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Review Article

Advances in Injectable Polysaccharide Hydrogels for Site-Specific Drug Delivery

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ABSTRACT

Injectable polysaccharide hydrogels are emerging as promising platforms for sitespecific drug delivery because they can be administered minimally invasively, conform to complex tissue geometries, and form *in situ* depots for sustained local drug release. This review summarizes recent advances in injectable systems based on chitosan, alginate, hyaluronic acid, dextran, and cellulose derivatives, with emphasis on their sources, structural features, and suitability for injectable formulations. Key hydrogel formation strategies-including physical, chemical, enzymatic, and stimulitriggered crosslinking-are discussed alongside critical physicochemical and biological properties that govern injectability, mechanical performance, swelling, and biocompatibility. Drug loading approaches and diffusion-, degradation-, and stimuliresponsive release mechanisms are outlined, with applications highlighted in cancer therapy, tissue engineering, regenerative medicine, wound healing, and localized infection control. Emerging smart and hybrid nanocomposite hydrogels, together with current challenges in stability, scalability, reproducibility, and regulation, are considered to frame future directions for successful clinical translation of these versatile biomaterials.

Keywords: Biocompatibility, Injectable hydrogels, Polysaccharides, Site-specific drug delivery, Stimuli-responsive systems.

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INTRODUCTION

Injectable hydrogels are now considered one of the key platforms in modern drug delivery, offering a clear advantage over conventional dosage forms by forming directly at the desired site in the body. They are administered as a flowable solution and then transform into a gel after injection, which reduces the need for invasive procedures and helps keep the drug concentrated where it is needed most. The choice of polysaccharides and their specific properties used to formulate these injectable hydrogels are outlined in Table 1 and illustrated in Figure 1 (Parvin *et al.*, 2025).

Rationale for Injectable Hydrogels

The main advantage of injectable hydrogels is that they can be delivered in a minimally invasive way using ordinary needles or catheters, avoiding the need for surgical implantation. They can flow into and completely fill irregular defects, adjust to moving or soft tissues, and then slowly release the drug over days to months, which lowers dosing frequency and supports better patient adherence. This strategy is especially useful in situations like treating tumor margins or deep, hardtoreach wounds where accurate local placement of the formulation is essential. Polysaccharide-based systems commonly used for these applications, along with their key functional benefits, are summarized in Table 1 (Sarvepalli *et al.*, 2025).

Importance of Site-Specific Drug Delivery

Site-specific drug delivery helps reduce systemic side effects and the poor pharmacokinetic profiles often seen with oral or intravenous administration, because it allows therapeutic levels of the drug to be achieved directly at the diseased site while largely sparing healthy tissues. By taking advantage of mechanisms such as the Enhanced Permeability and Retention (EPR) effect or using active targeting approaches, this strategy can markedly improve treatment effectiveness, especially in complex diseases like cancer where offtarget exposure frequently leads to doselimiting toxicity. Injectable polysaccharide hydrogels, as summarized in Table

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1, offer a flexible platform to realize this kind of localized and controlled drug release (Zhao *et al.*, 2020).

Advantages of Polysaccharide-Based Systems

Polysaccharide hydrogels are particularly attractive because they are naturally abundant, relatively inexpensive, and closely resemble the extracellular matrix, which supports good biocompatibility and helps limit immune reactions. Unlike many synthetic polymers, they are broken down by the body's own enzymes (such as hyaluronidases), generating nontoxic degradation products. Their physicochemical properties can also be precisely adjusted, since their inherent functional groups allow for controlled crosslinking and drug conjugation. Several of the most commonly used polysaccharides and their key features relevant to injectable hydrogel design are summarized in Table 1. In addition, many of these materials already have FDA approval for other biomedical uses, which facilitates clinical translation, while intrinsic activities-such as the antimicrobial effects of chitosan or the cellsignaling functions of hyaluronic acid-offer further therapeutic benefits (Zhang *et al.*, 2025).

Polysaccharides Used in Injectable Hydrogels

Polysaccharides are key building blocks for injectable hydrogels because they are plentiful, structurally adaptable, and inherently compatible with biological tissues, making them ideal for minimally invasive drug delivery systems. Sourced from renewable natural materials, they can be classified according to their origin, chemical composition, and functional characteristics, offering a broad design toolbox for tailoring hydrogels to specific sites in the body, as outlined in Table 2 and illustrated in Figure 2 (El-Sayed *et al.*, 2022).

Natural Sources and Classification

Polysaccharides used in injectable hydrogels come from three main sources: plants, animals, and microorganisms. Plant-derived examples include cellulose from wood pulp and starch from cereals, animal-derived ones include chitin from crustacean shells and hyaluronic acid obtained from rooster combs or produced by fermentation, while microbial/bacterial sources include materials such as xanthan gum and gellan gum. This broad range of origins is complemented by several ways of classifying them, for example into homopolysaccharides, which are made of a single type of monosaccharide (such as amylose), and heteropolysaccharides, which contain different monosaccharide units (such as alginate). They can also be grouped by charge: anionic polymers like alginate, cationic ones like chitosan, and neutral ones like dextran. This structural and physicochemical diversity allows formulation scientists to finetune gelation behavior and performance, with plant-derived polysaccharides contributing to sustainability and microbially produced polymers offering high purity and better control for biomedical applications (Mohammed *et al.*, 2021).

