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IN SITU GELS: A COMPREHENSIVE REVIEW OF MECHANISMS, POLYMERS, AND THERAPEUTIC APPLICATIONS

Dr. K. S. Srilatha[1]*, M. Jahnavi[2], Anusha S.[3], Lakshmi Devi[4], Sachin H. S.[5], V. Saravana Kumar[6]

*[1]Professor and HOD Department of Pharmaceutics, Shridevi Institute of Pharmaceutical Sciences Tumkur, Karnataka.
[2,3,4,5,6]Students of 8th Sem Department of Pharmaceutics, Shridevi Institute of Pharmaceutical Sciences Tumkur, Karnataka.

***Corresponding Author: Dr. K. S. Srilatha**

Professor and HOD Department of Pharmaceutics, Shridevi Institute of Pharmaceutical Sciences Tumkur, Karnataka.

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ABSTRACT

In-situ gel technology is a promising drug delivery strategy that undergoes a 'sol to gel' transition upon administration, providing controlled and prolonged drug release. These gels are composed of cross-linked 3D networks of polymers, with hydrogels being a specific type of absorbing water while retaining their shape. Gelation can be triggered by various stimuli, such as temperature, pH, ions, and light. They offer several advantages like improved patient compliance, extended drug residence time, localized drug delivery, etc, but also have some disadvantages like drug degradation and limited mechanical strength. *In-situ* gel falls into three categories: temperature-sensitive, ion-sensitive, and pH-sensitive, but multi-responsive gels that respond to multiple stimuli have better drug release characteristics. The mechanism of *in-situ* gel formation involves physical and chemical mechanisms. There are various applications of in-situ gel, like ocular drug delivery, nose-to-brain delivery, etc. In this review, we have discussed the types, and mechanisms of *in-situ* gel & use of *in-situ* gel in the treatment of different diseases through various routes like buccal, vaginal, ocular, nasal, etc., along with its use in targeted drug delivery.

KEYWORDS: In situ gel, Thermosensitive nature, bioavailability, Natural Polymer, Antifungal activity.

INTRODUCTION

In pharmacy, **gels** are semisolid dosage forms in which a liquid is immobilized within a three-dimensional network of a gelling agent. The composition of pharmaceutical gels typically includes the following components:

Table No. 1: Composition of Pharmaceutical gels.

Component	Function	Examples
Gelling agent	Forms the gel structure and provides viscosity	Carbopol (Carbomer), Hydroxypropyl methylcellulose (HPMC), Sodium carboxymethyl cellulose (NaCMC), Poloxamer 407, Xanthan gum, Sodium alginate, Gelatin
Solvent (Vehicle)	Dissolves or disperses ingredients	Purified water, Ethanol, Propylene glycol, Glycerin
Active pharmaceutical ingredient (API)	Produces the therapeutic effect	Diclofenac, Lidocaine, Clindamycin, Metronidazole, Ketoprofen
Humectant	Prevents drying and improves moisture retention	Glycerin, Sorbitol, Propylene glycol
Preservative	Prevents microbial growth	Methylparaben, Propylparaben, Benzalkonium chloride, Phenoxyethanol
pH Adjuster /	Adjusts pH and helps gel	Triethanolamine, Sodium hydroxide, Citric acid

Neutralizer	formation	
Stabilizer / Antioxidant	Prevents oxidation and improves stability	Sodium metabisulfite, Butylated hydroxytoluene (BHT), Ascorbic acid
Chelating agent (optional)	Enhances stability by binding metal ions	Disodium EDTA
Coloring and Flavoring agents (optional)	Improve appearance and acceptability (especially oral gels)	Approved pharmaceutical colors and flavors
Fragrance (optional)	Improves odor in topical gels	Suitable cosmetic fragrances

Composition of gel

Gels consist of a solid three-dimensional network that spans the volume of a liquid medium and ensnares it through surface tension effects. This internal network structure is made up of physical bonds (physical gels) or chemical bonds (chemical gels), as well as crystallites or other junctions that remain intact within the extending fluid. Virtually any fluid can be used as an extender including water (hydrogels), oil, and air (aerogel). Both by weight and volume, gels are mostly fluid in composition and thus exhibit densities similar to those of their constituent liquids. Edible jelly is a common example of a hydrogel and has approximately the density of water.[1]

