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IN SITU GEL: AN INNOVATIVE STRATEGY FOR CONTROLLED AND TARGETED DRUG DELIVERY

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ABSTRACT

Conventional drug delivery systems often suffer from limitations such as low bioavailability, poor site specificity, and systemic side effects. In response to these challenges, in situ gel systems have emerged as a promising alternative, offering controlled and sustained drug release through physiological triggers like temperature, pH, and ionic strength. These systems remain in a sol state during administration and undergo gelation upon exposure to specific physiological conditions, enhancing drug residence time and therapeutic efficacy. Various approaches—thermosensitive, pH-sensitive, and ion-activated—have been explored using both natural and synthetic polymers. In situ gels have demonstrated versatility across multiple routes of administration, including ocular, nasal, injectable, vaginal, and buccal delivery, significantly improving patient compliance. Recent advancements incorporating nanocarriers have further enhanced the efficiency of these systems. Despite their potential, challenges such as polymer toxicity and formulation consistency remain. This review discusses the mechanisms, formulation strategies, polymers used, applications, and evaluation parameters of in situ gels, while highlighting current innovations and future research directions in this dynamic field.

KEYWORDS: In situ gel, Floating drug delivery systems (FDDS), Thermosensitive gelation, pH-responsive polymers, Ion-activated systems, Controlled drug release.

INTRODUCTION

In situ gel drug delivery systems have been recognized as an innovative approach for achieving controlled and sustained drug release, presenting notable benefits when compared to traditional dosage forms. These systems are initially in a sol state and transition to a gel

state upon administration at the targeted site. Gelation can be instigated by multiple stimuli, such as variations in temperature, changes in pH, or the presence of specific ions, facilitating localized and extended drug release.[1] A significant breakthrough within this domain is the creation of floating in situ gels, which are specifically formulated to float within the gastric environment. This buoyancy allows for prolonged gastric retention time, subsequently enhancing the bioavailability of medications predominantly absorbed in the stomach. The floating effect is often realized by incorporating effervescent agents or by utilizing polymers that create low-density gels upon interaction with gastric fluids.[2] The unique gelation mechanisms and the physicochemical characteristics of the utilized polymers contribute to the controlled drug release features of in situ gels. By carefully selecting polymers and formulation techniques, it is feasible to achieve zero-order release kinetics, thereby reducing variability in drug plasma levels and improving therapeutic outcomes.[3] This review will investigate the progress made in in situ gel drug delivery systems, focusing specifically on floating formulations and their impact on controlled drug release. We will analyze the various polymers used, the gelation mechanisms, and the factors that affect drug release profiles, as well as the potential applications and challenges faced by these systems, offering a thorough overview of their current state and future potential within pharmaceutical sciences.[4]

MECHANISM OF GELATION

In situ gel systems are formulated to remain in a liquid state prior to administration and undergo gelation when exposed to specific physiological stimuli. This transition enhances the residence time of the drug at the site of application and allows for controlled drug release. Based on the nature of the triggering stimulus, in situ gels are primarily categorized into three types: thermosensitive, pH-sensitive, and ion-activated systems.

1. Thermosensitive Gelation

Sol-gel transition: When temperatures change, certain polymers may undergo a sol-gel transition. In a liquid solution, these polymers can create a stable gel network at a specific temperature. A widely used polymer in temperature-sensitive in-situ gel systems is poly (N-isopropyl acrylamide acid) (PNIPAAm), which can gel when the temperature exceeds a certain threshold known as the Lower Critical Solution Temperature (LCST). Ambient temperature changes can lead to the development of in-situ gels. For example, during injection applications, a decrease in body temperature can result in the cooling of the injected polymer solution, thereby facilitating the formation of a stable gel.[5]

2. pH-Sensitive Gelation

pH-Sensitive Polymers: Some polymers demonstrate sensitivity to pH changes, transitioning from a liquid form to a gel state when exposed to different pH levels. Examples include polyacrylate, alginate, and methyl cellulose, which can gel at designated pH thresholds. The formation of gels is influenced by alterations in the interactions between polymer chains due to pH shifts. Environmental pH Changes: Certain in-situ gels can solidify in response to fluctuations in the surrounding pH. For example, in-situ drug delivery gels that incorporate acidic polymers will experience a decrease in pH within the stomach's acidic environment, resulting in gel formation that facilitates the release of the contained medications.[6]

