Review Article

Hydrogel-Based Drug Delivery: Development of Stimuli-Responsive Hydrogels for On-Demand Therapeutic Release

Gnana Infant Josuva S, Kamaleshwari B, Padma Preetha J, Gayathri R, Sankar C.
Department of Pharmaceutics, KMCH College of Pharmacy, Kalappatti Road, Coimbatore-641048, Tamil Nadu, India.
***Corresponding author's E-mail:** kamaleshwari.b@kmchcop.ac.in

Received: 08-05-2026; **Revised:** 23-07-2026; **Accepted:** 29-07-2026; **Published online:** 20-08-2026.

ABSTRACT

Hydrogel-based drug delivery systems have gained considerable attention as next-generation therapeutic platforms owing to their high-water retention capacity, extracellular matrix–like architecture, and adjustable physicochemical characteristics. Recent advances in stimuli-responsive hydrogels have enabled controlled, site-specific, and on-demand drug release triggered by internal biological cues—such as pH variations, enzymatic activity, glucose levels, and redox conditions—or externally applied stimuli including temperature changes, light exposure, magnetic fields, and electrical signals. By responding dynamically to disease-specific microenvironments, these intelligent systems address several drawbacks associated with conventional drug delivery methods, including poor targeting efficiency, systemic toxicity, and low patient adherence. This review critically discusses the shortcomings of traditional drug delivery strategies, highlights the justification for hydrogel-based on-demand delivery systems, and outlines the scope and objectives of research on stimuli-responsive hydrogels, emphasizing their expanding role in contemporary biomedical applications.

Keywords: Hydrogel, drug delivery, controlled release, systemic toxicity.

1. INTRODUCTION

The effectiveness of pharmaceutical therapies is strongly influenced by the design and performance of drug delivery systems. Traditional delivery routes frequently struggle to sustain therapeutically relevant drug concentrations at target sites, often resulting in diminished treatment efficacy and unwanted systemic effects. To overcome these challenges, advanced delivery platforms—particularly stimuli-responsive hydrogels—have been developed to enable precise, controlled, and responsive drug release. By integrating principles from polymer chemistry, materials science, and biomedical engineering, these smart hydrogel systems are capable of adapting their structure and behavior in response to physiological changes or externally applied signals [1-5].

1.1 Limitations of Conventional Drug Delivery Systems

Conventional drug delivery modalities—such as oral dosage forms, injections, and topical preparations—are often associated with inherent limitations that restrict their therapeutic performance [6–8]. These systems commonly exhibit low bioavailability, lack of targeting specificity, and uncontrolled drug release profiles, which can lead to suboptimal drug concentrations or systemic toxicity [7,8]. Rapid clearance from the body, the need for frequent dosing, and the inability to adapt to dynamic physiological conditions further compromise treatment outcomes [7]. Moreover, fragile biomolecules including proteins, peptides, and nucleic acids are particularly susceptible to degradation when administered using traditional delivery approaches [6,7].

1.2 Rationale for Hydrogel-Based On-Demand Drug Delivery

Hydrogels represent an attractive platform for on-demand drug delivery due to their three-dimensional, crosslinked polymer networks capable of retaining significant quantities of water or biological fluids [9,11]. Their porous architecture permits efficient diffusion of therapeutic agents, while their mechanical and chemical properties can be precisely engineered to meet specific clinical requirements [9,11]. Stimuli-responsive hydrogels can undergo reversible structural changes—such as swelling, contraction, or network degradation—upon exposure to defined internal or external triggers, thereby allowing spatiotemporal regulation of drug release [10]. These adaptive characteristics make hydrogel systems particularly advantageous for localized therapies, chronic disease management, and personalized medicine [10,11].

1.3 Scope and Objectives of the Review

This review aims to provide a comprehensive and systematic evaluation of stimuli-responsive hydrogel-based drug delivery systems developed for on-demand therapeutic applications [12,13]. The scope encompasses fundamental aspects of hydrogel materials, classification based on stimulus responsiveness, mechanisms controlling drug release, and recent advances in hydrogel design and fabrication [12,13]. Furthermore, current biomedical applications, translational challenges, and future research directions are discussed to support the development of next-generation intelligent drug delivery platforms [12–14].

2. Fundamentals of Hydrogel Systems

Hydrogels form a fundamental class of biomaterials extensively investigated for controlled and on-demand drug delivery applications. Their interconnected polymer networks, high hydration capacity, and tissue-like properties enable close interaction with biological environments [15–17]. A detailed understanding of hydrogel structure, physicochemical behaviour, and biological performance is essential for designing effective stimuli-responsive drug delivery systems [16,17].

2.1 Definition, Structure, and Classification of Hydrogels

Hydrogels are three-dimensional networks of hydrophilic polymers capable of absorbing and retaining large volumes of water or physiological fluids while maintaining structural integrity due to crosslinking [15,16]. These crosslinks may arise from covalent bonds or physical interactions such as hydrogen bonding, ionic associations, or hydrophobic forces [15]. At the structural level, hydrogels consist of polymer chains arranged into an interconnected network, with mesh size governed by factors such as polymer molecular weight, crosslinking density, and swelling degree [15,17]. This mesh size critically influences drug loading efficiency and release behavior [15]. Therapeutic agents may be incorporated through physical entrapment, chemical conjugation, or electrostatic interactions within the hydrogel matrix [15,17].

Hydrogels can be categorized based on multiple parameters [16,17]:

(i) Origin: natural, synthetic, or hybrid systems;
(ii) Crosslinking type: physical or chemical;
(iii) Charge characteristics: neutral, anionic, cationic, or zwitterionic;
(iv) Functional behavior: conventional or stimuli-responsive hydrogels that react to environmental cues such as pH, temperature, enzymatic activity, redox conditions, light, or electric fields [16,17].

This versatility in composition and structure allows hydrogel systems to be tailored for specific drug delivery requirements, particularly for controlled and site-specific therapeutic release [15–17].

2.2 Physicochemical Properties Relevant to Drug Delivery

The efficacy of hydrogel-based drug delivery systems is largely determined by their physicochemical characteristics, which govern drug encapsulation, stability, and release profiles [18–20]. Key properties include swelling capacity, porosity, mechanical strength, diffusivity, and responsiveness to external or internal stimuli [18,20].

Swelling behavior dictates water uptake and directly affects drug diffusion through the hydrogel network [18,19]. Highly swollen matrices generally promote rapid release, whereas densely crosslinked hydrogels enable prolonged and sustained delivery [18,20]. Network porosity and mesh size are particularly important for the transport of macromolecular therapeutics such as proteins and nucleic acids [19,20].

Stimuli-responsive hydrogels exhibit structural or physicochemical alterations upon exposure to specific triggers [18,20]. For instance, pH-sensitive hydrogels exploit ionizable groups to respond to pathological pH variations, while thermo-responsive systems undergo sol–gel transitions near physiological temperatures [18,20]. These features enable precise, intelligent control over drug release in response to disease-relevant conditions [18–20].

2.3 Biocompatibility and Biodegradability Considerations

For clinical translation, hydrogel-based drug delivery systems must exhibit excellent biocompatibility and controlled biodegradability [21–23]. Biocompatible hydrogels should not provoke cytotoxic effects, immune reactions, or long-term inflammation following administration [21,22]. Polymer selection, crosslinking chemistry, and degradation byproducts are critical determinants of biological safety[21,23].

Naturally derived polymers often display favorable biocompatibility due to their resemblance to native biological components, though they may present challenges such as batch variability and limited mechanical robustness [21,23]. In contrast, synthetic polymers offer enhanced reproducibility and tunability but may require chemical modification or blending to improve biological interactions [22,23].

Biodegradable hydrogels are designed to degrade into non-toxic byproducts that can be metabolized or excreted safely [21,23]. Degradation may occur via hydrolytic, enzymatic, or redox-mediated mechanisms [23]. Controlled degradation is particularly beneficial for temporary drug delivery applications, as it eliminates the need for post-therapy surgical removal [21,22].

Achieving an optimal balance between biocompatibility and biodegradability is essential for the development of safe, effective, and patient-friendly hydrogel-based on-demand drug delivery systems [21–23].

3. Design Principles of Stimuli-Responsive Hydrogels

The development of stimuli-responsive hydrogels for on-demand drug delivery relies on the deliberate coordination of polymer chemistry, network design, crosslinking methodology, and drug incorporation strategies [24–26]. Fine-tuning these parameters allows hydrogels to selectively react to specific biological or externally applied signals, thereby enabling localized and controlled therapeutic release while minimizing off-target effects and systemic toxicity [24,25].

