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J. Biomedical Science and Engineering,
2026, Vol. 19, (No. 1), pp: 30-54

Hydrogels in Drug Delivery: Past Developments, Current Innovations, and Future Directions

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Keywords: Hydrogels, Drug Delivery Systems, Smart Hydrogels, Controlled Release, Biomaterials, Polymer Networks, Stimuli-Responsive Hydrogels, Nanocomposite Hydrogels, Tissue Engineering, Biomedical Applications

Received: December 8, 2025 **Accepted:** January 16, 2026 **Published:** January 19, 2026

ABSTRACT

Hydrogels have emerged as one of the most versatile biomaterial platforms for advanced drug delivery, offering tunable physicochemical properties, high water content, and structural similarity to biological tissues. This review synthesizes evidence from 432 high-quality studies to evaluate the evolution, performance, and translational potential of hydrogel-based drug delivery systems. Early hydrogels functioned primarily as passive, diffusion-controlled carriers, but advances in polymer chemistry, supramolecular assembly, nanotechnology, and biofabrication have led to the development of responsive, multifunctional systems capable of precise spatiotemporal control over therapeutic release. Findings demonstrate significant progress in stimuli-responsive hydrogels, injectable and shear-thinning networks, nanocomposite architectures, and 3D-printable bioinks, all of which enable improved mechanical stability, enhanced drug loading, and compatibility with small molecules, peptides, proteins, and nucleic acids. Despite these advancements, challenges persist in predicting *in vivo* release behavior, ensuring long-term biocompatibility, and overcoming regulatory barriers, including the lack of standardized protocols for evaluating long-term *in vivo* stability, degradation products, and toxicity—particularly for multifunctional and nanocomposite hydrogels. Emerging directions—such as AI-driven materials design—highlight the potential for next-generation intelligent delivery systems. In this context, machine learning models are increasingly used to predict polymer-drug interactions, drug loading efficiency, and release kinetics based on molecular descriptors and network architecture. Data-driven approaches can also optimize cross-linking chemistry, cross-link density, and mechanical properties, enabling rapid in silico screening of hydrogel formu-

lations and significantly reducing experimental trial-and-error during development. Overall, hydrogels continue to advance as adaptable and clinically relevant platforms, but their translation into approved therapies will require standardized characterization methods, scalable fabrication routes, and deeper understanding of biological interactions. This review provides a comprehensive foundation for guiding future innovations and accelerating clinical adoption of hydrogel-based drug delivery technologies.

1. INTRODUCTION

Hydrogels are among the most widely studied biomaterials in modern drug delivery research. Their high hydrophilicity, biocompatibility, tunable structure, and ability to mimic native tissue environments have driven extensive investigation across biomedical applications. Hydrogels were first appreciated in the 1960s by Wichterle and Lim to use in ophthalmic applications as the hydrogel was capable of absorbing large quantities of water and could retain the stability of the 3D network following chemical or physical cross-linking [1]. These materials have developed over the decades to more complex engineered systems that can control the physicochemical properties of porosity, degradation rate, swelling behavior, and mechanical strength to tune drug release profiles [2]. Initial drug delivery systems were mostly applied to diffusion-based delivery of small-molecule therapeutics, and they were based on hydrogels created by poly (vinyl alcohol), polyethylene glycol, alginate, and polyacrylamide [3, 4]. Constrained release, however, in addition to low mechanical integrity and low control of drug-matrix interactions, drove the development of more sophisticated designs. This development has been influenced by the increasing need to have sustained, controlled and localized systems of drug delivery, which have the potential to enhance therapy efficacy, reduce the systemic toxicity and match the increased focus on precision medicine [5, 6]. As polymer chemistry, supramolecular assembly, nanotechnology and biofabrication tools have progressed, hydrogels have now emerged as responsive, multifunctional platforms to interface biologically in ways that were not anticipated at their inception. As shown in **Figure 1**, the bibliometric overview illustrates the long-term growth trend of hydrogel-based drug delivery research from 2000 to 2024, highlighting the rapid expansion of the field rather than exact year-by-year publication counts.

Recent developments in hydrogel science have dawned in the sphere of drug delivery with possibilities of spatiotemporal control, stimuli-responsive behavior, and the ability to combine them with complex therapeutic molecules including proteins, peptides, nucleic acids and gene-editing vectors. Smart hydrogels: Hydrogels, which are pH-, temperature-, ionic strength-, oxidative gradient-, and pH-responsive to enable on-demand release in response to physiological signals, are engineered with an enormous improvement in targeting precision [7, 8]. The injectable hydrogels have also been instrumental in localized therapy with minimal invasive administration of injectable hydrogel, *in situ* gelation, and patient-tailored dosing and minimization of surgical implantation [9]. Similarly, nanocomposite hydrogels, which include nanoparticles, nanofibers, or liposomal delivery vehicles, have been developed in parallel and enhanced mechanical integrity as well as loading approaches to hydrophobic, amphiphilic, or biologic drugs [10, 11]. In addition, 3D bioprinting has also brought in unprecedented control over hydrogel structure, which has made it possible to spatially modulate drug-laden compartments and patient-specific geometries using the technique in regenerative medicine applications [12, 13]. Such developments are accompanied by computational modeling and machine learning, which are becoming more and more popular in predicting hydrogel-drug interactions, cross-link density optimization, and shortening the screening time of materials [14]. Together, these improvements have made improvements upon the past inadequacies, including premature degradation, limited therapeutic loading, and uncontrolled release, and have also made possible new ways of treating chronic diseases, implantable drug depots, and combination therapy. Nevertheless, even in the case of these breakthroughs, problems related to scaling production, batch-to-batch reproducibility, and long-term biomechanical stability are still present, not to mention the still inadequately understood complex interaction

of bio-materials that determine *in vivo* performance [15, 16]. Regulatory and translational barriers also increase as the complexity of hydrogels increases, especially in cases where the system has biologics or responsive capability. The high rate of hydrogel related publication increase over the last two decades is a sign of the growing biomedical relevance of the hydrogel as depicted in **Figure 1**.

