ***LCST mechanism****:* Below the LCST, polymers such as poly(N-isopropylacrylamide) (PNIPAAm) and Pluronic-type poloxamers (PEO–PPO–PEO) form hydrated coils in the sol state through hydrogen bonding with water. Heating above the LCST (approximately 32–37°C) promotes dehydration and hydrophobic association, driving micelle aggregation and gel network formation (10,9).
3. ***UCST mechanism****:* In contrast, polymers such as poly(N-acryloylglycinamide) — less commonly used in in situ applications — gel on cooling as hydrogen bonding strengthens (9).
4. ***Pharmaceutical relevance:*** This behaviour suits subcutaneous or intranasal administration; for example, Pluronic F127 (20% w/v) undergoes a sol-gel transition at approximately 25°C and can extend the release of hydrophobic drugs, such as itraconazole, when incorporated into solid dispersions (14).
5. **pH-sensitive transitions:** Changes in pH alter the protonation state of ionisable groups, thereby modifying chain solubility and intermolecular interactions (8).

a. *Mechanism:* Anionic polymers such as carbopol and gellan gum remain soluble at low pH (protonated carboxyl groups) but gel at physiological pH (7.4) as deprotonation reduces electrostatic repulsion and permits hydrogen bonding and cross-linking. Cationic polymers, such as chitosan, instead swell at low pH due to protonation of amine groups (9).

b. *Pharmaceutical relevance:* pH-responsive gelation enhances mucoadhesion and can improve antifungal bioavailability by exploiting the mildly acidic microenvironment of tumours (pH ≈ 6.5); carbopol 934P (0.5%) combined with HPMC is used, for example, in vaginal gel formulations (8).

6. **Ion-activated transitions:** Divalent cations promote rapid gelation through ionic cross-linking.

a. *Mechanism:* Polysaccharides such as alginate and gellan gum carry carboxylate groups on their uronic acid residues. These remain soluble in the presence of monovalent ions (Na^+) but form "egg-box" junctions within seconds on exposure to Ca^{2+} or Mg^{2+}, producing a three-dimensional gel network (10).

b. Low-acyl gellan gum (0.5–1%), used in ocular formulations, gels almost instantaneously on contact with cations that mimic tear fluid composition.

c. *Pharmaceutical relevance:* Ion-activated gelation overcomes solubility limitations associated with solid dispersions and extends residence time in nasal insulin formulations by exploiting endogenous ions, such as nasal or salivary Ca^{2+} (9).

7. **Enzyme- and redox-responsive transitions:** Biochemical stimuli enable site-specific gelation. Enzymatic cleavage — for example, by matrix metalloproteinases present in the tumour microenvironment — can cleave peptide-linked polymers, exposing hydrophobic domains that drive self-assembly and gelation of alginate-peptide conjugates. Redox-responsive systems exploit the elevated glutathione concentration within tumour cytosol (approximately 10 mM, compared with roughly 2 μM extracellularly) to reduce disulfide-cross-linked polymers, such as PEG-thiol conjugates, converting them from a sol to a micellar gel state. These mechanisms support tumour-selective drug delivery; redox-sensitive paclitaxel solid dispersions formulated with Pluronic micelles are one example exploiting this gradient (13).

Polymers used (natural and synthetic)

Both natural and synthetic polymers are used in in situ gel formulation. These polymers undergo a sol-gel transition in response to changes in temperature, pH, or ionic concentration within the body, allowing a liquid solution to convert, after administration, into a matrix capable of sustained and controlled drug release (14).

Natural polymers: pectin, chitosan, alginic acid, guar gum, xanthan gum, gellan gum, xyloglucan.

Synthetic polymers: carbopol, poloxamer (Pluronic), polyethylene glycol (PEG), polycaprolactone, hydroxypropyl methylcellulose (HPMC), poly (DL-lactic acid) (13, 14).

Quality by design (QbD) and formulation optimisation

Quality by Design (QbD) offers a systematic, risk-based approach for developing reliable in situ gel formulations, helping to ensure consistent gelation performance and

drug release, including for solubility-enhanced systems such as solid dispersions (16).

QTPP and CQAs

The Quality Target Product Profile (QTPP) for in situ gels typically specifies a syringeable sol state at room temperature (<25C), rapid gelation under physiological conditions (37C, pH 7.4, or in the presence of relevant ions), sustained release (e.g., 80% drug released over 8-24 h), adequate mucoadhesion (>1000 dyne/cm2), and biocompatibility. Corresponding Critical Quality Attributes (CQAs) include gelation temperature/time (10-60 s), viscosity (sol: 1-100 cP; gel: >1000 cP), mucoadhesive strength, gel strength (25-50 s retention), drug content uniformity (95-105%), and release profile at 1, 4, and 24 h, assessed against USP standards (16,17).

Design of Experiments (DoE) for optimisation

Design of Experiments (DoE) is used to identify Critical Material Attributes (CMAs), such as polymer ratios (e.g., poloxamer 407, 15-25%; gellan gum, 0.2-0.6%; HPMC, 0.1-0.3%), and their effects on CQAs. A 3-squared full factorial design testing two factors at three levels (e.g., gellan gum concentration as X1, HPMC concentration as X2) generates nine experimental runs suitable for response surface methodology (RSM) and ANOVA. Box-Behnken designs (12-15 runs) reduce the experimental burden while still mapping the design space for an optimum formulation - for example, an optimised composition of 0.4% gellan gum and 0.1% HPMC yielding 94% drug release with acceptable viscosity and rapid gelation (17).