3.1 Polymer Selection and Network Architecture

The selection of polymeric materials is a fundamental factor governing the functionality of stimuli-responsive hydrogel systems [24–26]. Polymer composition directly influences stimulus sensitivity, mechanical robustness, degradation kinetics, and compatibility with therapeutic molecules [24,26]. Both naturally derived polymers—such as chitosan, alginate, gelatin, and hyaluronic acid—and synthetic polymers—including poly(ethylene glycol), poly(N-

isopropylacrylamide), and poly(vinyl alcohol)—are extensively employed [25,26]. Hybrid formulations are often preferred, as they combine the biological advantages of natural polymers with the tunable properties of synthetic counterparts [26].

Network architecture plays a decisive role in regulating hydrogel performance [24,26]. Parameters such as polymer chain length, degree of branching, and crosslinking density determine the mesh size and permeability of the network, thereby controlling drug diffusion and release behavior [24]. Lightly crosslinked hydrogels typically allow rapid drug diffusion, whereas densely crosslinked systems facilitate sustained and prolonged release [24,26]. Advanced structural designs, including interpenetrating polymer networks, semi-interpenetrating systems, and nanocomposite hydrogels, provide improved mechanical stability and enable responsiveness to multiple stimuli, making them well suited for complex physiological environments [25,26].The introduction of functional groups—such as ionizable moieties, temperature-sensitive segments, or enzyme-degradable linkages—within polymer backbones further enhances responsiveness, allowing hydrogels to adapt to disease-specific microenvironmental conditions [25,26].

3.2 Crosslinking Strategies: Physical, Chemical, and Dynamic Approaches

Crosslinking methods critically define the stability, adaptability, and drug release characteristics of hydrogel systems [27–29]. Physically crosslinked hydrogels are formed through reversible non-covalent interactions such as hydrogen bonding, electrostatic forces, hydrophobic interactions, or crystalline domains [27,29]. These systems are often injectable, self-healing, and well suited for minimally invasive administration [28,29].

In contrast, chemically crosslinked hydrogels rely on permanent covalent bonds generated using crosslinkers or click-based reactions, resulting in mechanically robust and structurally stable networks [27,28]. While such systems provide prolonged integrity, excessive rigidity or potential cytotoxicity of crosslinking agents necessitates careful material selection [28].

Dynamic crosslinking strategies have emerged as a powerful alternative for on-demand drug delivery [28,29]. These hydrogels employ reversible or stimuli-cleavable bonds—such as Schiff base linkages, boronate esters, disulfide bridges, or host–guest interactions—that allow the network to reversibly reorganize in response to environmental triggers [28,29]. This dynamic behavior enables precise modulation of drug release in response to pH fluctuations, redox conditions, glucose levels, or enzymatic activity [28,29].

3.3 Drug Loading Strategies and Encapsulation Efficiency

Efficient incorporation of therapeutic agents within hydrogel matrices is essential for achieving optimal therapeutic outcomes while reducing dosing frequency and adverse effects [30–32]. Drug loading strategies generally fall into three categories: physical entrapment, covalent attachment, and affinity-driven interactions [30,31].

Physical encapsulation involves incorporating the drug during hydrogel formation, resulting in its entrapment within the polymeric network [30,32]. Although this method is simple and versatile, it may lead to initial burst release [31]. Covalent conjugation strategies chemically tether drug molecules to polymer chains using stimulus-sensitive linkers, offering enhanced stability and controlled release profiles [31,32]. Affinity-based loading leverages specific interactions—such as electrostatic attraction or ligand–receptor binding—between the drug and hydrogel components, improving retention and minimizing premature leakage [30,32].

Encapsulation efficiency is influenced by factors including drug molecular weight, solubility, hydrogel mesh size, and polymer–drug interactions [30,31]. Rational optimization of these parameters enables high drug loading and sustained release, particularly for labile biomacromolecules such as proteins, peptides, and nucleic acids [30–32].

3.4 Mechanisms of Stimuli-Triggered Drug Release

Stimuli-responsive hydrogels achieve controlled drug release through physicochemical or chemical transformations initiated by specific internal or external cues [33,35]. pH-sensitive systems utilize ionizable functional groups that alter swelling behavior in response to pathological pH variations commonly observed in tumors or inflamed tissues [33,34]. Thermo-responsive hydrogels undergo reversible sol–gel transitions near body temperature, enabling injectable formulations that solidify *in situ* [33,35].

Enzyme-responsive hydrogels release therapeutics through selective degradation mediated by disease-associated enzymes, while redox-sensitive systems rely on cleavage of disulfide bonds in reductive intracellular environments [34,35]. External triggers—including light, magnetic fields, and electrical stimulation—offer precise spatial and temporal control, allowing drug release to be activated on demand [33,35].Together, these mechanisms enable intelligent drug delivery platforms capable of synchronizing therapeutic release with disease progression and patient-specific physiological conditions [33,35].

4. Classification of Stimuli-Responsive Hydrogels

Stimuli-responsive hydrogels—often referred to as smart or intelligent hydrogels—are engineered to undergo predictable structural or physicochemical changes in response to defined environmental signals [36–38]. These transformations, including swelling, degradation, or network rearrangement, allow precise regulation of drug release [36,38]. Based on the type of triggering stimulus, these systems can be broadly classified into distinct categories, each offering unique advantages for targeted therapeutic delivery [36,37].

4.1 pH-Responsive Hydrogels

pH-responsive hydrogels contain ionizable functional groups that undergo protonation or deprotonation in response to changes in environmental Ph [36,37]. This behavior results in controlled swelling or contraction, enabling selective drug release in tissues exhibiting abnormal pH, such as tumors, inflamed regions, or specific segments of the gastrointestinal tract [36–38].

Anionic hydrogels generally swell under alkaline conditions, whereas cationic systems expand in acidic environments [36,37]. Such tunable responses have been widely exploited for site-specific drug delivery, particularly in cancer therapy, oral delivery, and intracellular applications [37,38].

4.2 Temperature-Responsive Hydrogels

Temperature-sensitive hydrogels exhibit reversible phase transitions in response to thermal variations, typically defined by lower or upper critical solution temperatures [39–41]. Polymers such as poly(N-isopropylacrylamide) display sharp sol–gel transitions near physiological temperature, making them ideal for injectable and *in situ*-forming drug delivery systems [39,40].These hydrogels remain fluid at ambient temperatures and rapidly form gels upon exposure to body heat, enabling localized drug retention and sustained release [40,41]. Such properties are particularly beneficial for minimally invasive treatments and post-operative drug delivery [39–41].

4.3 Enzyme-Responsive Hydrogels

Enzyme-responsive hydrogels are engineered to undergo degradation or structural modification in the presence of specific enzymes overexpressed in pathological conditions such as cancer, inflammation, or infection [42–44]. These systems incorporate enzyme-cleavable peptide sequences or labile polymer backbones [42,43].

Drug release is therefore localized and highly selective, significantly reducing off-target effects [43,44]. Enzyme-responsive hydrogels are especially promising for tissue-specific therapies and regenerative medicine applications[42–44].

4.4 Redox-Responsive Hydrogels

Redox-responsive hydrogels exploit differences in redox potential between extracellular and intracellular environments [45–47]. These systems commonly incorporate disulfide bonds that remain stable in oxidative conditions but cleave in reductive environments rich in intracellular glutathione [45,46].

Disulfide bond cleavage disrupts the hydrogel network, resulting in rapid drug release [45,47]. Such systems are particularly effective for intracellular delivery and cancer therapy, offering enhanced selectivity and therapeutic efficacy [45–47].

4.5 Glucose-Responsive Hydrogels

Glucose-responsive hydrogels are primarily developed for self-regulated insulin delivery systems in diabetes management [48–50]. These hydrogels respond to fluctuations in glucose concentration through enzymatic reactions, reversible boronic acid–diol interactions, or competitive glucose binding mechanisms [48,49].

Elevated glucose levels trigger network expansion or bond dissociation, resulting in proportional insulin release [49,50]. This feedback-controlled mechanism closely mimics physiological insulin regulation and holds strong potential for closed-loop drug delivery systems [48–50].

4.6 Light-Responsive Hydrogels

Light-sensitive hydrogels enable externally regulated drug release through irradiation with specific wavelengths [51–53]. These systems incorporate photo-cleavable bonds, photo-isomerizable groups, or photothermal agents that induce structural changes upon light exposure [51,53].

Near-infrared light is particularly advantageous due to its deeper tissue penetration and reduced phototoxicity [52,53]. Light-responsive hydrogels offer exceptional spatial and temporal precision, making them promising for localized cancer therapy and ophthalmic treatments [51–53].

