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Chitosan-Based *In-Situ* Gels for Topical Drug Delivery: A Review of Mechanisms, Applications, and Future Prospects

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ABSTRACT: Topical drug delivery systems are rapidly evolving to enhance therapeutic efficacy and patient compliance. Among these, *in-situ* gelling systems that transition from a sol to a gel state in response to physiological stimuli have emerged as a highly promising platform. This review provides a comprehensive analysis of chitosan, a natural polysaccharide, as a cornerstone polymer for the development of advanced *in-situ* gels. This paper, based on a systematic literature review of 63 articles published between 2015 and 2025, explores the formulation, characterization, and application of these intelligent delivery systems. Key findings highlight chitosan's exceptional properties, including biocompatibility, biodegradability, and mucoadhesion, which are crucial for effective topical therapy. The review details the primary gelation mechanisms, such as pH, temperature, and ion sensitivity that enable controlled, localized drug release. Furthermore, it summarizes extensive preclinical evidence demonstrating the versatility of chitosan-based gels in various applications, including ocular, nasal, wound healing, and even nose-to-brain drug delivery, where they significantly improve bioavailability and prolong residence time. While challenges like poor solubility and weak mechanical strength persist, innovative solutions involving polymer blending and chemical modification are effectively expanding their functional capabilities. This review concludes that chitosan-based in-situ gels represent a sophisticated and adaptable platform poised to advance next-generation, non-invasive therapeutics.

Keywords: Chitosan; in-situ gel; topical drug delivery; mucoadhesive polymer; stimuli-responsive

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INTRODUCTION

Recent advancements in pharmaceutical technology have catalyzed the development of innovative topical drug delivery systems designed to enhance therapeutic efficacy while prioritizing patient compliance and comfort. Among these, *in-situ* gels have emerged as a promising approach, capable of undergoing a sol-to-gel transition upon exposure to physiological stimuli such as changes in pH, temperature, or ionic strength (Kalaria et al., 2023). This unique transformation offers the advantage of controlled drug release and prolonged residence time at the site of administration, particularly beneficial for the management of chronic conditions such as wounds, infections, and ophthalmic diseases.

Chitosan was chosen as the focus of this review due to its status as a plentiful, non-toxic, and FDA-cleared natural polymer. Its distinct cationic nature facilitates superior mucoadhesion. Moreover, its biological functionality, including antimicrobial and biodegradable properties, alongside its responsiveness to external stimuli and recent chemical enhancements, positions it as a leading candidate for contemporary topical therapeutic delivery. Chitosan, a naturally derived polysaccharide from chitin, has gained considerable attention as a key polymer in *in-situ* gel formulations due to its excellent biocompatibility, biodegradability, mucoadhesive properties, and inherent antimicrobial activity (Barati et al., 2018; Irimia, Dinu-Pîrvu, et al., 2018). Studies have demonstrated that chitosan can be effectively combined with various responsive polymers, such as poloxamer 407, gellan gum, and carbopol, to create stable gel systems that adapt to physiological conditions (Elmotasem & Awad, 2020; Kadam et al., 2017). These combinations not only enhance the physical properties of the gel, such as viscosity and mechanical strength, but also broaden its therapeutic potential, including intranasal, ophthalmic, and dermatological delivery.

Despite these promising developments, several critical gaps remain in the literature regarding chitosan-based *in-situ* gels. Although these systems hold considerable promise, their translation into clinical practice remains hampered by several challenges, including concerns about long-term stability, maintaining gel integrity during sterilisation processes, and the complexity of regulatory requirements. This review responds to a growing demand for non-invasive therapeutic strategies to manage chronic conditions in an increasingly ageing population, with particular emphasis on ocular, nasal, and dermal routes of administration. Despite the rapid growth in research on chitosan-based in-situ gels, the available literature remains scattered, particularly regarding formulation strategies and clinical applicability. By consolidating current knowledge of gelation mechanisms and therapeutic uses, this review serves as a comprehensive reference, identifies key research gaps, and facilitates the advancement of these technologies toward real-world clinical implementation. Furthermore, there is a lack of comprehensive comparative data on their therapeutic efficacy and pharmacokinetic profiles in preclinical and clinical settings. Therefore, this review aims to evaluate the potential of chitosan in topical *in-situ* gel formulations, explore its gelation mechanisms and clinical applications, and provide a critical analysis of current challenges and future directions in the development of chitosan-based drug delivery systems.

METHODS

This study used a literature review to analyze scientific journals and research papers on the development of chitosan-based *in situ* gels for topical drug delivery. The literature was systematically retrieved through reputable databases, including PubMed

and Google Scholar. The search strategy involved the use of keywords such as “chitosan”, “in-situ gel”, “chitosan-based *in-situ* gel”, and “topical drug delivery”, with a publication year filter between 2015 and 2025. The selection of relevant articles was conducted in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) framework. As a first step, duplicate entries were identified and removed using the Mendeley reference management tool, yielding 87 distinct records. Titles and abstracts were then reviewed to determine their relevance to the study topic, and any disagreements between reviewers were settled through mutual discussion. Subsequently, the full texts of the remaining articles were evaluated against predetermined inclusion and exclusion criteria. Studies were omitted if they: (1) were not accessible in full-text format, (2) did not directly focus on chitosan-based in-situ gel systems intended for topical or mucosal drug delivery, (3) consisted of conference proceedings or review papers, or (4) provided insufficient information regarding formulation development or characterization parameters. The methodological quality of the included studies was evaluated using an adapted checklist designed for experimental pharmaceutical research. Data were systematically extracted using a uniform template encompassing key aspects such as formulation components, gelation mechanisms, characterization techniques, drug release behaviour, and therapeutic or application-related outcomes. A flowchart illustrating the article selection process is presented in Figure 1.