QbD has been applied to optimise in situ gels for several administration routes, most notably in nasal delivery and ion-activated ocular systems.

Nasal gellan gum/HPMC in situ gel for fluoxetine

Using a 3-squared factorial design with gellan gum (X1) and HPMC (X2) as factors, an ion-sensitive nasal in situ gel of fluoxetine hydrochloride was optimised. The selected formulation (0.4% gellan gum, 0.1% HPMC) showed rapid gelation in simulated nasal fluid, high mucoadhesion, and 94.24% ex vivo drug release; in vivo pharmacodynamic testing confirmed an enhanced antidepressant effect with no histological evidence of nasal damage. Increasing either polymer concentration raised viscosity and mucoadhesive strength but reduced the percentage of drug released (14, 18).

Other QbD-optimised in situ gels

Comparable QbD workflows - proceeding from QTPP definition through CQA identification, risk assessment, and DoE - have more recently been applied to ocular in situ gels containing antifungal or antibiotic actives (e.g., posaconazole or chloramphenicol), where polymer ratios (gellan gum, carbopol, or HPMC, alone or combined with thermosensitive solubilising polymers) were optimised using factorial or Box-Behnken designs to achieve target gelation temperature, clarity, and sustained release (>80% at 24 h) with acceptable ocular tolerability. These studies generally aim to limit burst release, maintain adequate corneal drug levels, and preserve appropriate pH and viscosity for patient comfort by varying ion-sensitive and viscosity-modifying polymers within a defined design space (17).

Types of drug delivery systems using in situ gel formulations

Recent advances and applications

In situ gel formulations are increasingly moving toward "smart," multi-stimuli-responsive, and nanotechnology-integrated systems designed to extend the functional lifetime of the formulation at the site of action. These systems support targeted, sustained, and controlled release across nasal, oral, parenteral, and ocular routes. Current research emphasises novel polymer chemistries, nanotechnology-enhanced "nano-in-situ gels," and patient-tailored designs intended to produce highly responsive, long-acting, and individualised delivery systems, particularly for high-value drugs (17).

Smart stimuli-responsive systems: Recent work has focused on polymers that respond to endogenous stimuli - pH, ions, enzymes, and redox potential - as well as exogenous triggers such as temperature, magnetic fields, and light, enabling on-demand sol-gel transformation and controlled release (18).

Nano-in-situ gels: Incorporating nanocarriers such as nanoparticles, nanogels, liposomes, or niosomes within an in situ gel matrix produces a "nano-in-situ gel" system with improved drug solubility, stability, permeation, and control over sustained release (19).

Tissue engineering and biomaterials applications: Long-acting in situ gels are being optimised for specific routes - ocular, rectal, vaginal, oral, and injectable - by tuning polymer composition, trigger type, and cross-

linking density to extend release from days to months. Emerging precision-medicine applications include anti-inflammatory and anti-infective microenvironment-responsive hydrogels and scaffold-integrated systems that adapt to the dosage form required (18).

Applications by route and clinical/preclinical status

In situ gel systems have advanced across multiple platforms and are increasingly represented in clinical and preclinical studies spanning metabolic, ocular, vaginal, oral, and nasal indications. The primary goal in each case is to achieve long-acting local or mucosal delivery that improves efficacy and convenience relative to conventional formulations or repeated injections (20).

Although challenges such as inconsistent in vivo gelation persist, clinical and preclinical evidence across routes generally shows improved residence time and bioavailability relative to conventional dosage forms. Representative studies, organised by route and indication, are summarised below (20).

Ocular in situ gels

Ion- and pH-triggered gels prolong precorneal retention for glaucoma therapy and antifungal treatment (7).

Nasal CNS delivery

Temperature- and ion-responsive gels enable targeted nose-to-brain delivery of CNS-active drugs (21).

Injectable cancer/depot systems

Thermosensitive depots have been explored for tuberculosis and chemotherapy applications (22).

Oral mucoadhesive gels

These formulations aim to address poor compliance in the treatment of oral wounds and ulcers (28).

Critical example: a failure/safety signal

A thermosensitive docetaxel PLGA-PEG in situ gel developed as an injectable prostate cancer depot showed a promising 4-week in vitro release profile, but was cleared unexpectedly rapidly in humans owing to a suboptimal LCST (>39C), producing only a 1.5-fold increase in bioavailability relative to intravenous administration and injection-site inflammation in 20% of patients. This finding was mitigated by reformulating with LCST-modifying excipients, and it underscores the need for QbD-based, human-representative gelation testing before clinical translation (29).

Diabetes: nasal in situ gel insulin and antidiabetic gels

Clinical and preclinical studies indicate that intranasal insulin gels provide rapid, painless delivery while avoiding systemic hypoglycaemia, offering a potential alternative to subcutaneous injection. Intranasal in situ gels incorporating antidiabetic agents such as repaglinide in solid lipid nanoparticle-loaded gels have been reported to enhance both brain and systemic exposure (7).