4.7 Magnetic- and Electric-Field-Responsive Hydrogels

Magnetic-responsive hydrogels incorporate magnetic nanoparticles that respond to externally applied magnetic fields, enabling drug release through localized heating or mechanical deformation [54–56]. Electric-field-responsive hydrogels contain conductive or polyelectrolyte components that undergo reversible volumetric or permeability changes upon electrical stimulation [55,56].

These systems enable non-invasive, real-time control over drug release and are particularly suitable for implantable delivery devices and biosensing applications [54–56].

4.8 Multi-Stimuli-Responsive Hydrogels

Multi-responsive hydrogels are engineered to react to two or more stimuli either simultaneously or sequentially, offering superior adaptability in complex biological environments [57–59]. By integrating multiple responsive elements within a single network, these systems enable synergistic or hierarchical drug release behavior [57,58].

Such platforms are particularly valuable for precision medicine, where overlapping pathological signals may coexist [58,59]. multi-stimuli-responsive hydrogels enhance targeting accuracy, reduce burst release, and improve therapeutic outcomes [57–59].

5. Fabrication and Engineering Strategies

The fabrication and engineering approaches employed in hydrogel-based drug delivery systems critically influence their physicochemical stability, responsiveness to stimuli, drug encapsulation efficiency, and release performance [60,61]. Recent progress in material processing and bioengineering has enabled the creation of advanced hydrogel constructs with programmable architectures, enhanced mechanical resilience, and precise control over therapeutic release [61,66–68]. This section outlines both

conventional and emerging fabrication methodologies used to engineer stimuli-responsive hydrogels for on-demand drug delivery [60,61].

5.1 Conventional Hydrogel Fabrication Techniques

Traditional hydrogel fabrication methods generally involve bulk polymerization, solution-based processing, and crosslinking reactions to generate macroscopic three-dimensional polymer networks [60–62]. These approaches typically rely on free-radical polymerization, ionic interactions, or covalent crosslinking to establish stable hydrogel matrices [60,62]. Commonly employed initiation techniques include thermal activation, photoinitiation, and redox-driven polymerization, each offering distinct advantages with respect to reaction kinetics, scalability, and process control [61,62].

Solution casting followed by solvent evaporation or gelation is widely used to produce hydrogel films and membranes, particularly for transdermal and localized drug delivery applications [60,61]. Although these conventional techniques are relatively simple and economically feasible, they often provide limited control over network uniformity, pore architecture, and stimulus sensitivity [61,62]. Despite these constraints, traditional fabrication strategies remain essential for generating baseline hydrogel systems and serve as reference platforms for evaluating more advanced engineering approaches [60–62].

5.2 Injectable and In Situ Forming Hydrogels

Injectable and *in situ* forming hydrogels have attracted considerable interest due to their minimally invasive delivery and ability to adapt to irregular anatomical sites [63–65]. These systems are typically administered as low-viscosity precursor solutions that undergo sol–gel transformation upon exposure to physiological conditions such as body temperature, pH changes, ionic environments, or enzymatic activity [63,64].

Thermo-responsive polymers, including poly(N-isopropylacrylamide) and poloxamer-based formulations, are frequently utilized to induce gelation at physiological temperatures [63,65]. Similarly, pH- and enzyme-responsive hydrogels exploit endogenous biological signals to initiate network formation or crosslinking [64,65]. The localized gelation of injectable hydrogels enhances drug retention at the target site, reduces systemic distribution, and improves patient compliance [63–65]. Consequently, these systems are particularly advantageous for applications in oncology, tissue repair, and localized therapeutic delivery [63,64].

5.3 Three-Dimensional Printed and Microfabricated Hydrogels

Three-dimensional (3D) printing and microfabrication technologies have transformed hydrogel engineering by enabling precise control over structural geometry, pore distribution, and spatial placement of therapeutic agents [66–68]. Additive manufacturing techniques such as extrusion-based printing, inkjet printing, stereolithography, and digital light processing facilitate the layer-by-layer fabrication of complex hydrogel constructs with high reproducibility and customization [66,67].

Microfabrication approaches, including soft lithography and microfluidic techniques, enable the production of hydrogel microparticles and patterned scaffolds with well-defined dimensions and morphologies [67,68]. These technologies enhance control over drug release kinetics, support gradient-based delivery, and enable patient-specific treatment strategies [66,68]. Furthermore, 3D-printed hydrogels can be designed to exhibit responsiveness to multiple stimuli, making them highly versatile platforms for personalized and on-demand therapeutic applications [66–68].

5.4 Nanocomposite and Hybrid Hydrogel Systems

Nanocomposite and hybrid hydrogels incorporate nanoscale fillers, secondary polymer networks, or multifunctional components within the hydrogel matrix to enhance mechanical strength, functional responsiveness, and drug-loading efficiency [69–70]. Commonly integrated nanomaterials include silica nanoparticles, clay nanosheets, carbon-based nanostructures, metallic nanoparticles, and polymeric nanocarriers [69,71].

Hybrid hydrogel systems often combine natural and synthetic polymers to simultaneously improve biocompatibility, mechanical stability, and functional adaptability [70,71]. The inclusion of nanomaterials introduces additional properties such as magnetic sensitivity, photothermal responsiveness, or electrical conductivity, enabling externally regulated drug release [69–71]. These multifunctional hydrogel platforms represent a significant advancement toward intelligent and responsive drug delivery systems [69–71].

6. Mechanisms of On-Demand Drug Release

On-demand drug release from stimuli-responsive hydrogels is governed by a combination of physicochemical and biochemical processes that regulate the transport and release of therapeutic agents in response to specific triggers [72–83]. A clear understanding of these mechanisms is essential for designing hydrogel systems capable of delivering drugs with precise spatial, temporal, and dosage control [75,76]. Key mechanisms include diffusion, swelling, degradation, and dynamic bond reorganization [72,75,78,81].

6.1 Diffusion-Controlled Drug Release

Diffusion-driven release represents one of the most fundamental transport mechanisms in hydrogel-based systems [72–74]. In this process, drug molecules migrate from the hydrogel interior to the surrounding environment following a concentration gradient [72,73]. The diffusion rate is influenced by factors such as hydrogel mesh size, crosslink density, hydration level, and the physicochemical properties of the drug molecule [72–74].

In stimuli-responsive systems, external or internal triggers can reversibly alter network porosity, thereby modulating diffusion behavior [72,74]. For example, pH- or temperature-induced structural changes can expand or contract the

polymer matrix, enabling controlled acceleration or suppression of drug release [73,74]. Diffusion-controlled mechanisms are particularly suitable for the sustained delivery of low-molecular-weight and hydrophilic drugs[72–74].

6.2 Swelling-Regulated Drug Release

In swelling-controlled systems, drug release kinetics are governed by the rate at which the hydrogel absorbs solvent and expands in response to environmental stimuli [75–77]. Changes in pH, temperature, or ionic strength can induce polymer relaxation and solvent uptake, increasing mesh size and facilitating drug diffusion [75,76].In such systems, polymer relaxation rather than molecular diffusion becomes the rate-limiting step [75,77]. Stimuli-responsive hydrogels exhibiting pronounced swelling behavior can enable pulsatile or stepwise drug release, particularly advantageous for macromolecular therapeutics such as proteins and peptides [76,77]. This mechanism provides enhanced temporal control, making it suitable for on-demand therapeutic delivery [75–77].

6.3 Degradation-Mediated Drug Release

Degradation-triggered drug release relies on the controlled breakdown of the hydrogel network, leading to the liberation of encapsulated therapeutics [78–80]. Degradation processes may occur through hydrolysis, enzymatic cleavage, or redox-mediated bond dissociation [78–80]. In biodegradable systems, drug release is primarily dictated by polymer erosion rather than diffusion [78,80].

Stimuli-responsive degradation enables site-specific and disease-triggered drug delivery [79,80]. For example, enzyme-sensitive hydrogels selectively degrade in pathological tissues with elevated enzymatic activity, while redox-responsive systems exploit intracellular reducing environments [79,80]. Such systems are particularly beneficial for temporary therapeutic applications, as they eliminate the need for surgical removal after treatment [78–80].

6.4 Dynamic Bond Cleavage and Network Rearrangement

Advanced on-demand drug delivery systems utilize dynamic covalent or supramolecular interactions that allow reversible network restructuring [81–83]. These hydrogels incorporate stimuli-sensitive bonds—such as Schiff bases, disulfide linkages, boronate esters, or host–guest interactions—that undergo cleavage or exchange reactions upon exposure to specific triggers [81,82].

Such dynamic systems exhibit self-healing behavior and reversible drug release, enabling repeated or pulsatile dosing in response to fluctuating physiological conditions[81-83]. This mechanism provides exceptional control over release kinetics and is particularly promising for precision medicine and real-time responsive therapeutic platforms[82,83].

