Current Pharmaceutical Research (CPR)
Vol 2, Issue 2, April-June 2026
Journal Homepage: https://cpr.org.in/

Smart Stimuli-Responsive Injectable Hydrogels for Precision Drug Delivery: Design, Mechanisms, and Emerging Applications

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Keywords

Smart hydrogels; Injectable systems; Stimuli-responsive; Precision drug delivery.

Abstract

Smart stimuli-responsive injectable hydrogels are new generation of drug delivery systems that promise to revolutionize the field of drug delivery by combining the benefits of minimally invasive drug delivery systems with spatial and temporal control over drug release. This report aims to summarize the recent advances in the design of stimuli-responsive injectable hydrogels, including the polymer backbone, such as polysaccharide-derived hyaluronic acid, and synthetic poly(NIPAM), poly(PEG), and poly(zwitterionic)s, as well as the various cross-linking chemistries, including Schiff base, Michael addition, and physical cross-linking, that enable the design of injectable hydrogels that undergo a solution-to-gel transition in situ in response to various stimuli, such as pH, redox, enzymes, light, ultrasound, and temperature, among others. This review aims to provide a comprehensive summary of the current advances, mechanisms, and perspectives of smart stimuli-responsive injectable hydrogels, including their applications in oncology, ophthalmology, and neurology, as well as their successful outcomes in completely curing tumours, 75% tumour regression using a GSH-responsive peptide gel, and significant functional repair in spinal cord injury repairs using microenvironment-responsive matrices, among many other applications of injectable hydrogels in drug delivery systems. The translation of injectable hydrogels into the clinic, however, is currently hampered by the difficulties in long-term biocompatibility profiling, large-scale sterile production, and regulatory hurdles associated with combination drug products.

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Article Info
Received: 10 April 2026, Received in revised form: 28 July 2026, Accepted: 28 July 2026, Available online: 30 July 2026; Volume: 2; Issue: 2; Pages: 181–191.

ISSN: 3049-2955/The authors © 2026, under exclusive license to the Sprout Publication.
DOI: https://doi.org/10.63785/2026.2.2.181191

1. Introduction

1.1. Concept and Minimally Invasive Advantages

Injectable hydrogels are a form of flowable formulation, generally existing as a liquid or low-viscosity paste before administration. They can be introduced into the body through catheters or needles, where they subsequently undergo gelation to form a solid matrix at the injection site [1]. This approach offers several advantages over conventional delivery methods. Injectable hydrogels are minimally invasive, allowing administration without the need for surgical procedures and making them particularly suitable for treating irregular or deep tissue defects [2]. They also enable localized and sustained drug release, ensuring that therapeutic agents are delivered directly to the target site at high concentrations while reducing systemic exposure and associated adverse effects [3]. Furthermore, injectable hydrogels provide excellent flexibility, as their mechanical and physicochemical properties can be tailored by selecting appropriate polymer backbones and controlling the cross-linking density to match the requirements of the target tissue [4].

1.2. Stimuli-Responsive Behaviour in Physiological and Pathological Environments

The "smart" attribute of these hydrogels refers to their ability to respond to specific biochemical or physical stimuli. For example, pathological microenvironments often exhibit distinct characteristics, such as the acidic pH of tumor or ischemic tissues (typically around 6.5-6.8), elevated levels of reactive oxygen species in inflammatory environments, or the overexpression of enzymes such as matrix metalloproteinases and proteases [5]. Smart hydrogels exploit these unique microenvironmental cues to trigger the controlled release of therapeutic agents or undergo degradation in response to these stimuli, thereby enabling more precise and targeted drug delivery [6].

Figure 1 illustrates the concept of injectable smart hydrogels, highlighting minimally invasive administration as a liquid precursor followed by *in situ* gelation at the target site. The hydrogel responds to physiological and external stimuli, including pH, temperature, enzymes, ROS, light, and redox conditions, enabling localized, controlled, and sustained therapeutic delivery with enhanced treatment efficacy [7].