Figure

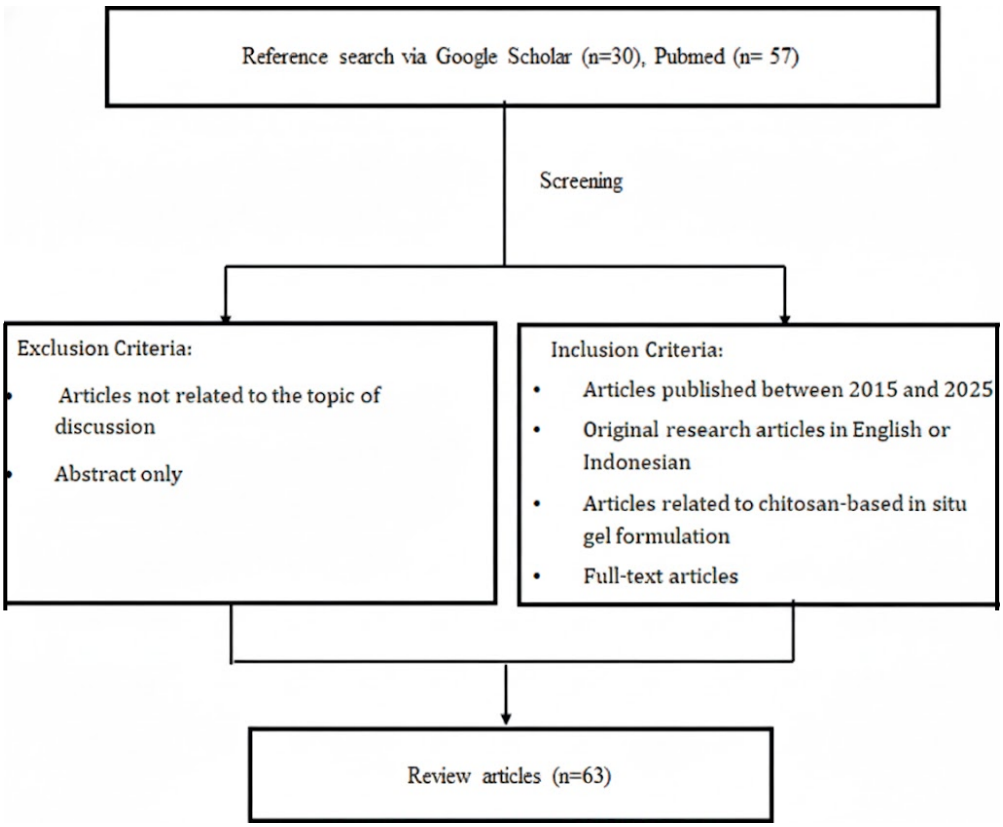

Figure 1. Flow of Research Methods

RESULT AND DISCUSSION

The flowchart in Figure 2 outlines a three-phase systematic process for the development and evaluation of a chitosan-based *in-situ* gel for topical drug delivery: formulation design, gel characterization, and preclinical evaluation. The first phase, formulation design of the chitosan-based *in-situ* gel, is the initial step in the development process, where the initial gel formula is carefully designed. This process involves selecting appropriate polymers, such as the appropriate type of chitosan and any other necessary polymers, deciding on the active pharmaceutical ingredient and how to incorporate it into the gel, and establishing the procedure for preparing the formulation. The result of this phase is a preliminary gel formula that is ready for evaluation in the next stage. Chitosan, a biopolymer derived from chitin, is commonly used due to its non-toxic, biodegradable, and biocompatible properties (Louisa et al., 2022; Mohammed et al., 2017). In the context of topical drug delivery, chitosan formulations can be optimized by modifying their physicochemical characteristics. For example, chitosan nanoparticles can improve drug solubility, stability, and bioavailability when designed correctly (Herdiana et al., 2022; Huang et al., 2017). Various methods, such as ionic cross-linking or emulsion-droplet coalescence, can be employed to prepare chitosan nanoparticles with tailored properties for efficient drug release (Garg et al., 2019). Moreover, the incorporation of hydrophilic additives can enhance the performance of chitosan gels, enabling sustained and controlled drug release (Al-najjar & Hussain, 2017).

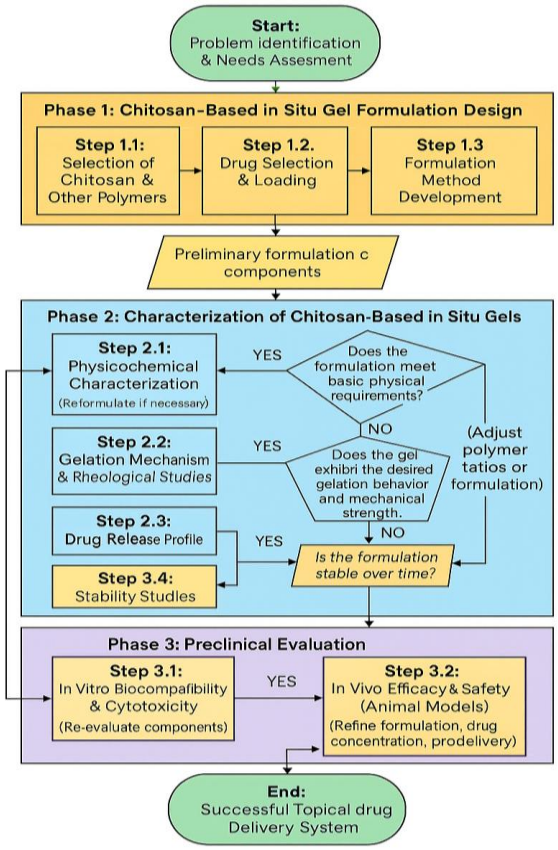

Figure 2. Chitosan-Based *In-Situ* Gel Development Process for Topical Drug Delivery

In Phase 2, gel characterization, the preliminary formula undergoes rigorous testing to ensure it meets the required standards. This crucial stage involves a series of evaluations, including physicochemical and rheological tests to assess the gel's basic properties, flow, and mechanical strength; studies of the drug release profile to understand the rate of drug delivery; and stability studies to assess whether the formulation remains effective over time. Techniques such as rheology can provide insights into the gel's flow characteristics and stability (Kurniawansyah et al., 2018). The degradation behaviour of chitosan, influenced by environmental factors and the presence of enzymes like lysozyme, can be studied to understand the kinetics of drug release under physiological conditions (Lončarević et al., 2017). Furthermore, *in-situ* gels must exhibit appropriate mucoadhesive properties to facilitate prolonged contact with the target site and enhance drug absorption (Liu et al., 2020). A key feature of this phase is its iterative nature, driven by feedback loops. If the formulation fails any test, for instance, by being unstable or lacking the correct strength, it must be adjusted or completely reformulated, sending the process back to an earlier step for refinement.

In the preclinical evaluation phase, a stable gel formulation is tested for safety and effectiveness before human trials. This is done first through in vitro cell-based tests to assess toxicity, followed by in vivo tests in animal models to confirm its therapeutic effect. The goal of this entire process is to develop a successful, safe, and effective topical drug delivery system, prepared for further clinical trials. The final phase involves preclinical evaluation of the chitosan-based gel, focusing on its biocompatibility, safety, and therapeutic effectiveness. Studies involving animal models provide crucial data on pharmacokinetics, therapeutic efficacy, and potential systemic side effects (Reddy et al., 2021; Siddique et al., 2015). For instance, targeted delivery systems using chitosan have shown promise in reducing systemic adverse effects associated with conventional therapies (Siddique et al., 2015). Preclinical models can help validate the formulation's performance, with particular attention to evaluating inflammation or irritation at the application site (Chuah et al., 2022). Additionally, assessing the gel's stability over time and under varying storage conditions is necessary to ensure long-term efficacy in real-world applications (Suryani et al., 2024). The preclinical and clinical applications of chitosan-based in-situ gels across different disease models can be seen in Table 3.