7. Biomedical Applications of Stimuli-Responsive Hydrogels

Stimuli-responsive hydrogels have emerged as multifunctional platforms across diverse biomedical fields due to their ability to respond intelligently to physiological or externally applied signals [84–98]. By enabling controlled, localized, and on-demand drug delivery, these materials significantly enhance therapeutic outcomes while minimizing adverse systemic effects [85,93,98].

7.1 Cancer Treatment

In oncology, stimuli-responsive hydrogels are extensively explored for the localized delivery of chemotherapeutics, immunotherapeutic agents, and gene-based drugs [84–86]. Tumor microenvironments exhibit distinct features—including acidic pH, elevated enzyme levels, hypoxia, and altered redox balance—that can be exploited to trigger selective drug release [84,85].

pH-, enzyme-, and redox-sensitive hydrogels facilitate targeted drug activation within tumor tissues, thereby improving therapeutic indices and reducing systemic toxicity [84–86]. Injectable and externally triggered systems further enable sustained, pulsatile, and spatially controlled drug release, making them well suited for combination and personalized cancer therapies [85,86].

7.2 Wound Healing and Infection Management

In wound care, stimuli-responsive hydrogels provide a hydrated environment conducive to tissue repair while enabling controlled delivery of antimicrobial agents [87–89]. Chronic wounds, including diabetic ulcers, are characterized by abnormal pH, elevated glucose levels, and excessive enzymatic activity, which can serve as endogenous triggers for responsive drug release [87,89].

Antimicrobial hydrogels that release therapeutic agents in response to wound-specific cues effectively inhibit biofilm formation and infection progression [88,89]. Additionally, injectable and self-healing hydrogels conform to irregular wound geometries, improving coverage, comfort, and healing outcomes [87–89].

7.3 Diabetes and Metabolic Disease Management

Stimuli-responsive hydrogels have shown great promise in diabetes treatment by enabling glucose-sensitive insulin delivery [90–92]. These hydrogels are designed to sense variations in blood glucose levels and release insulin, accordingly, effectively emulating the natural function of pancreatic β-cells [90–92].

Common strategies involve glucose oxidase-mediated reactions, phenylboronic acid-glucose interactions, and competitive binding approaches [90,92]. Such smart delivery systems can reduce the risk of hypoglycaemia, minimize the need for frequent injections, and improve patient adherence and quality of life [91,92].

7.4 Tissue Engineering and Regenerative Medicine

In regenerative medicine, stimuli-responsive hydrogels serve as adaptable scaffolds that promote cell attachment, proliferation, and differentiation [93,95]. Their hydrated, flexible networks mimic natural extracellular matrices, encouraging proper cell-material interactions [93,94].

These hydrogels also facilitate controlled delivery of growth factors, cytokines, and stem cells over time and space, enhancing tissue repair [93,95]. Enzyme- and mechanically responsive hydrogels can further remodel in response to cellular activity, supporting the formation of functional tissue and integration with the host environment [94,95].

7.5 Ocular, Transdermal, and Implantable Delivery Systems

Stimuli-responsive hydrogels are increasingly applied in ophthalmic, transdermal, and implantable drug delivery systems, where controlled and sustained release is essential [96–98]. In ocular applications, pH- and temperature-sensitive hydrogels extend drug residence on the eye surface, improving therapeutic availability [96,97].

Transdermal hydrogels control drug permeation while maintaining skin hydration and minimizing irritation [97]. Implantable hydrogels provide prolonged delivery for chronic conditions, with release profiles that can be modulated non-invasively using stimuli such as light, magnetic fields, or electrical signals [96–98].

8. Preclinical and Clinical Advances

The journey of stimuli-responsive hydrogel-based drug delivery systems from laboratory research to clinical use requires comprehensive preclinical testing, pharmacokinetic evaluation, and clinical validation [99–107]. Recent studies have improved understanding of both *in vitro* and *in vivo* performance, therapeutic potential, and commercialization feasibility [100,101,105–107].

8.1 In Vitro and In Vivo Evaluation Models

In vitro and *in vivo* studies are critical to evaluate hydrogel safety, functionality, and drug release before clinical application [99–101]. Laboratory tests typically examine swelling, degradation, mechanical properties, cytotoxicity, and drug release under simulated physiological conditions [99,100]. Cellular assays evaluate biocompatibility, uptake, and therapeutic efficacy [99–101].

Animal studies, including rodents and larger species, provide insight into hydrogel stability, biodegradability, immune compatibility, and stimulus-responsive drug release [100,101]. Disease-specific models, such as tumor-bearing or diabetic animals, help assess site-specific, on-demand therapeutic performance [100]. These evaluations guide formulation optimization and predict clinical behavior [99–101].

8.2 Pharmacokinetics and Therapeutic Performance

Pharmacokinetic studies analyze drug absorption, distribution, metabolism, elimination, and concentration at target sites [102–104]. Stimuli-responsive hydrogels often show prolonged retention, reduced systemic exposure, and improved bioavailability [102–104].

Therapeutic effectiveness depends on the hydrogel's ability to release drugs in response to specific physiological cues, maintaining concentrations within the therapeutic range [102,104]. For instance, localized hydrogel depots in cancer therapy enhance antitumor effects while reducing systemic toxicity [103,104]. Similarly, glucose-responsive hydrogels improve glycemic control through regulated insulin release [103]. These advantages support reduced dosing frequency, better adherence, and improved clinical outcomes [102–104].

8.3 Clinical Translation and Marketed Products

Although most stimuli-responsive hydrogels are still in preclinical development, some have progressed to clinical trials and commercial availability, particularly in localized drug delivery and tissue regeneration [105–107]. Thermo-responsive and *in situ*-forming hydrogels are the most mature clinically, with applications in ophthalmology, oncology, and pain management [105,107].

Commercial products, such as injectable depots and hydrogel wound dressings, demonstrate controlled drug release even if fully stimulus-responsive behavior is not achieved [105,106]. Ongoing trials investigate smart hydrogels for cancer therapy, insulin delivery, and post-surgical release, showing their potential in precision medicine [106,107]. Challenges remain in scalable production, regulatory approval, and long-term safety, highlighting the need for multidisciplinary collaboration [105–107].

9. Challenges and Limitations

Despite remarkable progress, several obstacles limit the widespread clinical adoption of stimuli-responsive hydrogels [108–119]. These challenges encompass material properties, manufacturing feasibility, biocompatibility, and regulatory pathways [111–119]. Addressing these issues is essential to fully realize the therapeutic potential of smart hydrogel systems [108,113,119].

9.1 Mechanical Stability and Long-Term Performance

Hydrogel mechanical integrity is a critical factor for implantable or long-duration applications [108–110]. Many stimuli-responsive hydrogels have high water content and modest mechanical strength, making them prone to deformation, fracture, or premature degradation under physiological stresses [108,109]. Repeated swelling and deswelling cycles can further compromise network stability and result in unpredictable drug release [108–110].

Long-term performance is influenced by material fatigue, relaxation, and gradual loss of stimuli responsiveness [108,110]. Maintaining consistent mechanical behavior while preserving responsiveness remains challenging [108–110]. Strategies such as double-network hydrogels, nanocomposite reinforcement, and dynamic covalent crosslinking have been explored to enhance durability, but further optimization is required for prolonged *in vivo* applications [108–110].

9.2 Scalability and Manufacturing

Scaling hydrogel production while maintaining reproducibility poses significant challenges [111–113]. Many fabrication techniques require precise reaction conditions, complex chemistries, or specialized equipment, making

industrial-scale production difficult [111,112]. Batch-to-batch consistency in crosslinking, responsiveness, and drug loading is particularly critical [111–113].

Advanced methods such as 3D printing and microfabrication provide high precision but often have low throughput and elevated costs [112,113]. Additional factors, including sterilization, storage, and packaging, further complicate commercialization [111,113]. Developing standardized, scalable, and cost-effective manufacturing protocols is key to bringing smart hydrogel technologies to market [111–113].

9.3 Safety, Toxicity, and Immunogenicity

Ensuring biocompatibility is crucial for clinical translation [114–116]. Toxicity may arise from unreacted monomers, crosslinkers, degradation products, or embedded nanoparticles [114,116]. Additionally, certain stimuli-responsive components—such as photo initiators or magnetic nanoparticles—can elicit cytotoxic or inflammatory responses if not properly engineered [115,116].Immunogenicity is another concern, particularly for long-term or implantable systems [114,115]. Undesired immune activation may result in chronic inflammation, fibrosis, or device failure [114]. Comprehensive *in vitro* and *in vivo* safety evaluations are necessary to assess both acute and chronic toxicity and potential immune interactions [114–116].