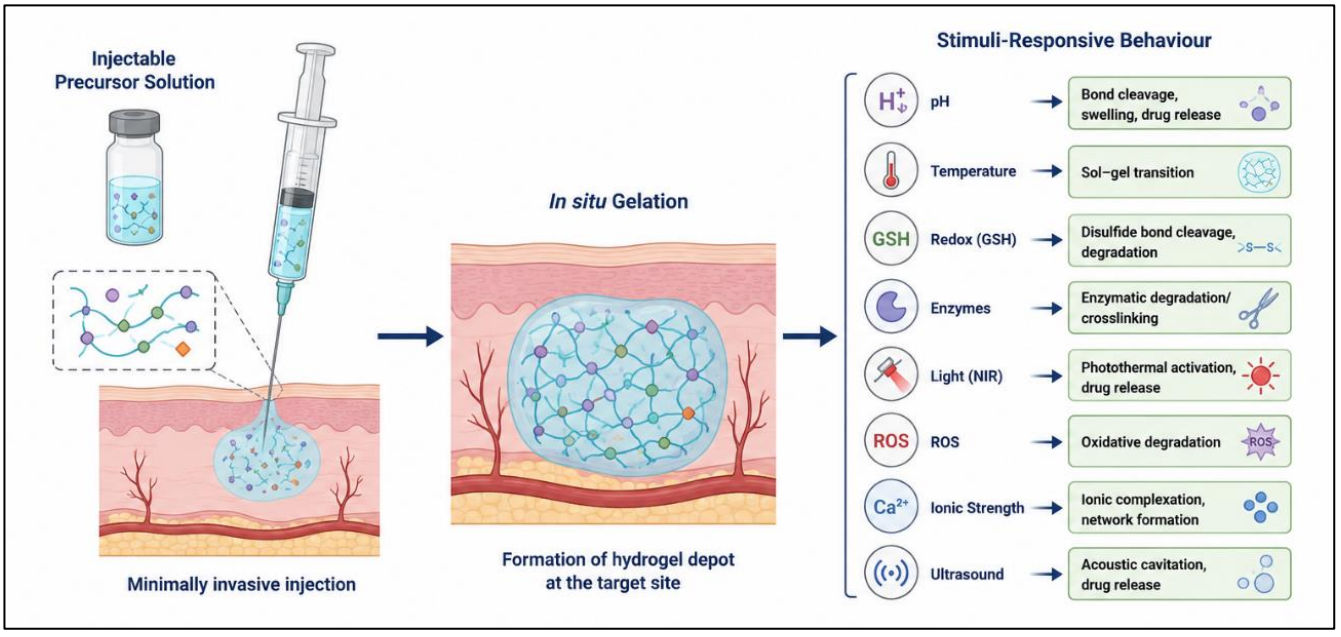

Figure 1: Schematic illustration of injectable smart hydrogels.

2. Design and Fabrication Strategies

2.1. Polymeric Backbones and Crosslinking Chemistries

The choice of polymeric backbone plays a crucial role in determining the biocompatibility, mechanical strength, degradation behavior, and stimulus responsiveness of injectable hydrogel systems [8].

Natural polysaccharides such as hyaluronic acid, chitosan, alginate, and agarose are widely employed because of their excellent biocompatibility, biodegradability, and bioactivity [9]. Modified derivatives of hyaluronic acid, including thiol-functionalized hyaluronic acid (HA-SH) and tyrosine-modified hyaluronic acid (HA-Tyr), are frequently utilized to enable enzymatic crosslinking. Chitosan is also commonly combined with synthetic polymers, such as poly(N-isopropylacrylamide) (PNIPAM), to improve the mechanical and thermoresponsive properties of hydrogels [10].