3. Ion-Sensitive Gelation

Ionic Bond Development: Some polymers are capable of forming gels by bonding with specific ions, which results in ionic bond formation. Gelatin is a frequently used polymer in in-situ gel systems. In these systems, calcium ions are used to create stable cross-links among the gelatin chains, thereby producing a strong gel. Ion-Induced Viscosity Modification: The incorporation of certain ions into a polymer solution can change its viscosity and encourage gel formation. For example, adding calcium or sodium ions can enhance the viscosity of an alginate solution, leading to the formation of a stable alginate gel.[7,8]

TYPES OF POLYMERS USED IN IN SITU GELS

The performance of in situ gel systems largely depends on the selection of suitable polymers, which determine the system’s gelation behavior, mechanical strength, biocompatibility, and drug release profile. Both **natural** and **synthetic polymers** are used, depending on the required gelation mechanism and route of administration.[9]

1. Natural Polymers

Natural polymers offer advantages such as biodegradability, non-toxicity, and mucoadhesiveness, making them favorable for in situ gel formulations.

- **Gellan gum**: An ion-sensitive polysaccharide derived from *Pseudomonas elodea*, commonly used in ophthalmic and oral gels. It forms a gel in the presence of cations like Na^+ and Ca^{2+}
- **Alginate**: Another ion-sensitive polymer extracted from brown seaweed, forms gels in the presence of divalent cations, particularly Ca^{2+}

- **Chitosan**: A pH-sensitive polymer that gels in mildly alkaline environments. It also exhibits antimicrobial properties and enhances permeability.[10]

2. Synthetic Polymers

Synthetic polymers are often used to achieve precise control over gelation temperature and drug release kinetics.

- **Poloxamers (Pluronic® F127, F68)**: Thermosensitive triblock copolymers of polyethylene oxide and polypropylene oxide. They are liquid at room temperature and form gels at body temperature
- **Carbopol**: A pH-sensitive synthetic polymer that forms gels at neutral to alkaline pH. Often used in combination with HPMC to improve viscosity and stability .
- **Polyacrylic acid derivatives**: Exhibit pH-responsive gelation and are useful for oral and topical applications.

The choice and combination of polymers must be tailored based on the drug's physicochemical properties, intended route, and desired therapeutic effect. The use of polymer blends (e.g., gellan gum with carbopol or HPMC) is also common to achieve synergistic gelation and improved performance.[11,12]

COMMONLY USED EXCIPIENT IN INSITU GEL PREPARATION

1. Gelling Agents

These polymers undergo sol-to-gel transition in response to specific stimuli, forming the gel matrix upon administration:

- **Thermoreversible Gelling Agents**: Poloxamers (e.g., Poloxamer 188, Poloxamer 407) exhibit gelation upon temperature increase, making them suitable for oral in situ gel formulations.
- **pH-Responsive Gelling Agents**: Carbopol 934P is a synthetic polymer that forms gels when the pH is raised, aiding in controlled drug release.
- **Ion-Activated Gelling Agents**: Gellan gum and sodium alginate form gels in the presence of specific ions like calcium, providing sustained drug release.[13]

2. Viscosity Enhancers

These excipients modify the viscosity of the formulation, ensuring ease of administration and stability:

- **Hydroxypropyl Methylcellulose (HPMC)**: Used to enhance viscosity and improve mucoadhesive properties, thereby prolonging the residence time of the gel in the oral cavity.
- **Hydroxyethyl Cellulose (HEC)**: Serves a similar function as HPMC, contributing to the gel's viscosity and stability.[14]

3. Mucoadhesive Agents

These agents promote adhesion to the mucosal surfaces, enhancing the residence time of the gel:

- **Carbopol 934P**: In addition to its gelling properties, it enhances mucoadhesion through hydrogen bonding with mucosal tissues.
- **Chitosan**: A natural polymer that forms gels and exhibits strong mucoadhesive properties, facilitating prolonged drug retention.[15]

4. pH Modifiers

These excipients adjust the pH of the formulation to optimize the gelation process and drug stability:

- **Triethanolamine (TEA)**: Used to adjust the pH of Carbopol-based gels to the desired range, ensuring proper gelation and stability.[16]

5. Preservatives

These agents prevent microbial growth, ensuring the safety and longevity of the formulation:

- **Methylparaben**: A commonly used preservative in oral formulations to inhibit microbial growth.

