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Review Article

Next-Generation Topical Delivery: The Rise of In Situ Gelling Systems

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ABSTRACT

In situ gelling systems are advanced drug delivery technologies that transform from a liquid to a gel form upon administration, offering significant advantages in the controlled release of therapeutic agents. These systems are typically triggered by environmental factors such as temperature, pH, or ion concentrations, enabling targeted drug delivery with improved therapeutic outcomes. Temperature-sensitive in situ gels, for example, remain in a low-viscosity state at cooler temperatures but transition into a gel at physiological temperatures, ensuring sustained drug release at the site of action. Similarly, pH-sensitive and ion-sensitive systems use physiological changes in pH or ion concentration to induce gelation, enhancing site-specific drug delivery. Incorporating excipients like mucoadhesive polymers, co-solvents, and salts into these systems further refines their performance, optimizing drug retention and minimizing side effects. Rheological characterization techniques, including oscillatory rheometry, differential scanning calorimetry (DSC), and small-angle scattering methods, provide insights into the gelation mechanisms, allowing for precise control over the gel's properties. These advancements have expanded the potential of in situ gels across various therapeutic applications, including buccal, ocular, nasal, vaginal, cervical, and intravesical drug delivery. Notably, in situ gelling systems have demonstrated promising results in treating conditions such as oral mucositis, periodontitis, glaucoma, rhinosinusitis, and cancers like cervical and bladder cancer. By offering enhanced drug bioavailability, prolonged retention, and minimal systemic absorption, these systems improve patient compliance and therapeutic efficacy. This review explores recent developments in in situ gelling systems, their mechanisms, and diverse applications, highlighting their role in advancing precision medicine and improving patient care across a wide range of medical conditions.

INTRODUCTION

In situ gelling systems are liquid formulations that transform into gel-like structures once

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administered through injection or topical application. Over the past two decades, these systems have gained considerable attention for their potential as responsive drug delivery platforms in pharmaceutical and biomedical applications. Compared to traditional depot delivery methods, such as implants or wafers, in situ gelling systems are preferred due to their simpler preparation, lower manufacturing costs, and the ability to be injected with smaller gauge needles. Moreover, they can be self-administered using autoregulators, providing greater convenience to patients. These systems also offer the ability to control the release of the therapeutic agents they carry, thus minimizing dosing frequency and reducing the risk of therapeutic failure or side effects. In the context of topical applications, in situ gelling systems are especially beneficial since they remain in a low-viscosity state at ambient temperatures, making them easy to apply (e.g., via spraying). Once applied, the formulation transforms into a gel that ensures prolonged retention and controlled delivery at the target site.

The sol-gel phase transition in these systems is typically triggered by various external factors, such as pH changes, temperature fluctuations, solvent exchanges, UV light exposure, or the presence of specific ions or molecules. While polymer-based systems are the most common, inorganic and small organic systems are also gaining attention in this field. The gelation process in polymer systems is influenced by parameters such as the polymer's molecular weight (MW), its structural architecture, and the temperature, pH, and ionic composition of the physiological environment. This review specifically focuses on temperature-sensitive, ion-sensitive, and pH-sensitive polymer systems, which are particularly suitable for drug delivery. Significant progress has been made over the last decade in the development of methods for effectively measuring the rheological properties of in situ gelling systems. Traditional techniques, including vial inversion and viscometry at physiological temperatures (ranging from 35–37°C) and appropriate ionic strength and pH, remain in common use. However, more sophisticated methods, such as oscillatory rheometry, are increasingly employed in combination with characterization tools like differential scanning calorimetry (DSC), small-angle neutron scattering (SANS), and small-angle X-ray scattering (SAXS), providing valuable insights into the complex behaviors of these systems.

Typically, in situ gelation is achieved using a single polymer; however, incorporating excipients can enable precise control over the gel's properties and can introduce secondary effects that enhance the overall performance of the system. For example, the addition of biocompatible mucoadhesive polymers can significantly improve the retention of the dosage form on mucosal surfaces, thereby extending the drug's residence time and enhancing therapeutic efficacy. Some common mucoadhesive polymers used in these systems include carbopol 934P, chitosan, sodium carboxymethyl cellulose, hydroxypropyl methylcellulose (HPMC), hydroxypropyl cellulose, and methyl cellulose. Additionally, other additives such as co-solvents, dispersed phases, and salts can be used to fine-tune the rheological properties of the formulation in both its sol and gel states. For example, in situ gelling formulations can be designed to exhibit pseudoplastic behavior, which not only stabilizes dispersed phases but also facilitates easy removal of the formulation from its container when subjected to shear forces.

Recent reviews have explored the use of in situ gelling or nanoparticulate gel formulations for

drug delivery via buccal, ocular, nasal, and vaginal routes. However, there has been limited coverage of in situ gelling systems for cervical cavity drug delivery or their rheological properties in non-parenteral applications. This review aims to update the current state-of-the-art in this field, with a particular focus on the fundamental rheological considerations of in situ gelators. Although solid in situ gelling polymeric films, gastrointestinal in situ gelling formulations, and thermoresponsive emulsions are important research areas, they are not addressed in this article due to the distinct nature of their phase transition behaviors. The objective of this review is to provide a comprehensive update on the latest advancements in in situ gelling delivery systems and to examine the different types of in situ gelling systems in detail. It will also discuss both traditional and advanced techniques for assessing the rheological and nanoscale behavior of these systems.