1. Based on the Nature of the Liquid Phase

a. Hydrogels

- Contain **water** as the dispersion medium.
- Most common pharmaceutical gels.
- Non-greasy, cooling, and easily washable.
- **Examples:** Carbopol gel, HPMC gel, aloe vera gel.

b. Organogels (Oleogels)

- Contain **organic solvents or oils** as the dispersion medium.
- Suitable for lipophilic drugs.
- **Examples:** Lecithin organogel, Pluronic lecithin organogel (PLO).

c. Xerogels

- Formed by removing the liquid from a gel, leaving a dry porous structure.
- Can absorb liquid and reform a gel.
- **Examples:** Silica gel, dried gelatin sponge.

2. Based on the Number of Phases

a. Single-phase Gels

- Consist of one continuous phase with uniformly distributed gelling agent.
- Usually transparent.
- **Examples:** Carbopol gel, HPMC gel.

b. Two-phase Gels (Magmas)

- Consist of solid particles dispersed in a liquid.
- Often opaque.
- **Examples:** Aluminium hydroxide gel, Bentonite magma.

3. Based on the Cross-Linking

a. Physical Gels

- Formed by weak intermolecular forces such as hydrogen bonding or ionic interactions.
- Reversible on heating or cooling.
- **Examples:** Gelatin gel, Agar gel.

b. Chemical Gels

- Formed by covalent cross-linking.
- Permanent and irreversible.
- **Examples:** Cross-linked polyacrylamide gel.

4. Based on Route of Administration

- **Topical gels:** Applied to the skin (e.g., diclofenac gel).
- **Oral gels:** Used in the mouth or swallowed (e.g., antacid gels).
- **Ophthalmic gels:** Applied to the eyes.
- **Nasal gels:** Administered through the nose.
- **Vaginal gels:** Used for local treatment or contraception.
- **Rectal gels:** Used for local or systemic drug delivery.

***IN SITU* GEL**

This is a drug delivery system that is administered as a liquid but undergoes gelation at the site of administration due to physiological triggers such as changes in pH, temperature, or ionic concentration. This transformation allows the formulation to remain at the target site for an extended period, improving drug residence time, bioavailability, and therapeutic effectiveness while reducing dosing frequency.

In situ gel systems have gained significant attention in pharmaceutical research because they combine the ease of administration of liquid dosage forms with the prolonged retention and controlled drug release characteristics of gels. These systems are widely used for ophthalmic, nasal, oral, rectal, vaginal, and injectable drug delivery. The gel formation is typically achieved using polymers that respond to environmental stimuli, such as Sodium alginate, Carbopol 934, Poloxamer 407, Gellan gum, and Chitosan.

The major advantages of *in situ* gel systems include:

- Easy administration and improved patient compliance.
- Prolonged residence time at the site of application.

- Sustained and controlled drug release.
- Enhanced bioavailability by reducing drug loss.
- Reduced frequency of administration and minimized systemic side effects.

Mechanisms of *In Situ* Gelation

In situ gel systems undergo a **sol-to-gel transition** when exposed to specific physiological or environmental stimuli. Depending on the trigger responsible for gel formation, *in situ* gelation can be classified into the following mechanisms.

1. Temperature-Triggered Gelation (Thermosensitive Gelation)

Temperature-sensitive *in situ* gels remain in a liquid state at room temperature and transform into a gel at body temperature (approximately 37°C). This gelation occurs due to changes in polymer solubility and molecular interactions as the temperature increases. Common thermosensitive polymers include Poloxamer 407, Poloxamer 188, and Methylcellulose.

Advantages

- Easy administration
- Rapid gel formation at the site of application
- Sustained drug release

2. pH-Triggered Gelation

pH-sensitive *in situ* gels undergo gelation when exposed to the physiological pH of the target site. These formulations remain liquid at acidic or neutral pH and form a gel when the pH changes, causing ionization and swelling of the polymer. Common pH-sensitive polymers include Carbopol 934, Carbopol 940, and Polyacrylic acid.