6. Other Excipients

- **Calcium Carbonate**: Acts as a gas-generating agent in floating in situ gels, aiding in gastric retention.

Sodium Citrate: Enhances the gelation process in ion-activated systems by facilitating ion exchange.[17]

ROUTES OF ADMINISTRATION AND APPLICATIONS

In situ gel systems have been successfully explored for various routes of administration. Their ability to provide prolonged residence time, controlled release, and localized drug

delivery makes them ideal for ophthalmic, nasal, oral, vaginal, rectal, and injectable formulations.

1. Ocular Drug Delivery

Ocular in situ gels provide a significant advantage over conventional eye drops, which suffer from rapid precorneal elimination. In situ gelling formulations, upon instillation into the conjunctival sac, undergo gelation due to tear fluid ions, temperature, or pH, thus increasing corneal contact time and bioavailability.[[18] Polymers such as gellan gum, xanthan gum, poloxamer, and carbopol are commonly used. Drugs like timolol maleate, ciprofloxacin, and pilocarpine have been effectively formulated into ocular in situ gels.[19]

2. Nasal Drug Delivery

The nasal route allows rapid drug absorption due to the rich vascularization of the nasal mucosa. However, rapid mucociliary clearance can limit drug residence time. In situ gels overcome this limitation by forming a gel upon contact with nasal mucosa, thus enhancing drug absorption and retention.[20] Thermosensitive and ion-activated polymers are particularly effective in nasal delivery of drugs such as insulin, sumatriptan, and midazolam.

3. Oral Drug Delivery

In situ oral gels offer benefits such as sustained drug release and improved gastric retention. The gelation typically occurs due to pH changes or ion interactions in the gastrointestinal tract.[21] Alginate and gellan gum-based in situ gels have been employed for delivering drugs like ranitidine, clarithromycin, and metronidazole to treat conditions such as peptic ulcers and H. pylori infections.

4. Vaginal and Rectal Delivery

In situ gels for vaginal and rectal administration provide localized drug delivery with enhanced mucoadhesion and prolonged residence time. These systems are especially useful for treating infections or delivering hormones while minimizing systemic side effects. Thermosensitive and pH-sensitive gels have been formulated for drugs like clotrimazole, progesterone, and metronidazole.[22]

5. Parenteral (Injectable) Systems

Injectable in situ gels are used for sustained systemic or local drug release. After injection, the sol transitions into a gel depot at the site of administration, enabling prolonged drug

release. Biodegradable polymers such as PLGA, poloxamer, and chitosan are widely used in formulations for proteins, peptides, anti-inflammatory agents, and anticancer drugs.[23]

ADVANTAGES AND DISADVANTAGES OF IN SITU GELS

In situ gel systems provide numerous benefits for controlled and localized drug delivery, but certain formulation and physiological challenges must also be considered.

Advantages[24,25]

- **Prolonged Drug Release**: These systems maintain the drug at the site of administration for an extended period, allowing for sustained and controlled drug delivery
- **Improved Bioavailability**: Increased retention time at mucosal sites enhances drug absorption and therapeutic efficacy.
- **Convenient Administration**: The sol–gel transition enables easy administration as a liquid that forms a gel in situ under physiological conditions.
- **Minimized Systemic Exposure**: Localized delivery helps reduce systemic side effects and improves site-specific action.
- **Patient Compliance**: Due to less frequent dosing and ease of use, in situ gels are generally well accepted by patients.

Disadvantages[26,27]

- **Environmental Sensitivity**: Gelation depends on stimuli such as pH, temperature, or ions, which can vary among individuals and affect reliability.
- **Formulation Complexity**: Development requires careful selection and optimization of polymers, triggers, and drug compatibility.
- **Drug Loading Limitations**: High polymer concentration may restrict the amount of drug that can be effectively incorporated.
- **Potential Irritation**: Some excipients or preservatives may cause tissue irritation, especially with ocular or nasal use.