Common Polymers (Chitosan, Alginate, Hyaluronic Acid, Dextran, Cellulose Derivatives)

Chitosan is obtained by deacetylating chitin from crustacean shells and is a positively charged polysaccharide with amino groups that give it pHresponsive behavior, strong mucoadhesion, and inherent antimicrobial properties, making it particularly suitable for injectable hydrogels at wound sites, where it can form a gel *in situ* in the presence of βglycerophosphate (Zhao *et al.*, 2023).

Alginate is a negatively charged polysaccharide extracted from brown algae that quickly forms hydrogels through ionic crosslinking with divalent cations such as Ca^{2+} or Ba^{2+}; its excellent waterholding capacity and good biocompatibility make it a popular choice for injectable depots in applications like tumor therapy and cartilage repair.

Hyaluronic Acid (HA), a glycosaminoglycan sourced from animal tissues or produced by microbial fermentation, closely resembles the natural extracellular matrix, supports cell migration via interactions with CD44 receptors, and can be formulated into shearthinning injectable gels using chemistries

Table 1: Common polysaccharides used in injectable hydrogels for site-specific drug delivery.

Polysaccharide	Natural Source	Key Properties	Typical Applications
Chitosan	Chitin (crustacean shells)	Biodegradable, mucoadhesive, pH-sensitive	Cancer therapy, wound healing (Muthu *et al.*, 2021).
Alginate	Brown seaweed	Mild gelation, biocompatible, ion-sensitive	Cell encapsulation, tissue engineering (Umekar *et al.*, 2025).
Hyaluronic acid	Animal tissues, microbial fermentation	High biocompatibility, bioactive	Joint delivery, cancer targeting. (Espah Borujeni *et al.*, 2025).
Dextran	Bacterial fermentation	Water-soluble, easily modifiable	Controlled drug release (Baek *et al.*, 2025).
Cellulose derivatives	Plant sources	Mechanical strength, stability	Sustained-release formulations (Marinho, 2025).

such as thiol-maleimide crosslinking, which is especially useful for ophthalmic and intraarticular injections.

Dextran is a glucosebased polysaccharide produced by bacteria; it is highly watersoluble and chemically stable, with relatively low viscosity and an enzymedegradable backbone, making it well suited for incorporation into thermosensitive hydrogel blends designed for sustained release of proteins and other biologics.

Cellulose derivatives, such as carboxymethyl cellulose and hydroxypropyl cellulose, are created by chemically modifying plantderived cellulose, allowing fine control over viscosity and, in some cases, thermoreversible gelation; these features improve injectability and performance when they are used in composite hydrogels, for example in the management of chronic wounds.

Hydrogel Formation and Crosslinking Mechanisms

Hydrogel formation in injectable polysaccharide systems depends on carefully controlled crosslinking, which drives the transition from a flowing sol to a solid gel and thereby supports both easy injection and *in situ* depot formation at the target site. These crosslinking mechanisms must balance reversibility, rate of gelation, and longterm stability, with physically crosslinked systems generally offering superior biocompatibility and chemically crosslinked systems providing greater mechanical robustness and persistence, as illustrated in Table 3 and Figure 3a (Sabarees *et al.*, 2026).

Physical Crosslinking

Physical crosslinking relies on noncovalent interactions-such as ionic gelation (for example, alginate with Ca^{2+} forming characteristic "eggbox" structures), hydrogen bonding, hydrophobic interactions, or stereo complex formation-to build the hydrogel network. These interactions give the material shearthinning behavior for easy injection and allow the gel to recover and "selfheal" after administration. Because the network is reversible, gelation is usually very fast (often within less than a minute) and does not generate toxic byproducts, which is advantageous in clinical use, although such physically crosslinked gels can be less mechanically robust over the long term when subjected to sustained stress (Yu *et al.*, 2021).

Chemical Crosslinking

Chemical crosslinking creates permanent covalent bonds within the hydrogel network through reactions such as Michael addition, Schiff base formation between aldehyde and amine groups, or photopolymerization of methacrylated polysaccharides under UV light. Crosslinkers like genipin or glutaraldehyde can generate mechanically robust gels with adjustable crosslinking density, which enhances elasticity (with storage modulus values that can reach around 10^4 Pa) and improves drug retention. However, these systems must be carefully optimized and thoroughly purified to minimize any residual crosslinker, as this can lead to cytotoxicity and compromise the safety of the final formulation (Jayachandran *et al.*, 2022).

Enzymatic and Stimuli-Triggered Gelation

Enzymatic gelation uses biological catalysts such as transglutaminase or Horseradish Peroxidase (HRP), together with hydrogen peroxide, to oxidize tyrosine residues on suitably modified polysaccharide chains, forming hydrogel networks under

Table 2: Polysaccharides commonly used in injectable hydrogels for site-specific drug delivery

Polysaccharide	Natural Source	Classification / Charge	Key Properties	Typical Injectable Hydrogel Applications
Chitosan	Deacetylated chitin from crustacean shells	Cationic heteropolysaccharide	pH-responsive, mucoadhesive, antimicrobial, biodegradable; amino functional groups enable chemical modification.	Wound healing, localized cancer therapy, mucosal drug delivery.
Alginate	Brown algae (marine source)	Anionic heteropolysaccharide	Rapid ionic gelation (Ca^{2+}/Ba^{2+}), high water retention, biocompatible.	Injectable depots, cartilage repair, tumor-targeted delivery.
Hyaluronic Acid	Animal tissues or bacterial fermentation	Anionic glycosaminoglycan	ECM mimicry, bioactive (CD44 interaction), shear-thinning, enzymatically degradable.	Ophthalmic injections, joint delivery, cancer targeting.
Dextran	Bacterial fermentation	Neutral homopolysaccharide	High solubility, low viscosity, enzyme-degradable, chemically versatile.	Sustained protein and peptide delivery.
Cellulose Derivatives (CMC, HPC, HPMC)	Plant cellulose (wood pulp, cotton)	Neutral / weakly anionic	Tunable viscosity, thermoreversible gelation, mechanical stability.	Chronic wound management, injectable composite hydrogels.