Cancer: injectable in situ gels

Several injectable in situ hydrogel systems have reached advanced preclinical evaluation in solid tumours, administered intratumorally or into resection cavities to provide sustained local chemotherapy or immunotherapy (7).

Ocular disorders: approved and emerging uses

Ocular in situ gels, particularly ion-activated systems, are among the most clinically and preclinically advanced applications and are represented in several marketed products. Recent clinical and preclinical studies of drug-loaded ocular in situ gels report improved permeation, 8-12 h of sustained release, and enhanced antimicrobial or antiviral efficacy (23).

Across ocular, nasal, oral, and injectable routes, in situ gels generally improve real-world efficacy by increasing residence time, bioavailability, and patient compliance relative to conventional formulations and repeated injections. The ocular and nasal routes currently provide the strongest evidence for improved comfort, compliance, and reduced dosing frequency, while oral and injectable applications primarily contribute prolonged systemic exposure and localised therapeutic effects (23).

Ocular routes: In situ gels containing ciprofloxacin or ganciclovir improve corneal permeation and provide 8-12 h of sustained, controlled release.

Reviews report that extended precorneal retention and fewer daily instillations translate into improved compliance, comfort, and adherence in chronic conditions such as glaucoma (24).

Nasal routes: Thermosensitive or ion-activated in situ gels show a faster onset of action, greater brain or systemic exposure, and reduced dosing frequency compared with oral tablets or simple solutions in clinical and preclinical studies. Reviews highlight needle-free administration as enabling rapid onset and ease of self-administration, improving patient acceptance and potential adherence, particularly for CNS and metabolic indications (24, 25).

Oral routes: For poorly soluble drugs or drugs intended for local action, oral in situ gels can improve bioavailability and prolong drug action, contributing to more stable plasma levels and improved symptom control in clinical and preclinical studies. Mucoadhesive oral gels may reduce dosing frequency and are expected to improve long-term adherence, although large-scale clinical data remain limited (25).

Injectable and implantable routes: Injectable in situ hydrogels used in cancer therapy and depot systems sustain local drug levels, inhibit tumour growth, and reduce dosing frequency in animal models.

These systems have the potential to improve quality of life by replacing repeated injections or infusions with a single long-acting administration, although comprehensive patient-reported outcome data from late-phase trials remain limited (26).

Regulatory, Safety, and Quality Considerations

Regulatory agencies generally treat in situ gels as modified-release or depot systems and apply existing quality, safety, and efficacy frameworks, although the novel polymers and complex drug-polymer combinations involved often extend development and review timelines.

Key challenges include demonstrating biocompatibility, controlling batch-to-batch variability, and developing analytical methods that can reliably predict in vivo gelation performance (27).

Regulatory status and guidance: Regulators note that relatively few in situ gel-forming products have received full marketing authorisation as new drug applications, with essentially no approved generic equivalents to date - reflecting the complexity of demonstrating equivalence for these systems. Such products are typically regulated under existing modified-release and parenteral depot frameworks and require comprehensive chemistry, manufacturing, and controls (CMC) data (26).

FDA guidance: In situ gels and depot systems are evaluated by the FDA under both New Drug Applications (NDAs) and Abbreviated New Drug Applications (ANDAs), with particular emphasis on in vitro release testing (IVRT) for characterising gel/depot-formed products. Draft guidance issued in 2024 specifies that test and reference products must form stable gels prior to IVRT, that discriminatory methods must be validated for the relevant gelation trigger (pH, temperature, or ions), and that inconsistent gelation is grounds for rejection; as of 2024, approximately 15 NDAs and 4 ANDAs had been authorised for such products. CQAs such as gel strength and release rate, as influenced by polymer ratios, are defined within a QbD design space (26).

EMA and other agencies: Under the European Pharmacopoeia gel monographs, the EMA generally regards multi-stimuli-responsive polymers as "novel excipients," requiring biocompatibility data and in vivo gelation evidence, such as gamma scintigraphy. In India, the CDSCO requires 12-month stability data and simulated-fluid gelation testing for approval through hybrid application pathways. There is currently no dedicated ICH Q8/Q9 guidance specific to in situ gel systems, although QbD principles are generally recommended for scale-up (28).

Safety and biocompatibility requirements: Comprehensive biocompatibility and local tolerance data are required for gel-forming polymers, covering irritation, inflammation, and chronic toxicity, particularly for synthetic and semi-synthetic materials. Ganciclovir in situ gel studies, for example, have demonstrated good tolerability and prolonged safe ocular residence. Scale-up must maintain sterility and controlled gelation parameters to avoid batch variability in drug release, both of which are treated as key safety and quality risk factors (28).

Key testing requirements: Polymers must be assessed for sensitisation (ISO 10993-10), irritation (HET-CAM for ocular use, target score <1.0), cytotoxicity (ISO 10993-5, MTT or LIVE/DEAD assay, target <Grade 2), and genotoxicity (Ames test/micronucleus assay, negative result required). For injectable and implantable formulations with contact exceeding 24 h, additional testing includes haemocompatibility (ISO 10993-4, <5% haemolysis), pyrogenicity (LAL assay, <20 EU/device), and subchronic toxicity (ISO 10993-11, no inflammation at 14/28 days). Extractables and leachables profiling is required under USP <1663>/<1664> for erosion-related

degradation products, such as poloxamer metabolites and gellan gum oligomers (30).