The development of *in-situ* gel systems based on chitosan offers a smart, innovative solution for topical drug delivery. With its unique physicochemical profile, particularly its positive surface charge, chitosan enables strong adhesion to mucosal surfaces, improved drug absorption, and longer retention time at the target site. Table 1 highlights the remarkable versatility of chitosan as a polymer in advanced drug delivery systems. It effectively demonstrates how different physicochemical properties of chitosan are strategically harnessed to achieve specific, desirable outcomes in a formulation. Core properties such as being cationic (positively charged), mucoadhesive (the ability to adhere to mucous membranes), and biocompatible are consistently shown to be advantageous. For example, the cationic nature facilitates interaction with negatively charged biological surfaces, such as the cornea, while mucoadhesion extends the drug's residence time at the application site, thereby increasing its potential effectiveness (Badran et al., 2024; Zafar et al., 2022). Furthermore, the table illustrates how modifying chitosan or combining its properties leads to "smart" and highly functional materials. Properties such as thermosensitivity and rapid gelation are crucial for creating *in-situ* gels that can be applied as a liquid and then transform into a gel at body temperature. This allows for sustained drug release and improved patient comfort (Asfour et al., 2021; Song et al., 2018). By tuning

characteristics like cross-linking, particle size (nanoparticles), or hydrophobicity, researchers can create formulations with enhanced stability, better tissue penetration, and controlled release profiles tailored for specific applications, such as treating eye infections or ensuring long-lasting drug delivery (Kalaria et al., 2023; Modi et al., 2021).

In terms of gelation behaviour, chitosan is known for its environmental responsiveness. It undergoes sol–gel transitions in response to physiological triggers such as pH, temperature, or ionic strength, allowing it to form gels after administration. This characteristic provides significant clinical convenience, as the formulation can be applied in liquid form and transforms into a gel at the site of action. Table 2 describes several key "stimuli-responsive" mechanisms through which chitosan can form an in-situ gel, an innovative system that transitions from a liquid to a gel upon encountering physiological conditions. This approach is highly advantageous for drug delivery, as a low-viscosity solution can be easily administered (e.g., as an eye drop or nasal spray) and then thickens at the target site, ensuring prolonged contact and sustained drug release. The table highlights common triggers, such as changes in pH (gelling at the eye's neutral pH), temperature (gelling at body temperature), and the presence of specific ions (ionic cross-linking).

Delving deeper, the table explains that specific molecular interactions drive these gelation mechanisms. For example, thermo-responsive gelation is often due to increased hydrophobic interactions at body temperature, while ion-sensitive systems rely on ionic cross-linking between the positively charged chitosan and negatively charged polymers. Beyond these physical transitions, the table also discusses chemical modifications of chitosan, such as carboxymethylation (CMC). This strategy alters the fundamental properties of the polymer, thereby increasing its solubility and biocompatibility and expanding its use beyond drug delivery to advanced applications, including tissue engineering for corneal and skin reconstruction (Xu et al., 2018). Overall, the table effectively showcases a range of strategies, from physical stimulus-response to chemical alteration, used to tailor chitosan for specific biomedical functions.

The versatility of chitosan-based *in-situ* gels has been demonstrated across wide range of preclinical and clinical models. Formulations have shown superior performance in improving drug bioavailability, enhancing residence time, and reducing systemic exposure. These outcomes have been observed in treatments for eye diseases, nasal disorders, mucosal ulcers, and even central nervous system conditions. demonstrates the broad therapeutic utility of chitosan-based formulations across a wide spectrum of medical applications. It highlights how these systems are not limited to one area but have been successfully developed for indications ranging from ocular disorders, such as eye ulcers and posterior eye diseases, to wound healing, cancer therapy, and nasal drug delivery. The "Key Results" column consistently points to significant improvements over conventional methods. Common advantages include dramatically increased bioavailability of drugs, prolonged or controlled release, and enhanced retention at the target site, ultimately leading to better therapeutic outcomes, such as faster wound closure or significant tumor reduction (Gholizadeh et al., 2019; Ibrahim et al., 2016; Piotrowska & Orzechowska, 2024).

Furthermore, the table demonstrates chitosan's versatility in enabling various routes of administration, including challenging ones such as nose-to-brain delivery. Formulations for intranasal administration have been shown to effectively treat local conditions such as allergic rhinitis and, more impressively, to deliver drugs such as lorazepam to the brain to manage status epilepticus, bypassing the blood-brain barrier (Taymouri et al., 2020). This highlights chitosan's role as a potent permeation enhancer. The diverse test models, ranging from in vitro setups to rabbits, sheep, and mice,

underscore the extensive preclinical validation these advanced drug delivery systems have undergone, demonstrating their potential for future clinical use.

Table 1. Physicochemical Properties and Functional Advantages of Chitosan in *In-Situ* Gel Formulations

Physicochemical Properties of Chitosan	**Excellence in Formulation**	**Referefences**
Cationic, Cross-linked, Mucoadhesive, Biocompatible	Nanoparticle stability, increased local retention, compatibility with drugs	(Kalaria et al., 2023)
Biodegradability, Bioadhesion, Biocompatibility	Safe for topical application, environmentally friendly, extends residence time	(Zafar et al., 2022)
Cationic, Thermo-sensitive Gel, Physiological pH	Increased bioavailability, antimicrobial properties, sustained release	(Asfour et al., 2021)
Cationic, Biocompatibility, Biodegradability	Penetration into the cornea is increased, optimal drug release	(Paulsamy et al., 2018)
Thermosensitive, Crosslinking, Fast Gelation	Gelation at physiological pH, controlled drug release, easy to modify	(Song et al., 2018)
Mucoadhesive, Fast Gelation, Ocular Compatible	Small microparticles, high corneal permeability, non-irritating	(Khan et al., 2018)
Hydrophobic Interaction, Bioadhesive	Long lasting in the eyes, high adhesion strength	(Modi et al., 2021)
Mucoadhesive, High Viscosity, Cationic	Corneal absorption increases, negative charge interaction	(Badran et al., 2024)
.Antibacterial, Amorphous, Colloidal Stability	High stability, benefits for eye infections	(Ameeduzzafar et al., 2018)
Viscosity Enhancer, Fast Gelation	Gel forms faster, gel hardness is lower	(Fathalla et al., 2022)
Nanoparticles, Bioadhesive Coating	Longer retention, natural decomposition without toxicity	(Ibrahim et al., 2015)
Phase Conversion, Cationic	Corneal formulation retention is increased, safe, non-irritating	(L. Wang et al., 2021)

Table 2. Gelation Mechanisms of Chitosan-Based *In-Situ* Gels: Environmental Triggers, Functions, and Observed Effects