Applications

- Ophthalmic drug delivery
- Oral and nasal formulations

3. Ion-Activated Gelation

Ion-sensitive in situ gels are formed in the presence of physiological ions such as calcium (Ca^{2+}), sodium (Na^{+}), potassium (K^{+}), or magnesium (Mg^{2+}). These ions interact with specific polymers, leading to cross-linking and gel formation. Common ion-sensitive polymers include Sodium alginate, Gellan gum, and Pectin.

Advantages

- Simple gelation mechanism
- Excellent mucoadhesion
- Prolonged drug retention

4. Solvent Exchange-Induced Gelation

In solvent exchange systems, gel formation occurs when the solvent in the formulation diffuses into the surrounding biological fluid while water diffuses into the formulation. This exchange decreases polymer solubility, causing precipitation and gel formation. This mechanism is commonly used in injectable depot formulations for sustained drug release.

5. Enzyme-Induced Gelation

Certain biodegradable polymers undergo gelation in the presence of specific enzymes found in body tissues. Enzymatic reactions create cross-links between polymer chains, resulting in gel formation. This mechanism is mainly used in tissue engineering, regenerative medicine, and targeted drug delivery.

6. Photo-Induced Gelation

Photo-sensitive polymers form gels when exposed to light of a specific wavelength, usually ultraviolet (UV) or visible light, in the presence of a photoinitiator. Light exposure initiates polymerization or cross-linking, producing a stable gel. This technique is widely applied in tissue engineering, wound healing, and localized drug delivery.

Polymer selection is, without overstating it, the single most consequential decision in *in situ* gel formulation design. The trigger mechanism, the gelation kinetics, the mechanical properties of the resulting gel, the mucoadhesive behaviour, the drug release profile, and the tolerability at the administration site — all of these are downstream consequences of the polymer or polymer combination chosen. Getting this decision right requires understanding not just what a polymer does under idealised laboratory conditions, but how it behaves in the messy physiological environment of the tear film, the nasal cavity, or the periodontal pocket. This section reviews the major polymer classes used in *in situ* gel systems, their formulation-relevant physicochemical properties, and the rationale behind combination approaches that now dominate the literature.

Table No. 2: Indicating natural polymers its concentration used in formulations.

Polymers	Trigger	Concentration	Gel, Temperature /PH	Mucoadhension	Drugs example
Gellan gum	Ionic	0.1-1.0%w/v	RT-37 C [ions]	Moderate	Timolol
Sodium alginate	Ionic[ca2+]	1-3%w/v	RT[Ca2+ trigger]	High	Ofloxacin
Chitosan	PH[alkaline]	0.5%w/v	Ph > 6.5	Very high	Gatifloxacin
Pectin	Ionic[ca2+]	1.5%w/v	Gastric ph 1.2	Moderate	Metformin
Xyloglucan	Temperature	1-2%w/v	25 -37 c	Low-moderate	Pilocarpine
Guar gum	Enzymatic	0.5-2.0%w/v	Colonic enzymes	Moderate	5-ASA
Xanthan gum	Ionic/shear	0.1-1.0%w/v	Variable	Moderate	Diclofenac

Table No. 3: Indicating Synthetic polymers and its applications.

Synthetic polymers	Gelation mechanism	Applications	Advantages
Poloxamer 407	Temperature sensitive	Ophthalmic, nasal ,rectal , vaginal and injectable	Liquid at low temperature, gels at body temperature, biocompatible
Poloxamer 188	Temperature sensitive	Combined with poloxamer 407	Adjusts gelation temperature and viscosity
Poly{N-isopropylacrylamide}	Temperature sensitive	Injectable drug delivery, tissue engineering	Sharp sol-gel transition near body temperature
Polyethylene glycol	Cross-linking or copolymer formation	Injectable hydrogels	Hydrophilic, biocompatible, low toxicity
Polyvinyl alcohol	Chemical or physical cross linking	Ocular and wound dressings	Good film-forming ability, biocompatibility
Polyvinyl acid	PH-sensitive	Ophthalmic and oral formulations	Sweels and gels at physiological ph
Carbapol 934	PH-sensitive	Ophthalmic, nasal	High mucosadhesion and viscosity
Carbapol 940	PH- sensitive	Controlled drug delivery	Excellent gel strength and clarity

Recent Advances and Emerging Trends

In situ gels are advanced drug delivery systems that undergo a phase transition from sol (liquid) to gel upon exposure to physiological stimuli such as temperature, pH, or ionic strength. These systems have gained significant attention due to their ability to provide controlled drug release, prolonged residence time, improved bioavailability, and enhanced patient compliance.