Genuine generic equivalents of approved in situ gel products remain scarce, and most marketed products are still single-source, illustrating the difficulty of replicating these systems relative to conventional dosage forms such as tablets (24).

Barriers to generic in situ gels: In situ gels depend on intricate, often multicomponent polymer networks in which non-linear changes in polymer grade, molecular weight distribution, or impurity profile can affect viscosity, mucoadhesion, and gelation temperature. Simple in vitro tests - viscosity at a single shear rate, gelation temperature in buffer, or basic IVRT - may not adequately predict in vivo residence time, spreading, or drug release, because reproducing the underlying microstructure (micelles, junction zones, ion-cross-linking density), and hence in vivo gelation kinetics, is difficult even when Q1/Q2 sameness is achieved on paper. Consequently, regulators often require more extensive comparative in vitro data, and occasionally in vivo/pharmacokinetic data, than for conventional generics. Combined with the need for complex characterisation techniques (rheology, microstructural analysis, in situ imaging), this has slowed the development of approved generic in situ gels despite the availability of reference products (24).

Challenges for new polymers and combinations

New drug-polymer combinations intended for in situ gel formulation must demonstrate that altered release profiles do not compromise safety or efficacy, generally requiring a full clinical development pathway rather than a simple reformulation exercise. A further limitation is the lack of standardised test methods for characterising smart, stimuli-responsive gelation (25).

Ensuring safety requires minimising local and systemic toxicity, confirming that polymers and their degradation products are biocompatible and biodegradable, maintaining formulation stability through controlled polymer chemistry, and using stabilisers and appropriate storage conditions to prevent degradation, phase separation, or loss of gelation performance over time (25).

Toxicity and local safety: Most hydrogels used in in situ gel formulation have high water content and are structurally similar to soft tissue, which generally supports good cytocompatibility and low local irritation. Safety concerns instead arise from residual monomers, cross-linking agents, organic solvents, and degradation products, which can cause inflammation, cytotoxicity, or systemic effects if not tightly controlled and adequately removed or qualified (32).

Polymer biodegradability and fate: Biodegradable hydrogels are designed to break down into non-toxic, excretable fragments once drug delivery is complete. Key formulation challenges include tuning the degradation rate to match the intended therapeutic window, avoiding the accumulation of non-degradable residues, and ensuring that degradation does not alter local pH or trigger chronic inflammation (32).

Formulation stability and degradation control: Stability of in situ gels can be compromised by hydrolysis, oxidation, or aggregation of embedded nanoparticles, with corresponding changes in rheology or gelation temperature during storage. Stability studies typically monitor drug content, viscosity, and gelation behaviour across a range of particle sizes, temperatures, and humidity conditions over extended periods (30).

Practical safety-by-design strategies: Recommended approaches include selecting GRAS-listed or clinically established polymers, minimising the use of reactive cross-linkers, and rigorously characterising degradation products through combined in vivo and in vitro testing for irritancy and organ toxicity (30).

Formulation and manufacturing challenges

Practical challenges in the formulation and manufacture of in situ gels include scale-up, assurance of sterility, stability under varying storage conditions, and batch-to-batch reproducibility (31).

Scale-up challenges: Translating laboratory processes to industrial scale requires close control of mixing, temperature, and reaction kinetics to preserve polymer properties, gelation behaviour, and drug loading. Large-scale manufacturing can introduce variability through uneven temperature distribution, inconsistent mixing, oxygen exposure, and equipment limitations, making process optimisation and monitoring essential to maintaining product quality during scale-up (30).

Sterility and aseptic processing: Ensuring sterility is critical, particularly for injectable and ophthalmic gels. Two principal approaches are used: terminal sterilisation

(autoclaving or gamma irradiation) and aseptic processing. Terminal sterilisation generally provides higher sterility assurance, but heat-sensitive polymers may be adversely affected by autoclaving, making gamma irradiation preferable in such cases; aseptic processing instead relies on stringent control of raw materials, equipment sterilisation, and environmental monitoring to avoid contamination (31).

Stability considerations: Variations in temperature and humidity are key challenges affecting in situ gel stability, contributing to polymer hydrolysis, oxidation, drug degradation, or nanoparticle aggregation, all of which can alter viscosity, gelation temperature, and release characteristics. Stability studies monitor these factors over extended periods, with formulation strategies - such as the inclusion of antioxidants - used to extend shelf life and preserve efficacy (33).

Batch-to-batch reproducibility: Consistent manufacturing is essential for predictable gelation, drug release, and therapeutic effect. Variability can arise from differences in raw material quality, mixing time, temperature control, and operator technique (32).

Overall, overcoming these challenges requires a multidisciplinary approach that integrates formulation science, quality assurance, and regulatory compliance to ensure product safety and efficacy (4). Analytical techniques commonly used to characterise in situ gel formulations include rheological assessment, evaluation of swelling behaviour, gelation time measurement, and drug release kinetics, among others (33).