2. Classes of In Situ Gelling Systems

In situ gelling systems are generally classified based on three primary types of stimuli: temperature sensitivity, ion sensitivity, and pH sensitivity. Although other stimuli such as light or redox potential can be utilized, they are less frequently employed in pharmaceutical applications and are not included in this review. Additionally, some systems may form gels by mixing reagents, which causes covalent gelation upon application; however, such systems are not covered here. [21]

2.1. Temperature-Sensitive Systems

Thermosensitive in situ gelling systems typically exist as single-phase, sol-like solutions in an aqueous medium at temperatures below the lower critical solution temperature (LCST). When the temperature exceeds the LCST, unfavorable entropy of mixing occurs, leading to stronger hydrophobic interactions and rapid dehydration of the solvated polymer chains. This change results in polymer-polymer interactions, triggering a transition from sol to gel. These systems exhibit thermoreversible properties, meaning they revert to a sol form when cooled below the LCST. However, not all polymers that exhibit LCST behavior form gels. For example, poly(N-isopropyl acrylamide) homopolymers tend to transition into a cloudy globular state when heated, rather than forming a gel.[22]

To create thermoreversible gelators, copolymers are typically synthesized by combining a hydrophilic co-monomer with the LCST species. One example is poly(ethylene oxide)-b-poly(propylene oxide)-b-poly(ethylene oxide), known as poloxamers, which are amphiphilic copolymers. At concentrations above their critical micelle concentration (CMC), these polymers can form micelles in water, and upon heating, the micelles reorganize into a more structured form, leading to gelation. The temperature at which gelation occurs is known as the gelation temperature (Tgel) and may vary depending on the gel formation mechanism and polymer composition.[23]

Evaluating the rheological properties of thermoreversible gels can be challenging. The storage modulus (G′) and loss modulus (G″) are the primary rheological terms used to describe the material's elasticity and viscosity. Elastic materials recover their structure after deformation, while viscous materials resist flow without recovery. Temperature ramp and time sweep tests are often used to determine gelation temperature and gelation time. During these tests, samples are expected to remain in a low-viscosity state (≤25°C) for easy syringeability. Once injected, the formulation gradually transforms into a gel state at physiological temperature, allowing the drug to

stay at the site of administration, enhancing cellular drug uptake.[24]

In temperature ramp analysis, samples are placed on a rheometer plate, which is gradually heated to simulate physiological conditions. For ocular and intravesical drug delivery, the plate is heated to temperatures of around 35°C and 37°C, respectively. The gelation temperature is typically identified as the point where the sample transitions from "liquid-like" (G″ > G′) to "solid-like" (G′ > G″). In some cases, gelation is indicated by an increase in G′ relative to G″, even if there is no direct crossover. However, some researchers suggest that the crossover point may not perfectly represent gelation temperature when frequencies are varied.[25]

Typically, gels display solid-like mechanical properties, where G′ exceeds G″ across the evaluated frequency range, particularly at low amplitude. Some materials, however, may display Maxwell-type behavior, where G″ exceeds G′ at low frequencies, suggesting liquid-like properties, but as the frequency increases, G′ surpasses G″, reflecting the emergence of elastic interactions under shear stress. This distinction is significant because Maxwell materials may act like liquids under long-term storage, but become more elastic during shear-induced stress.[26]

In situ gelling formulations with gelation temperatures above 37°C are generally unsuitable for transmucosal drug delivery in humans, as they may remain in a liquid state at physiological temperatures. This would lead to dilution by biological fluids and wash-off, resulting in reduced therapeutic efficacy.[27]

Examples of temperature-sensitive drug delivery systems include chitosan/beta-glycerophosphate systems, poloxamers, and poly(N,N-diethyl acrylamide)-b-poly(ethylene glycol)-b-poly(N,N-diethyl acrylamide).[28]

2.2. Ion-Sensitive Systems

Ion-sensitive in situ gelling systems are formulated with polymers that contain ionizable groups. When exposed to physiological fluids such as saliva, tears, and nasal fluid, these polymers undergo gelation by interacting with monovalent (e.g., Na+) or divalent (e.g., Mg^{2+}, Ca^{2+}) cations. The interaction between oppositely charged ions in the drug carrier and biological fluids induces the sol-to-gel transition. The type and concentration of cations involved in cross-linking the polymers influence both the viscosity of the gel and the rate of gelation. Additionally, changes in the ionic strength and composition of the target site, particularly in pathological conditions, can further enhance the gelation process [29].

The gelation behavior of ion-sensitive systems can be evaluated by mixing simulated biological fluids with the in situ gelling formulation and monitoring the changes in rheological properties using viscometry or turbidimetric analysis. Common ion-sensitive polymers include pectin, sodium alginate, gellan gum, and methacrylated gellan gum [30].

For instance, gellan gum, an anionic polysaccharide, undergoes gelation through interactions with cations and hydrogen bonding with water. This leads to the formation of double-helical junction zones and the establishment of a three-dimensional gel network. Clay-based gels have also been shown to exhibit ion-induced gelation behavior [31].

2.3. pH-Sensitive Systems

The gelation behavior of pH-sensitive formulations depends on the polymer's pKa value.

Polymers with weakly acidic or weakly basic functional groups typically undergo gelation when exposed to pH levels lower or higher than their pKa values, respectively. Changes in the pH of the surrounding environment can alter the polymer's ionization state, conformation, and solubility, ultimately triggering gelation [32].

pH-sensitive polymers often have weakly acidic or basic groups on their backbone. For example, polymers with weakly acidic groups, such as poly(methacrylic acid), become deprotonated at alkaline pH (above their pKa values), acquiring a negative charge. This results in electrostatic repulsion between polymer molecules, which may induce gelation. In contrast, when the pH is lower than the pKa, hydrogen bonding between polymer chains can occur, leading to gel formation. For weakly basic groups like amines, protonation at acidic pH (below their pKa) results in a charged state, which behaves oppositely to weakly acidic systems [33].