Types of Gelation Mechanisms	Mechanism Description	Pharmaceutical Function of Chitosan	Observed Effects	References
pH-Triggered Gelation	Chitosan solution dissolves at acidic pH and turns into a gel at physiological pH (e.g. eye fluid pH 7.4)	*In-situ* sol-gel transition- Increased bioavailability- Permeation enhancer	Fluconazole permeation increased by 3.5x. Formulation retention on the ocular surface increased significantly	(Gupta et al., 2007)
Thermo-Responsive Gelation	The mixture of chitosan and β - glycerophosphate forms a gel at body temperature (37°C) due to hydrophobic interactions and decreased electrostatic repulsion.	- Gelling at body temperature- Viscosity enhancer- Prolonged antiglaucoma effect	- Delayed release up to 42 days (PIL)- Antifibrotic effect and high biocompatibility	(Vigani et al., 2020)(Zhou et al., 2015)
Ion-Sensitive Gelation	Ionic interactions between chitosan (polycationic) and polyanions (e.g., TPP, gellan gum) cause cross-linking and gelation.	- High mucoadhesive properties- Enhanced intranasal permeation- Controlled drug release	- Rufinamide absorption into the brain is significantly increased	(Dalvi et al., 2021)
Hydrogen & Hydrophobic Interactions	Secondary interactions between polymer chains (chitosan–poloxamer or chitosan–mucus) strengthen the gel network.	- Extended mucoadhesive retention- Sustained drug release- Enhanced gel stability	- Slower FLU release than free solution- Increased mechanical strength of gel	(Nilsen-NyBgaard et al., 2015)(Kadam et al., 2017)
Sol–Gel Transition (Thermal-Induced)	H-GCS dissolves at low temperatures and forms a gel when approaching body temperature due to the dominance of hydrophobic interactions.	- Effective as a thermosensitive eye drop system- Temperature-specific viscosity control	- Bioavailability of levofloxacin is drastically increased (AUC is higher than the regular solution)	(Shi et al., 2019)
Modified Chitosan (CMC/CMCTS)	Carboxymethylation increases polymer solubility and interactions.	- High transparency- Support for corneal epithelial cell growth- Application in tissue engineering	- Used in corneal reconstruction and skin/bone regeneration	(Xu et al., 2018)

Despite these promising findings, several challenges remain. Chitosan's poor solubility at physiological pH, its relatively weak mechanical strength, and issues with gel homogeneity limit its application in some settings. However, researchers have proposed a variety of modifications and formulation techniques to overcome these limitations. These include polymer blending, chemical derivatization, and crosslinking strategies to enhance gel stability, control drug release, and enable targeted therapy. As shown in Table 4, each challenge has been met with innovative solutions, reinforcing chitosan's potential as a flexible and adaptive material in pharmaceutical technology (Valachová & Šoltés, 2021). This table provides a clear overview of the inherent challenges in developing chitosan-based *in-situ* gels and the innovative solutions researchers have implemented to overcome them. A primary theme is addressing the fundamental limitations of pure chitosan, such as its poor solubility at physiological pH and its weak mechanical structure. or instance, the addition of β-glycerophosphate (BGP) stabilizes the formulation and allows it to form a gel at the body's neutral pH, while blending it with polymers such as Poloxamer or cross-linkers enhances its mechanical strength and extends drug release time (Jiang et al., 2016).

Beyond overcoming fundamental limitations, the table showcases advanced strategies that significantly expand chitosan's functionality for sophisticated biomedical applications. Chemical modification of the chitosan backbone is a key strategy, such as synthesizing derivatives to improve solubility or adding hydrophobic groups to enable the carrying of fat-soluble drugs, which is crucial for tumour targeting (Gugleva et al., 2022; Shou et al., 2020).

Furthermore, solutions are tailored to specific therapeutic goals, such as incorporating materials to enhance tissue adhesion or using advanced manufacturing techniques, including 4D bioprinting, to create highly structured carriers with precise control over drug release. These innovations effectively transform chitosan from a simple polymer into a versatile and highly functional platform for advanced drug delivery and tissue engineering.

Altogether, the reviewed findings emphasize chitosan’s multifunctionality as both a drug delivery vehicle and a bioactive excipient, capable of adapting to diverse physiological environments while maintaining biocompatibility, mucoadhesion, and sustained-release performance. Supported by a broad spectrum of preclinical evidence and innovative formulation strategies, these characteristics underscore chitosan’s relevance across current and emerging pharmaceutical technologies. As the field continues to evolve, these insights lay a solid foundation for drawing meaningful conclusions about the therapeutic value, formulation versatility, and translational potential of chitosan-based *in-situ* gels in modern drug delivery systems.

Table 3. Preclinical and Clinical Applications of Chitosan-Based *In-Situ* Gels Across Different Disease Models

Indication	Formulation & Active Drug	Test Model	Key Results	References
Anterior & posterior eye disorders	*In-situ* gel of chitosan nanoparticles + Celecoxib	Female Sprague-Dawley rat	Bioavailability ↑ (4.8–29.7x), stable 24.56 months, undetectable in plasma	(Ibrahim et al., 2016)
Wound & anti-inflammatory	H_2O_2-producing dual-enzyme system	Mouse fibroblast cells	Neutrophil elastase ↓ 40–60%	(Huber et al., 2017)
Topical ocular insulin	MP-INS + Chitosan/poloxamer gel	Male Wistar rat	↑ tear volume, corneal cell protection, INS bioavailability ↑	(Cruz-Cazarim et al., 2019)
Eye ulcer	Ketorolac tromethamine + Chitosan + Carbopol 940	Rabbit	Bioavailability ↑, irritation does not occur	(Irimia, Ghica, et al., 2018)
Tramadol controlled release	Chitosan-based tramadol-HCl *in-situ* gel	In vitro	Slow release, high stability, good texture	(Barati et al., 2018)
Allergic rhinitis (nasal)	CPM + chitosan (nasal *in-situ* gel)	Rabbit (in vivo), sheep/goat (ex vivo)	Cmax ↑ 4–5x, duration of action 8 hours	(Kumar et al., 2019)
Eye infection	Chitosan + *Orthosiphon stamineus extract*	In vitro	Ideal pH, moderate antimicrobial activity	(Sheshala et al., 2022)
Colorectal cancer	NP PLGA + TA/Vitamin E + chitosan	Mouse	Tumor ↓ significant, intestinal histology improved	(Piotrowska & Orzechowska, 2024)
Tumor sonodynamics	TCPP-CAT + chitosan/GP	BALB/c mice	Molecular retention ↑ up to 96 hours	(She et al., 2021)
Tooth remineralization	Chitosan + NaF + nano-HAp	In vitro	Fast sol–gel (30 s), stable 90 days	(Rafiee et al., 2024)
Epistaxis (nosebleed)	TXA + chitosan + β-GP	Sheep (mucosal wound)	Wound closure 6x faster	(Gholizadeh et al., 2019)
Stomach disease	Ranitidine + alginate-chitosan + Ca^{2+}	Dog	Gastric residence time ↑ from normal (~2 hours)	(Belhadji et al., 2018)
intranasal CPM	CPM + chitosan + Carbopol 934 + NaCMC	Sheep mucosa	Permeation flux ↑ >2x (with oleic acid)	(Viswanadhan Vasantha et al., 2023)
Status epilepticus (intranasal to the brain)	Lorazepam in NLC + Gel	Male Wistar rat	Significant ↓ seizures (compared to control & LZM-gel)	(Taymouri et al., 2020)
Cerebral ischemia	Naringenin + nanoemulsion-gel *in-situ*	Male Wistar rats, goat mucosa	Brain NRG bioavailability ↑ significantly	(Ahmad et al., 2020)