Synthetic polymers provide greater control over hydrogel properties and functionalization. PNIPAM is one of the most extensively studied thermoresponsive polymers because its lower critical solution temperature (LCST) lies close to physiological temperature (32-37°C), enabling temperature-triggered sol-gel transitions [11]. Polyethylene glycol (PEG), along with its copolymers such as PEG-PCL and PEG-PLA, serves as a versatile platform for covalent modification and bioorthogonal crosslinking reactions [12]. Other synthetic polymers, including polyzwitterions (e.g., polycarboxybetaines), polyvinylpyrrolidone (PVP), polylactic acid (PLA), polyglycolic acid (PGA), and poly(lactic-co-glycolic acid) (PLGA), are extensively used in biomedical applications, particularly in ophthalmic and neurological drug delivery [13].

Peptide-based hydrogels, especially those formed from short self-assembling peptides, have gained considerable attention because of their excellent biocompatibility, inherent biodegradability, and high bioactivity [14]. These peptides spontaneously assemble into injectable hydrogel networks and can be engineered to respond to specific stimuli, such as redox conditions or enzymatic activity, making them attractive candidates for advanced drug delivery and

tissue engineering applications [15].

2.2. In Situ-Gelling Mechanisms (Chemical vs. Physical)

Hydrogels can be broadly classified according to their crosslinking mechanism into physically crosslinked and chemically crosslinked systems, each exhibiting distinct structural and functional characteristics [16]. Physical crosslinking involves the formation of hydrogel networks through reversible non-covalent interactions, including hydrogen bonding, hydrophobic interactions, ionic interactions, and host–guest inclusion complexes. These hydrogels are generally reversible, exhibit shear-thinning behavior, and possess excellent injectability, allowing them to flow under applied stress and rapidly recover their structure after injection [17]. Thermogelling systems are a common example, in which hyaluronan–Pluronic F-127 complexes undergo sol–gel transition in the presence of calcium ions, remaining fluid at low temperatures while forming mechanically stable gels at physiological temperature. Another important class is supramolecular hydrogels, which are assembled through dynamic non-covalent interactions and exhibit desirable properties such as self-healing, injectability, and rapid structural recovery [18].

Chemical (covalent) crosslinking relies on the formation of permanent covalent bonds between polymer chains, resulting in hydrogels with enhanced mechanical strength, structural stability, and prolonged degradation profiles [19]. Common crosslinking strategies include Schiff base reactions, Michael addition reactions, enzyme-mediated crosslinking, and bioorthogonal polymerization. Schiff base chemistry utilizes dynamic imine bonds formed between amino-functionalized polymers, such as gelatin, and aldehyde-containing polymers, such as oxidized dextran or oxidized hyaluronic acid, producing hydrogels that remain stable while responding to changes in environmental pH [20]. Enzyme-mediated crosslinking, particularly using horseradish peroxidase (HRP), enables rapid gelation under physiological conditions through the formation of dityrosine linkages. Bioorthogonal polymerization methods, such as strain-promoted azide–alkyne cycloaddition (SPAAC), allow PEG-based hydrogels to be formed in situ with highly controlled network architectures, making them especially suitable for biomedical and drug delivery applications [21].

2.3. Nanocomposite and Hybrid Smart Hydrogels

The incorporation of nanoparticles into hydrogel matrices further enhances their functionality by imparting unique physicochemical and therapeutic properties. These multifunctional nanocomposite hydrogels have attracted considerable attention for applications in controlled drug delivery, tissue engineering, and regenerative medicine [22].

Photothermal nanoparticles, such as copper sulfide (CuS) and polydopamine (PDA), serve as efficient photothermal transducers that enable hydrogels to respond to near-infrared (NIR) light. Upon NIR irradiation, these nanoparticles generate localized heat, which can trigger on-demand drug release or be combined with photothermal therapy (PTT) for synergistic treatment, particularly in cancer applications [23].

Conductive nanomaterials, including molybdenum disulfide (MoS_2) and polyaniline (PANI), impart electrical conductivity to hydrogel systems. These conductive hydrogels facilitate electrical signal transmission across damaged tissues, making them especially valuable for neural tissue engineering and nerve regeneration, where electrical stimulation plays a critical role in functional recovery [24].