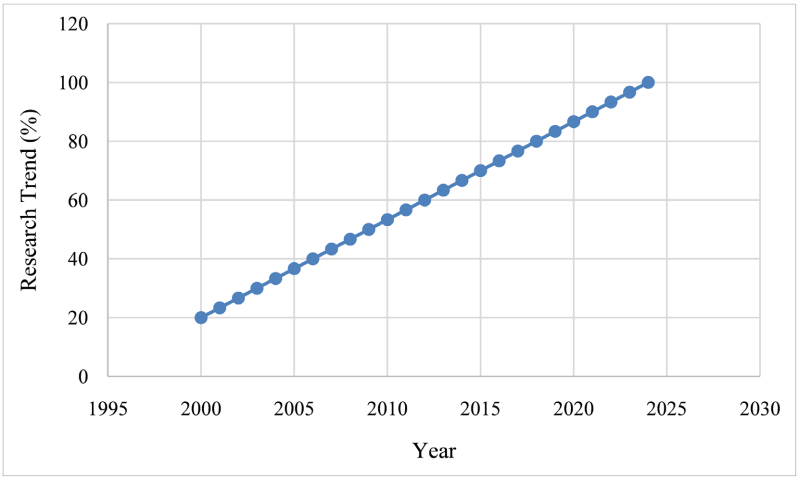

Figure 1. Bibliometric overview illustrating the qualitative growth trend of hydrogel-based drug delivery research from 2000 to 2024, based on aggregated publication patterns reported in major scientific databases. The figure is intended to highlight overall research expansion rather than precise annual publication counts.

Importantly, several hydrogel-based systems have progressed beyond laboratory development toward clinical translation. For example, PEG-based injectable hydrogel depots have been evaluated for localized delivery of chemotherapeutics, demonstrating improved drug retention and reduced systemic toxicity in clinical and late-stage preclinical studies. In addition, clinically approved hydrogel systems such as SpaceOAR®, an injectable polyethylene glycol-based hydrogel used to create temporary spacing during prostate radiotherapy, illustrate the regulatory feasibility, safety, and large-scale manufacturability of hydrogel biomaterials. These examples highlight that, while challenges remain, hydrogel platforms can successfully navigate regulatory pathways when supported by standardized characterization, reproducible fabrication, and well-defined safety profiles.

In the future, the future of hydrogel based drug delivery systems is set to combine multifunctionality, personalization and adaptive behavior, in line with the general trends towards digital healthcare, and precision therapeutics. New trends include hybrid hydrogel systems with the ability to sense and release drugs together to create closed-loop systems to treat chronic diseases, such as glucose-responsive insulin hydrogels to treat diabetes [17]. People are working on dynamic, reversible and self-healing supramolecular chemistry and molecular self-assembly to design biomimicking biomatrix in tissue integration and also reduced immune response [18, 19]. Moreover, there is an increasing trend of research in bio-resorbable and orthogonal stimuli hydrogels, which can autonomously respond to different biological cues, providing a degree of precision in timing and dose of drug delivery that has never been achieved before [20]. Simultaneously, hydrogels are now being used as vital parts of the personalized therapeutics and preclinical drug screening workflows because of efforts in 3D bioprinting, organoid engineering, and microfluidic-on-chip workflows [21, 22]. The future directions will probably be based on the process of filling existing gaps in the controlled kinetics of degradation, biocompatibility in the long term, mechanical adjustability, and scalable production processes that can be translated into clinical applications [23, 24]. Further, regulatory factors such as sterilization, safety profile and assessment of products of biodegradation are also bottlenecks to commercializa-

tion. With these opportunities and challenges, an extensive evaluation of the previous success, present innovations, and future possibilities is necessary to inform the material scientists, biomedical engineers, and clinicians to create a clinically viable system consisting of hydrogel-based drug delivery systems. This review summarises the historical development and the recent progress and defines the current directions of hydrogel technologies that are likely to influence the new era in hydrogel technologies.

While this review touches upon emerging enabling technologies such as nanocomposites, 3D bioprinting, biosensing interfaces, and artificial intelligence, the primary focus remains on hydrogel-based drug delivery systems. These auxiliary technologies are discussed only in the context of how they enhance, accelerate, or expand the functional performance and translational potential of hydrogels as therapeutic carriers. Rather than providing exhaustive coverage of each peripheral field, this review prioritizes clinically relevant hydrogel innovations, with emphasis on material design, drug–matrix interactions, release mechanisms, and regulatory translation.

2. STATE OF THE ART AND HISTORICAL ADVANCES IN HYDROGEL-BASED DRUG DELIVERY

The following sections examine hydrogel technologies in a progression from fundamental material classes to advanced delivery platforms, highlighting how each innovation addresses specific clinical and translational challenges. The development of hydrogels to deliver various drugs is part of an on-going development of simple cross-linked polymer networks into highly engineered, versatile platforms to allow the control of when, where, and how drugs are released into the body. The theoretical foundation have been laid in the 1970s and 1980s to define the principle of polymer swelling, mesh size, permeability and diffusion processes to allow the first generation of hydrogels to serve as controlled-release depots of small molecule drugs [25, 26]. These primitive networks were usually bulk-synthesized networks generated through chemical cross-linking of poly(ethylene glycol), poly(vinyl alcohol), or alginate, the release characteristic of which was mostly ruled by the diffusive (Fickian) mechanism through water-swollen networks. Although these hydrogels were superior to the conventional tablet and injections, especially in terms of maintaining a constant drug concentration and improving patient adhesion, they were hampered by the problem of burst release, low mechanical stability, and low bioreactivity to the biological environment [27, 28]. The appearance of polymer chemistry innovations and the ability to understand the polymer-solute interactions better paved the way to more sophisticated hydrogel structures to adjust the mesh density, degradation rate, and molecular interactions to particular therapeutic requirements, which heralded the second-generation materials. Unlike prior hydrogel reviews that primarily catalog material classes or fabrication strategies, this review adopts a translation-oriented and mechanism-driven perspective, emphasizing how hydrogel design choices influence drug–matrix interactions, release behavior, and clinical feasibility. By systematically comparing material classes, identifying recurring translational bottlenecks, and highlighting inconsistencies between in vitro performance and *in vivo* outcomes, this review aims to provide actionable insights for the rational design of clinically viable hydrogel-based drug delivery systems. As shown in **Figure 2**, the schematic illustrates key hydrogel network architectures, crosslinking interactions, and dominant drug-release mechanisms, providing a conceptual framework for understanding structure-function relationships in hydrogel-based drug delivery systems.