Table 4. Challenges and Innovative Solutions in the Development of Chitosan-Based *In-Situ* Gels

Main Challenges	Proposed Solution	Development Prospects	Reference
Chitosan only dissolves at low pH	Addition of β - glycerophosphate (BGP) as a pH and temperature sensitive agent	Stable *in-situ* gel formulation at physiological pH	(Jiang et al., 2016)
Mechanical weaknesses of pure chitosan hydrogel	Combination with PVA and glutaraldehyde (GA)	Sustained release for tumor therapy	(Stoleru et al., 2022)
Low physical integrity	Addition of clove oil (CEO) for superporous structure	Two-level morphology for flexibility and pH-sensitive swelling	(Valachová & Šoltés, 2021)
Limited solubility of chitosan	Synthesis of water-soluble derivatives such as CM-chitosan	Advanced formulation with controlled release	(Shou et al., 2020)
Poor tissue adhesion in the wound	Multifunctional HBCS-C hydrogel	Rapid hemostatic with thermosensitive gelation	(Jalani et al., 2015)
Poor homogeneity of CH–HA at pH 7	Use BGP for gradual neutralization	Tough hydrogel for cartilage regeneration	(Feyissa et al., 2023)
Low stability in physiological fluids (SALG-CS)	Double crosslinking + optimal SALG/CS ratio	High biodegradability and good thermal stability	(Z. Wang et al., 2024)
Non-uniform pore size & low cell charge	Thermosensitive chitosan 4D bioprinting	High precision cell carrier with structure control	Jiang et al., 2016
Uncontrolled drug release	Modification of CS gel with interpenetration system	Intratumoral controlled release	(Ram Garg et al., 2019)
Low bioavailability of ophthalmic drugs	CS gel *in-situ* thermogelling for eyes	Precorneal retention increased	(Caramella et al., 2015)
Low elasticity of CS/GP in the vagina	High bioactive & mucoadhesive activity	Candidate for treatment of vaginal mucositis	(Abdeltawab et al., 2020)
Weak mechanical properties of Poloxamer	Poloxamer + chitosan combination	Ophthalmic drug delivery with extended residence time	(Iacob et al., 2021)
Chitosan only binds hydrophilic drugs	Modification of chitosan chains with hydrophobic groups	Lipophilic drug entrapment & tumor targeting	(Gugleva et al., 2022)
Does not affect gel erosion time	Addition of chitosan for bioadhesion	Antibacterial activity increased	(Sabino et al., 2021)
Lack of evidence of long-term biocompatibility	Further study of chitosan gel injection	Broader evaluation for clinical applications	(Sabino et al., 2021)

CONCLUSION

Chitosan-based *in-situ* gels are an innovative, multifunctional platform for topical drug delivery, leveraging their unique biocompatibility, mucoadhesion, and responsiveness to physiological triggers like pH and temperature. These properties enable localised, sustained drug release, thereby enhancing therapeutic outcomes and patient comfort. Preclinical studies have validated their versatility across many applications, including ocular, nasal, and even brain-targeted delivery. Although challenges like poor solubility exist, innovative solutions such as polymer modification and advanced gel design continue to overcome these limitations, solidifying chitosan's role in developing next-generation, non-invasive medicines

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AUTHOR CONTRIBUTION

WA: Searching articles from database, write manuscript in introduction, methods, and results and discussion,
FA: Refining the introduction, methods, results and discussion, writing the conclusion and abstract.

REFERENCES

Abdeltawab, H., Svirskis, D., & Sharma, M. (2020). Formulation strategies to modulate drug release from poloxamer based in situ gelling systems. In *Expert Opinion on Drug Delivery* (Vol. 17, Issue 4, pp. 1–49). Taylor and Francis Ltd. https://doi.org/10.1080/17425247.2020.1731469

Ahmad, N., Ahmad, R., Ahmad, F. J., Ahmad, W., Alam, M. A., Amir, M., & Ali, A. (2020). Poloxamer-chitosan-based Naringenin nanoformulation used in brain targeting for the treatment of cerebral ischemia. *Saudi Journal of Biological Sciences*, *27*(1), 500–517. https://doi.org/10.1016/j.sjbs.2019.11.008

Al-najjar, B. Y., & Hussain, S. A. (2017). Chitosan Microspheres for the Delivery of Chemotherapeutic Agents: Paclitaxel as a Model. *Asian Journal of Pharmaceutical and Clinical Research*, *10*(8), 15. https://doi.org/10.22159/ajpcr.2017.v10i8.18765

Ameeduzzafar, Imam, S. S., Abbas Bukhari, S. N., Ahmad, J., & Ali, A. (2018). Formulation and optimization of levofloxacin loaded chitosan nanoparticle for ocular delivery: In-vitro characterization, ocular tolerance and antibacterial activity. *International Journal of Biological Macromolecules*, *108*, 650–659. https://doi.org/10.1016/j.ijbiomac.2017.11.170

Asfour, M. H., Abd El-Alim, S. H., Awad, G. E. A., & Kassem, A. A. (2021). Chitosan/β-glycerophosphate in situ forming thermo-sensitive hydrogel for improved ocular delivery of moxifloxacin hydrochloride. *European Journal of Pharmaceutical Sciences*, *167*, 1–10. https://doi.org/10.1016/j.ejps.2021.106041

Badran, M. M., Alsubaie, A., Salem Bekhit, M. M., Alomrani, A. H., Almomen, A., Ibrahim, M. A., & Alshora, D. H. (2024). Bioadhesive hybrid system of niosomes and pH sensitive in situ gel for itraconazole ocular delivery: Dual approach for efficient treatment of fungal infections. *Saudi Pharmaceutical Journal*, *32*(12), 1–13. https://doi.org/10.1016/j.jsps.2024.102208

Barati, M., Mohammadi Samani, S., Pourtalebi Jahromi, L., Ashrafi, H., & Azadi, A. (2018). Controlled-release in-situ gel forming formulation of tramadol containing chitosan-based pro-nanogels. *International Journal of Biological Macromolecules*, *118*, 1449–1454. https://doi.org/10.1016/j.ijbiomac.2018.06.152

Belhadji, L., HadjSadok, A., & Moulai-Mostefa, N. (2018). Design and characterization of calcium-free in-situ gel formulation based on sodium alginate and chitosan. *Drug Development and Industrial Pharmacy*, *44*(4), 662–669. https://doi.org/10.1080/03639045.2017.1408640