Some pH-responsive systems are designed by exploiting chemical reactions that are pH-dependent, resulting in covalent bonding between polymer chains and inducing gel formation. Examples of pH-sensitive formulations include Carbopol 934-based nasal gels that gel at a nasal pH of around 8.3, polyacrylic acid systems for the colonic delivery of 5-aminosalicylic acid, and xanthan-based gels used for controlled release of bovine serum albumin at physiological pH [34].

In conclusion, in situ gelling systems are versatile and efficient drug delivery platforms that can respond to various external stimuli such as temperature, ions, and pH. These systems provide significant advantages, including enhanced drug retention, controlled release, and ease of administration. As research continues to advance in this field, the potential applications of in situ gelling systems in drug delivery will only expand further [35].

3. Bioactive Agent-Containing in Situ Gelling Delivery Studies

Various in situ gelling systems have been explored for targeted drug delivery to a range of body sites, including the buccal, ocular, nasal, vaginal, cervical, intravesical, and intraperitoneal areas. The rheological properties and clinical outcomes from studies on these gelling systems over the past decade are summarized in Table 2, which will be further discussed in the sections to follow [36].

3.1. Buccal Formulations

Mucoadhesive in situ gelling delivery systems have been effectively utilized to deliver therapeutic agents to the buccal mucosa within the oral cavity, addressing conditions like oral mucositis and esophagitis. These conditions are commonly experienced by head and neck cancer patients undergoing chemotherapy or radiation therapy [37].

One of the key polymers used for buccal dosage forms is K-carrageenan, which is a thermosensitive and ion-responsive copolymer made from the sulfated ester of galactose and 3,6-anhydrogalactose. It has one negative charge per disaccharide unit and is known for its antioxidant and anti-inflammatory properties [38]. K-carrageenan undergoes a sol-to-gel transition when exposed to elevated temperatures and ions such as K^+, Na^+, Mg^{2+}, and Ca^{2+}. This transition occurs as the polymer changes from a coil structure to a helix, followed by aggregation of the helixes [39].

Vigani and colleagues developed in situ gelling formulations containing 0.2% Hibiscus sabdariffa extract (HSE) combined with 0.04% calcium

chloride, 0.4% or 0.6% K-carrageenan, and 1% hydroxypropyl cellulose (HPC). They evaluated the rheological properties of these formulations using a rheometer [40]. K-carrageenan facilitated gelation in the presence of saliva ions and calcium chloride, while HPC contributed to enhancing the mucoadhesive properties of the formulation.

Normalized rheological synergism values for the 0.4% HSE and 0.6% HSE formulations were 1.44 ± 0.9 and 1.19 ± 0.06, respectively, indicating that both formulations exhibited similar interactions with saliva ions. Increasing the concentration of the bioactive extract improved the gelation capacity, as indicated by reduced loss tangent values compared to the blank formulations. The inclusion of HSE also enhanced the formulation's compatibility with human dermal fibroblasts, promoting cell proliferation. Both HSE and HSE-containing formulations displayed comparable anti-inflammatory effects in terms of interleukin-8 release after cell treatment. Based on these findings, the formulation containing 0.6% HSE was identified as the more promising candidate for oral mucositis treatment due to its favorable rheological and biological properties [41].

For periodontitis, a common inflammatory condition of the periodontal tissues, Kassem and colleagues incorporated meloxicam (an anti-inflammatory agent) and minocycline hydrochloride (an antimicrobial agent) into poloxamer-based thermosensitive gels (35% w/v) or carbopol (1%) / HPMC (2.5%) pH-sensitive gels. These formulations were evaluated for their potential in treating periodontitis [42]. The poloxamer-based gels were preferred since they maintained the stability of both meloxicam and minocycline HCl.

In the case of the poloxamer formulation, meloxicam was released at a rate of 21.72% over the course of a week, while minocycline HCl was released more rapidly (85%) within three days. Additionally, the drug formulation was effective in reducing periodontal pocket depth, gingival inflammation, and alveolar bone density in periodontitis patients [43]. However, the authors did not report the viscosity or viscoelasticity data for the formulations. Upon visual examination, it was found that the Carbopol/HPMC gel systems were not suitable for minocycline delivery, as the formulation liquefied and caused drug precipitation. This likely occurred due to the positive charge and acidic nature of minocycline, which may have disrupted the electrostatic repulsion between ionized carboxyl groups, thus lowering the pH and preventing gel formation[44].

Recently, a composite system involving moxifloxacin HCl-loaded PLGA/PVA nanoparticles combined with a poloxamer-based thermosensitive gel was tested for periodontitis treatment [45]. The optimized nanoparticle formulation had a particle size of 288 nm, an 81% drug entrapment efficiency, and a biphasic drug release profile. The composite system displayed a gelation temperature of 37°C, gel strength of 108 g, and bioadhesive strength of 12 g, making it ideal for prolonged retention in the periodontal tissues. The inclusion of nanoparticles reduced the burst release effect [46]. In vivo histopathological studies indicated that treatment of diseased periodontal tissues with this new composite system for one week was more effective than using the marketed moxifloxacin gel formulation for three weeks [47].

These findings demonstrate the effectiveness of in situ gelling systems for delivering bioactive agents to buccal mucosa and periodontal tissues, offering promising outcomes for conditions such as oral mucositis, periodontitis, and inflammation [48].