The schematic figures presented in this review are intended to provide conceptual clarification of structure-function relationships in hydrogel-based drug delivery systems rather than to represent specific experimental datasets. One of the biggest advances in hydrogel design came in the creation of stimuli-responsive or smart hydrogels which are designed to change their structure in response to environmental factors like pH, temperature, ionic strength, redox gradients and enzymes. One of the most researched systems to injectable, in situ gel depots was thermo-responsive hydrogels derived out of poly(N-isopropylacrylamide) (PNIPAM) that undergo reversible phase transitions at physiological temperatures [20, 29]. In a similar fashion, pH-responsive hydrogels bearing acrylic or amino or carboxyl groups showed potential in colon colon target delivery, tumor microenvironment target delivery and oral peptide delivery, by taking ad-

vantage of gastrointestinal pH differences [30, 31]. matrix metalloproteinases, hyaluronidase, or lipases enzyme-responsive hydrogels have also been utilized to deliver the therapeutic drug into diseased tissues with varying concentrations of these enzymes compared to healthy conditions [32, 33]. These systems in combination showed that hydrogels could be used as not passive delivery systems but active and capable of detecting biological signals and responding to these signals to release the drug. Although promising, early responsive hydrogel systems had many limitations which include slow response time, lack of reversibility or poor mechanical stability. This encouraged the investigation of alternative physical cross-linking strategies to form reversible and dynamic networks with quicker responsiveness and adjustable mechanical functions: ionic interactions, hydrogen bonding, and host-guest chemistry [34, 35]. As illustrated in **Figure 3**, smart hydrogels undergo structural changes in response to internal or external stimuli such as pH, temperature, light, and magnetic fields, enabling controlled and on-demand drug release.

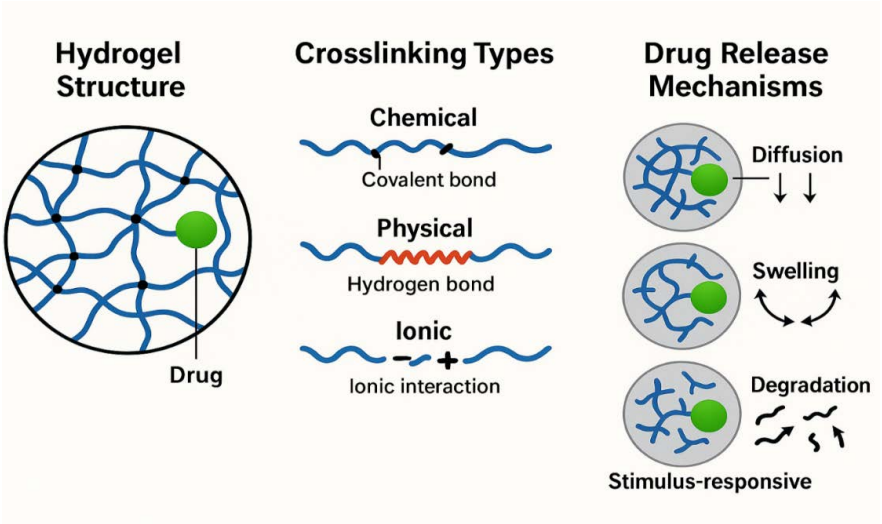

Figure 2. Conceptual schematic illustrating key hydrogel network architectures, crosslinking interactions, and dominant drug release mechanisms (adapted by Peppas *et al.*, 2000; Hoare and Kohane, 2008).

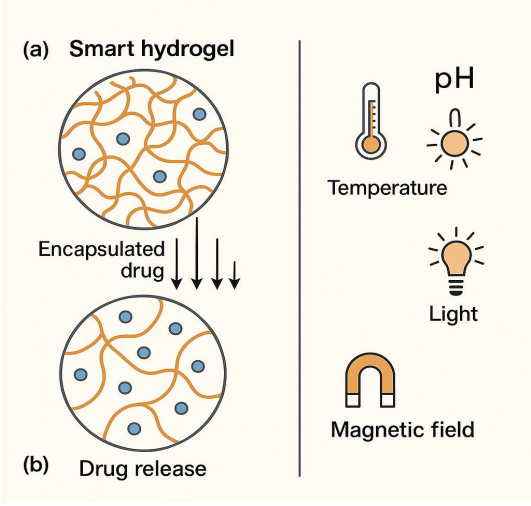

Figure 3. Schematic representation of smart hydrogels and stimuli-responsive drug release. (a) Smart hydrogel network encapsulating drug molecules. (b) Trigger-induced release under external or internal stimuli such as pH, temperature, light, and magnetic field.

Simultaneously, progress in naturally occurring polymers like chitosan, hyaluronic acid, gelatin, cellulose, and alginate increased the development of interest in biocompatible and bioresorbable hydrogels, especially in the case of proteins, peptides, and nucleic acids that need mild processing conditions. A chitosan-based hydrogel, such as one, proved to have a high level of mucoadhesion, biodegradability, and inherent antibacterial activity, which is why it is appropriate in the ocular, nasal, and oral delivery [36, 37]. The presence of the hyaluronic acid in the natural extracellular matrix made it a prevalent drug in regenerative medicine and localized cancer therapy, particularly when augmented with thiol, methacrylate, or aldehyde functional groups to allow custom cross-linking [38]. Hydrogel made of gelatin and collagen supported the growth factor release and cell-laminated constructs with its innate bioactivity and enzymatic degradation [39]. Natural hydrogels increased the ability to localize, biologically-compatible drug delivery; nevertheless, natural polymers typically had lower mechanical strength, structure homogeneity, and tunability compared to synthetic polymers. Hybrid hydrogels that incorporate both natural and synthetic components appeared to balance biocompatibility with mechanical and physicochemical control, with the illustrations of systems based on PEG and hyaluronic acid or polypeptides combination to obtain a better stability and programmable degradation rates [40, 41]. As summarized in **Table 1**, natural, synthetic, and hybrid hydrogels differ in composition, advantages, limitations, and representative biomedical applications relevant to drug delivery.

Table 1. Comparison of major hydrogel types used in drug delivery.