Hydrogels also function as reservoirs for advanced nanocarriers, enabling sustained and controlled secondary release of therapeutic nanoparticles such as lipid nanoparticles, polymeric micelles, dendrimers, and transferosomes [25]. This hierarchical delivery strategy enhances drug stability, prolongs therapeutic efficacy, and improves bioavailability. For instance, transferosome-loaded hydrogels have demonstrated effective transdermal insulin delivery, resulting in significant reductions in blood glucose levels in experimental animal models [26].

Table 1 summarizes the major design and fabrication strategies of injectable smart hydrogels used in biomedical applications. Natural and synthetic polymeric backbones provide biocompatibility, tunable mechanical properties, and controlled biodegradation, while peptide-based hydrogels mimic the extracellular matrix to support tissue regeneration. Physical crosslinking offers reversible gelation, injectability, and self-healing properties, whereas chemical crosslinking improves structural stability and long-term performance [27]. Incorporating functional nanomaterials, including photothermal nanoparticles, conductive nanomaterials, and nanocarrier-loaded systems, further enhances stimuli responsiveness, controlled drug release, electrical conductivity, and therapeutic efficacy, making these hydrogels promising platforms for advanced drug delivery and regenerative medicine [28]

Table 1: Design and fabrication strategies for injectable smart hydrogels.

S. No.	Strategy	Components/Examples	Mechanism	Advantages	Representative Applications	References
1.	Natural polymeric backbones	Hyaluronic acid (HA), Chitosan, Alginate, Agarose	Biocompatible biodegradable polymer matrices; enzymatic or ionic gelation	Excellent biocompatibility, biodegradability, bioactivity	Drug delivery, wound healing, cartilage regeneration	[29]
2.	Modified natural polymers	HA-SH, HA-Tyr, Chitosan-PNIPAM	Thiol-mediated or enzyme-mediated crosslinking; thermoresponsive gelation	Enhanced mechanical strength, injectability, stimulus responsiveness	Injectable tissue engineering scaffolds, controlled drug release	[30]
3.	Synthetic polymeric backbones	PNIPAM, PEG, PEG-PCL, PEG-PLA, PVP, PLA, PGA, PLGA	Thermoresponsive phase transition or covalent crosslinking	Tunable mechanical properties, reproducible synthesis, controlled degradation	Ophthalmic, neurological, and sustained drug delivery	[31]
4.	Peptide-based hydrogels	Self-assembling peptides	Molecular self-assembly through non-covalent interactions	High bioactivity, biodegradability, ECM-mimicking microenvironment	Tissue engineering, regenerative medicine, cell delivery	[32]
5.	Physical crosslinking	Hydrogen bonding, ionic interactions, hydrophobic interactions, host–guest complexes	Reversible non-covalent interactions	Injectable, shear-thinning, self-healing, reversible gelation	Minimally invasive injectable hydrogels	[33]
6.	Chemical crosslinking	Schiff base, Michael addition, HRP-mediated crosslinking, SPAAC	Formation of covalent polymer networks	Superior mechanical stability, prolonged degradation, controlled network architecture	Long-term drug delivery and implantable biomaterials	[34]
7.	Photothermal nanocomposite hydrogels	CuS nanoparticles, Polydopamine (PDA)	NIR-induced photothermal conversion	On-demand drug release, combined photothermal therapy	Cancer therapy, localized chemotherapy	[35]
8.	Conductive nanocomposite hydrogels	MoS_2, Polyaniline (PANI)	Electrical signal conduction within hydrogel matrix	Promotes nerve regeneration and electrical stimulation	Neural tissue engineering, cardiac tissue repair	[36]
9.	Hybrid nanocarrier-loaded hydrogels	Lipid nanoparticles, Polymeric micelles, Dendrimers, Transferosomes	Secondary sustained release of encapsulated nanocarriers	Improved drug stability, prolonged release, enhanced bioavailability	Transdermal insulin delivery, targeted drug delivery, regenerative medicine	[37]