Evaluation

- **Rheology and viscosity:** Viscometers and rheometers are used to characterise flow behaviour, viscosity, and the gelation-induced changes accompanying the sol-to-gel transition at different temperatures (12).
- **Gelation time and gelation temperature:** Gelation time is determined by placing the solution in simulated physiological fluid and recording the time required for the sol-to-gel transition. Gelation temperature is determined by gradually heating or cooling the solution until gel formation is observed (11).
- **Swelling and gelling capacity:** Swelling studies assess water uptake by the gel over time in simulated fluids, providing information on gelation stability and drug release potential; gelling capacity is evaluated by mixing the formulation with simulated body fluids and assessing gel firmness and the duration of gel integrity (8).
- **Drug release kinetics:** In vitro drug release is studied using dissolution apparatus or membrane diffusion cells with simulated physiological fluids, monitoring drug concentration over time to model diffusion- and erosion-controlled release mechanisms (12).
- **Other assessments:** Additional evaluations include clarity, pH, homogeneity, sterility testing, and particle size analysis for nano-in-situ gel systems (34).

Comparative Analysis with Conventional Systems

Market Products and Industrial Perspective

Market trends and commercial products: Growth in the global in situ gel drug delivery market is driven mainly by the rising prevalence of chronic ophthalmic disease - glaucoma alone is projected to affect 111 million people by 2040 - an ageing population that benefits from fewer instillations, and increasing demand for long-acting injectables in oncology and tuberculosis owing to a preference for minimally invasive treatment. The global market was valued at approximately USD 2.12 billion in 2024 and is projected to grow at a compound annual growth rate of 8.6% to reach approximately USD 4.47 billion by 2033 (35).

Additional pipeline examples: Periodontal depots of the Arestin/Atridox type (doxycycline or minocycline in PLGA-based, in situ-forming systems) are used to treat periodontitis locally; a liquid is injected into periodontal pockets and gels to provide 1-4 weeks of local antibiotic release, reducing pocket depth and bacterial load compared with scaling alone (2). Injectable bone and tissue-engineering hydrogels, based on in situ-forming gelatin, PEG, or hyaluronic acid networks, are being developed as minimally invasive fillers for bone defects and cartilage repair, combining thermosensitive or enzyme-cross-linked gelation with osteoconductive particles or BMP-mimetic peptides to promote regeneration and local growth factor delivery (1). For oral mucositis and periodontal maintenance, in situ oral and dental care gels - for example, chlorhexidine or herbal actives formulated as thermosensitive or mucoadhesive in situ gels - are also under investigation; the sol is applied to the oral cavity and gels on contact with the mucosa or in response to temperature (1). Industry interest in in situ gelation technology remains strong and continues to grow, driven by demand for sustained delivery, patient-friendly dosing, and route flexibility.

Table.1 Natural polymers and their primary gelation mechanism

Polymer	Key property	Primary mechanism	Example application
Gellan Gum	Ion-activated (Ca2+ egg-box)	Erosion-controlled	Ophthalmic timolol gels
Alginate	Ion-sensitive (Ca2+/Mg2+)	Swelling/erosion	Wound dressings, oral matrices
Chitosan	pH-sensitive (cationic)	Swelling-controlled	Mucoadhesive nasal insulin gels
Carbopol 934P	pH-sensitive (anionic)	Swelling/non-Fickian	Vaginal antifungal gels
HPMC	Hydrophilic swelling	Swelling/diffusion	Oral solid dispersions (felodipine)

Table.2 Synthetic polymers and their primary gelation mechanism

Polymer	Key property	Primary mechanism	Example application
Pluronic F127	LCST (~25C, 20% w/v)	Diffusion-controlled	Subcutaneous hydrophobic drug depots
PNIPAAm	LCST (~32C)	Swelling/non-Fickian	Intratumoral paclitaxel release
PEG-PLGA	Biodegradable, erosion-based	Erosion-controlled	Long-acting injectables (risperidone)
Carbopol	pH-sensitive	Swelling/non-Fickian	Vaginal and ophthalmic gels
Polycaprolactone	Hydrophobic degradation	Diffusion/erosion	Solid dispersion matrices

Table.3 DoE approaches used in in situ gel optimisation

DoE type	Factors/levels	Runs	Use case example
2-squared Factorial	2 factors, 2 levels	4+	Binary polymer screening
3-squared Full factorial	2 factors, 3 levels	9	Gellan gum/HPMC ratio for nasal gels
Box-Behnken	3 factors, 3 levels	12-15	Poloxamer/gellan/HPMC ternary systems