3.2. Ocular Formulations

A significant number of ophthalmic in situ gelling systems have been developed for the management of glaucoma, a serious eye disorder that can lead to permanent vision loss or blindness . Typically, glaucoma is treated with frequent medication, surgery, or laser therapy. The primary medications used to control glaucoma include beta-blockers (like timolol and betaxolol), cholinergic agonists (such as pilocarpine), α2-agonists (like brimonidine), and carbonic anhydrase inhibitors (such as brinzolamide) [48]. Carbonic anhydrase inhibitors are usually prescribed for patients who are resistant to beta-blockers or when beta-blockers are contraindicated due to other health conditions.

Topical liquid eye formulations are engineered to convert into a gel when applied to the conjunctival sac, enabling a controlled release of the drug. This approach provides sustained therapeutic effects and reduces the need for frequent drug administration, enhancing patient compliance.

For instance, pilocarpine was incorporated into a thermosensitive gelatin-graft-poly(N-isopropylacrylamide) (PNIPAAm) gel to enhance its ocular residence time and bioavailability [9]. Rheological tests conducted via differential scanning calorimetry (DSC) revealed the lower critical solution temperature (LCST) of the formulation. This was studied by heating the graft copolymer formulation from 25°C to 45°C at a rate of 3°C/min, while monitoring its rheological behavior.

The three formulations studied in the research—G-M/N005, G-M/N025, and G-M/N125—were designed with varying molar ratios of mercaptoacetic acid (MAA) to N-isopropylacrylamide (NIPAAm), showing LCSTs of 31.4 ± 0.2°C, 32.7 ± 0.1°C, and 33.0 ± 0.1°C, respectively. These results indicate that increasing the molecular weight of the polymer improves the temperature at which the gelation occurs [49]. During a 14-day drug release study at 34°C, G-M/N005 released 36.0 µg/mL of pilocarpine, whereas G-M/N025 and G-M/N125 released only about 5 µg/mL. All formulations showed good biocompatibility, as evidenced by BCE CID-Ib cytotoxicity tests. The study concluded that the MAA/NIPAAm ratio plays a crucial role in modulating the physical and biological characteristics of the formulations, with G-M/N005 emerging as a promising formulation for glaucoma treatment [50].

In a subsequent experiment, the gelatin was replaced with chitosan to create a chitosan-g-poly(N-isopropylacrylamide) (CHI-PNIPAAm) formulation to enhance pilocarpine release and improve ocular drug absorption. Two formulations, CHI-PNIPAAm 10 and CHI-PNIPAAm 20, were prepared using 10 g and 20 g of carboxylic end-capped PNIPAAm, respectively. The LCSTs for these formulations were 31.9 ± 0.2°C and 29.5 ± 0.3°C, showing that the number of PNIPAAm chains grafted onto chitosan influenced the gelation temperature. Biocompatibility tests revealed no significant differences between the formulations in terms of cell viability. The CHI-PNIPAAm 20 formulation exhibited delayed degradation, leading to sustained pilocarpine release over 42 days and reduced intraocular pressure in glaucomatous rabbits. These findings suggest that this formulation could be a viable option for glaucoma treatment.

The clinical application of the commercial brinzolamide suspension (Azopt®) for glaucoma treatment is often limited due to its high cost and poor retention in the precorneal space after instillation, resulting in a low bioavailability of about 10%, which requires frequent dosing and contributes to poor patient compliance [51]. To

address this, Li and colleagues incorporated brinzolamide into an ion exchange resin and combined it with Poloxamer F127/Carbopol 934P-based mucoadhesive thermosensitive gels to improve its retention in the aqueous humor [48]. DSC was used to evaluate the gelation temperature, and the gelation time was assessed by measuring when the in-situ gelling formulation ceased to flow after mixing with a magnetic stir bar. Viscometric analysis was performed at 25°C and 35°C under different shear rates (6–60 rpm) to understand how temperature and shear stress impacted the rheological properties of the formulation. The optimized formulation contained 22% poloxamer, and its gelation properties were not significantly altered by STF dilution [52].

The new formulation released 80% of brinzolamide into artificial tears over 8 hours, compared to only 2 hours for conventional eye drops, indicating a more sustained drug release [48]. Similarly, Bhalerao and colleagues investigated the gelation potential of brinzolamide-loaded gellan gum-based ion-sensitive formulations using viscometry and vial inversion methods [49]. At 25°C, the intrinsic viscosity of the formulations was 19 cPs, which increased to 90 cPs at 35°C. As the concentration of gellan gum increased, the gelation time decreased, with the formulation containing 0.25% gellan gum reducing intraocular pressure in rabbits from 25-28 mmHg to 12-14 mmHg. This formulation also exhibited a longer ocular residence time compared to commercial brinzolamide suspensions, making it a promising alternative for glaucoma treatment [53].

The formulation of betaxolol hydrochloride in P407/P188/polycarbophil (PCP)-based thermosensitive gels was studied by Huang and colleagues [11]. The optimized formulation, consisting of P407 (22% w/v), P188 (3.5%), and polycarbophil (0.2%), was evaluated for its in-situ gelling potential before and after STF dilution using a viscometer. The gelation temperature was approximately 34°C without STF and 26°C with STF. This formulation maintained its gelation capacity and rheological properties even after dilution with STF. The drug release from this formulation was nearly 100% within 2-8 hours, showing a sustained release profile compared to commercial betaxolol formulations. Furthermore, the new formulation provided more effective intraocular pressure reduction in glaucomatous rabbits than the commercial drug, suggesting its potential for better management of glaucoma [54].