3. Stimuli-Responsive Mechanisms

Stimuli-responsive hydrogels, also known as smart hydrogels, undergo reversible physicochemical changes in response to specific internal or external stimuli, enabling controlled and site-specific therapeutic delivery [38]. Internal stimuli include variations in pH, enzyme activity, reactive oxygen species (ROS), glucose concentration, and redox conditions that are characteristic of pathological tissues such as tumors, inflamed regions, or diabetic wounds [39]. These biological cues trigger hydrogel swelling, degradation, or structural rearrangement, resulting in the controlled release of encapsulated drugs [40]. External stimuli, including temperature, light, magnetic fields, ultrasound, and electrical signals, provide precise spatiotemporal control over hydrogel behavior [41]. Thermoresponsive polymers such as poly(N-isopropylacrylamide) undergo sol–gel transitions near physiological temperature, while near-infrared (NIR)-responsive nanocomposite hydrogels generate localized heat for on-demand drug release. The ability to respond selectively to disease-specific microenvironments enhances therapeutic efficacy, minimizes systemic toxicity, and makes stimuli-responsive hydrogels highly promising platforms for targeted drug delivery, tissue engineering, wound healing, and regenerative medicine [42].

Table 2 summarizes the major stimuli-responsive mechanisms that govern the behavior of injectable smart hydrogels under physiological and external

triggers. Different stimuli, including pH, temperature, redox conditions, enzymes, light, reactive oxygen species (ROS), ionic strength, and ultrasound, induce specific physicochemical changes such as bond cleavage, sol-gel transition, degradation, or photothermal activation [43]. These responses are mediated by functional motifs such as Schiff base linkages, disulfide bonds, thioketal groups, and thermosensitive polymers [44]. Representative hydrogel systems exploit these mechanisms to achieve site-specific gelation, controlled drug release, and enhanced therapeutic efficacy, highlighting their potential for precision drug delivery, tissue engineering, and regenerative medicine [45].

Table 2: Summary of stimuli-responsive mechanisms and representative systems

S. No.	Stimulus	Response Mechanism	Representative Systems	Responsive Motif	References
1.	pH	Bond cleavage, swelling	Gelatin/Oxidized Dextran, Chitosan, PNIPAM	Schiff base, Hydrazone	[19]
2.	Temperature	Sol–gel transition	PNIPAM, Pluronic F-127, PEG–polyester	Thermosensitive segments	[46]
3.	Redox (GSH)	Disulfide bond cleavage	Peptide hydrogels, PEG hydrogels	Disulfide, Diselenide	[47]
4.	Enzyme	Enzymatic degradation/crosslinking	HA derivatives, Gelatin	HRP, MMP-cleavable peptides	[48]
5.	Light (NIR)	Photothermal activation	CuS- or PDA-loaded hydrogels	CuS, PDA, Photo-crosslinkers	[49]
6.	ROS	Oxidative degradation	ROS-responsive polymers	Thioketal, Boronic ester	[50]
7.	Ionic Strength	Ionic complexation	Alginate, Ionic hydrogels	Ca^{2+}, Multivalent ions	[51]
8.	Ultrasound	Acoustic cavitation	Injectable nanocomposite hydrogels	Microbubbles, Sonosensitive carriers	[52]