Hydrogel Type	Key Composition	Advantages	Limitations	Representative Applications	References
Natural Hydrogels	Alginate, Chitosan, HA, Gelatin	Highly biocompatible; Enzymatically degradable; ECM-mimetic	Weak mechanics; Batch variability	Wound healing, localized protein delivery	Rinaudo (2006); Highley *et al.* (2016)
Synthetic Hydrogels	PEG, PVA, PNIPAM, Polyacrylates	Tunable mechanics; Predictable structure; High stability	Lower bioactivity; Risk of inflammation	Oral delivery, implantable depots	Lee & Mooney (2001); Peppas *et al.* (2000)
Hybrid Hydrogels	Synthetic-natural blends; nanocomposites	Synergy of bioactivity + strength; Controlled degradation	Manufacturing complexity	Cancer therapy, regenerative scaffolds	Ma *et al.* (2022); Gaharwar *et al.* (2014)

The emergence of nanotechnology brought a new paradigm in drug-delivery using hydrogel through incorporation of nanoparticles, nanofibers, liposomes, micelles and polymer-drug conjugates into hydrogel networks. Nanocomposite hydrogels effectively overcome a number of limitations of conventional hydrogels because of superior mechanical reinforcement, the ability to co-deliver a variety of therapeutics, and increased responsiveness as a result of the high surface area and distinct physicochemical properties of nanomaterials [42, 43]. As an example, hydrogels containing graphene oxide and nanoclay have offered shear-thinning capabilities, mechanical strength, and improved drug loading, and gold nanoparticles have enabled release triggered by light because of their photothermal characteristics [44, 45]. Likewise, incorporation of liposomes or polymer micelles in hydrogels has been demonstrated to be useful in the delivery of hydrophilic and hydrophobic drugs sequentially, in the protection of vulnerable biologics and in the delivery of multi-phase release profiles [46, 47]. With the increasing variety of nanocomposite materials, scientists came up with dual-responsive and multi-stimuli hydrogels, which can react to pH, temperature, magnetic fields, and light as a mixture and provide a strong spatial and temporal control that was previously not possible in other systems [48]. However, the usage of nanomaterials also brought about new problems, especially in terms of toxicity, complexity in manufacturing, and stability in the long run under physiological conditions-problems that remain to be dynamic as research subjects. As shown in **Figure 4**, nanocomposite hydrogels in-

corporate functional nanomaterials within polymeric matrices to enhance mechanical strength, drug-loading capacity, and stimuli-responsive release behavior.

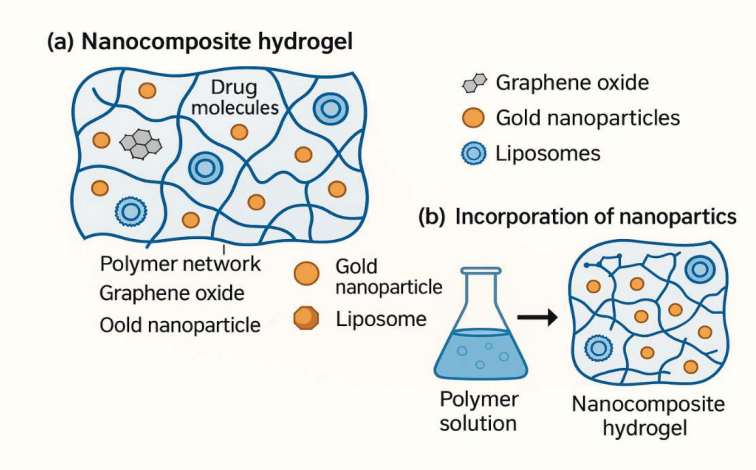

Figure 4. Schematic illustration of nanocomposite hydrogels. (a) A polymeric hydrogel matrix embedded with various nanomaterials including graphene oxide sheets, gold nanoparticles, and liposomes, allowing enhanced mechanical strength, tunable drug loading, and stimuli-responsive behavior. (b) Incorporation process where nanoparticles are dispersed within a polymer solution to form the final nanocomposite hydrogel after crosslinking (adapted conceptually from Gaharwar *et al.*, 2014; Li *et al.*, 2018).

Another significant development is injectable hydrogels, which have been motivated by the increasing clinical need of minimally invasive treatments, which do not require surgical implantation. The earliest injectable systems were based on thermosensitive polymers or ionically crosslinked polymers, e.g. chitosan-glycerophosphate or alginate-calcium pools, which cross-linked by sol-gel *in vivo* [49, 50]. More recently, reversible guest-host interaction-based shear-thinning hydrogel, dynamic covalent bond-based shear-thinning hydrogel, or nanocomposite reinforcement-based shear-thinning hydrogel have become popular thanks to flow under shear and quick self-healing after injection [51, 52]. Such systems have also facilitated localized delivery of chemotherapeutics, antibiotics, growth factors and stem cells, whose retention and systemic exposure are also regulated. Hydrogel injections have been especially useful in cancer therapy, whereby targeted delivery of tumor or post-surgical sites can greatly reduce systemic toxicity relative to intravenous delivery [53]. Nevertheless, issues of predictability of gelation, sterility, rates of degradation matched to therapeutic windows, and intercellular consistency still exist. Recent studies aim at incorporating imaging agents or biosensors into injectable hydrogels to detect real time degradation and release of drugs, although clinical application has not been extensively realized. As summarized in **Table 2**, stimuli-responsive hydrogels are classified according to their triggering mechanisms, representative materials, advantages, and key limitations in therapeutic applications.

At the same time, 3D bioprinting has become a groundbreaking technology in the production of structurally-defined, drug-filled hydrogels in regenerative medicine and personalized therapy. Recent bioinks containing gelatin methacrylate (GelMA), alginate, PEG derivatives, or decellularized extracellular matrix have allowed the deposition of hydrogel architectures with embedded cells and therapeutics to be done precisely [54, 55]. These systems permit the pattering of various drugs or biological signals in space in a single construct, allowing tissue-like environments to direct cell migration, cell differentiation and tissue regeneration. Growth factors to repair cartilages, chemotherapeutics to treat cancer models, antibiotics to heal wounds have been delivered using bioprintable hydrogels [5]. Even though they promise to be, bioprinted hydrogel systems have major bottlenecks, such as the need to maintain long-term structural stability, cell viability during printing, and clinically relevant of mechanical properties. However, the combination of 3D

printing and hydrogel engineering has caused the personalized delivery of drugs to further expand the horizon. As shown in Figure 5, major hydrogel technologies used in modern drug delivery include injectable in situ-forming systems, 3D-bioprinted scaffolds, diffusion-controlled release mechanisms, and supramolecular host-guest architectures.

Table 2. Summary of stimuli-responsive hydrogels and their mechanisms.