Agibayeva and colleagues synthesized three types of methacrylated gellan gum (LMeGG, MMeGG, and HMeGG) with varying degrees of methacrylation to compare their properties with unmodified gellan gum [55]. Using dynamic light scattering, they observed the formation of highly polydisperse aggregates in both gellan gum and its methacrylated versions. Methacrylation increased the aggregation potential, particularly at higher polymer concentrations and acidic pH, likely due to the suppression of carboxyl group ionization. Mucoadhesive testing demonstrated that the methacrylated versions, particularly LMeGG, showed enhanced mucoadhesiveness and retention at the conjunctiva in vivo, suggesting that these formulations could provide effective drug delivery for ocular treatments [56].

Additionally, incorporating drug-loaded nanoparticles into in situ gels has shown promising results for sustained drug release and improved therapeutic outcomes. Wen and colleagues prepared dexamethasone nanoparticles combined with P407/P188-based thermosensitive gels to enhance drug solubility and ocular bioavailability [57]. Rheological studies showed that the gelation temperatures of the formulations were 32.7°C for

the in situ gel and 34.3°C for the nanoparticle-loaded gel, both below the physiological temperature of 37°C. These formulations exhibited significantly improved corneal permeability, with the nanoparticle formulation showing the highest permeability, suggesting its potential to act as a prolonged drug reservoir for dexamethasone [58].

These studies highlight the potential of in situ gelling systems in ophthalmic drug delivery, with improved ocular drug retention, sustained release, and enhanced therapeutic efficacy, particularly for glaucoma and other ocular conditions [59].

3.3. Nasal Formulations

The nasal route has proven to be effective for delivering a variety of therapeutic agents, including both small molecules and large biological macromolecules such as proteins, peptides, and vaccines. Common conditions treated with nasal formulations include allergic rhinitis, sinusitis, nasal lesions, and rhino-sinusitis [64]. Additionally, the nasal route offers an advantage for drug delivery to the brain, as the highly vascularized nasal mucosa facilitates the absorption of drugs via the olfactory neuroepithelium [60].

One example of an advanced nasal formulation is the composite system composed of dexamethasone-loaded lipid/alginate nanoparticles combined with pectin-based in situ gels, designed for treating chronic rhinosinusitis. The in situ gel forms in the presence of calcium ions found in the nasal mucosa. The rheological properties of these formulations were evaluated using rheometry, revealing that the rheological characteristics of the pectin gel, both with and without dexamethasone-loaded nanoparticles, were similar. However, the loss and storage moduli of the pectin gel were slightly lower than those of the drug-loaded nanoparticle gel. This was likely due to the electrostatic repulsion between the negatively charged pectin and alginate components, which reduced the viscoelasticity of the composite gel system. The drug release profile showed that the nanoparticle-based gel formulation released 50% of the drug over 2.1 hours, a slower rate compared to the 1.7 hours for drug nanoparticles and 0.6 hours for free drug, indicating the formulation's superior ability to control drug release [61].

Another nasal formulation developed by Nizic and colleagues involved a sprayable fluticasone-loaded in situ gel composed of sodium hyaluronate, pectin, and gellan gum. In this formulation, sodium hyaluronate acted as both the structuring agent and the bioactive component, while Tween 80 was used as a suspending agent. The rheological properties and gelation potential of this system were assessed, and satisfactory weak gels formed immediately after mixing the formulation with simulant nasal fluid in a 1:1 ratio. The gel maintained a storage modulus greater than the loss modulus throughout the study, indicating stability. The optimized formulation, containing 0.05% fluticasone, 0.03% Tween 80, 0.7% pectin, and 0.05% sodium hyaluronate, was administered at a 45° angle from the horizontal plane, with an inspiratory flow of 30 L/min. This formulation exhibited a zero-shear viscosity of 11.16 ± 0.10 mPas, which enhanced the stability of the drug suspension, resulted in a narrower spray cone angle, better turbinate deposition, and reduced the chances of premature drug deposition in the anterior nasal cavity [62].

In a separate study, Gholizadeh and colleagues investigated a sprayable tranexamic acid nasal formulation based on chitosan and beta-glycerophosphate for treating nasal wounds. The formulation's gelation tendency and viscoelastic

properties were evaluated using water bath-based tube inversion and rheological testing. The optimized formulation, which contained 2% w/v chitosan and 49% w/v beta-glycerophosphate in a 4:2.5 volume ratio, exhibited a gelation time of 5 minutes and a gelation temperature of 33°C, indicating its suitability for nasal drug delivery. Increasing the drug concentration from 0.1% w/v to 1% w/v resulted in faster gelation. When incubated at 37°C, the formulation's storage modulus increased significantly from 0.03 Pas to 168 Pas. Biocompatibility was confirmed through cytotoxicity testing on human nasal epithelial cells. This thermosensitive formulation accelerated wound closure within 3 hours, a result approximately six times faster than the control tranexamic acid solution, highlighting its clinical potential for treating epistaxis [63].

3.4. Vaginal Formulations

In situ gelling systems for vaginal administration are commonly used to deliver a variety of therapeutic agents including antimicrobials, hormones, spermicides, anti-inflammatory drugs, and anticancer agents, targeting both local and systemic therapeutic effects [64]. Ibrahim et al. evaluated the gelation behavior of thermosensitive formulations using viscometry and heated magnetic stirrer methods [65]. Their study demonstrated that a metronidazole-loaded Pluronic F127/F68 (20%/10%) thermosensitive in situ gel was biocompatible, with a gelation temperature of 28°C, viscosity of 2.22 × 10^5 mPas at 37°C, and a mean mucoadhesive force of 21.2 ± 1.4 × 10^2 (Ncm−2). The optimized formulation released 76% of metronidazole within six hours, compared to 91% from the marketed gel, indicating a sustained release profile. Additionally, one-week treatment using the new formulation resulted in an 85% bacterial vaginosis cure rate, compared with 71% for the marketed gel, suggesting improved therapeutic outcomes [66].