4. Drug Delivery Applications

4.1. Cancer Chemo- and Immuno-Therapeutics

Smart injectable hydrogels have emerged as promising platforms for localized cancer therapy by enabling controlled drug release, prolonged retention at the tumor site, and reduced systemic toxicity. Their ability to respond to tumor-specific stimuli, such as acidic pH, elevated glutathione (GSH), and reactive oxygen species (ROS), allows precise and on-demand release of therapeutic agents [53]. GSH-responsive peptide hydrogels have demonstrated selective intracellular release of doxorubicin (DOX), resulting in significant tumor regression in preclinical breast cancer models [54]. To further enhance therapeutic efficacy, multifunctional nanocomposite hydrogels incorporating photothermal agents such as copper sulfide (CuS) or polydopamine (PDA) enable combined chemotherapy and photothermal therapy (PTT). Upon near-infrared (NIR) irradiation, these systems generate localized heat, accelerating drug release while simultaneously inducing thermal ablation of tumor cells [55]. Injectable self-healing hydrogels have also been developed to provide sustained release of chemotherapeutic drugs over extended periods, maintaining therapeutic concentrations at the tumor site [56].

In addition, hydrogel-based localized immunotherapy platforms have shown considerable promise by delivering immune checkpoint inhibitors, cytokines, and chemokines directly into the tumor microenvironment, thereby enhancing cytotoxic T-cell infiltration, overcoming immunosuppression, and improving antitumor immune responses while minimizing systemic immune-related adverse effects [57].

4.2. Localized Delivery for Inflammatory and Infectious Diseases

Injectable smart hydrogels have shown significant potential for the localized treatment of inflammatory and infectious diseases by providing sustained drug release and responding to disease-specific microenvironmental cues [58]. In inflammatory conditions, dual-responsive hydrogels capable of sensing both reactive oxygen species (ROS) and matrix metalloproteinases (MMPs) have demonstrated sequential therapeutic delivery [59]. These systems initially release antioxidant nanodrugs to reduce oxidative stress and subsequently deliver regenerative biomolecules, such as vascular endothelial growth factor (VEGF), in response to elevated MMP activity, thereby suppressing inflammation while promoting tissue repair and functional recovery [60]. For infectious diseases, hydrogel-based drug delivery systems have been extensively investigated for the localized administration of antimicrobial and antiviral agents

[61]. The incorporation of advanced nanocarriers, including lipid nanoparticles and transferosomes, enhances drug stability, tissue penetration, and retention at the infection site [62]. Such nanocomposite hydrogels have successfully delivered drugs including acyclovir and miconazole, providing prolonged release, improved skin accumulation, enhanced antimicrobial efficacy, and reduced dosing frequency compared with conventional topical formulations [63].

4.3. Ocular, Neural, and Transdermal Applications

Injectable smart hydrogels have gained considerable attention for ocular, neural, and transdermal drug delivery owing to their ability to prolong drug retention, provide sustained release, and improve therapeutic efficacy [64]. In ocular applications, thermoresponsive hydrogels based on hyaluronan–Pluronic F-127 and chitosan-graft-poly(N-isopropylacrylamide) have demonstrated prolonged release of drugs such as brinzolamide, dexamethasone, and sunitinib, thereby extending precorneal residence time and reducing dosing frequency for the management of glaucoma and age-related macular degeneration [65]. Nanocomposite hydrogels incorporating poly(butyl cyanoacrylate) (PBCA) and cerium oxide nanoparticles have also shown significant neuroprotective effects by reducing retinal ganglion cell loss and mitigating oxidative stress-induced retinal damage. Supramolecular polymer–nanoparticle hydrogels further enhance ocular therapy through sustained intraocular drug release [66].

In neural tissue engineering, stimuli-responsive conductive hydrogels loaded with bioactive molecules such as Wnt5a promote axonal regeneration and functional recovery following spinal cord injury by responding to the acidic injury microenvironment. Injectable self-healing hydrogels carrying stem cells and neuroprotective drugs have also improved motor function and nerve conduction in preclinical models. For transdermal delivery, hydrogels containing lipid-based nanocarriers, including solid lipid nanoparticles and transferosomes, enhance skin penetration and provide sustained systemic delivery of therapeutics such as acyclovir and insulin, resulting in prolonged therapeutic efficacy and improved patient compliance [67].