Table 3: Hydrogel Formation and Crosslinking Mechanisms in Injectable Polysaccharide Hydrogels.

Crosslinking Mechanism	Type of Interaction	Typical Polysaccharides / Systems	Key Features	Advantages	Limitations
Physical Crosslinking	Non-covalent (ionic, hydrogen bonding, hydrophobic interactions, stereocomplexation)	Alginate-Ca^{2+}, chitosan, cellulose derivatives, HA	Reversible networks, rapid sol-gel transition (<1 min), shear-thinning, self-healing.	High biocompatibility, no toxic crosslinkers, easy injectability.	Lower mechanical stability, possible premature dissolution under stress.
Ionic Gelation (subtype)	Electrostatic interactions ("egg-box" model)	Alginate-Ca^{2+} / Ba^{2+}	Fast gelation, tunable stiffness via ion concentration.	Mild conditions, clinically acceptable.	Ion exchange *in vivo* may weaken gels.
Chemical Crosslinking	Covalent bonds (Schiff base, Michael addition, photopolymerization)	Methacrylated HA, oxidized dextran, chitosan	Permanent networks, high elasticity (G′ up to 10^4 Pa), controlled crosslink density.	Enhanced mechanical strength, prolonged drug retention.	Risk of cytotoxicity if crosslinkers or initiators are not optimized.
Chemical Crosslinkers	Small-molecule or photo-initiated	Genipin, glutaraldehyde, UV-activated systems	Stable 3D networks, tunable degradation.	Durable hydrogels for long-term delivery.	Requires strict control of reaction conditions.
Enzymatic Crosslinking	Enzyme-mediated covalent bonding	HA-tyramine, gelatin-polysaccharide hybrids	Mild reaction (1-5 min), *in situ* gelation.	Excellent biocompatibility, tissue-friendly.	Cost of enzymes, sensitivity to local conditions.
Stimuli-Triggered Gelation	pH, temperature, light, enzyme-responsive	Chitosan-β-glycerophosphate, MMP-sensitive HA	On-demand gelation, environment-responsive behavior.	Site-specific and adaptive drug delivery.	Complex design, variability in biological environments.

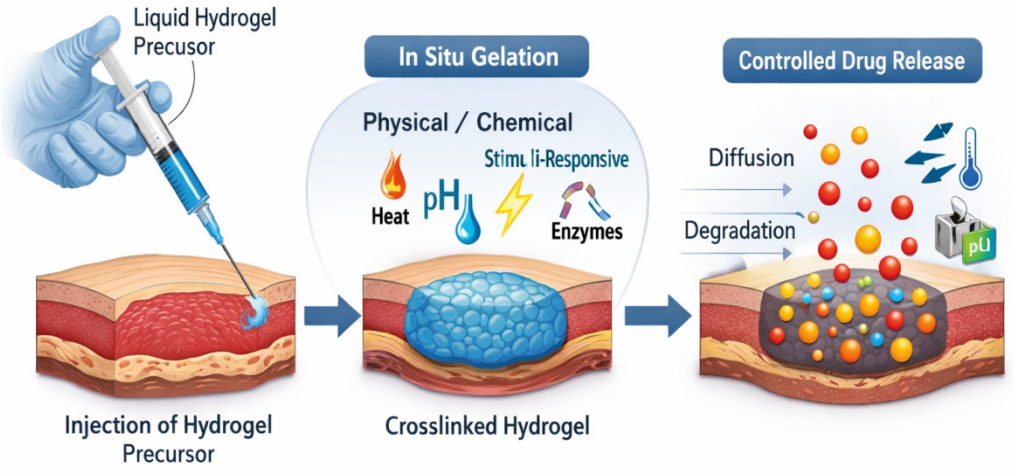

Figure 1: Schematic illustration of injectable polysaccharide hydrogel based site specific drug delivery.

very mild, cellfriendly conditions within a few minutes (typically 1-5 min). In parallel, stimuliresponsive systems are designed to gel or remodel in response to specific environmental cues-for example, pHsensitive hydrazone bonds that cleave in the acidic milieu of tumors, thermosensitive chitosan-glycerophosphate formulations that gel at body temperature, lightactivated chemistries, or matrices containing enzymecleavable peptide sequences such as those recognized by Matrix Metalloproteinases (MMPs). Together, these strategies enable ondemand gelation and adaptable drug release profiles that can dynamically match changing physiological or pathological microenvironments (Sabarees *et al.*, 2026).

Physicochemical and Biological Properties

Injectable polysaccharide hydrogels are designed with specific physicochemical and biological properties that make them highly effective for sitespecific drug delivery, combining easy flow during injection with sufficient structural integrity once

in place. These properties can be finely tuned by adjusting the polymer type, the degree and nature of crosslinking, and local environmental conditions so that the resulting gels closely resemble the characteristics of native tissues, as summarized in Table 4 and illustrated in Figure 3b (Nishiguchi, 2024).