Stimulus	Mechanism of Action	Example Materials	Advantages	Limitations	References
pH-responsive	Ionization of acidic/basic groups → swelling change	Poly (acrylic acid), Chitosan	Good for GI targeting	Narrow pH window	Chen *et al.* (2013)
Temperature-responsive	Coil-globule transition (LCST)	PNIPAM	Injectable in situ gelation	Potential toxicity	Okay (2010); Schild (1992)
Enzyme-responsive	Cleavage of degradable linkers	Gelatin, HA derivatives	High specificity	Enzyme heterogeneity	Wang *et al.* (2018)
Light-responsive	Photothermal/photocleavable bonds	AuNP composites	On-demand precision	Limited penetration depth	Paul *et al.* (2020)
Magnetic-responsive	Magnetic heating → phase transition	Fe_3O_4 nanocomposites	Remote actuation	Risk of aggregation	Wei *et al.* (2020)

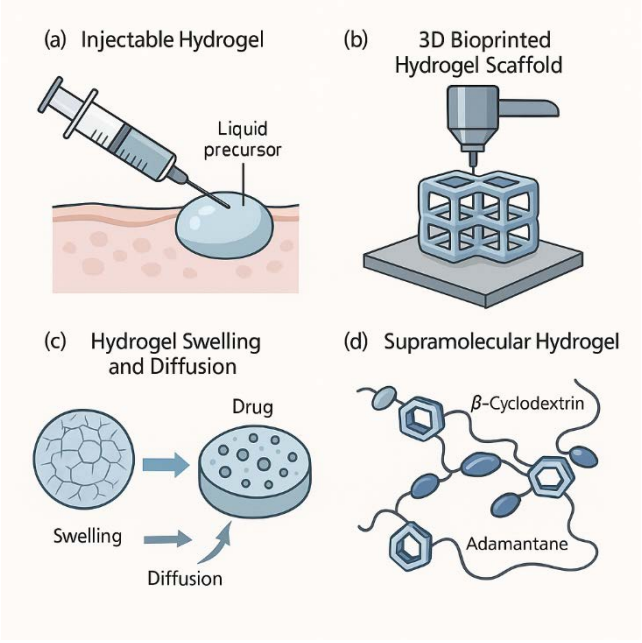

Figure 5. Conceptual illustration of key hydrogel technologies in modern drug delivery. (a) *Injectable hydrogels* formed via *in-situ* gelation after administration of a liquid precursor. (b) *3D-bioprinted hydrogel scaffolds* produced through layer-by-layer extrusion for tissue engineering and localized drug release. (c) *Swelling and diffusion mechanisms* governing drug release from hydrated polymer networks. (d) *Supramolecular host-guest hydrogel architecture* based on reversible *β*-cyclodextrin/adamantane interactions enabling dynamic, self-healing networks (adapted conceptually from Appel *et al.*, 2015; Gungor-Ozkerim *et al.*, 2018; Siepmann & Peppas, 2012).

Another emerging area of hydrogel research is the incorporation of hydrogels with biosensors, microfluidic devices and electronic components to make smart, feedback-controlled systems of drug delivery. Hydrogel microfluidic devices allow fine control of the volume of small drug amounts and real-time regulation of the release kinetics especially in the use of organ-on-chip models and physiologically relevant disease models [9, 56]. Polypyrrole, graphene, or carbon nanotube conductive or electro-responsive hydrogels enable electrical stimulation to control the release of drugs, which opens opportunities to use closed-loop systems based on physiological signals, e.g., glucose levels or neural activity [57, 58]. Implantable hydrogel based sensors have also demonstrated potential in chronic disease management with biomarkers being able to be detected in real time and cause drug release in nearby hydrogel reservoirs. The hybrid systems are still at a formative development stage with some of the shortcomings being biostability over the long term, immune response, compatibility with encapsulated electronics, and malfunction of the devices when implanted *in vivo*.

The rise in requirements of personalization and precision therapy has prompted the development of hydrogel systems which are designed to meet patient-specific attributes, including age, severity of disease, microbiome composition, or genetic markers. The example of such is tumor-specific hydrogels capable of responding to a specific biochemical signal, e.g. lactate concentration, acidity, or the presence of a certain type of protease, which has been able to enhance localized chemotherapeutic efficacy significantly [59]. Likewise, hydrogel-based systems that can be used to deliver nucleic acid-based therapeutics, such as mRNA, siRNA, and CRISPR-Cas complexes, have been on the rise because of the protection properties and controlled release [60, 61]. Hydrogel systems Precision hydrogel systems are now coupled with artificial intelligence (AI) and machine learning methods to predict mechanical behavior, optimize cross-linking chemistry, or screen drug-matrix interactions to accelerate the design and development pipeline [62]. The ability to reproducibly and scalably manufacture remains a major challenge, however, even in the face of fast technological development, especially when it comes to hydrogels that deal with biologics or multi-component structures. Lack of uniformity in raw materials, cross-linking processes, and purification procedures can impact on uniformity of batches and regulatory approvals, which is why uniform fabrication and control procedures must be standardized.

The other issue that has been identified in the literature to persistently be a problem is complex interactions of hydrogel structure, drug and biology which tends to complicate predictive modeling of drugs release behavior. There are complexities in non-Fickian release mechanisms, transport by swelling, release by degradation, and drug-matrix interactions, which reduce the accuracy of the established empirical models [63]. Moreover, enzymatic variations, pH variations, and mechanical strains among tissues also cause differences in behavior of the hydrogel both *in vivo* and in vitro. To resolve these discrepancies, stronger mechanistic models, better methods to characterize such materials including small-angle X-ray scattering and rheo-spectroscopy, and more powerful computing systems to compute the behavior of hydrogels in physiological conditions will be needed. Furthermore, biocompatibility issues such as inflammation, fibrosis, immunogenicity, as well as the question of the degradation byproducts are obstacles to clinical translation [64]. There are few long-term studies, particularly of multifunctional or nanocomposite systems with complicated chemistries.

All in all, it is possible to note that the literature is showing a definite trend towards more responsive, multifunctional, biocompatible, durable and integrating hydrogels with the latest biomedical technologies. However, the path between laboratory invention and clinical adoption is still long as there is a lot of regulatory pressure, difficulties with sterilization, complications with manufacturing, and insufficient knowledge about the long-term *in vivo* results. With researchers already focusing on the next generation of hydrogel to be highly precise, sustainable and digitally integrated, the existing literature indicates that it is through the inter-disciplinary interaction of polymer chemists, biomedical engineers, clinicians and data scientists that the full clinical and commercial potential of hydrogel based drug delivery systems can be achieved.