Figure 2 presents the major biomedical applications of injectable smart hydrogels. Following localized administration, the hydrogel depot provides sustained and controlled drug release for cancer treatment, inflammatory and infectious diseases, ocular therapy, neural regeneration, and transdermal delivery. These systems enhance therapeutic efficacy, improve patient compliance, and minimize systemic toxicity [68].

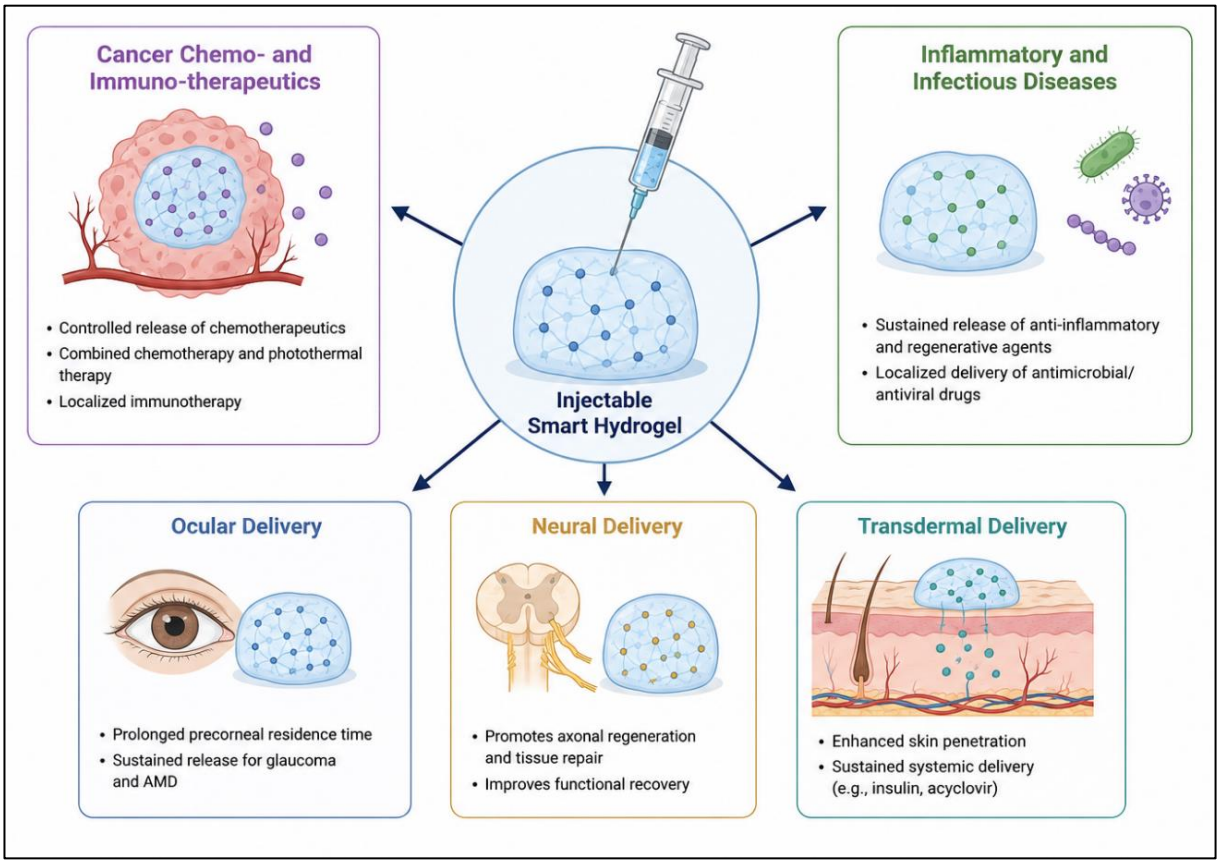

Figure 2: Schematic illustration of the major drug delivery applications of injectable smart hydrogels.