EVALUATION PARAMETERS FOR IN SITU GEL FORMULATIONS

The evaluation of in situ gel formulations is crucial for ensuring that the final product meets the desired therapeutic outcomes, such as controlled drug release, ease of administration, and patient compliance. The following evaluation parameters are commonly employed to assess the quality and effectiveness of these formulations:

1. Clarity and Appearance

The clarity of the in-situ gel formulation is an important factor, especially for ocular, nasal, and injectable gels, as the presence of particulate matter or cloudiness may affect the patient's comfort and the product's acceptance. In ocular formulations, clarity is especially critical to avoid irritation or discomfort upon application. A clear, transparent formulation indicates that the active pharmaceutical ingredient (API) and excipients are well-solubilized and homogeneous, ensuring consistent performance. This is typically observed visually, and any precipitates or turbidity should be noted as they may suggest instability or improper formulation.[28]

2. pH Measurement

The pH of in situ gel formulations plays a significant role in their performance, especially for formulations intended for mucosal or ocular administration. The pH should be compatible with the physiological conditions of the site of administration. For example, ocular formulations should ideally have a pH range of 6.5–7.5 to match the natural pH of the eye (around 7.4), which helps prevent irritation. If the pH deviates significantly, it can cause discomfort, mucosal irritation, or reduced drug bioavailability. The pH of the formulation is measured using a pH meter or pH indicator strips to ensure it falls within the acceptable range for the intended application.[29]

3. Gelling Capacity and Gelation Time

One of the most critical evaluation parameters for in situ gels is their gelling capacity, which is the ability of the formulation to transition from a liquid to a gel state under physiological conditions (such as changes in temperature, pH, or ion concentration). This property is important for ensuring prolonged drug residence at the site of action.

The gelation time is the time it takes for the sol to undergo gelation after application or exposure to physiological conditions. This is typically tested by placing the formulation in an environment simulating the body's conditions (e.g., 37°C for temperature-sensitive systems or pH 7.4 for pH-sensitive systems) and observing the time taken for the gelation process to occur. The gelation should occur rapidly enough to ensure quick drug release and long enough to maintain residence time at the site of action.[30]

4. Viscosity and Rheological Behavior

Viscosity plays a key role in the performance of in situ gel formulations. It affects both the ease of administration (e.g., spreading or ease of injection) and the release of the drug from the gel. Rheological studies provide a detailed understanding of the flow behavior of the gel, which is crucial for its functionality. Ideally, in situ gels should exhibit pseudoplastic or shear-thinning behavior, meaning that the viscosity decreases under shear stress (such as during blinking in ocular applications or swallowing for oral gels). This allows the gel to flow easily upon administration and then return to a thicker gel state at the site of application for sustained drug release. Viscosity is typically measured using a Brookfield viscometer or a rotational viscometer, and flow behavior can be analyzed using the Herschel-Bulkley model or other rheological equations.[30]

5. Drug Content Uniformity

To ensure that the in-situ gel formulation delivers a consistent and accurate dose of the drug, drug content uniformity is evaluated. This test involves determining the uniform distribution of the drug throughout the gel, ensuring that each dose administered provides the correct amount of active pharmaceutical ingredient (API). Drug content can be measured using UV spectrophotometry, HPLC (High-Performance Liquid Chromatography), or HPTLC (High-Performance Thin-Layer Chromatography). These methods provide an accurate measurement of drug concentration and confirm the uniformity of the formulation.[31]

6. In Vitro Drug Release Studies

In vitro drug release studies are essential for understanding the release kinetics and ensuring that the formulation provides sustained drug delivery over time. These studies simulate the physiological environment using Franz diffusion cells, dialysis membranes, or modified USP dissolution apparatus to evaluate how the drug is released from the gel matrix. The release profile is typically studied under conditions that mimic the biological environment (e.g., pH 7.4 for ocular and nasal gels). Various models, such as zero-order kinetics, first-order kinetics, or Higuchi model, are used to analyze the drug release rate and determine whether the release follows a controlled, sustained pattern.[31]