Caramella, C. M., Rossi, S., Ferrari, F., Bonferoni, M. C., & Sandri, G. (2015). Mucoadhesive and thermogelling systems for vaginal drug delivery. In *Advanced Drug Delivery Reviews* (Vol. 92, pp. 39–52). Elsevier B.V. https://doi.org/10.1016/j.addr.2015.02.001

Chuah, L., Loo, H.-L., Goh, C. F., Fu, J., & Ng, S. (2022). *Chitosan Based Drug Delivery Systems for Skin Atopic Dermatitis: Recent Advancements and Patent Trends*. https://doi.org/10.21203/rs.3.rs-1812044/v1

Cruz-Cazarim, E. L. C., Cazarim, M. S., Ogunjimi, A. T., Petrilli, R., Rocha, E. M., & Lopez, R. F. V. (2019). Prospective insulin-based ophthalmic delivery systems for the treatment of dry eye syndrome and corneal injuries. *European Journal of Pharmaceutics and Biopharmaceutics*, *140*, 1–10. https://doi.org/10.1016/j.ejpb.2019.04.014

Dalvi, A., Ravi, P. R., & Uppuluri, C. T. (2021). Rufinamide-Loaded Chitosan Nanoparticles in Xyloglucan-Based Thermoresponsive In Situ Gel for Direct Nose to Brain Delivery. *Frontiers in Pharmacology*, *12*, 1–13. https://doi.org/10.3389/fphar.2021.691936

Elmotasem, H., & Awad, G. E. A. (2020). A stepwise optimization strategy to formulate in situ gelling formulations comprising fluconazole-hydroxypropyl-beta-cyclodextrin complex loaded niosomal vesicles and Eudragit nanoparticles for enhanced antifungal activity and prolonged ocular delivery. *Asian Journal of Pharmaceutical Sciences*, *15*(5), 1–20. https://doi.org/10.1016/j.ajps.2019.09.003

Fathalla, Z., Mustafa, W. W., Abdelkader, H., Moharram, H., Sabry, A. M., & Alany, R. G. (2022). Hybrid thermosensitive-mucoadhesive in situ forming gels for enhanced corneal wound healing effect of L-carnosine. *Drug Delivery*, *29*(1), 374–385. https://doi.org/10.1080/10717544.2021.2023236

Feyissa, Z., Edossa, G. D., Gupta, N. K., & Negera, D. (2023). Development of double crosslinked sodium alginate/chitosan based hydrogels for controlled release of metronidazole and its antibacterial activity. *Heliyon*, *9*(9), 1–17. https://doi.org/10.1016/j.heliyon.2023.e20144

Garg, U., Chauhan, S., Nagaich, U., & Jain, N. (2019). Current Advances in Chitosan Nanoparticles Based Drug Delivery and Targeting. *Advanced Pharmaceutical Bulletin*, *9*(2), 195–204. https://doi.org/10.15171/apb.2019.023

Gholizadeh, H., Messerotti, E., Pozzoli, M., Cheng, S., Traini, D., Young, P., Kourmatzis, A., Caramella, C., & Ong, H. X. (2019). Application of a Thermosensitive In Situ Gel of Chitosan-Based Nasal Spray Loaded with Tranexamic Acid for Localised Treatment of Nasal Wounds. *AAPS PharmSciTech*, *20*(7), 1–12. https://doi.org/10.1208/s12249-019-1517-6

Gugleva, V., Michailova, V., Mihaylova, R., Momekov, G., Zaharieva, M. M., Najdenski, H., Petrov, P., Rangelov, S., Forys, A., Trzebicka, B., & Momekova, D. (2022). Formulation and Evaluation of Hybrid Niosomal In Situ Gel for Intravesical Co-Delivery of Curcumin and Gentamicin Sulfate. *Pharmaceutics*, *14*(4), 1–23. https://doi.org/10.3390/pharmaceutics14040747

Gupta, H., Jain, S., Mathur, R., Mishra, P., Mishra, A. K., & Velpandian, T. (2007). Sustained ocular drug delivery from a temperature and pH triggered novel in situ gel system. *Drug Delivery*, *14*(8), 507–515. https://doi.org/10.1080/10717540701606426

Herdiana, Y., Wathoni, N., Shamsuddin, S., & Muchtaridi, M. (2022). Drug Release Study of the Chitosan-Based Nanoparticles. *Heliyon*, *8*(1), e08674. https://doi.org/10.1016/j.heliyon.2021.e08674

Huang, G., Liu, Y., & Chen, L. (2017). Chitosan and Its Derivatives as Vehicles for Drug Delivery. *Drug Delivery*, *24*(2), 108–113. https://doi.org/10.1080/10717544.2017.1399305

Huber, D., Tegl, G., Mensah, A., Beer, B., Baumann, M., Borth, N., Sygmund, C., Ludwig, R., & Guebitz, G. M. (2017). A Dual-Enzyme Hydrogen Peroxide Generation Machinery in Hydrogels Supports Antimicrobial Wound Treatment. In *ACS Applied Materials and Interfaces* (Vol. 9,

Issue 18). https://doi.org/10.1021/acsami.7b03296

Iacob, A. T., Lupascu, F. G., Apotrosoaei, M., Vasincu, I. M., Tauser, R. G., Lupascu, D., Giusca, S. E., Caruntu, I. D., & Profire, L. (2021). Recent biomedical approaches for chitosan based materials as drug delivery nanocarriers. In *Pharmaceutics* (Vol. 13, Issue 4, pp. 1–36). MDPI AG. https://doi.org/10.3390/pharmaceutics13040587

Ibrahim, M. M., Abd-Elgawad, A.-E. H., Soliman, O. A.-E., & Jablonski, M. M. (2015). Natural Bioadhesive Biodegradable Nanoparticle-Based Topical Ophthalmic Formulations for Management of Glaucoma. *Translational Vision Science & Technology*, *4*(3), 1–13. https://doi.org/10.1167/tvst.4.3.12

Ibrahim, M. M., Abd-Elgawad, A. E. H., Soliman, O. A. E., & Jablonski, M. M. (2016). Stability and Ocular Pharmacokinetics of Celecoxib-Loaded Nanoparticles Topical Ophthalmic Formulations. *Journal of Pharmaceutical Sciences*, *105*(12), 1–11. https://doi.org/10.1016/j.xphs.2016.09.019

Irimia, T., Dinu-Pîrvu, C. E., Ghica, M. V., Lupuleasa, D., Muntean, D. L., Udeanu, D. I., & Popa, L. (2018). Chitosan-based in situ gels for ocular delivery of therapeutics: A state-of-the-art review. In *Marine Drugs* (Vol. 16, Issue 10, pp. 1–23). MDPI AG. https://doi.org/10.3390/md16100373