Injectability and Rheological Behavior

For an injectable hydrogel, good injectability means that the material flows easily through a syringe but quickly regains its structure once inside the body. In practical terms, this is achieved through shearthinning behavior: the viscosity drops markedly under the high shear conditions of injection and then the gel rapidly recovers its elastic character within seconds after the shear is removed. Systems based on chitosan and βglycerophosphate are a classic example of thermosensitive, thixotropic formulations-they can pass smoothly through fine needles (around 25-30 G) at room temperature and then form a stable gel at body temperature (about 37°C), which is essential for accurate placement in restricted sites such as tumors or joint cavities (Wu *et al.*, 2024).

Biocompatibility and Biodegradability

Polysaccharide-based hydrogels generally show very good biocompatibility, which is reflected in high cell viability (often above 95% in standard assays such as MTT) and low levels of inflammatory cytokine release, partly because their structures resemble components of the natural extracellular matrix and several of them are already used in approved medical products (for example, alginate-based wound dressings). Their biodegradability is mainly driven by enzymatic hydrolysis: hyaluronidases break down hyaluronic acid with an *in vivo* halflife on the order of 1-2 days, lysozymes slowly cleave chitosan over weeks, and alginate lyases act on specific guluronate-rich segments of alginate, generating small, biocompatible metabolites such as glucuronic acid that are readily handled by normal metabolic pathways and do not accumulate in the body (Sharma & Bhende, 2024).

Swelling and Mechanical Strength

Swelling in polysaccharide hydrogels can be very pronounced, with many formulations absorbing several times their dry weight in water-often in the range of roughly 5- to 20-fold within a few hours because of their hydrophilic functional groups and nanosized mesh structure. This high swelling capacity promotes the diffusion of nutrients and metabolic waste through the gel,

Table 4: Physicochemical and Biological Properties of Injectable Polysaccharide Hydrogels.

Property	Key Parameters / Ranges	Representative Systems	Functional Significance in Drug Delivery
Injectability	Shear-thinning behavior; viscosity reduction from >10^3 Pa·s to <10 Pa·s at shear rates <10 s^{-1}.	Chitosan-β-glycerophosphate, HA-based hydrogels.	Enables smooth extrusion through fine needles (25-30G) and minimally invasive administration.
Rheological Recovery	Rapid recovery of storage modulus (G′ > G″, tan δ < 1) within seconds after injection.	Thermosensitive chitosan systems.	Ensures *in situ* gelation and retention at the target site.
Thermosensitivity	Sol at room temperature, gelation at 37°C.	Chitosan-β-glycerophosphate.	Precise localization in confined tissues (tumors, joints).
Biocompatibility	Cell viability >95% (MTT assay); low cytokine induction (IL-6 <50 pg/mL).	Alginate, HA, chitosan.	Minimizes inflammation and toxicity; suitable for clinical use.
Regulatory Acceptance	FDA-approved or clinically used polysaccharides.	Alginate (wound dressings), HA (injectables)	Facilitates translational and regulatory approval.
Biodegradability	Enzymatic degradation: HA (1-2 days), chitosan (weeks), alginate (via lyases).	HA, chitosan, alginate.	Controlled matrix erosion and safe metabolite clearance.
Swelling Behavior	Swelling ratio 500-2000%; mesh size 10-100 nm.	Hydrophilic polysaccharide networks.	Promotes nutrient diffusion and drug transport while maintaining depot integrity.
Mechanical Strength	Compressive modulus 0.1-500 kPa.	Alginate-Ca^{2+} (10-50 kPa), HA-thiol gels.	Matches mechanical properties of soft tissues.
Self-Healing Ability	Fracture energy >100 J/m^2.	HA-thiol and dynamic covalent networks.	Enhances durability under physiological stresses.

Table 5: Drug Loading and Release Mechanisms in Injectable Polysaccharide Hydrogels.

Category	Mechanism	Key Features	Outcome
Drug Loading	Physical entrapment	70-95% loading efficiency	Simple, suitable for hydrophilic drugs
	Electrostatic complexation	Charge-based reversible binding	Reduced burst release
	Covalent conjugation	Stable chemical linkage	Long-term retention
	Affinity binding	Cyclodextrin-guest interactions	Tunable, reversible release
	Nanoparticle integration	PLGA-loaded hydrogels	High payload for hydrophobic drugs
Drug Release	Diffusion-controlled	Fickian transport (D_eff/D_0 ≈ 0.1-0.5)	Short-term release (days)
	Degradation-controlled	Enzymatic erosion (1-5%/day)	Sustained release
	Stimuli-responsive	pH, temperature, enzymes	Site-specific, on-demand delivery