Table.4 Representative polymers and drugs by administration route

Route	Example polymers	Example drugs
Oral	Carbopol 934, chitosan, gellan gum, gum karaya, HPMC, hyaluronic acid esters, methylcellulose, methylpyrrolidinone, pectin, poloxamer, Pluronic F-127, sodium alginate, trimethyl chitosan, xyloglucan	Ambroxol, articaine HCl, benzydamine HCl, cimetidine, indomethacin, paracetamol, theophylline
Nasal	Acacia, carbomer/carbopol 934, carrageenan, chitosan, CMC, gellan gum, gum karaya, HEC, HPMC, pectin, PEG, poloxamer, PVA, PVP, sodium alginate, tragacanth	Acetaminophen, chloramphenicol, insulin, ketorolac, melatonin, metoclopramide, midazolam, oxymetazoline, oxytocin, salbutamol, zolmitriptan
Ocular	Carbomer/carbopol 940, carrageenan, chitosan, gelatin, gellan gum, HPMC, HEC, sodium alginate, Pluronic F-127, poloxamer, PVA, PVP, xanthan gum, xyloglucan	Aceclofenac, ciprofloxacin, diclofenac, dorzolamide, fluconazole, indomethacin, methazolamide, ofloxacin, pilocarpine, timolol, voriconazole
Rectal and vaginal	Carbopol, chitosan, gelatin, HEC, HPC, HPMC, methylcellulose, PEG, Pluronic F-127, poloxamer, polycarbophil, PVP, sodium alginate, sodium CMC, starch	Acetaminophen, acyclovir, chloramphenicol, clotrimazole, doxorubicin, 5-fluorouracil, insulin, metronidazole, nimesulide, oxybutynin, oxytocin, quinine
Parenteral	Cellulose acetate, chitosan, gelatin, PEG, poloxamer, sodium alginate, sodium hyaluronate	Doxorubicin, 5-fluorouracil, paclitaxel

Table.5 Stimuli-responsive in situ gel systems and outcomes

Stimulus/type	Polymer system	Route/site	Model drug/payload	Key outcome
pH + temperature	Pluronic + carbopol	Tumour/injectable	Doxorubicin	Dual-trigger release, reduced systemic toxicity
Enzyme (MMP-responsive)	Peptide-cross-linked PEG hydrogel	Tumour	Paclitaxel or cisplatin	Tumour-specific degradation, increased local concentration
Redox (wound ROS/GSH)	Disulfide-cross-linked hydrogel	Chronic wound	Antibiotic/growth factor	On-demand release, faster wound closure
Ion + nanoparticles	Gellan gum + drug-loaded nanoparticles	Ocular	Antifungal (e.g., azole)	Increased corneal retention and bioavailability
Thermosensitive nano-in-situ	PNIPAAm or poloxamer + micelles	Intra-articular	NSAID or corticosteroid	Prolonged joint residence, fewer injections
Bone defect, enzyme/pH	Injectable smart hydrogel + nano-HA	Bone defect	BMP-mimetic peptide	Increased bone regeneration, controlled degradation

Table.6 Ocular in situ gel studies

Formulation	Species/phase	Key findings
Gellan gum brimonidine (ion-activated)	Rabbit (preclinical)	6 h sustained release; 3-fold increase in AUC vs. drops; non-irritant on HET-CAM testing
Poloxamer/ganciclovir (thermosensitive)	Rabbit (preclinical)	12 h release; increased permeability vs. commercial formulation; no evidence of toxicity

Table.7 Nasal in situ gel studies

Formulation	Species/phase	Key findings
Gellan gum/HPMC fluoxetine (QbD, 3-squared DoE)	Rat (pharmacodynamic)	94% ex vivo release; enhanced antidepressant effect vs. solution; no nasal damage
Poloxamer nasal antifungal	Ex vivo porcine mucosa	6-fold increase in flux; 8 h steady release

Table.8 Injectable in situ gel studies

Formulation	Species/phase	Key findings
Poloxamer 407 anti-TB (rifampicin)	Rat (preclinical)	Sustained release beyond 7 days; reduced dosing frequency
PLGA-PEG doxorubicin (dual-responsive)	Mouse tumour model	Tumour-specific release; 2-fold reduction in systemic toxicity

Table.9 Oral in situ gel studies

Formulation	Species/phase	Key findings
Poloxamer/carbopol choline salicylate	Rabbit oral ulcer	Ulcer healing within 5 days vs. 8 days for control; shear-thinning and mucoadhesive

Table.10 Selected approved in situ gel products

Product/example	Agency/status	Route/key notes
Timoptic-XE (timolol gel)	FDA (NDA approved)	Ocular; ion-activated, first approved in 2000
Pilopine HS (pilocarpine)	FDA (approved)	Ocular gel; pH-sensitive
Eligard (leuprolide PLGA)	FDA/EMA (approved)	Subcutaneous depot; thermosensitive

Table.11 Route-specific biocompatibility testing

Route	Critical tests	Acceptance criteria
Ocular	HET-CAM, BCOP, ICE (ISO 10993-23), rabbit Draize test	Non-irritant (score 0-0.9), >90% cell viability
Nasal/injectable	Intracutaneous reactivity, 14-day systemic toxicity (IP)	No oedema/erythema (>Grade 0); Cmax below therapeutic threshold
Oral mucosal	Reconstructed human epidermis (RhE) irritation (EpiDerm), mucoadhesion shear testing	Viability >50%; adhesion >500 dyne/cm2

Table.12 In situ gels vs. conventional dosage forms

Parameter	In situ gels	Tablets	Ointments	Injections
Bioavailability	High	Moderate	Variable	High
Patient compliance	High	Moderate	Low-moderate	Moderate
Sustained release	Yes	Sometimes	Sometimes	Yes
Ease of use	Moderate-high	High	Low	Moderate
Manufacturing cost	Moderate	Low	Low	High