7. Sterility (for Ocular/Injectable Gels)

For ophthalmic and injectable in situ gels, sterility is a critical parameter. Any microbial contamination in these products can lead to serious complications, such as infection or inflammation. Therefore, sterility testing is mandatory and is usually performed following the

guidelines provided by USP or BP. This test ensures that no viable microorganisms are present in the formulation. Bacterial endotoxins and pyrogenicity tests may also be conducted to ensure the formulation does not induce an immune response upon administration.[29]

8. Stability Studies

Stability studies are conducted to assess the long-term physical, chemical, and microbiological stability of in situ gel formulations. These studies simulate real-life storage conditions, including accelerated stability testing at higher temperatures (e.g., 40°C or 45°C) and long-term stability testing at controlled conditions (e.g., 25°C or 30°C). Parameters such as gel appearance, pH, viscosity, drug content, and drug release profiles are monitored over time. Stability testing helps predict the shelf life of the product and provides insight into the appropriate storage conditions required to maintain the formulation's integrity and performance.[30]

RECENT ADVANCES IN IN SITU GEL FORMULATIONS

In recent years, in situ gel formulations have gained significant attention due to their ability to provide controlled, sustained, and targeted drug release. Advancements in materials, techniques, and applications have enhanced the versatility and effectiveness of in situ gels. Below are some of the key recent innovations in the field:

1. Development of New Polymers

Advances in the development of novel polymers have expanded the range of stimuli-responsive in situ gels. For instance, biodegradable polymers such as poly(lactic-co-glycolic acid) (PLGA), chitosan, and gelatin are increasingly being explored for their ability to degrade safely in the body while providing controlled release of drugs. These polymers are particularly useful in applications like ocular, nasal, and parenteral delivery, where safety and biocompatibility are paramount. Recent work has focused on enhancing the mechanical properties and drug release profiles of these polymers to extend their applications.[32]

2. Nanotechnology Integration

The integration of nanotechnology with in situ gel systems has resulted in significant improvements in drug delivery efficiency. Nanoparticles, such as liposomes, nanospheres, and nanosuspensions, have been incorporated into in situ gels to improve drug solubility, stability, and bioavailability. Additionally, nanoparticles offer the advantage of increasing the gel's penetration ability at the site of action, particularly in ocular and skin delivery systems.

This combination also enhances the controlled release of drugs by encapsulating the drug in the nanoparticles, which gradually release the drug over time once the gel forms in situ.[33]

3. Advanced Drug Release Kinetics

Recent research has focused on fine-tuning the drug release kinetics of in situ gels. By modifying the polymer concentration, cross-linking density, and the type of solvent used, researchers have developed formulations that release drugs in a zero-order, Higuchi, or first-order manner, depending on the therapeutic needs. This enables more precise control over the release profile, which is especially important for drugs with narrow therapeutic windows. For example, the development of thermoresponsive gels based on poloxamers and Pluronic® has led to gels that undergo rapid gelation at body temperature, resulting in sustained release over extended periods.[34]

4. Targeted Drug Delivery Systems

Targeted drug delivery is one of the most exciting applications of in situ gels. Advances in ligand-receptor interactions and nanoparticle targeting have enabled the development of gels that release drugs specifically at targeted sites, such as tumors or inflamed tissues. Mucoadhesive polymers are now being used to enhance the retention time of in situ gels on mucosal surfaces, such as the nasal or ocular mucosa. Additionally, stimuli-responsive gels can release drugs in response to specific environmental triggers, such as pH, temperature, or ionic strength, thus providing an intelligent drug delivery system.[35]

5. Smart and Multifunctional In Situ Gels

The concept of "smart" or multifunctional in situ gels has emerged, wherein the gel not only provides controlled drug release but also incorporates additional functions like antimicrobial properties, anti-inflammatory effects, or tissue regeneration. For example, chitosan-based gels have been combined with antibiotics for enhanced wound healing, while hydrogel systems containing growth factors have been developed for tissue engineering applications. The multifunctionality of these gels provides therapeutic benefits beyond just drug delivery.[36]

6. In Vivo Applications and Clinical Trials

Recent advances in the in vivo applications of in situ gels have led to promising results in clinical trials. For instance, ocular in situ gels for the sustained release of drugs like latanoprost and timolol have been tested, showing improved patient compliance and

therapeutic efficacy. Nasal gels for the delivery of vaccines and biologics have also demonstrated enhanced stability and mucosal absorption in clinical studies. Moreover, injectable in situ gels for cancer therapy are under investigation, aiming to provide localized drug release directly at the tumor site, minimizing systemic side effects.[37]

CHALLENGES AND FUTURE PERSPECTIVES

Despite the promising advantages of in situ gel drug delivery systems, several challenges remain that must be addressed for their broader clinical translation and commercialization. Additionally, ongoing research continues to explore new directions to enhance their performance and applicability.