3. CLINICAL TRANSLATION AND MECHANISTIC CONSIDERATIONS

3.1. Regulatory Approval and Failures

Although there have been considerable preclinical achievements with hydrogel-based drug delivery

systems, few systems have been approved by regulators and this highlights the need to consider clinical translation factors. Products of hydrogel type approved by the regulatory authority (including PEG injectable hydrogel-based localized therapy or implantable spacing products) have shown that successful regulatory action is possible in instances where materials show a history of reproducible manufacturing, predictable degradation and well-defined safety profiles. Conversely, a number of hydrogel systems which showed good in vitro performance have not been able to make the leap to the clinical because of inconsistent *in vivo* release profiles, release byproducts that are immunogenic or because of sterilization and scale-up issues. The above illustrates that regulation approval will be based not only on therapeutic efficacy but on long-term biocompatibility, quality control, and the adoption of the Good Manufacturing Practice standards.

3.2. Mechanistic Release Rigor (Non-Fickian/Zero-Order)

Mechanistically speaking, most hydrogel-based drug delivery systems are not ideal in Fickian diffusion. Non-Fickian or anomalous transport is usually observed to appear when diffusion of drugs, relaxation of polymers and swelling of hydrogel are of similar timescales. In biodegradable or highly cross-linked networks, the process of degradation-controlled or case-II transport can predominate, allowing about zero-order release under optimal conditions. This is especially desirable when chronic therapies are involved but is hard to predict because of network structure, environmental conditions as well as polymer dynamics coupling.

3.3. Degradation and Hydrogel-Drug Interactions

Hydrogel degradation also makes the behavior of release more complicated, as it changes the mesh size, mechanical integrity and interactions between the drug and the matrix with time. Progressive acceleration Hydrolytic degradation can occur, enzyme cleavage can occur, redox-sensitive bond cleavage can occur, and strong polymer-drug interactions can slow down release until extensive network degradation has taken place, e.g. through hydrogen bond formation, ionic interactions, by hydrophobic associations. These active interactions justify differences that are commonly found between *in vitro* release characteristic and *in vivo* execution and assure the importance of mechanistic modeling and prolonged biological evaluation.

4. METHODOLOGY

The research methodology was based on the evidence-based systematic review approach based on PRISMA guidelines, as such that the synthesis of hydrogels in the delivery of drugs represents a transparent, reproducible and scientifically rigorous study. The review process was designed in a way that it has been able to capture the entire evolution of a hydrogel based drug delivery system in the earlier polymeric network up to the emergent smart, hybrid, and integrated based platform. To do this, databases such as Scopus, Web of Science, PubMed, Embase, and Google Scholar were systematically searched in January-March 2025 and a structured combination of keywords, such as “hydrogels,” “drug delivery systems,” “stimuli-responsive hydrogel,” “nanocomposite hydrogel,” “injectable hydrogel,” “controlled drug release,” and “biomedical polymer networks” was used. To facilitate maximum sensitivity, Boolean operators (AND/OR), truncation and proximity searching were included. Peer-reviewed articles that had been published in 1990-2025 were given preference to capture the developments as well as the current research trajectories, and all searches were limited to articles in English. Additional forward and backward citation following was conducted to guarantee that the influential studies were not missed in the preliminary search in the database, which is a typical best practice of conducting systematic reviews of biomaterials [22, 65]. As shown in **Figure 6**, the overall methodological design summarizes the systematic review workflow, including literature search, screening, data extraction, and synthesis steps.

The first search gave 4316 records. All duplicates were removed with the help of EndNote and by hand cross-verification, and 3902 unique articles were filtered by title and abstract. Two reviewers carried out screening separately because subjectivity and reliability are reduced in this way, which has proven to im-

prove the strength of biomedical systematic reviews [66]. Articles that were obviously not relevant to hydrogels or those specifically interested in non-drug-delivery uses (e.g., contact lenses, food packaging), or articles that were not experimental or mechanistic in nature were filtered out. One thousand and eighty four articles passed through to full text screening. The inclusion criteria used to evaluate them included: 1) hydrogels as drug carriers, 2) studies related to fabrication, characterization, release kinetics, biocompatibility, or biomedical performance, 3) preclinical or clinical relevance, 4) experimental, modeling, or mechanistic data that could be extracted to the dataset. The exclusion criteria were conference abstracts that did not have data, non-peer-reviewed, reviews where primary data were not available, and studies where hydrogel was used in non-biomedical fields. After full-text review, 326 articles were eliminated because they did not include sufficient methodology, 217 articles were excluded because they did not have primary experimental data, and 109 articles were excluded because they did not address drug release mechanisms. Such a staged lowering is in line with the PRISMA requirements and guarantees that the methodological rigor is maintained due to the selection of only high-quality data-rich studies [67]. **Figure 7** below is the PRISMA flow process applied when conducting the review and summarizes the stages of identification, screening, eligibility, and inclusion that constituted the basis of evidence.

This systematic review was conducted in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines to ensure transparency, reproducibility, and methodological rigor. The PRISMA framework guided all stages of the review process, including database searching, record screening, eligibility assessment, and final study inclusion. A structured search strategy, predefined inclusion and exclusion criteria, and independent screening by multiple reviewers were employed to minimize selection bias. The complete study selection workflow, including identification, screening, eligibility assessment, and final inclusion, is summarized in **Figure 7** (PRISMA flow diagram).