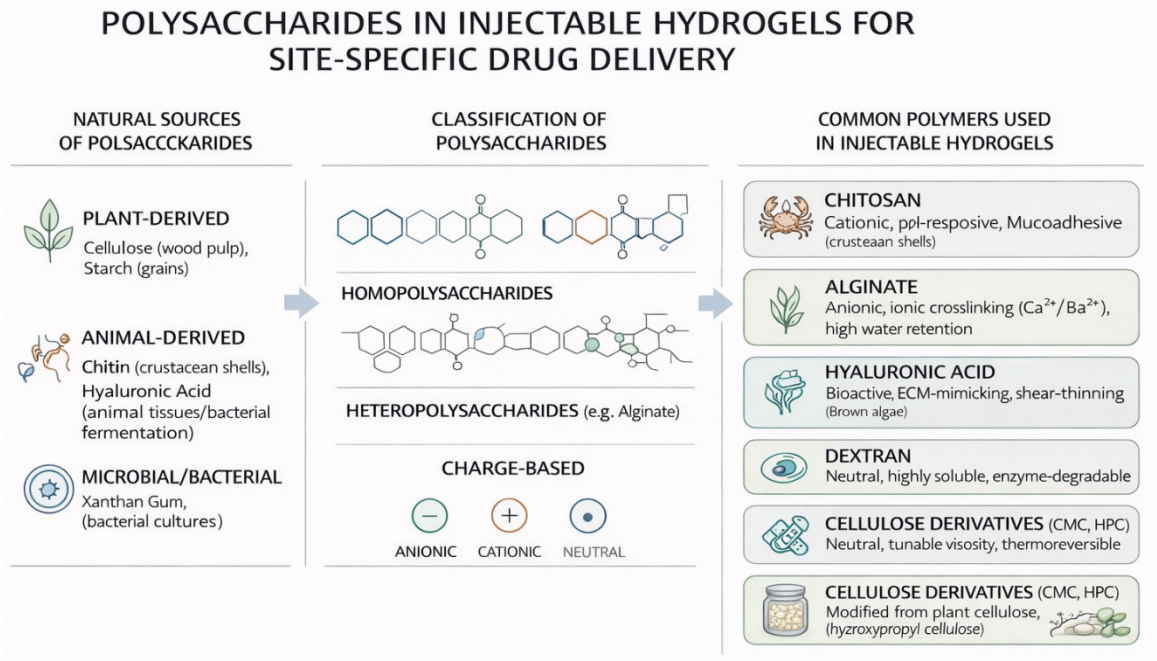

Figure 2: Polysaccharide in injectable hydrogels for site specific drug delivery system.

but is typically moderated by the degree of crosslinking so that drug release remains controlled rather than occurring as an initial burst.

In terms of mechanics, these hydrogels can be tuned to cover a wide spectrum of stiffness values, from very soft (comparable to brain tissue) to much stiffer (approaching cartilage), with compressive moduli spanning from fractions of a kilopascal up to several hundred kilopascals depending on the formulation. For example, alginate gels crosslinked with calcium ions can be adjusted into the tens of kilopascals range through ionic "cluster" formation, while hyaluronic acid systems crosslinked via thiol chemistry can form selfhealing networks with high fracture energy, meaning they can dissipate substantial mechanical stress without failing.

Drug Loading and Release Mechanisms

Polysaccharide hydrogels facilitate precise drug loading and controlled release, enabling sustained therapeutic levels at target sites while minimizing systemic exposure. These mechanisms leverage the hydrogel's porous network (pore sizes 10-200 nm) and tunable chemistry to achieve zero- to first-order kinetics over hours to months as mentioned in Table 5 and Figure 4 (Lei *et al.*, 2022).

Site-Specific and Targeted Drug Delivery Applications

Encapsulation Strategies

Drug loading into injectable polysaccharide hydrogels can be achieved through several complementary strategies, each offering different levels of control and stability. One of the simplest is physical entrapment during *in situ* gelation, where

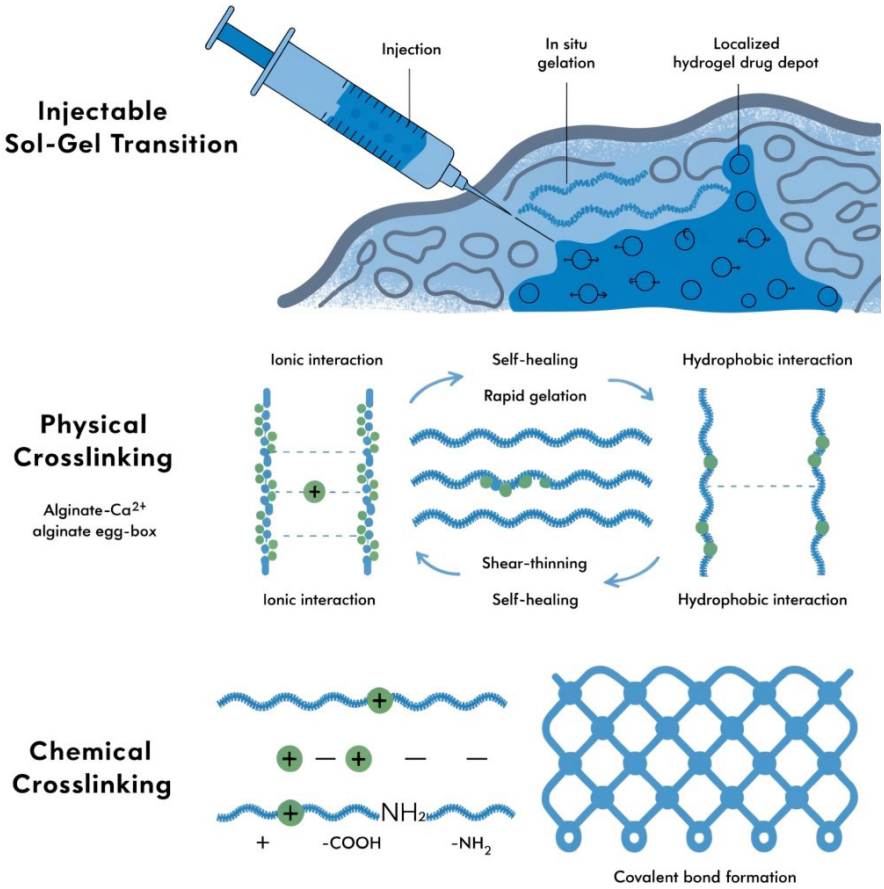

Figure 3a: Mechanisms of Injectable Polysaccharide Hydrogel Formation and *in situ*.

the drug is mixed with the polymer solution before injection so that, as the sol turns into a gel in the body, the molecules become immobilized within the network; this approach is especially effective for hydrophilic small molecules and often results in high loading efficiency (Ahmed, 2015).