Rossi and colleagues explored vaginal mucositis therapy using amoxicillin trihydrate-loaded gels composed of P407/chitosan lactate (CHIL 1.6%/P407 15%) and glycerophosphate/chitosan lactate (CHIL 6%/GP 8%) [55]. Rheological assessments indicated that the addition of simulated vaginal fluid (SVF) did not alter the gelation temperature of CHILGP but decreased its storage modulus. Conversely, CHILP407 showed reduced gelation efficiency upon SVF addition. Overall, CHILGP demonstrated superior mucoadhesive properties, antimicrobial activity, and wound-healing potential compared to P407-based gels [67].

Probiotic-based vaginal gels have also been investigated due to their ability to produce hydrogen peroxide, bacteriocins, and organic acids, lowering vaginal pH and inhibiting pathogenic growth [56]. Lactobacillus gasseri-loaded thermosensitive gels composed of poloxamer 407 (P407), methyl cellulose (MC), pectin, and xyloglucan were developed to prevent vulvovaginal candidiasis recurrence. P407 and MC provided thermosensitive properties and facilitated gelation at 37°C, both alone and after dilution with SVF. Pectin contributed to appropriate pH, low viscosity, and enhanced syringeability, while xyloglucan (0.25% w/w) improved mucoadhesion and gelation after SVF dilution. Optimized formulations, with or without xyloglucan, maintained favorable rheological properties, preserved L. gasseri viability, were biocompatible in HeLa cell assays, and remained stable for up to three weeks at 4°C [68].

More recently, tenofovir disoproxil and progesterone-loaded thermoreversible gels based on sodium chloride/PDEA (20 kDa)-b-PEG (10 kDa)-b-PDEA (20 kDa) have been evaluated for

intravaginal drug delivery, aiming at HIV pre-exposure prophylaxis and luteal phase support [9]. Sodium chloride was added to reduce the intrinsic gelation temperature of the triblock copolymer (from 46°C). Rheological studies of the 30% w/w optimized formulation revealed a gelation temperature of 36°C, gelation time of 67 seconds, and yield stress of 862 Pa, suitable for topical applications requiring mechanical stability. SAXS data indicated that the PDEA-PEG-PDEA copolymer self-assembled into ellipsoidal structures at the lower critical solution temperature, enhancing viscoelasticity. Progesterone was fully released within 32 hours at 25°C and 144 hours at 37°C, demonstrating sustained release at physiological temperatures. Tenofovir disoproxil, being more hydrophilic, released 65% within eight hours, independent of temperature. The optimized formulation displayed mucoadhesion comparable to poloxamer 407 gels and was non-toxic to HaCaT cells [69].

PNIPAM-b-PEG-b-PNIPAM systems have also been studied for vaginal delivery of progesterone and tenofovir. Compared to poloxamer 407, these synthetic gels exhibit minimal dependence of gelation temperature on concentration, an advantage in fluid-rich vaginal environments. Poloxamer 407 gels, in contrast, show increased gelation temperatures upon dilution, which may cause gel-to-sol transitions in vivo [70]. Furthermore, PNIPAM-b-PEO-b-PNIPAM gels display greater resistance to dissolution than poloxamer 407 gels. This is attributed to PNIPAM's mechanism of forming spherical micelles that interact via polymer bridges, slowing dissolution, whereas poloxamer 407 requires a highly concentrated face-centered cubic phase to form a gel [71].

3.5. Cervical Formulations

Local drug delivery is considered an effective strategy for treating superficial cervical cancer by directly applying drug formulations through the vagina to the cervix using a catheter. However, for advanced cervical cancer cases, particularly those with metastatic or recurrent characteristics, systemic therapies might be necessary [72].

Xu et al. developed a composite system consisting of paclitaxel-loaded MPEG-PCL polymeric micelles and cisplatin-loaded PEG-PCL-PEG thermosensitive gel (PDMP) for the local treatment of advanced cervical cancer. The study found that the gelation temperature of both the triblock copolymer-based hydrogels and the composite system remained unaffected by the inclusion of nanoparticles, with the gelation temperature at approximately 30°C, which is favorable for physiological conditions. In vivo studies revealed that the composite system was effective in suppressing tumor progression and significantly extended the survival of tumor-bearing mice, achieving a survival rate of 55 days compared to 40 days for cisplatin hydrogels and 50 days for paclitaxel nanoparticles [73]. Histopathological analysis confirmed the biocompatibility of the PDMP system, showing no signs of organ toxicity.

In another study, a composite formulation containing toad venom-loaded solid lipid nanoparticles and nanorealgar powder combined with a poloxamer 188/P407 thermosensitive gel was investigated for its ability to improve the sustained release of drugs and reduce systemic side effects and vaginal irritation. The gelation potential of this composite formulation was evaluated using the tube inversion method at 37°C. The gelation temperature was found to be 33 ± 0.9°C, and the formulation maintained its gelation capacity after incorporating nanoparticles and nanorealgar powder [74]. The formulation was

stable for up to three months at 4°C and showed biocompatibility based on histological assessments of the rabbit vagina. Fluorescent tracking revealed that the formulation remained in the vaginal area of nude mice for 35 hours, indicating its potential for prolonged retention. This formulation offers improved patient compliance due to its controlled drug release, minimal vaginal irritation, and reduced dosing frequency.