Recent Advances in *In Situ* Gels

1 Smart Stimuli-Responsive Polymers

Recent developments focus on **stimuli-responsive polymers** that precisely respond to environmental triggers such as temperature, pH, ions, and enzymes. These systems enable rapid gelation and sustained drug release at the target site.

2 Nano-Integrated In Situ Gels

Integration of **nanotechnology** (nanoparticles, liposomes, nanoemulsions, and nanogels) into in situ gel systems has significantly improved:

- Drug stability
- Targeted delivery
- Permeability across biological barriers

Nanoparticle-loaded in situ gels have shown enhanced therapeutic efficacy, particularly in ocular and cancer treatments.

3 Mucoadhesive In Situ Systems

The incorporation of **mucoadhesive polymers** (e.g., chitosan, carbopol) enhances adhesion to mucosal surfaces, leading to:

- Increased residence time
- Improved drug absorption
- Reduced dosing frequency

4 Injectable In Situ Forming Depots

Recent research includes **injectable in situ gels** that form drug depots after administration, enabling:

- Long-term sustained drug release
- Reduced systemic toxicity
- Improved patient compliance

5 Multi-Responsive (Dual/Triple Stimuli) Systems

Advanced systems now respond to **multiple stimuli (e.g., pH + temperature + ions)**, offering highly controlled and site-specific drug release.

2. Emerging Trends in *In Situ* Gel Technology

1 Personalized and Precision Medicine

In situ gels are being tailored for **patient-specific drug delivery**, enabling customized dosing and targeted therapy, particularly in oncology and chronic diseases.

2 Biodegradable and Natural Polymer-Based Gels

There is a growing shift toward **biodegradable and eco-friendly polymers** such as:

- Hyaluronic acid
- Xanthan gum
- Guar gum

These improve safety, reduce toxicity, and enhance biocompatibility.

3 Ocular and CNS Targeted Delivery

In situ gels are widely explored for:

- **Ocular delivery** (glaucoma, infections)
- **Nose-to-brain delivery** for CNS disorders

They overcome barriers like rapid clearance and low bioavailability.

4 Tissue Engineering and Regenerative Medicine

Emerging applications include:

- Scaffold formation for tissue repair
- Wound healing systems
- Controlled growth factor delivery

These systems act as both **drug carriers and structural biomaterials**.

5 Hybrid Hydrogel Systems

Combination of **physical and chemical cross-linking** leads to hybrid hydrogels with improved:

- Mechanical strength
- Stability
- Controlled drug release

6 Advanced Drug Delivery Routes

New routes being explored include:

- Vaginal and rectal delivery
- Intravesical (bladder) delivery
- Periodontal drug delivery

These provide localized therapy with minimal systemic side effects.

CONCULSION

In situ gels have emerged as a versatile and promising drug delivery system due to their unique ability to undergo phase transition in response to physiological stimuli such as pH, temperature, and ionic strength. This property enables prolonged residence time at the site of administration, improved bioavailability, and controlled drug release, thereby enhancing therapeutic efficacy. A wide range of natural and synthetic polymers, including alginate, chitosan, poloxamers, and carbopol, have been extensively explored to design stimuli-responsive systems with desirable rheological and mucoadhesive properties.

The underlying mechanisms governing sol–gel transition play a critical role in determining the performance of in situ gels, with each trigger offering specific advantages for targeted applications. These systems have demonstrated significant potential across multiple routes of administration, including ocular, nasal, oral, injectable, and transdermal delivery, addressing limitations associated with conventional dosage forms.

Despite their advantages, challenges such as formulation stability, reproducibility, scale-up, and regulatory considerations remain areas requiring further investigation. Future research should focus on the development of multifunctional, patient-friendly, and precision-targeted in situ gel systems by integrating advanced technologies such as nanocarriers and smart polymers. Overall, in situ gels represent a progressive platform in drug delivery, with substantial scope for innovation and clinical translation in modern therapeutics.

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