Electrostatic complexation takes advantage of charge interactions, for example pairing a negatively charged polysaccharide like alginate with a positively charged drug such as doxorubicin, thereby forming stable ionic complexes within the gel. For even more durable attachment, drugs particularly proteins or peptides can be covalently linked to the polymer backbone using chemistries like click reactions or Schiff base formation, which tether the therapeutic to the matrix and allow controlled cleavage under physiological conditions (Caló *et al.*, 2015).

Affinity-based approaches introduce specific binding motifs into the hydrogel, such as cyclodextrin units that can host hydrophobic guest molecules like adamantane; in hyaluronic acid matrices, these reversible host-guest interactions allow tunable, noncovalent binding and release. In addition, incorporating drug-loaded nanoparticles (for example, PLGA nanospheres) into the polysaccharide network provides an extra level of control and can greatly increase the loading and sustained release of poorly soluble or hydrophobic agents (Li *et al.*, 2020).

Injectable polysaccharide hydrogels are particularly effective for sitespecific delivery because they can flow into and adapt to complex tissue shapes, then form a stable depot that releases drugs locally over prolonged periods. Their architecture closely mimics the extracellular matrix, which supports cell infiltration, neovascularization, and tissue integration, thereby enhancing therapeutic outcomes across a range of clinical indications, as summarized and illustrated in Figure 5 (Liao *et al.*, 2025).

Cancer Therapy

In cancer therapy, injectable polysaccharide hydrogels can be placed directly within or around a tumor to deliver drugs such as doxorubicin or paclitaxel, which helps achieve much higher drug concentrations at the tumor site than with standard systemic administration while limiting exposure of healthy tissues. By combining this local delivery with passive mechanisms like the enhanced permeability and retention effect and active targeting-for example, using aptamermodified chitosan hydrogels-these systems can substantially boost intratumoral drug accumulation compared with intravenous dosing (Liu *et al.*, 2025).

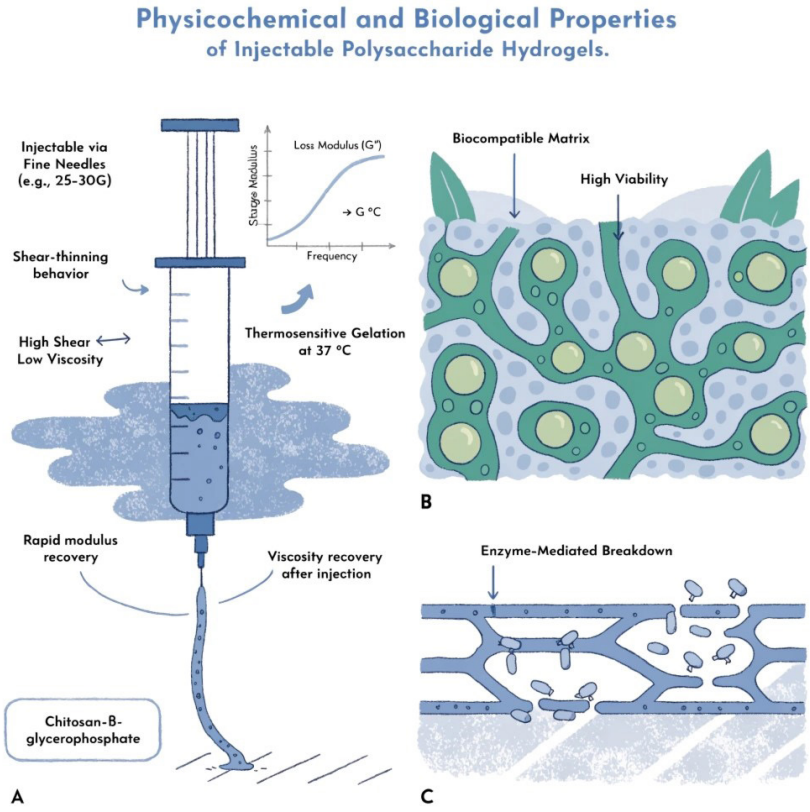

Figure 3b: Physicochemical and biological properties of injectable polysaccharide hydrogels.