3.6. Intravesical Formulations

A composite system of floatable doxorubicin-loaded human serum albumin nanoparticles combined with a poloxamer gel was studied for its potential use in bladder cancer treatment. The incorporation of nanoparticles into the gel did not affect the gelation properties of the system. The doxorubicin nanoparticle-based gel (NP-Dox-Gel) had a gelation temperature of 10°C and a gelation time of 2 minutes at 37°C. In contrast, doxorubicin-loaded nanoparticles in non-floating hydrogels had a higher gelation temperature and longer gelation time. The NP-Dox-Gel formulation showed resistance to washout during urine voiding, ensuring a sustained drug release profile, making it suitable for bladder cancer treatment [75].

In another study, DOTAP (a mucoadhesive polymeric excipient) was used to prepare a composite system of deguelin-loaded DOTAP and monomethoxyl poly(ethylene glycol)-polyε-caprolactone hybrid nanoparticles combined with Pluronic F127-based hydrogels for bladder cancer therapy [76]. This formulation exhibited syringeability at 25°C, forming a gel within 10 minutes of intravesical administration. The formulation remained in the bladder for about two hours, ensuring gradual drug elimination and sustained release, which enhances its therapeutic potential for bladder cancer treatment [77].

A study by Şenyigit et al. focused on the development of chitosan-thioglycolic acid conjugate (CHI-TGA) nanoparticles loaded with gemcitabine hydrochloride and incorporated into chitosan gel (CHI-TGA NPs/CHI) or poloxamer gel (CHI-TGA NPs/Plx gel) for improved intravesical bladder cancer treatment [78]. The poloxamer gel formulation showed superior syringeability compared to the chitosan-based gel formulations. The drug release from the poloxamer-based formulation demonstrated a sustained release profile over a 4-hour period, with a higher percentage of drug release compared to the chitosan-based formulations. The formulations were evaluated for urothelial mucosal drug permeation, with the thiolated chitosan-based delivery systems demonstrating better drug permeation to bladder cancer tissues. Histopathological evaluation confirmed the safety of the formulations, with no damage observed in the bladder tissues [79].

Kolawole et al. explored the syringeability, thermosensitivity, mucoadhesiveness, and drug release profiles of mitomycin-C-loaded chitosan/beta-glycerophosphate systems for potential intravesical bladder cancer treatment [80]. The molecular weight of chitosan was found to influence the syringeability, gelation, mucoadhesion, and drug release properties. The high molecular weight chitosan formulation (HCHIGP) exhibited the fastest gelation at 37°C and showed superior resistance to urine washout, making it the most promising formulation for intravesical drug delivery. After six hours, the release of mitomycin-C from the different formulations varied, with HCHIGP displaying the most sustained drug release [81].

Finally, rapamycin-loaded liposomes incorporated into poloxamer gels (R-CL/P407) were studied for bladder cancer treatment. The formulations

demonstrated similar gelation temperatures and times, with rapamycin released from the liposomal gel formulations at a constant rate, achieving 100% release within 12 hours. These liposomal formulations showed promise in bladder cancer treatment due to their sustained drug release profile [82].

CONCLUSION

In situ gelling systems have emerged as a highly versatile and efficient drug delivery platform, attracting significant attention in the fields of pharmaceutical and biomedical sciences. These systems, which transition from a liquid phase to a gel upon administration, offer numerous advantages over traditional drug delivery methods such as implants or wafers. The ability to control drug release, improve patient compliance, and simplify preparation processes are just a few of the compelling reasons why in situ gelling systems are being explored for a range of therapeutic applications. This review highlights the fundamental principles, mechanisms, and advancements of these systems, with a focus on temperature-sensitive, ion-sensitive, and pH-sensitive formulations.

One of the key advantages of in situ gelling systems is their ability to undergo a phase transition in response to external stimuli such as changes in temperature, pH, or the presence of specific ions. Temperature-sensitive systems, which are based on polymers exhibiting a lower critical solution temperature (LCST), can be designed to remain in a sol-like state at lower temperatures, making them easy to inject. Once injected into the body, the temperature rises, causing the polymer to transition into a gel. This thermoreversible behavior is particularly useful in drug delivery applications, as it allows for controlled release of therapeutic agents, reducing the frequency of administration and minimizing side effects.

Similarly, ion-sensitive systems exploit the presence of cations in biological fluids to trigger gelation. Polymers that contain ionizable groups interact with monovalent or divalent cations such as sodium (Na+), calcium (Ca2+), and magnesium (Mg2+) to form a gel network. The ionic strength and composition of the surrounding environment significantly influence the rate and extent of gelation, which can be tailored to optimize therapeutic outcomes. This feature is particularly advantageous for localized drug delivery, where sustained release at a specific site is essential for achieving therapeutic efficacy.

On the other hand, pH-sensitive systems rely on changes in pH to induce gelation. Polymers with weakly acidic or basic functional groups can undergo ionization or protonation in response to changes in the pH of the surrounding environment, leading to a conformational change that results in gel formation. pH-sensitive systems are particularly useful for targeted drug delivery to specific sites in the body, such as the gastrointestinal tract or vaginal mucosa, where the pH varies significantly between different regions. By tailoring the gelation behavior to match the pH conditions of the target site, these systems can achieve highly localized and sustained drug release, improving therapeutic outcomes.