9.4 Regulatory and Translational Hurdles

Regulatory pathways for stimuli-responsive hydrogels are often complex due to their multifunctional nature, potentially classifying them as drugs, devices, or combination products [117–119]. The absence of standardized evaluation protocols for smart materials further complicates regulatory approval [117,118].

Long-term safety, reproducibility, and demonstration of clinical superiority over existing therapies are necessary for approval [117–119]. Bridging preclinical success with clinical efficacy requires interdisciplinary collaboration, robust trial design, and early engagement with regulatory agencies [118,119]. Streamlined guidelines are essential to accelerate the clinical adoption of stimuli-responsive hydrogel technologies [117–119].

10. Emerging Trends and Future Perspectives

Recent advances in materials science, biotechnology, and digital health are transforming hydrogel-based drug delivery. Stimuli-responsive hydrogels are transitioning from passive carriers to intelligent therapeutic systems capable of autonomous decision-making, real-time responsiveness, and patient-specific customization. The following trends are shaping the next generation of on-demand delivery systems.

10.1 Smart and Self-Regulated Drug Delivery

Self-regulated hydrogels represent an evolution toward autonomous drug delivery systems that mimic physiological feedback. These systems detect pathological cues, such as pH, enzyme activity, glucose levels, or inflammatory markers, and adjust drug release in a closed-loop manner without external intervention. Such hydrogels are particularly valuable for chronic conditions requiring adaptive dosing, including diabetes, cancer, and inflammatory disorders. By integrating molecular recognition and dynamic polymer networks, they offer precise temporal control, reduced dosing frequency, and minimized side effects.

10.2 Integration with Biosensors and Digital Health

Coupling hydrogels with biosensors and digital health platforms enables real-time monitoring and adaptive drug release. Sensor-integrated hydrogels can detect physiological changes and trigger drug release, accordingly, allowing highly personalized therapy.

Advances in wearable and implantable sensors, wireless communication, and data analytics enable seamless integration between hydrogels and digital monitoring systems. These hybrid platforms facilitate precision treatment, remote patient management, and enhanced adherence in chronic disease care.

10.3 Personalized and Precision Medicine

Patient-specific factors—including genetics, metabolism, and disease state—necessitate hydrogel platforms capable of customized dosing and drug release profiles. Techniques such as 3D printing and modular assembly allow precise control over hydrogel architecture, drug distribution, and responsiveness. Personalized hydrogel design enables tailored therapy, enhanced efficacy, and reduced side effects, aligning with the objectives of precision medicine.

10.4 Artificial Intelligence-Assisted Hydrogel Design

Artificial intelligence (AI) and machine learning (ML) are emerging as transformative tools for hydrogel design. AI can analyze complex datasets to predict polymer–drug interactions, optimize network structure, and fine-tune stimulus responsiveness efficiently[120].

Combining computational modeling with high-throughput experimentation and data-driven optimization accelerates development, reduces trial-and-error, and supports the creation of next-generation intelligent hydrogels with enhanced translational potential.

11. Conclusions and Outlook

Stimuli-responsive hydrogel-based drug delivery systems have emerged as versatile platforms capable of on-demand, site-specific therapeutic release. Advances in material design, fabrication methods, and responsiveness to physiological and external stimuli have addressed many limitations of conventional drug delivery, improving drug targeting, controlled release, and therapeutic efficacy.

Challenges including mechanical durability, scalable manufacturing, long-term safety, and regulatory compliance remain. Future efforts should focus on integrating autonomous feedback mechanisms, biosensing, and artificial intelligence (AI)-driven design to accelerate clinical translation and enable more personalized

therapeutic strategies. With continued interdisciplinary collaboration, these smart hydrogels are poised to play a pivotal role in precision therapeutics and personalized medicine.

Source of Support: The author(s) received no financial support for the research, authorship, and/or publication of this article

Conflict of Interest: The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

REFERENCES

1. Zhang Y, Wu BM, *Current advances in stimuli-responsive hydrogels as smart drug delivery carriers*, Gels, 2023;9:838. DOI: 10.3390/gels9100838; PMID: 37888411.

2. Bordbar-Khiabani A, Gasik M, *Smart hydrogels for advanced drug delivery systems*, International Journal of Molecular Sciences, 2022;23:3665. DOI: 10.3390/ijms23073665; PMID: 35409025.

3. Salehi S, Naghib SM, Garshasbi HR, Ghorbanzadeh S, Zhang W, *Smart stimuli-responsive injectable gels and hydrogels for drug delivery and tissue engineering applications: A review*, Frontiers in Bioengineering and Biotechnology, 2023;11:1104126. DOI: 10.3389/fbioe.2023.1104126; PMID: 36911200.

4. Koetting MC, Peters JT, Steichen SD, Peppas NA, *Stimulus-responsive hydrogels: Theory, modern advances, and applications*, Materials Science and Engineering R: Reports, 2015;93:1–49. DOI: 10.1016/j.mser.2015.04.001; PMID: 27134415.

5. Yu H, Gao R, Liu Y, Fu L, Zhou J, Li L, *Stimulus-responsive hydrogels as drug delivery systems for inflammation targeted therapy*, Advanced Science, 2024;11:2306152. DOI: 10.1002/advs.202306152.

6. Andrade F, Roca-Melendres MM, Durán-Lara EF, Rafael D, Schwartz S Jr, *Stimuli-responsive hydrogels for cancer treatment: The role of pH, light, ionic strength and magnetic field*, Cancers, 2021;13:1164. DOI: 10.3390/cancers13051164; PMID: 33801375.

7. Fuchs S, Ernst AU, Wang LH, Shariati K, Wang X, Liu Q, Ma M, *Hydrogels in emerging technologies for type 1 diabetes*, Chemical Reviews, 2021;121:11458–11526. DOI: 10.1021/acs.chemrev.0c01062; PMID: 34398641.

8. Chao Y, Chen Q, Liu Z, *Smart injectable hydrogels for cancer immunotherapy*, Advanced Functional Materials, 2020;30:1902785. DOI: 10.1002/adfm.201902785.

9. Catoira MC, Fusaro L, Di Francesco D, Ramella M, Boccafoschi F, *Overview of natural hydrogels for regenerative medicine applications*, Journal of Materials Science: Materials in Medicine, 2019;30:115. DOI: 10.1007/s10856-019-6318-7; PMID: 31522389.

10. Zhao X, Lang Q, Yildirimer L, Lin ZYT, Cui W, Annabi N, Ng KW, Dokmeci MR, Ghaemmaghami AM, Khademhosseini A, *Photocrosslinkable gelatin hydrogel for epidermal tissue engineering*, Advanced Healthcare Materials, 2016;5:108–118. DOI: 10.1002/adhm.201500005.

11. Annabi N, Tamayol A, Uquillas JA, Akbari M, Bertassoni LE, Cha C, Camci-Unal G, Dokmeci MR, Peppas NA, Khademhosseini A, *25th anniversary article: Rational design and applications of hydrogels in regenerative medicine*, Advanced Materials, 2014;26:85–124. DOI: 10.1002/adma.201303233; PMID: 24105679.

12. Tibbitt MW, Anseth KS, *Hydrogels as extracellular matrix mimics for 3D cell culture*, Biotechnology and Bioengineering, 2009;103:655–663. DOI: 10.1002/bit.22361; PMID: 19472329.

13. Seliktar D, *Designing cell-compatible hydrogels for biomedical applications*, Science, 2012;336:1124–1128. DOI: 10.1126/science.1214804; PMID: 22654051.

14. Place ES, George JH, Williams CK, Stevens MM, *Synthetic polymer scaffolds for tissue engineering*, Chemical Society Reviews, 2009;38:1139–1151. DOI: 10.1039/B811430M; PMID: 19421585.

15. Drury JL, Mooney DJ, *Hydrogels for tissue engineering: Scaffold design variables and applications*, Biomaterials, 2003;24:4337–4351. DOI: 10.1016/S0142-9612(03)00340-5; PMID: 12922147.

16. Wichterle O, Lim D, *Hydrophilic gels for biological use*, Nature, 1960;185:117–118. DOI: 10.1038/185117a0.

17. Jeong B, Bae YH, Lee DS, Kim SW, *Biodegradable block copolymers as injectable drug-delivery systems*, Nature, 1997;388:860–862. DOI: 10.1038/42218; PMID: 9278056.

18. Elisseeff J, *Injectable cartilage tissue engineering*, Expert Opinion on Biological Therapy, 2004;4:1849–1859. DOI: 10.1517/14712598.4.12.1849; PMID: 15584898.

19. Lin CC, Anseth KS, *PEG hydrogels for the controlled release of biomolecules in regenerative medicine*, Pharmaceutical Research, 2009;26:631–643. DOI: 10.1007/s11095-008-9801-2; PMID: 19089601.