A. Challenges

1. Formulation Complexity

Designing an in situ gel formulation requires careful selection of stimuli-responsive polymers and excipients to ensure precise sol–gel transition under physiological conditions. Achieving the desired gelation temperature, pH sensitivity, and ionic responsiveness while maintaining drug stability and bioavailability can be complex. Additionally, ensuring batch-to-batch consistency in the gelling behavior is challenging during scale-up and manufacturing.[38]

2. Limited Drug Loading Capacity

Many polymers used in in situ gels have limited drug solubilization capacity, especially for poorly water-soluble drugs. This restricts the range of drugs that can be effectively delivered using these systems. Moreover, incorporating high drug loads may affect the rheological properties and gelling behavior of the formulation.[39]

3. Sterility and Microbial Stability

Sterility is particularly critical for ocular and parenteral in situ gels, and maintaining aseptic conditions throughout production and packaging processes is a major concern. In addition, biodegradable polymers may degrade over time, potentially impacting microbial stability and shelf-life unless appropriate preservatives are used.[40]

4. Regulatory and Standardization Issues

There is currently a lack of well-defined regulatory guidelines specific to in situ gels, which poses a challenge in obtaining approval from regulatory authorities. Furthermore, analytical

techniques for characterizing gelling behavior, drug release kinetics, and in vivo performance need standardization to ensure consistency across studies and manufacturers.[40]

B. Future Perspectives

1. Smart and Responsive Systems

The future of in situ gels lies in the development of "smart" or multi-responsive systems that can respond to multiple physiological triggers simultaneously, such as pH, temperature, and enzymatic activity. Such systems will offer site-specific and on-demand drug release, improving therapeutic outcomes and minimizing side effects.[41]

2. Personalized Drug Delivery

The integration of in situ gels with personalized medicine is a promising area. Tailoring the formulation to individual patients based on their physiological conditions, disease state, or genetic makeup could lead to precision-targeted therapies, especially in cancer, autoimmune, and ocular diseases.[41]

3. 3D Printing and Advanced Fabrication

Advanced 3D printing and microfabrication technologies offer new opportunities to create customized in situ gel-based implants and devices. These methods allow precise control over the shape, porosity, and drug distribution within the gel matrix, enabling next-generation implantable delivery systems.[42]

4. Integration with Nanomedicine

Combining in situ gel technology with nanoparticles, liposomes, and micelles can overcome solubility and targeting limitations. Future research is expected to focus on multi-layered or composite gels with embedded nanocarriers for enhanced drug penetration, stability, and targeted delivery, especially in cancer and brain-related therapies.[42]

5. Clinical Translation and Commercialization

For successful clinical translation, further research is needed on in vivo pharmacokinetics, toxicity profiling, and long-term stability. Collaboration between academia, industry, and regulatory bodies will be essential to streamline the development pipeline and bring more in situ gel products to market.

CONCLUSION

In situ gel drug delivery systems represent a significant advancement in pharmaceutical science, addressing the limitations of conventional delivery methods through their unique ability to transition from liquid to gel upon administration. Their application across various routes, coupled with sustained drug release and improved patient compliance, underscores their clinical potential. The integration of novel polymers and nanocarrier technologies has further expanded their scope and effectiveness. However, for these systems to reach their full potential, challenges such as toxicity, scalability, and regulatory approval must be systematically addressed. Future research should focus on the development of smart, biodegradable, and multi-stimuli-responsive polymers, as well as personalized in situ gel systems tailored to individual patient needs. With continued innovation and optimization, in situ gels are poised to become a cornerstone in next-generation drug delivery platforms.

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