5. Challenges and Translational Perspectives

5.1. Biocompatibility, Biodegradability, and Toxicity

Despite their remarkable therapeutic potential, the clinical translation of injectable smart hydrogels is primarily constrained by safety considerations. Biocompatible and biodegradable polymers, including hyaluronic acid, gelatin, chitosan, and self-assembling peptides, are preferred because they degrade into non-toxic metabolites through natural enzymatic or hydrolytic pathways [69].

However, multifunctional hydrogels often incorporate synthetic polymers, chemical crosslinkers, and responsive nanoparticles, such as copper sulfide (CuS) and polydopamine (PDA), whose long-term biocompatibility and degradation profiles remain incompletely understood [70]. Residual monomers, degradation products, and nanoparticle accumulation may induce cytotoxicity, oxidative stress, or undesirable immune responses. Furthermore, most preclinical investigations have focused on short-term therapeutic efficacy, whereas comprehensive long-term studies evaluating biodistribution, biodegradation, chronic toxicity, immunogenicity, and pharmacokinetics under Good Laboratory Practice (GLP) conditions remain limited. Addressing these safety concerns is essential before widespread clinical implementation [71].

5.2. Scalability and Regulatory Hurdles

The large-scale manufacturing of injectable smart hydrogels presents significant technical and regulatory challenges. Industrial production requires stringent control over polymer synthesis, crosslinking efficiency, sterilization, storage stability, and batch-to-batch reproducibility while preserving injectability and stimulus responsiveness. Maintaining consistent gelation kinetics and drug-loading efficiency during scale-up is particularly challenging [72]. From a regulatory perspective, most smart hydrogel formulations are classified as combination products because they integrate biomaterials, therapeutic agents, and, in many cases, functional nanoparticles or biological components. This classification necessitates extensive evaluation of material quality, manufacturing consistency, pharmacokinetics, toxicology, and clinical performance, increasing both development time and regulatory complexity [73]. The establishment of standardized manufacturing protocols, quality control parameters, and internationally harmonized regulatory guidelines will be crucial for accelerating the successful clinical translation and commercialization of smart injectable hydrogel systems [74].

6. Discussion

This area of research is progressing towards "multi-smart" materials, which can respond effectively to multiple stimuli. For example, the controlled release of therapeutic agents, such as ROS scavengers and growth factors, regulates sophisticated biological events such as tissue regeneration following SCI. Nevertheless, the "translational gap" between the laboratory and the clinic persists, indicating that, although the preclinical data are impressive, showing almost complete eradication of tumors and functional recovery, human clinical trial data for these smart stimuli-responsive materials are lacking in the current literature.

Conclusion

A unique opportunity for precise medication administration exists through smart stimuli-responsive injectable hydrogels, which increase therapeutic efficacy and minimize systemic side effects by virtue of their ability to form stable depot formulations and release agents in response to specific stimuli. Their promise has been realized through the successful application of these materials in preclinical models of brain repair, cancer, and eye disease. Overcoming challenges associated with biocompatibility, scalability, and regulatory approval will be necessary for the therapeutic benefits of these innovative materials to be realized.

Acknowledgements

The authors thank the Management and Higher officials of Sri Ramachandra Institute of Higher Education and Research (SRIHER) for providing necessary infrastructure for carrying out this review work. They also thank Principal, Sri Ramachandra Faculty of Pharmacy (DST-FIST Sponsored Department), SRIHER for the constant motivation and encouragement towards the completion of the review work.

Author Contributions

SRS: Conceptualization; **BJ:** Investigation; **RS:** Data curation; **AR:** Writing – original draft, supervision.

Declaration of Interest statement

The authors declare no financial or non-financial conflict of interests.

Funding

Not applicable

Ethics approval and consent to participate

Not applicable

AI Declaration

The author declares that no artificial intelligence (AI) tool was used to generate or draft the scientific content of this manuscript. Grammarly AI was used solely to improve the language, grammar, readability, and clarity of the manuscript. The author carefully reviewed and edited all suggested changes and takes full responsibility for the accuracy, originality, and integrity of the final content.

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