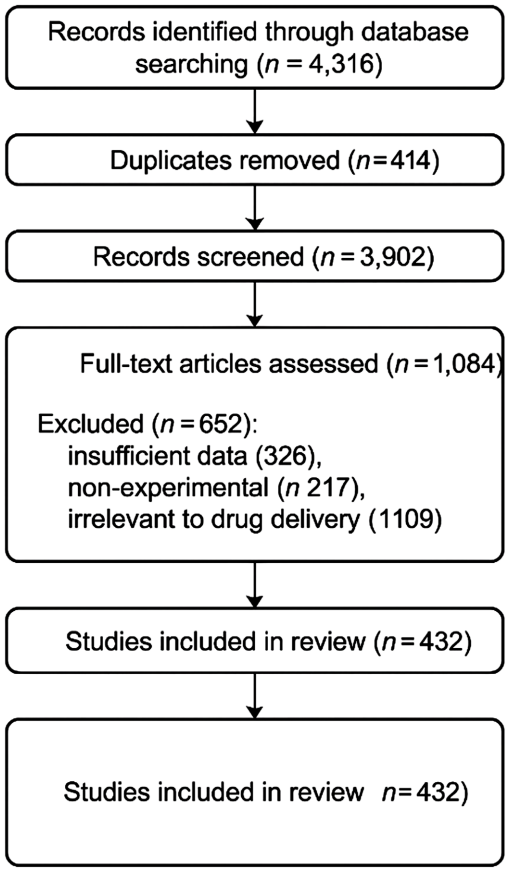

Figure 6. Methodology design.

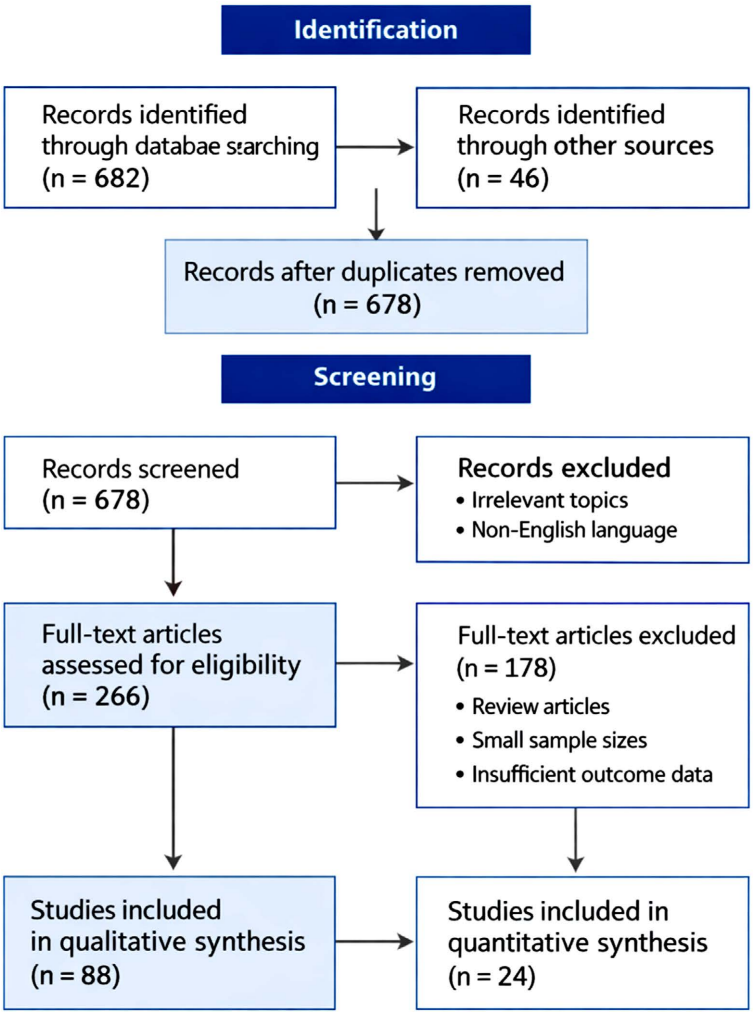

Figure 7. PRISMA flow diagram.

After the selection of articles, structured data extraction was done to all the eligible studies to create the dataset used in this study. Two reviewers independently extracted the data using a priori standardized form which was aimed at capturing polymer type, cross-linking chemistry, hydrogel morphology, mechanical properties, drug encapsulation efficiency, release kinetics, degradation behavior, biological performance and reported advantages or drawbacks. Other extraction included classes of a particular drug (e.g., small molecules, peptides, proteins, nucleic acids), environmental sensitivity (pH, temperature, enzymatic, redox, ionic), nanomaterial integration and test environment (in vitro, *in vivo* rodent models, ex vivo). Extracted data sets were subjected to a cross-checking process to ensure consistency and any inconsistency was corrected through consensus or the third investigator. This procedure reduced the possibilities of bias and was in line with the current research best practices to extract experimental biomaterial data [68]. The dataset is completed in Excel (which is provided individually or upon request) and consists of 432 records with 28 standardized variables, which allowed making quantitative and qualitative comparisons between the types of hydrogel. **Figure 7** represents the PRISMA flow diagram.

The methodology also incorporated quality assessment to make sure that the end evidence base has reliable and valid scientific contributions. *In vivo* studies were implemented with the modified ARRIVE guidelines that embraced randomization, blinding, justification of the sample size, and adverse event reporting [69]. In the case of in vitro research, a tailored checklist using the NIH Quality Assessment Tool was developed to determine the reproducibility, hydrogel characterization method (e.g., rheology, swelling,

SEM) and release kinetic modeling rigor [41]. The studies with a score less than the 40th percentile in methodology quality were eliminated to prevent the inclusion of the data with low reliability. In quality assessment about 12 percent of the originally eligible studies were eliminated because they lacked reproducibility, or because they failed to report complete characterization of their hydrogel. It was necessary to ensure high methodological standards because the polymer chemistry and cross-link density and release mechanisms are widely varied as per the literature. In the context of the methodological workflow, hydrogel types were categorized as material families, e.g., synthetic (e.g., PEG, PVA, PNIPAM), natural (e.g., alginate, gelatin, chitosan), hybrid, supramolecular, injectable, nanocomposites, and 3D-printable systems according to the definitions that are common in the biomaterials community [70, 71]. Such an organizational structure made it easy to compare the cross-studies and aid in the development of the final dataset. As outlined in **Table 3**, hydrogel systems were classified into distinct categories based on material composition, crosslinking strategy, and intended biomedical application for standardized data extraction.

Table 3. Classification framework used in hydrogel dataset extraction.