Table.13 In situ gels vs. conventional drops/solutions and solid dispersions

Parameter	Conventional drops/solutions	In situ gels	Solid dispersions (tablets)
Residence time	1-5 min (ocular/nasal)	4-24 h (extended via gelation)	N/A (systemic absorption)
Bioavailability	Low (20-40%)	2-4x higher (via mucoadhesion)	High for BCS Class II drugs (2-5x)
Dosing frequency	4-8x/day	1-2x/day	1-2x/day
Onset of action	Rapid (<5 min)	5-15 min (post-gelation)	30-60 min (gastric)
Need for healthcare supervision	Low (self-administered)	Low-moderate (injectables)	Low (oral)
Suitability for biologics/peptides	Poor (enzymatic degradation)	Good (mucosal protection)	Poor (GI degradation)
Manufacturing complexity	Simple	Moderate (polymer blending)	High (spray drying/hot-melt extrusion)
Cost	Low	Moderate-high	High

Table.14 In situ gels vs. tablets, ointments, and injections - broader comparison

Parameter	In situ gels	Tablets	Ointments	Injections
Bioavailability	Often enhanced by prolonged residence and controlled release at the site of action, reducing first-pass metabolism (e.g., nasal, ocular)	Variable; limited by solubility and first-pass metabolism	Limited to local effect; poor systemic absorption	High for systemic delivery but limited by rapid clearance
Patient compliance	Improved by reduced dosing frequency and painless, non-invasive administration (nasal, ocular)	Generally good, but frequent dosing and swallowing difficulties can reduce compliance	Moderate; messy application and sensory discomfort may reduce adherence	Lower due to pain, needle phobia, and need for healthcare provider administration
Cost	Moderate to high; advanced polymers and manufacturing increase cost, but can reduce overall treatment expense by improving efficacy	Generally low-cost and widely available	Low to moderate, depending on formulation	High due to sterile manufacturing and administration costs
Safety	Generally safe with biodegradable polymers; localised delivery reduces systemic side effects; polymer toxicity risk if not well characterised	Safe, but systemic side effects are possible due to peak plasma concentrations	Local irritation and sensitisation possible	Risks of infection, tissue damage, and systemic reactions
Ease of use	Very convenient for self-administration via topical/nasal routes; injectable gels may require a healthcare setting	Very easy to use orally	Application can be inconvenient; requires skin site preparation	Requires trained personnel and a controlled environment

Table.15 Selected marketed and pipeline in situ gel products

Product name	Indication	Formulation type	Key features	Commercial/market notes
Timoptic-XE	Glaucoma	Ion-activated ocular gel	Sustained release, reduced dosing frequency	Widely marketed; strong sales in anti-glaucoma therapy
Betoptic S	Glaucoma	Ion-exchange resin + gel	Enhanced corneal retention	FDA-approved; used primarily in glaucoma
Ganciclovir gel	Viral ocular infections	Ion-activated ocular gel	Prolonged corneal residence, improved efficacy	Marketed in some countries for advanced clinical use
Injectable PLGA/PEG depots	Hormonal therapy, cancer	Injectable hydrogels	Long-acting intratumoral/systemic delivery	Several products in use or development; growing pharmaceutical interest
Nasal insulin gels	Diabetes management	Thermosensitive nasal gel	Needle-free, rapid absorption	Experimental/early clinical stage; promising but not widely marketed

Table.16 Key commercial products

Product	Active ingredient	Route/type	Key advantage
Timoptic-XE	Timolol	Ocular (gellan gum, ion-activated)	Twice-daily dosing vs. six-hourly drops
Pilopine HS	Pilocarpine	Ocular (pH-sensitive gel)	Prolonged miosis; reduced dosing frequency
Eligard	Leuprolide	Subcutaneous (PLGA, thermosensitive)	1-6-month prostate cancer depot
Zirgan (ganciclovir)	Ganciclovir	Ocular (in situ forming)	Extended antiviral retention

Table.17 Priority research areas

Research area	Description
Oral in situ gel systems	Novel polymers and mucoadhesive strategies to improve oral bioavailability, gastric retention, and protection against enzymatic degradation
Protein and peptide delivery	Biocompatible gelation chemistries that maintain protein stability while enabling sustained, targeted release
Global regulatory harmonisation	Harmonising guidelines, quality standards, and approval pathways for complex in situ gel products worldwide

Fig.1 Schematic representation of drug release mechanisms from reservoir-type in situ gel systems.