Irimia, T., Ghica, M. V., Popa, L., Anuţa, V., Arsene, A. L., & Dinu-Pîrvu, C. E. (2018). Strategies for improving ocular drug bioavailability and cornealwound healing with chitosan-based delivery systems. In *Polymers* (Vol. 10, Issue 11, pp. 1–24). MDPI AG. https://doi.org/10.3390/polym10111221

Jalani, G., Rosenzweig, D. H., Makhoul, G., Abdalla, S., Cecere, R., Vetrone, F., Haglund, L., & Cerruti, M. (2015). Tough, in-situ thermogelling, injectable hydrogels for biomedical applications. *Macromolecular Bioscience*, *15*(4), 473–480. https://doi.org/10.1002/mabi.201400406

Jiang, Y., Meng, X., Wu, Z., & Qi, X. (2016). Modified chitosan thermosensitive hydrogel enables sustained and efficient anti-tumor therapy via intratumoral injection. *Carbohydrate Polymers*, *144*, 245–253. https://doi.org/10.1016/j.carbpol.2016.02.059

Kadam, A. T., Jadhav, R. L., Salunke, P. B., & Kadam, S. S. (2017). Design and Evaluation of Modified Chitosan Based in Situ Gel for Ocular Drug Delivery. *International Journal of Pharmacy and Pharmaceutical Sciences*, *9*(11), 87–91. https://doi.org/10.22159/ijpps.2017v9i11.20938

Kalaria, V. J., Saisivam, S., Alshishani, A., Aljariri Alhesan, J. S., Chakraborty, S., & Rahamathulla, M. (2023). Design and evaluation of in situ gel eye drops containing nanoparticles of Gemifloxacin Mesylate. *Drug Delivery*, *30*(1), 1–11. https://doi.org/10.1080/10717544.2023.2185180

Khan, S., Warade, S., & Singhavi, D. J. (2018). Improvement in Ocular Bioavailability and Prolonged Delivery of Tobramycin Sulfate Following Topical Ophthalmic Administration of Drug-Loaded Mucoadhesive Microparticles Incorporated in Thermosensitive in Situ Gel. *Journal of Ocular Pharmacology and Therapeutics*, *34*(3), 1–11. https://doi.org/10.1089/jop.2017.0079

Kumar, M., Upadhayay, P., Shankar, R., Joshi, M., Bhatt, S., & Malik, A. (2019). Chlorpheniramine maleate containing chitosan-based nanoparticle-loaded thermosensitive in situ gel for management in allergic rhinitis. *Drug Delivery and Translational Research*, *9*(6), 1017–1026. https://doi.org/10.1007/s13346-019-00639-w

Kurniawansyah, I. S., Sopyan, I., Wathoni, N., Fillah, D. L., & Praditya, R. U. (2018). Application and Characterization of in Situ Gel. *International Journal of Applied Pharmaceutics*, *10*(6), 34. https://doi.org/10.22159/ijap.2018v10i6.28767

Liu, Y., Sun, M., Wang, T., Chen, X., & Wang, H. (2020). Chitosan-based Self-assembled Nanomaterials: Their Application in Drug Delivery. *View*, *2*(1). https://doi.org/10.1002/viw.20200069

Lončarević, A., Ivanković, M., & Rogina, A. (2017). Lysozyme-Induced Degradation of Chitosan: The Characterisation of Degraded Chitosan Scaffolds. *Journal of Tissue Repair and Regeneration*, *1*(1), 12–22. https://doi.org/10.14302/issn.2640-6403.jtrr-17-1840

Louisa, M., Hawa, P., Purwantyastuti, P., Mardliyati, E., & Freisleben, H. (2022). Primaquine-Chitosan Nanoparticle Improves Drug Delivery to Liver Tissue in Rats. *Open Access Macedonian Journal of Medical Sciences*, *10*(A), 1278–1284. https://doi.org/10.3889/oamjms.2022.10005

Modi, D., Mohammad, Warsi, M. H., Garg, V., Bhatia, M., Kesharwani, P., & Jain, G. K. (2021). Formulation development, optimization, and in vitro assessment of thermoresponsive ophthalmic pluronic F127-chitosan in situ tacrolimus gel. *Journal of Biomaterials Science, Polymer Edition*, *32*(13), 1–26. https://doi.org/10.1080/09205063.2021.1932359

Mohammed, M., Syeda, J., Wasan, K. M., & Wasan, E. K. (2017). An Overview of Chitosan Nanoparticles and Its Application in Non-Parenteral Drug Delivery. *Pharmaceutics*, *9*(4), 53. https://doi.org/10.3390/pharmaceutics9040053

Nilsen-Nygaard, J., Strand, S. P., Vårum, K. M., Draget, K. I., & Nordgård, C. T. (2015). Chitosan: Gels and interfacial properties. In *Polymers* (Vol. 7, Issue 3, pp. 552–579). MDPI AG. https://doi.org/10.3390/polym7030552

Paulsamy, M., Ponnusamy, C., Palanisami, M., Nackeeran, G., Paramasivam, S. S., Sugumaran, A., Kandasamy, R., Natesan, S., & Palanichamy, R. (2018). Nepafenac loaded silica nanoparticles dispersed in-situ gel systems: Development and characterization. *International Journal of Biological Macromolecules*, *110*, 336–345. https://doi.org/10.1016/j.ijbiomac.2018.01.123

Piotrowska, U., & Orzechowska, K. (2024). Advances in Chitosan-Based Smart Hydrogels for Colorectal Cancer Treatment. In *Pharmaceuticals* (Vol. 17, Issue 10, pp. 1–27). Multidisciplinary Digital Publishing Institute (MDPI). https://doi.org/10.3390/ph17101260

Rafiee, A., Mozafari, N., Fekri, N., Memarpour, M., & Azadi, A. (2024). Preparation and characterization of a nanohydroxyapatite and sodium fluoride loaded chitosan-based in situ forming gel for enamel biomineralization. *Heliyon*, *10*(2), 1–10. https://doi.org/10.1016/j.heliyon.2024.e24217

Ram Garg, Vikas Kumar, & Vandana Sharma. (2019). Emerging Trends in Ocular Drug Delivery Special Reference to In Situ Ophthalmic Gel. *Pharmaceutical and Biosciences Journal*, *7*(3), 08–17. https://doi.org/10.20510/ukjpb/7/i3/185553

Reddy, C. M., Krishnan, S. P., & Reddy, C. B. (2021). A Mini-Review on Chitosan Microsphere Drug Delivery. *Journal of Pharmaceutical Research International*, 179–186. https://doi.org/10.9734/jpri/2021/v33i49a33318

Sabino, I. J., Lima-Sousa, R., Alves, C. G., Melo, B. L., Moreira, A. F., Correia, I. J., & de Melo-Diogo, D. (2021). Injectable in situ forming hydrogels incorporating dual-nanoparticles for chemo-photothermal therapy of breast cancer cells. *International Journal of Pharmaceutics*, *600*, 1–8. https://doi.org/10.1016/j.ijpharm.2021.120510