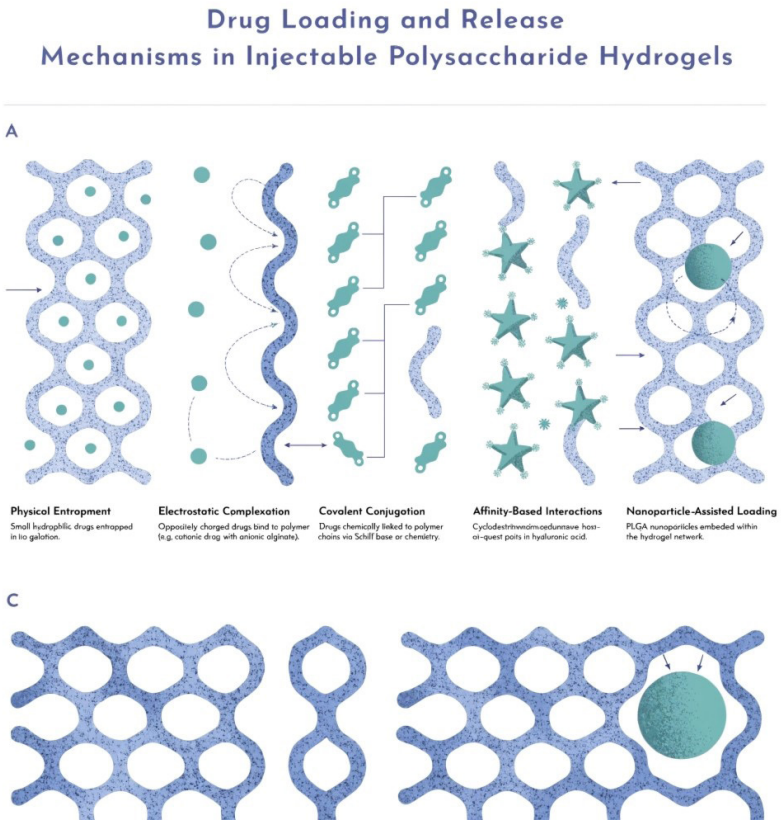

Figure 4: Drug loading and release mechanism in injectable polysachharide hydrogels.

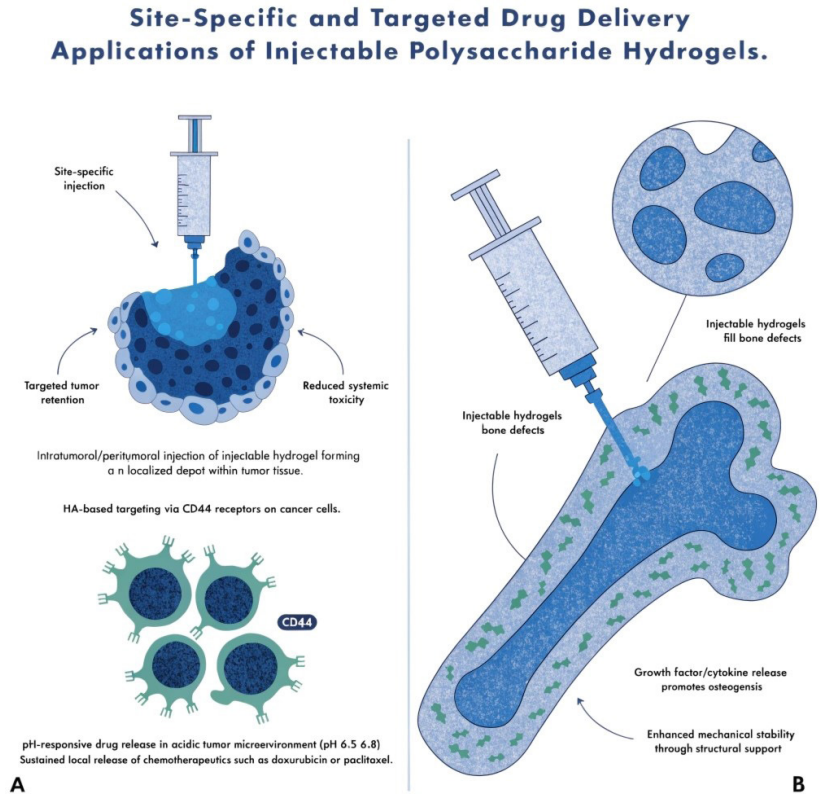

Figure 5: Site-specific and targeted drug delivery applications of injectable polysachharide hydrogels.

Tissue Engineering and Regenerative Medicine

For regenerative medicine, injectable polysaccharide hydrogels can be engineered to gradually deliver growth factors such as VEGF and BMP2 from dextran- or alginate-based matrices, supporting new blood vessel formation and bone regeneration in settings like criticalsized bone defects or myocardial infarction. By maintaining a controlled release over several weeks, these systems encourage progressive tissue ingrowth and functional recovery, often accompanied by substantial restoration of mechanical strength in the repaired region (Yasmin *et al.*, 2026).

Wound Healing and Localized Infections

Chitosan-alginate hydrogel dressings can be loaded with antimicrobial agents such as silver ions or vancomycin to treat chronic wounds, where their adhesive nature helps them stay in place and their ability to disrupt biofilms contributes to faster reepithelialization and overall wound closure. By maintaining intimate contact with the wound bed and providing sustained local drug release, these systems have been reported to markedly speed up healing compared with conventional dressings (Abdollahi *et al.*, 2025).

Recent Advances and Smart Injectable Hydrogels

Recent work on injectable polysaccharide hydrogels has focused on adding smart features that allow these materials to sense and respond to local physiological conditions, thereby improving the accuracy and control of sitespecific drug delivery. Between roughly 2020 and 2025, many systems have combined responsive chemistries (for example, pH-, redox-, or enzymecleavable linkages) with nanoengineered components, such as drugloaded nanoparticles or inorganic nanofillers, to achieve better spatiotemporal control, multimodal therapy, and improved mechanical performance compared with earlier, more static hydrogel formulations (Tian *et al.*, 2025).