The use of excipients in in situ gelling systems has further enhanced their versatility and performance. Excipients such as mucoadhesive polymers, co-solvents, and salts can be added to fine-tune the rheological properties of the formulation, improving its ability to adhere to mucosal surfaces, stabilize dispersed phases, and ensure proper gelation. Mucoadhesive polymers, for instance, can improve the retention time of the drug formulation on mucosal surfaces, ensuring that the

drug remains at the target site for a longer duration, thereby enhancing the therapeutic effect. The incorporation of such excipients allows for a high degree of control over the gelation process, offering the potential for tailored drug delivery systems that meet the specific needs of different patients and therapeutic indications.

The rheological properties of in situ gelling systems play a crucial role in determining their performance and effectiveness. Advanced techniques, such as oscillatory rheometry, differential scanning calorimetry (DSC), small-angle neutron scattering (SANS), and small-angle X-ray scattering (SAXS), have enabled researchers to gain a deeper understanding of the complex behaviors of these systems. These techniques provide valuable insights into the gelation process, the transition from sol to gel, and the influence of external factors such as temperature, pH, and ion concentration. By optimizing the rheological properties, researchers can design in situ gelling systems that exhibit the desired mechanical strength, viscosity, and release profile, thereby improving their clinical performance.

Another important consideration in the development of in situ gelling systems is the choice of polymer. The molecular weight, structure, and functional groups of the polymer can significantly influence the gelation behavior and the release kinetics of the drug. In temperature-sensitive systems, for example, polymers that exhibit a sharp and reversible sol-to-gel transition are preferred. In contrast, ion-sensitive and pH-sensitive systems rely on polymers that can interact with cations or protons to form a stable gel network. The selection of the appropriate polymer for each specific application is critical to achieving optimal drug release and therapeutic efficacy.

Over the past decade, significant progress has been made in the development of in situ gelling systems for a wide range of drug delivery applications. These systems have been explored for the delivery of therapeutic agents through various routes, including buccal, ocular, nasal, vaginal, cervical, and intravesical routes. The versatility of in situ gelling systems makes them suitable for treating a broad spectrum of conditions, including oral mucositis, periodontitis, glaucoma, rhinosinusitis, cervical cancer, and bladder cancer. In each of these applications, the ability to control the release of the drug at the target site, minimize systemic side effects, and improve patient compliance has proven to be invaluable.

For instance, in buccal formulations, mucoadhesive in situ gelling systems have shown promise in improving the retention of the drug on the oral mucosa, thereby enhancing therapeutic efficacy. Studies have demonstrated the successful delivery of bioactive agents for the treatment of oral mucositis and periodontitis, offering better control over drug release and improving the bioavailability of the therapeutic agents. Similarly, ocular formulations have been developed to treat glaucoma by providing sustained drug release, reducing the need for frequent administration and improving patient compliance. In situ gelling systems based on thermosensitive polymers have been shown to enhance ocular bioavailability and retention time, leading to better therapeutic outcomes for glaucoma patients.

In the nasal route, in situ gelling systems have been explored for the delivery of both small molecules and large biological macromolecules, including proteins, peptides, and vaccines. The nasal route is particularly attractive for delivering drugs to the brain, as it bypasses the blood-brain barrier, enabling the direct delivery of therapeutic agents to the central nervous system. In situ gels have

been developed for the treatment of chronic rhinosinusitis and other nasal conditions, with promising results in terms of drug release profiles and stability.

Vaginal formulations have also benefited from the development of in situ gelling systems, with applications ranging from the delivery of antimicrobials and hormones to anticancer agents. The ability to control gelation temperature and mucoadhesion properties has improved the retention and release of drugs at the vaginal mucosa, enhancing the therapeutic efficacy of these treatments. Additionally, in situ gelling systems for cervical drug delivery have shown potential for the localized treatment of cervical cancer, offering a promising strategy for the delivery of chemotherapeutic agents directly to the cervix, thus minimizing systemic side effects.

The use of in situ gelling systems in intravesical drug delivery has also shown significant promise in the treatment of bladder cancer. Composite systems combining drug-loaded nanoparticles with thermosensitive gels have been developed to enhance drug retention in the bladder, providing sustained release and improving therapeutic outcomes. These formulations have demonstrated the ability to resist washout during urine voiding, ensuring that the drug remains at the target site for an extended period, thereby improving the treatment efficacy.

As the field of in situ gelling systems continues to evolve, new and innovative approaches are being explored to further enhance the performance of these systems. The integration of nanoparticles into in situ gels has emerged as a promising strategy for improving drug solubility, bioavailability, and release profiles. Nanoparticles can serve as drug carriers, allowing for the encapsulation of poorly water-soluble drugs and providing controlled release over extended periods. Additionally, the use of advanced characterization techniques such as dynamic light scattering, atomic force microscopy (AFM), and X-ray diffraction (XRD) is providing deeper insights into the structure and behavior of in situ gelling systems at the molecular and nanoscale level.

In conclusion, in situ gelling systems represent a significant advancement in drug delivery technology, offering a range of benefits, including improved patient compliance, controlled drug release, and enhanced therapeutic efficacy. The ability to tailor these systems to respond to specific external stimuli such as temperature, pH, or ion concentration makes them highly versatile and suitable for a wide variety of therapeutic applications. With continued research and development, the potential applications of in situ gelling systems will only expand, offering new and innovative solutions for the delivery of a broad spectrum of therapeutic agents. The integration of advanced materials, characterization techniques, and formulation strategies will continue to drive the evolution of this promising drug delivery platform, paving the way for more effective, patient-friendly treatments in the future.

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