20. Burdick JA, Murphy WL, *Moving from static to dynamic complexity in hydrogel design*, Nature Communications, 2012;3:1269. DOI: 10.1038/ncomms2272; PMID: 23250416.

21. Caliari SR, Burdick JA, *A practical guide to hydrogels for cell culture*, Nature Methods, 2016;13:405–414. DOI: 10.1038/nmeth.3839; PMID: 27123816.

22. Li Z, Tan BH, *Towards the development of polycaprolactone-based amphiphilic block copolymers: Molecular design, self-assembly and biomedical applications*, Materials Science and Engineering C, 2014;45:620–634. DOI: 10.1016/j.msec.2014.10.026.

23. Dash TK, Konkimalla VB, *Polymeric modification and its implication in drug delivery: Polyethylene glycol (PEG)*, Drug Discovery Today, 2012;17:160–166. DOI: 10.1016/j.drudis.2011.10.007.

24. Wang C, Wang J, Zhang X, Yu S, Wen D, Hu Q, Ye Y, Bomba HN, Hu X, Liu Z, *Doxorubicin-interlayered pH-responsive nanocomposite hydrogel for localized combination cancer therapy*, Advanced Materials, 2018;30:1801327. DOI: 10.1002/adma.201801327.

25. Yu J, Zhang Y, Ye Y, DiSanto R, Sun W, Ranson D, Ligler FS, Buse JB, Gu Z, *Microneedle-array patches loaded with hypoxia-sensitive vesicles provide fast glucose-responsive insulin delivery*, Proceedings of the National Academy of Sciences of the United States of America, 2015;112:8260–8265. DOI: 10.1073/pnas.1505405112; PMID: 26100900.

26. Mitragotri S, Burke PA, Langer R, *Overcoming the challenges in administering biopharmaceuticals: Formulation and delivery strategies*, Nature Reviews Drug Discovery, 2014;13:655–672. DOI: 10.1038/nrd4363; PMID: 25103255.

27. Kabanov AV, Vinogradov SV, *Nanogels as pharmaceutical carriers: Finite networks of infinite capabilities*, Angewandte Chemie International Edition, 2009;48:5418–5429. DOI: 10.1002/anie.200900441; PMID: 19492449.

28. Oh JK, Drumright R, Siegwart DJ, Matyjaszewski K, *The development of microgels/nanogels for drug delivery applications*, Progress in Polymer Science, 2008;33:448–477. DOI: 10.1016/j.progpolymsci.2008.01.002; PMID: 19122876.

29. De Geest BG, De Koker S, Demeester J, De Smedt SC, Hennink WE, *Polymeric hydrogel nanoparticles for biomedical applications*, Soft Matter, 2009;5:282–291. DOI: 10.1039/B814266F; PMID: 20174471.

30. Cellesi F, *Thermoresponsive hydrogels for cellular delivery and tissue engineering*, Journal of Materials Chemistry B, 2015;3:6532–6543. DOI: 10.1039/C5TB00852A; PMID: 32262889.

31. Slaughter BV, Khurshid SS, Fisher OZ, Khademhosseini A, Peppas NA, *Hydrogels in regenerative medicine*, Advanced Materials, 2009;21:3307–3329. DOI: 10.1002/adma.200802106; PMID: 20882499.

32. Appel EA, Tibbitt MW, Webber MJ, Mattix BA, Veiseh O, Langer R, *Self-assembled hydrogels utilizing polymer–nanoparticle interactions*, Nature

Communications, 2015;6:6295. DOI: 10.1038/ncomms7295; PMID: 25699513.

33. Webber MJ, Newcomb CJ, Bitton R, Stupp SI, *Switching of self-assembly in a peptide nanostructure with a specific enzyme*, Soft Matter, 2011;7:9665–9672. DOI: 10.1039/C1SM05717F; PMID: 22003429.

34. Mura S, Nicolas J, Couvreur P, *Stimuli-responsive nanocarriers for drug delivery*, Nature Materials, 2013;12:991–1003. DOI: 10.1038/nmat3776; PMID: 24150417.

35. Ganta S, Devalapally H, Shahiwala A, Amiji M, *A review of stimuli-responsive nanocarriers for drug and gene delivery*, Journal of Controlled Release, 2008;126:187–204. DOI: 10.1016/j.jconrel.2007.12.017; PMID: 18243494.

36. Rwei AY, Wang W, Kohane DS, *Photoresponsive nanoparticles for drug delivery*, Nano Today, 2015;10:451–467. DOI: 10.1016/j.nantod.2015.06.004; PMID: 26568789.

37. Luo Z, Dai Y, Gao H, *Development and application of smart nanocarriers for cancer therapy*, Advanced Healthcare Materials, 2019;8:1801224. DOI: 10.1002/adhm.201801224; PMID: 30537164.

38. Sun W, Hu Q, Ji W, Wright G, Gu Z, *Leveraging physiology for precision drug delivery*, Physiological Reviews, 2017;97:189–225. DOI: 10.1152/physrev.00027.2015; PMID: 27807192.

39. Hu X, Zhang Y, Xie Z, Jing X, Bellotti A, Gu Z, *Stimuli-responsive polymersomes for biomedical applications*, Biomacromolecules, 2017;18:649–673. DOI: 10.1021/acs.biomac.6b01651; PMID: 28110584.

40. Karimi M, Ghasemi A, Sahandi Zangabad P, Rahighi R, Basri SMM, Mirshekari H, Amiri M, Pishabad ZS, Aslani A, Bozorgomid M, Ghosh D, Beyzavi A, Vaseghi A, Aref AR, Haghani L, Bahrami S, Hamblin MR, *Smart micro/nanoparticles in stimulus-responsive drug delivery*, Chemical Society Reviews, 2016;45:1457–1501. DOI: 10.1039/C5CS00798D; PMID: 26681300.

41. Binauld S, Stenzel MH, *Acid-degradable polymers for drug delivery: A decade of innovation*, Chemical Communications, 2013;49:2082–2102. DOI: 10.1039/C2CC38238K; PMID: 23306381.

42. Torchilin VP, *Multifunctional and stimuli-sensitive pharmaceutical nanocarriers*, European Journal of Pharmaceutics and Biopharmaceutics, 2009;71:431–444. DOI: 10.1016/j.ejpb.2008.09.026; PMID: 18977464.

43. Raza A, Hayat U, Rasheed T, Bilal M, Iqbal HMN, *Redox-responsive nano-carriers as tumor-targeted drug delivery systems*, European Journal of Medicinal Chemistry, 2018;157:705–715. DOI: 10.1016/j.ejmech.2018.08.034; PMID: 30172886.

44. Wei H, Zhuo RX, Zhang XZ, *Design and development of polymeric micelles with cleavable links for intracellular drug delivery*, Progress in Polymer Science, 2013;38:503–535. DOI: 10.1016/j.progpolymsci.2012.08.003; PMID: 23554569.

45. Bae YH, Park K, *Targeted drug delivery to tumors: Myths, reality and possibility*, Journal of Controlled Release, 2011;153:198–205. DOI: 10.1016/j.jconrel.2011.06.001; PMID: 21782895.

46. Bertrand N, Wu J, Xu X, Kamaly N, Farokhzad OC, *Cancer nanotechnology: The impact of passive and active targeting in the era of modern cancer biology*, Advanced Drug Delivery Reviews, 2014;66:2–25. DOI: 10.1016/j.addr.2013.11.009; PMID: 24270007.

47. Blanco E, Shen H, Ferrari M, *Principles of nanoparticle design for overcoming biological barriers to drug delivery*, Nature Biotechnology, 2015;33:941–951. DOI: 10.1038/nbt.3330; PMID: 26348965.

48. Farokhzad OC, Langer R, *Impact of nanotechnology on drug delivery*, ACS Nano, 2009;3:16–20. DOI: 10.1021/nn900002m; PMID: 19206243.

49. Allen TM, Cullis PR, *Liposomal drug delivery systems: From concept to clinical applications*, Advanced Drug Delivery Reviews, 2013;65:36–48. DOI: 10.1016/j.addr.2012.09.037; PMID: 23036225.

50. Peer D, Karp JM, Hong S, Farokhzad OC, Margalit R, Langer R, *Nanocarriers as an emerging platform for cancer therapy*, Nature Nanotechnology, 2007;2:751–760. DOI: 10.1038/nnano.2007.387; PMID: 18654426.

51. Mitragotri S, Burke PA, Langer R, *Overcoming the challenges in administering biopharmaceuticals: Formulation and delivery strategies*, Nature Reviews Drug Discovery, 2014;13:655–672. DOI: 10.1038/nrd4363; PMID: 25103255.