She, J., Zhou, X., Zhang, Y., Zhang, R., Li, Q., Zhu, W., Meng, Z., & Liu, Z. (2021). Thermo-Triggered In Situ Chitosan-Based Gelation System for Repeated and Enhanced Sonodynamic Therapy Post a Single Injection. *Advanced Healthcare Materials*, *10*(3), 1–10. https://doi.org/10.1002/adhm.202001208

Sheshala, R., Wai, N. Z., Said, I. D., Ashraf, K., Lim, S. M., Ramasamy, K., & Zeeshan, F. (2022). Poloxamer and Chitosan-Based In Situ Gels Loaded with Orthosiphon stamineus Benth. Extracts Containing Rosmarinic Acid for the Treatment of Ocular Infections. *Turkish Journal of Pharmaceutical Sciences*, *19*(6), 671–680. https://doi.org/10.4274/tjps.galenos.2021.40121

Shi, H., Wang, Y., Bao, Z., Lin, D., Liu, H., Yu, A., Lei, L., Li, X., & Xu, X. (2019). Thermosensitive glycol chitosan-based hydrogel as a topical ocular drug delivery system for enhanced ocular bioavailability. *International Journal of Pharmaceutics*, *570*, 1–7. https://doi.org/10.1016/j.ijpharm.2019.118688

Shou, Y., Zhang, J., Yan, S., Xia, P., Xu, P., Li, G., Zhang, K., & Yin, J. (2020). Thermoresponsive Chitosan/DOPA-Based Hydrogel as an Injectable Therapy Approach for Tissue-Adhesion and Hemostasis. *ACS Biomaterials Science and Engineering*, *6*(6), 1–26. https://doi.org/10.1021/acsbiomaterials.0c00545

Siddique, M. I., Katas, H., Amin, M. C. I. M., Ng, S.-F., Zulfakar, M. H., Buang, F., & Jamil, A. (2015). Minimization of Local and Systemic Adverse Effects of Topical Glucocorticoids by Nanoencapsulation: In Vivo Safety of Hydrocortisone–Hydroxytyrosol Loaded Chitosan Nanoparticles. *Journal of Pharmaceutical Sciences*, *104*(12), 4276–4286. https://doi.org/10.1002/jps.24666

Song, Y., Nagai, N., Saijo, S., Kaji, H., Nishizawa, M., & Abe, T. (2018). In situ formation of injectable chitosan-gelatin hydrogels through double crosslinking for sustained intraocular drug delivery. *Materials Science and Engineering C*, *88*, 1–12. https://doi.org/10.1016/j.msec.2018.02.022

Stoleru, E., Dumitriu, R. P., Ailiesei, G. L., Yilmaz, C., & Brebu, M. (2022). Synthesis of Bioactive Materials by In Situ One-Step Direct Loading of Syzygium aromaticum Essential Oil into Chitosan-Based Hydrogels. *Gels*, *8*(4), 1–20. https://doi.org/10.3390/gels8040225

Suryani, S., Chaerunisaa, A. Y., Joni, I. M., Ruslin, R., Aspadiah, V., Anton, A., Sartinah, A., & Ramadhan, L. O. A. N. (2024). The Chemical Modification to Improve Solubility of Chitosan and Its Derivatives Application, Preparation Method, Toxicity as a Nanoparticles. *Nanotechnology Science and Applications*, *Volume 17*, 41–57. https://doi.org/10.2147/nsa.s450026

Taymouri, S., Minaiyan, M., Ebrahimi, F., & Tavakoli, N. (2020). In-vitro and in-vivo evaluation of chitosanbased thermosensitive gel containing lorazepam NLCs for the treatment of status epilepticus. *IET Nanobiotechnology*, *14*(2), 148–154. https://doi.org/10.1049/iet-nbt.2019.0156

Valachová, K., & Šoltés, L. (2021). Versatile use of chitosan and hyaluronan in medicine. In *Molecules* (Vol. 26, Issue 4, pp. 1–15). MDPI AG. https://doi.org/10.3390/molecules26041195

Vigani, B., Rossi, S., Sandri, G., Bonferoni, M. C., Caramella, C. M., & Ferrari, F. (2020). Recent advances in the development of in situ gelling drug delivery systems for non-parenteral administration routes. In *Pharmaceutics* (Vol. 12, Issue 9, pp. 1–29). MDPI AG. https://doi.org/10.3390/pharmaceutics12090859

Viswanadhan Vasantha, P., Sherafudeen, S. P., Rahamathulla, M., Mathew, S. T., Murali, S., Alshehri, S., Shakeel, F., Alam, P., Sirhan, A. Y., & Narayana Iyer, B. A. (2023). Combination of Cellulose Derivatives and Chitosan-Based Polymers to Investigate the Effect of Permeation Enhancers Added to In Situ Nasal Gels for the Controlled Release of Loratadine and Chlorpheniramine. *Polymers*, *15*(5), 1–16. https://doi.org/10.3390/polym15051206

Wang, L., Pan, H., Gu, D., Sun, H., Chen, K., Tan, G., & Pan, W. (2021). A novel carbon dots/thermo-sensitive in situ gel for a composite ocular drug delivery system: Characterization, ex-vivo imaging and in vivo evaluation. *International Journal of Molecular Sciences*, *22*(18), 1–16. https://doi.org/10.3390/ijms22189934

Wang, Z., Jiang, C., Fan, Y., Hao, X., Dong, Y., He, X., Gao, J., Zhang, Y., Li, M., Wang, M., Liu, Y., & Xu, W. (2024). The application of a 4D-printed chitosan-based stem cell carrier for the repair of corneal alkali burns. *Stem Cell Research and Therapy*, *15*(1), 1–17. https://doi.org/10.1186/s13287-024-03653-z

Xu, W., Wang, Z., Liu, Y., Wang, L., Jiang, Z., Li, T., Zhang, W., & Liang, Y. (2018). Carboxymethyl chitosan/gelatin/hyaluronic acid blended-membranes as epithelia transplanting scaffold for corneal wound healing. *Carbohydrate Polymers*, *192*, 240–250. https://doi.org/10.1016/j.carbpol.2018.03.033

Zafar, A., Imam, S. S., Yasir, M., Alruwaili, N. K., Alsaidan, O. A., Warsi, M. H., Ullah, S. N. M. N., Alshehri, S., & Ghoneim, M. M. (2022). Preparation of NLCs-Based Topical Erythromycin Gel: In Vitro Characterization and Antibacterial Assessment. *Gels*, *8*(2), 1–18. https://doi.org/10.3390/gels8020116

Zhou, H. Y., Jiang, L. J., Cao, P. P., Li, J. B., & Chen, X. G. (2015). Glycerophosphate-based chitosan thermosensitive hydrogels and their biomedical applications. In *Carbohydrate Polymers* (Vol. 117, pp. 524–536). Elsevier Ltd. https://doi.org/10.1016/j.carbpol.2014.09.094.