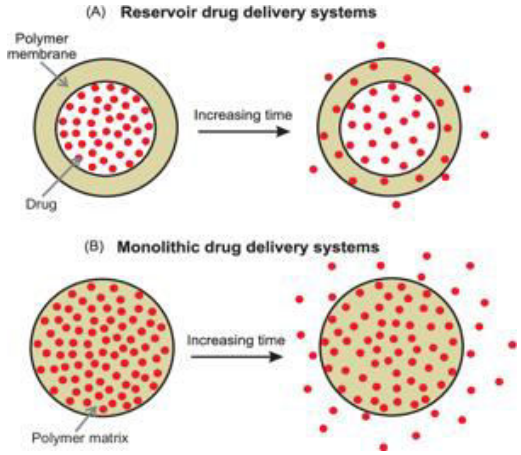
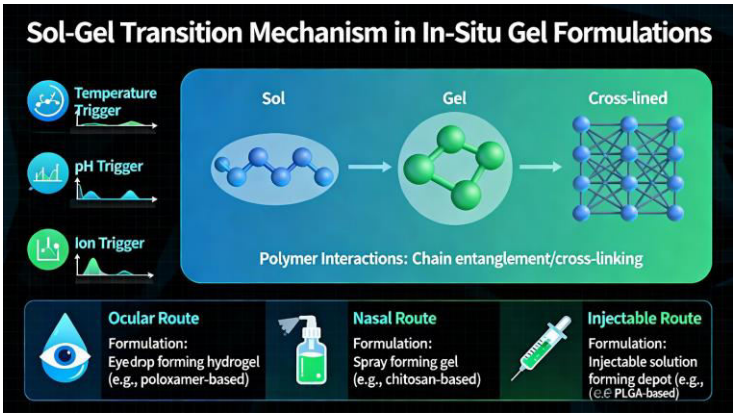


Fig.2 Schematic of sol-gel transition and in situ gel formulations for ocular, nasal, and injectable routes.



Pharmaceutical companies and research institutes are increasingly investing in smart polymer platforms, integrating nanotechnology, and pursuing scale-up of these systems (6).

Ongoing collaborations and consortia: Industry-academic partnerships continue to drive product innovation, launches, and regulatory submissions in the in situ gel drug delivery space, with several established pharmaceutical companies active in this area, reflecting sustained commercial interest and ongoing investment (5).

Future Directions (Smart, Nano, AI-Driven, Personalised Systems)

Future opportunities in in situ gel formulation lie at the intersection of emerging technologies and evolving clinical needs, particularly in personalised medicine, combination therapies, and artificial-intelligence-assisted formulation optimisation (7).

Personalised medicine: Advanced polymer and biomaterial platforms may allow in situ gel formulations to be customised to an individual patient's physiological status and disease profile. Such personalised gelation systems could, in principle, adjust gelation triggers, drug loading, and release kinetics based on a patient's genetic profile or biomarker status, potentially improving therapeutic precision and outcomes (36).

Combination therapies: In situ gels provide a matrix suited to co-delivering multiple therapeutic agents - drug-drug combinations, drug-biologic combinations, or drug-gene therapy combinations. Such multi-agent approaches could more effectively address complex diseases, including cancer, infection, and chronic inflammatory conditions, by combining local and sustained release within a single formulation (36).

AI-Powered Formulation Optimisation

Artificial intelligence and machine learning methods are increasingly applied to accelerate the design and optimisation of in situ gel formulations. AI models can predict polymer-drug interactions, gelation behaviour, stability, and release profiles from large datasets, reducing experimental burden and shortening development timelines (10). By training machine learning models on polymer-drug characteristics - such as molecular weight, hydrophilic-lipophilic balance, and charge density - together with DoE datasets, AI-assisted approaches can predict key formulation responses without requiring extensive additional experimentation (10).

Concrete AI applications for in situ gels

- *Predicting gelation temperature/time:* Inputs such as poloxamer 407 concentration (15-25%), HPMC concentration (0.1-0.5%), drug hydrophobicity (log P), and pH can be used to train neural networks or random forest models to predict LCST/UCST or ion-triggered gelation onset (target: 32-37C in <60 s), with reported model performance of R-squared > 0.95 on 3-squared factorial datasets (17).
- *Forecasting viscosity profiles:* Gradient boosting methods (e.g., XGBoost) or Gaussian process models applied to rheological DoE data (sol: <100 cP; gel: >5000 cP at low shear) can support inverse design for syringeability through 18-25G needles, incorporating polymer ratios, ionic strength, and temperature ramps (8).
- *Modelling drug release kinetics:* Mesh size (derived from polymer entanglement), erosion rate, and the Fickian diffusional exponent (n = 0.43-0.89) can be used as inputs to train support vector regression or artificial neural network models on in vitro release testing/USP II data from Box-Behnken designs, predicting percentage release at 1, 4, and 24 h with reported error below 5% within the QbD design space (17).

In situ gel systems have progressed from a conceptually simple sol-to-gel formulation strategy, first proposed in the 1970s, into a versatile drug delivery platform applicable across ocular, nasal, oral, vaginal, rectal, and parenteral routes. By forming a gel depot at the site of administration in response to temperature, pH, ionic strength, or biochemical triggers, these systems prolong residence time, sustain drug release, and improve patient compliance relative to conventional drops, solutions, or injections. The rational selection of biocompatible natural or synthetic polymers, supported increasingly by Quality by Design and Design of Experiments methodologies, remains central to achieving consistent gelation behaviour and predictable release. Several ocular and injectable products have reached the market and demonstrate the clinical viability of the approach, although batch-to-batch reproducibility, sterility assurance, and the general absence of approved generic equivalents continue to constrain wider adoption. Looking ahead, the convergence of nanotechnology-enabled "nano-in-situ gels," multi-stimuli-responsive

smart polymers, and artificial-intelligence-assisted formulation design is likely to accelerate the development of more precisely tuned, patient-specific systems, while continued regulatory harmonisation will be needed to support their broader clinical translation. Sustained interest from both industry and academia suggests that in situ gel technology will remain an important area of pharmaceutical research and development in the coming decade.

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