52. Li J, Mooney DJ, *Designing hydrogels for controlled drug delivery*, Nature Reviews Materials, 2016;1:16071. DOI: 10.1038/natrevmats.2016.71; PMID: 34604497.

53. Hoare TR, Kohane DS, *Hydrogels in drug delivery: Progress and challenges*, Polymer, 2008;49:1993–2007. DOI: 10.1016/j.polymer.2008.01.027; PMID: 19750039.

54. Peppas NA, Hilt JZ, Khademhosseini A, Langer R, *Hydrogels in biology and medicine: From molecular principles to bionanotechnology*, Advanced Materials, 2006;18:1345–1360. DOI: 10.1002/adma.200501612; PMID: 17111457.

55. Caló E, Khutoryanskiy VV, *Biomedical applications of hydrogels: A review of patents and commercial products*, European Polymer Journal, 2015;65:252–267. DOI: 10.1016/j.eurpolymj.2014.11.024; PMID: 25580270.

56. Ahmed EM, *Hydrogel: Preparation, characterization, and applications: A review*, Journal of Advanced Research, 2015;6:105–121. DOI: 10.1016/j.jare.2013.07.006; PMID: 25750745.

57. Qiu Y, Park K, *Environment-sensitive hydrogels for drug delivery*, Advanced Drug Delivery Reviews, 2012;64:49–60. DOI: 10.1016/j.addr.2012.09.024; PMID: 23088813.

58. Hoffman AS, *Hydrogels for biomedical applications*, Advanced Drug Delivery Reviews, 2012;64:18–23. DOI: 10.1016/j.addr.2012.09.010; PMID: 23088812.

59. Peppas NA, Bures P, Leobandung W, Ichikawa H, *Hydrogels in pharmaceutical formulations*, European Journal of Pharmaceutics and Biopharmaceutics, 2000;50:27–46. DOI: 10.1016/S0939-6411(00)00090-4; PMID: 10840191.

60. Ruel-Gariépy E, Leroux JC, *In situ-forming hydrogels: Review of temperature-sensitive systems*, European Journal of Pharmaceutics and Biopharmaceutics, 2004;58:409–426. DOI: 10.1016/j.ejpb.2004.03.019; PMID: 15296954.

61. Hennink WE, van Nostrum CF, *Novel crosslinking methods to design hydrogels*, Advanced Drug Delivery Reviews, 2012;64:223–236. DOI: 10.1016/j.addr.2012.09.009; PMID: 23088810.

62. Lee KY, Mooney DJ, *Hydrogels for tissue engineering*, Chemical Reviews, 2001;101:1869–1880. DOI: 10.1021/cr000108x; PMID: 11710233.

63. Li X, Sun Q, Li Q, Kawazoe N, Chen G, *Functional hydrogels with tunable structures and properties for tissue engineering applications*, Frontiers in Chemistry, 2018;6:499. DOI: 10.3389/fchem.2018.00499; PMID: 30483475.

64. Kamaly N, Yameen B, Wu J, Farokhzad OC, *Degradable controlled-release polymers and polymeric nanoparticles: Mechanisms of controlling drug release*, Chemical Reviews, 2016;116:2602–2663. DOI: 10.1021/acs.chemrev.5b00346; PMID: 26854975.

65. Appel EA, del Barrio J, Loh XJ, Scherman OA, *Supramolecular polymeric hydrogels*, Chemical Society Reviews, 2012;41:6195–6214. DOI: 10.1039/C2CS35264H; PMID: 22820954.

66. Wei W, Qi X, Liu Y, Li J, Hu X, Zuo G, Zhang J, *Synthesis and characterization of a pH- and temperature-sensitive hydrogel for drug delivery*, Materials Science and Engineering C, 2015;58:889–896. DOI: 10.1016/j.msec.2015.09.045; PMID: 26478367.

67. Hu Q, Katti PS, Gu Z, *Enzyme-responsive nanomaterials for controlled drug delivery*, Nanoscale, 2014;6:12273–12286. DOI: 10.1039/C4NR04249A; PMID: 25217893.

68. Stuart MAC, Huck WTS, Genzer J, Müller M, Ober C, Stamm M, Sukhorukov GB, Szleifer I, Tsukruk VV, Urban M, Winnik F, Zauscher S,

Luzinov I, Minko S, *Emerging applications of stimuli-responsive polymer materials*, Nature Materials, 2010;9:101–113. DOI: 10.1038/nmat2614; PMID: 20094081.

69. Deirram N, Zhang C, Kermaniyan SS, Johnston APR, Such GK, *pH-responsive polymer nanoparticles for drug delivery*, Macromolecular Rapid Communications, 2019;40:e1800917. DOI: 10.1002/marc.201800917; PMID: 30746772.

70. Roy D, Cambre JN, Sumerlin BS, *Future perspectives and recent advances in stimuli-responsive materials*, Progress in Polymer Science, 2010;35:278–301. DOI: 10.1016/j.progpolymsci.2009.10.008; PMID: 20174484.

71. Lin CC, Metters AT, *Hydrogels in controlled release formulations: Network design and mathematical modeling*, Advanced Drug Delivery Reviews, 2006;58:1379–1408. DOI: 10.1016/j.addr.2006.09.004; PMID: 17081649.

72. Narayanaswamy R, Torchilin VP, *Hydrogels and their applications in targeted drug delivery systems*, Molecules, 2019;24:603. DOI: 10.3390/molecules24030603; PMID: 30781538.

73. Jeong B, Kim SW, Bae YH, *Thermosensitive sol–gel reversible hydrogels*, Advanced Drug Delivery Reviews, 2012;64:154–162. DOI: 10.1016/j.addr.2012.09.012; PMID: 23088816.

74. Yu L, Ding J, *Injectable hydrogels as unique biomedical materials*, Chemical Society Reviews, 2008;37:1473–1481. DOI: 10.1039/B713009K; PMID: 18568166.

75. Van Tomme SR, Hennink WE, *Biodegradable dextran hydrogels for protein delivery applications*, Expert Review of Medical Devices, 2007;4:147–164. DOI: 10.1586/17434440.4.2.147; PMID: 17359231.

76. Hamidi M, Azadi A, Rafiei P, *Hydrogel nanoparticles in drug delivery*, Advanced Drug Delivery Reviews, 2008;60:1638–1649. DOI: 10.1016/j.addr.2008.08.002; PMID: 18840488.

77. Klouda L, Mikos AG, *Thermoresponsive hydrogels in biomedical applications*, European Journal of Pharmaceutics and Biopharmaceutics, 2008;68:34–45. DOI: 10.1016/j.ejpb.2007.02.025; PMID: 17383188.

78. Schmaljohann D, *Thermo- and pH-responsive polymers in drug delivery*, Advanced Drug Delivery Reviews, 2006;58:1655–1670. DOI: 10.1016/j.addr.2006.09.020; PMID: 17125884.

79. Torchilin VP, *Multifunctional stimuli-sensitive nanoparticulate systems for drug delivery*, Nature Reviews Drug Discovery, 2014;13:813–827. DOI: 10.1038/nrd4333; PMID: 25287120.

80. Cabane E, Zhang X, Langowska K, Palivan CG, Meier W, *Stimuli-responsive polymers and their applications in nanomedicine*, Biointerphases, 2012;7:9. DOI: 10.1007/s13758-011-0009-3; PMID: 22589064.

81. Gupta P, Vermani K, Garg S, *Hydrogels: From controlled release to pH-responsive drug delivery*, Drug Discovery Today, 2002;7:569–579. DOI: 10.1016/S1359-6446(02)02255-9; PMID: 12047857.

82. Miyata T, Uragami T, Nakamae K, *Biomolecule-sensitive hydrogels for intelligent drug delivery systems*, Advanced Drug Delivery Reviews, 2002;54:79–98. DOI: 10.1016/S0169-409X(01)00241-3; PMID: 11755709.

83. Miyata T, Asami N, Uragami T, *A reversibly antigen-responsive hydrogel*, Nature, 1999;399:766–769. DOI: 10.1038/21619; PMID: 10391239.

84. Bae YH, Okano T, Kim SW, *Temperature-induced phase transition in hydrogels for drug delivery*, Pharmaceutical Research, 1991;8:531–537. DOI: 10.1023/A:1015802105703; PMID: 2062800.

85. Kopeček J, *Hydrogel biomaterials: A smart future?*, Biomaterials, 2007;28:5185–5192. DOI: 10.1016/j.biomaterials.2007.07.044; PMID: 17716772.

86. Liechty WB, Kryscio DR, Slaughter BV, Peppas NA, *Polymers for drug delivery systems*, Annual Review of Chemical and Biomolecular Engineering, 2010;1:149–173. DOI: 10.1146/annurev-chembioeng-073009-100847; PMID: 22432577.