Stimuli-Responsive Systems (pH, Temperature, Enzymes)

Stimuli-responsive hydrogels dynamically alter structure in response to tumor or inflammatory microenvironments. pH-sensitive systems employ acid-labile bonds like hydrazones in HA-doxorubicin conjugates, disassembling at pH 6.5 to release 70-90% payload within hours, compared to stability at physiological pH 7.4. Temperature-responsive platforms, such as chitosan-PNIPAAm grafts with LCST ~32°C, gel upon body heat for intratumoral depots, while enzyme-triggered networks use MMP-9 cleavable peptides (e.g., GPLGLAG↓) in alginate matrices, achieving on-demand growth factor release during tissue remodeling (Protsak & Morozov, 2025).

Hybrid and Nanocomposite Hydrogels

Hybrid hydrogels combine polysaccharides with synthetic polymers or inorganic nanoparticles for synergistic properties. Chitosan-PEGDA networks boost mechanical resilience (fracture toughness >200 J/m^2), while nanocomposites embed gold nanorods or mesoporous silica in dextran gels for photothermal-chemotherapy synergy, elevating local temperatures to 45°C and eradicating 95% of cancer cells *in vivo*. PLGA-alginate hybrids enable dual burst-sustained release profiles, with clinical trials demonstrating 3-fold prolonged circulation in arthritis models (Mohanty *et al.*, 2023).

Challenges and Limitations

Despite remarkable progress, injectable polysaccharide hydrogels face significant hurdles that impede widespread clinical adoption, particularly in achieving consistent performance and regulatory approval. These challenges span material stability, manufacturing scalability, and standardization, necessitating innovative solutions for practical translation (Almawash *et al.*, 2022).

Stability and Scale-Up Issues

Stability concerns include premature gelation during storage, shear-induced degradation, or batch variability from natural polymer polydispersity (M_w 10^5-10^6 Da, PDI >2), leading to inconsistent injectability (viscosity fluctuations >50%). Scale-up from lab (mL) to industrial (L) batches struggles with uniform crosslinking-ionic alginate gels exhibit 20-30% modulus variation-and sterilization (autoclaving denatures HA), while lyophilization compromises rehydration and bioactivity, limiting shelf-life to months under refrigeration (Badruddoza *et al.*, 2023).

Reproducibility and Regulatory Concerns

Reproducibility suffers from source-dependent impurities (e.g., heavy metals in algal alginate) and ill-defined gelation kinetics, yielding variable drug release (CV >25% across batches). Regulatory hurdles demand extensive GMP validation, long-term biocompatibility data per ISO 10993, and clearance for endogenous degradation products, with FDA scrutiny on genipin crosslinkers' carcinogenicity delaying IND filings. Clinical translation lags, with <10% of preclinical hydrogels reaching Phase II due to immunogenicity risks in sensitive sites like the brain (Catoira *et al.*, 2020).

Future Perspectives and Clinical Translation (Brief)

Future injectable polysaccharide hydrogels will focus on smart, personalized, and clinically adaptable systems. Emerging trends include stimuli- and time-responsive (4D) hydrogels, AI-guided formulation design, gene delivery platforms, and advanced biofabrication techniques such as bioprinting for patient-specific therapy. From a translational standpoint, regulatory approvals, modular manufacturing platforms, and GMP-scale production are accelerating commercialization. With growing clinical trials and industry partnerships, injectable polysaccharide hydrogels are poised to become next-generation, on-demand drug delivery systems across oncology, regenerative medicine, and beyond.

CONCLUSION

Injectable polysaccharide hydrogels have gained significant attention as advanced platforms for site-specific drug delivery due to their biocompatibility, biodegradability, and ability to form in situ depots. Recent developments in chemical modification, crosslinking techniques, and stimuli-responsive designs have enhanced their mechanical strength, drug-loading efficiency, and controlled release performance. These systems offer improved localized therapeutic action while minimizing systemic toxicity, making them highly suitable for applications in oncology, wound healing, and regenerative medicine.

Despite promising preclinical outcomes, challenges related to large-scale production, sterilization, reproducibility, and regulatory approval remain. Continued interdisciplinary research and clinical validation are essential to translate these innovative hydrogel systems into safe and effective therapeutic solutions.

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ABBREVIATIONS

AI: Artificial Intelligence; **BMP-2:** Bone Morphogenetic Protein-2; **Ca^{2+}:** Calcium Ion; **CD44:** Cluster of Differentiation 44; **CMC:** Carboxymethyl Cellulose; **CV:** Coefficient of Variation; **Da:** Dalton; **EPR:** Enhanced Permeability and Retention; **FDA:** Food and Drug Administration; **G′:** Storage Modulus; **G″:** Loss Modulus; **GMP:** Good Manufacturing Practice; **HA:** Hyaluronic Acid; **HPC:** Hydroxypropyl Cellulose; **HPMC:** Hydroxypropyl Methylcellulose; **HRP:** Horseradish Peroxidase; **IL-6:** Interleukin-6; **IND:** Investigational New Drug; **ISO:** International Organization for Standardization; **LCST:** Lower Critical Solution Temperature; **MMP:** Matrix Metalloproteinase; **MTT:** 3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium Bromide; **Mw:** Molecular Weight; **PDI:** Polydispersity Index; **PEGDA:** Poly(ethylene.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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