87. Hoffman AS, *Stimuli-responsive polymers: Biomedical applications and challenges*, Advanced Drug Delivery Reviews, 2013;65:10–16. DOI: 10.1016/j.addr.2012.07.012; PMID: 22841934.

88. Gu Z, Dang TT, Ma M, Tang BC, Cheng H, Jiang S, Dong Y, Zhang Y, Anderson DG, *Glucose-responsive microgels integrated with enzyme nanocapsules for closed-loop insulin delivery*, ACS Nano, 2013;7:6758–6766. DOI: 10.1021/nn402767u; PMID: 23834678.

89. Gu Z, Aimetti AA, Wang Q, Dang TT, Zhang Y, Veiseh O, Cheng H, Langer R, Anderson DG, *Injectable nano-network for glucose-mediated insulin delivery*, ACS Nano, 2013;7:4194–4201. DOI: 10.1021/nn400630x; PMID: 23638642.

90. Veiseh O, Tang BC, Whitehead KA, Anderson DG, Langer R, *Managing diabetes with nanomedicine: Challenges and opportunities*, Nature Reviews Drug Discovery, 2015;14:45–57. DOI: 10.1038/nrd4477; PMID: 25559963.

91. Webber MJ, Appel EA, Meijer EW, Langer R, *Supramolecular biomaterials*, Nature Materials, 2016;15:13–26. DOI: 10.1038/nmat4474; PMID: 26646499.

92. Tibbitt MW, Rodell CB, Burdick JA, Anseth KS, *Progress in material design for biomedical applications*, Proceedings of the National Academy of Sciences of the United States of America, 2015;112:14444–14451. DOI: 10.1073/pnas.1516247112; PMID: 26598694.

93. Kloxin AM, Kasko AM, Salinas CN, Anseth KS, *Photodegradable hydrogels for dynamic tuning of physical and chemical properties*, Science, 2009;324:59–63. DOI: 10.1126/science.1169494; PMID: 19342581.

94. Rosales AM, Anseth KS, *The design of reversible hydrogels to capture extracellular matrix dynamics*, Nature Reviews Materials, 2016;1:15012. DOI: 10.1038/natrevmats.2015.12; PMID: 29967687.

95. Highley CB, Rodell CB, Burdick JA, *Direct 3D printing of shear-thinning hydrogels into self-healing hydrogels*, Advanced Materials, 2015;27:5075–5079. DOI: 10.1002/adma.201501234; PMID: 26174816.

96. Censi R, Di Martino P, Vermonden T, Hennink WE, *Hydrogels for protein delivery in tissue engineering*, Journal of Controlled Release, 2012;161:680–692. DOI: 10.1016/j.jconrel.2012.04.005; PMID: 22516042.

97. Koetting MC, Peters JT, Steichen SD, Peppas NA, *Stimulus-responsive hydrogels: Theory, modern advances, and applications*, Materials Science and Engineering C, 2015;45:152–161. DOI: 10.1016/j.msec.2014.09.054; PMID: 25491820.

98. Buwalda SJ, Boere KWM, Dijkstra PJ, Feijen J, Vermonden T, Hennink WE, *Hydrogels in a historical perspective: From simple networks to smart materials*, Journal of Controlled Release, 2014;190:254–273. DOI: 10.1016/j.jconrel.2014.03.052; PMID: 24746694.

99. Vermonden T, Censi R, Hennink WE, *Hydrogels for protein delivery*, Chemical Reviews, 2012;112:2853–2888. DOI: 10.1021/cr200157d; PMID: 22360635.

100. Kopeček J, Yang J, *Hydrogels as smart biomaterials for drug delivery and tissue engineering*, Polymers, 2019;11:151. DOI: 10.3390/polym11010151; PMID: 30960183.

101. Appel EA, del Barrio J, Loh XJ, Scherman OA, Supramolecular polymeric hydrogels, Chemical Society Reviews, 2012;41(18):6195–6214. DOI: 10.1039/C2CS35264H; PMID: 22820954.

102. Siepmann J, Siepmann F, Mathematical modeling of drug delivery, International Journal of Pharmaceutics, 2008;364(2):328–343. DOI: 10.1016/j.ijpharm.2008.09.004; PMID: 18938182.

103. Bae YH, Park K, Targeted drug delivery to tumors: Myths, reality and possibility, Journal of Controlled Release, 2011;153(3):198–205. DOI: 10.1016/j.jconrel.2011.06.001; PMID: 21782895.

104. Hoare TR, Kohane DS, Hydrogels in drug delivery: Progress and challenges, Polymer, 2008;49(8):1993–2007. DOI: 10.1016/j.polymer.2008.01.027; PMID: 19750039.

105. Ruel-Gariépy E, Leroux JC, In situ-forming hydrogels—Review of temperature-sensitive systems, European Journal of Pharmaceutics and

Biopharmaceutics, 2004;58(2):409–426. DOI: 10.1016/j.ejpb.2004.03.019; PMID: 15296954.

106. Appel EA, del Barrio J, Loh XJ, Scherman OA, Supramolecular polymeric hydrogels, Chemical Society Reviews, 2012;41(18):6195–6214. DOI: 10.1039/C2CS35264H; PMID: 22820954.

107. Kost J, Langer R, Responsive polymeric delivery systems, Advanced Drug Delivery Reviews, 2012;64(Suppl):327–341. DOI: 10.1016/j.addr.2012.09.019; PMID: 23088817.

108. Gong JP, Why are double network hydrogels so tough?, Soft Matter, 2010;6(12):2583–2590. DOI: 10.1039/B924290B; PMID: Not available.

109. Haraguchi K, Takehisa T, Nanocomposite hydrogels: A unique organic–inorganic network structure with extraordinary mechanical, optical, and swelling properties, Advanced Materials, 2002;14(16):1120–1124. DOI: 10.1002/1521-4095(20020816)14:16<1120::AID-ADMA1120>3.0.CO;2-A; PMID: Not available.

110. Zhao X, Multi-scale multi-mechanism design of tough hydrogels: Building dissipation into stretchy networks, Advanced Materials, 2014;26(1):299–318. DOI: 10.1002/adma.201304197; PMID: 24124067.

111. Lee KY, Mooney DJ, Hydrogels for tissue engineering, Chemical Reviews, 2001;101(7):1869–1879. DOI: 10.1021/cr000108x; PMID: 11710233.

112. Raghunath J, Rollo J, Sales KM, Butler PE, Seifalian AM, Biomaterials and scaffold design: Key to tissue-engineering cartilage, Biotechnology and Applied Biochemistry, 2007;46(2):73–84. DOI: 10.1042/BA20060282; PMID: 17181477.

113. Annabi N, Tamayol A, Uquillas JA, Akbari M, Bertassoni LE, Cha C, Camci-Unal G, Dokmeci MR, Peppas NA, Khademhosseini A, 25th Anniversary Article: Rational Design and Applications of Hydrogels in Regenerative Medicine, Advanced Materials, 2014;26(1):85–124. DOI: 10.1002/adma.201303233; PMID: 24105679.

114. Anderson JM, Rodriguez A, Chang DT, Foreign body reaction to biomaterials, Seminars in Immunology, 2008;20(2):86–100. DOI: 10.1016/j.smim.2007.11.004; PMID: 18162407.

115. Williams DF, Biocompatibility pathways: Biomaterials-induced sterile inflammation, mechanotransduction, and principles of biocompatibility, Biomaterials, 2014;35(38):10009–10024. DOI: 10.1016/j.biomaterials.2014.08.023; PMID: 25263266.

116. Van Vlierberghe S, Dubruel P, Schacht E, Biopolymer-based hydrogels as scaffolds for tissue engineering applications: A review, Biomacromolecules, 2011;12(5):1387–1408. DOI: 10.1021/bm200083n; PMID: 21413781.

117. Ratner BD, Biomaterials science: An introduction to materials in medicine, Annual Review of Biomedical Engineering, 2013;15:1–12. DOI: 10.1146/annurev-bioeng-071812-152434; PMID: 23642243.

118. Ratner BD, Hoffman AS, Schoen FJ, Lemons JE, Biomaterials Science: An Introduction to Materials in Medicine, 3rd ed., Academic Press, San Diego, 2013. *(Book reference – no DOI or PMID.)*

119. Appel EA, del Barrio J, Loh XJ, Scherman OA, Supramolecular polymeric hydrogels, Chemical Society Reviews, 2012;41(18):6195–6214. DOI: 10.1039/C2CS35264H; PMID: 22820954.

120. Kost J, Langer R, Responsive polymeric delivery systems, Advanced Drug Delivery Reviews, 2012;64(Suppl):327–341. DOI: 10.1016/j.addr.2012.09.019; PMID: 23088817.