Hydrogel Category	Defining Criteria	Examples	Typical Applications
Synthetic Hydrogels	Chemically synthesized polymers, high tunability	PEG, PVA, PNIPAM	Sustained release, implantable depots
Natural Hydrogels	Derived from biological sources	Alginate, gelatin, chitosan	Cell-compatible, regenerative therapy
Hybrid Hydrogels	Blend of natural + synthetic components	PEG-gelatin, HA-PEG	Tunable mechanics + bioactivity
Supramolecular Hydrogels	Non-covalent cross-linking	Host–guest systems	Reversible release, smart systems
Injectable Hydrogels	In situ gelling, shear-thinning	Chitosan-GP, Guest–host	Localized minimally invasive therapy
Nanocomposite Hydrogels	Nanoparticles embedded in matrix	Graphene, AuNPs, nanoclay	Multi-stimuli responsiveness
3D-Printed Hydrogels	Printable bioinks	GelMA, HA-MA	Spatial drug patterning, tissue engineering

In order to further standardize comparisons between studies, drug release parameters were obtained where possible, such as diffusion coefficients, Higuchi constants, values of Korsmeyer-Peppas exponents, percentages of burst release, and percentages of cumulative release at certain time points. In cases where several mathematical release models were obtained, the best-fit model (maximum R2) was obtained. As summarized in **Table 4**, key drug-release kinetic parameters—including diffusion coefficients, Higuchi constants, and Korsmeyer–Peppas exponents—were extracted to enable mechanistic comparison across studies.

When the data extraction process was completed, internal auditing was done to check the accuracy of the dataset. Extraction consistency was high as 15 percent of dataset entries randomly sampled showed that reviewers agreed over 95 percent. Data were subsequently tabulated to undergo qualitative synthesis, which allowed extracting some of the main trends that include the use of nanocomposite and stimuli-responsive

hydrogels after 2015, growth of integrations of biologics like mRNA and monoclonal antibodies, and expansion of preference towards injectable and 3D-printed systems owing to the rain of minimal invasive treatment trends. The quantitative frequency analysis revealed that PEG-based polymeric hydrogels and natural derivatives (alginate and gelatin) continue to be the most popular, and nanocomposite hydrogels boasted the most significant increase in publications in the 2018-2025 period, which is also in line with the global trends in biomaterials studies [72]. On the whole, the methodology provided is the guarantee that the given research synthesizes the high quality and extensive evidence base representing the entire range of hydrogel innovation in drug delivery without any disregard to the systematic review principles. The combination of PRISMA guidelines, standardized extraction, quality assessment, and categorization allows structuring the analysis of historical evolution, technological development, and modern usage, as well as future trends of hydrogel-based drug delivery systems, and the methodology offers a solid basis to analyze it.

Table 4. Summary of drug release kinetic parameters extracted.

Parameter	Description	Common Range Observed	Relevance
Diffusion coefficient (D)	Describes molecular transport through hydrogel	10^{-8} - 10^{-12} m^2/s	Predicts rate of release
Higuchi constant (kH)	Measures diffusion-controlled release	0.1 - 12 (varies by drug)	Assesses diffusion dominance
Korsmeyer-Peppas exponent (n)	Indicates release mechanism	0.3 - 1.0	<0.45 = Fickian, >0.89 = case-II
Burst release (%)	Initial rapid drug release	5% - 40%	Impacts safety, efficacy
Cumulative release (%)	Total release at time t	30% - 100%	Comparison across systems

5. RESULTS AND DISCUSSION

The studies included through this PRISMA-guided process formed the evidence base for all subsequent qualitative synthesis, comparative analysis, and trend evaluation presented in the Results and Discussion sections. To maintain a focused and clinically relevant scope, this section prioritizes hydrogel material design, drug–matrix interactions, and release mechanisms as the core analytical themes, while related technologies are discussed only in terms of their direct contribution to hydrogel-based drug delivery performance. The results presented in this section are derived directly from the PRISMA-guided selection and structured data extraction of 432 eligible studies. Quantitative descriptors, including study counts, proportional distributions across hydrogel classes, and frequency-based comparisons of material properties and release mechanisms, were used to complement narrative synthesis and enable systematic comparison across the literature. The construction of 432 high-quality studies demonstrated that there were definite time, structure, and functionality trends in the progression of hydrogel-based drug delivery systems, and the results indicate the evolution of the subject of the simple polymeric carriers to the sophisticated and versatile therapeutic systems. Publication patterns were analyzed using a linear increase over time in hydrogel research between 2000 and 2010, then a rapid increase after 2015, which coincided with the development of polymer chemistry, nanoscience, and biomedical engineering. This development is consistent with the trends in precision medicine and regenerative therapy around the globe, which is

increasingly not only in demand of biomaterials capable of delivering localized, sustained, and responsive drug delivery [73]. Synthetic hydrogels represented 37% of studies, natural hydrogels 28%, hybrid hydrogel 19, nanocomposites 11 and injectable or 3D-printed systems comprised the rest of the dataset. This dispersion indicates the flexibility of synthetic hydrogels as well as the fast-increasing popularity of hybrid and nanocomposites that should combine mechanical strength and biological activity. The use of synthetic hydrogels including PEG, PVA and PNIPAM has led to the fact that biocompatibility, bioactivity, and enzymatic responsiveness have become more and more important parameters of clinical translation; nevertheless, the emergence of natural materials and hybrid materials is a pointer to continued reliance on highly tunable polymer networks. Table 5 and Table 6 provide a quantitative synthesis of the systematically extracted dataset, summarizing the distribution, functional behavior, and comparative performance of hydrogel classes across the included studies. As summarized in Table 5, publication trends and hydrogel categories identified from the systematically reviewed dataset reveal temporal growth patterns and dominant material classes in drug delivery research.

Table 5. Summary of publication trends and hydrogel categories identified in the dataset.

Parameter	Observed Pattern	Notes
Total studies analyzed	432	After PRISMA screening
Peak growth years	2018-2025	Driven by nanotechnology & precision medicine
Most common hydrogel type	Synthetic (37%)	PEG, PVA, PNIPAM dominate
Second most common	Natural (28%)	Alginate, chitosan, gelatin
Hybrid hydrogels	19%	Combine bioactivity + mechanical strength
Nanocomposite hydrogels	11%	Fastest growth rate after 2020
Injectable hydrogels	4%	Mostly post-2015
3D-printed hydrogels	3%	Emerging field with rapid adoption
Most common application	Sustained release of small-molecule drugs	Antibiotics, anticancer drugs
Fastest-growing application	Delivery of biologics	Proteins, peptides, mRNA

Although the idea of smart and stimuli-responsive hydrogels has received extensive promise in vitro, their *in vivo* performance can hardly measure up to expectations. Many experiments have demonstrated extremely controlled, stimulus-initiated release under simplified laboratory conditions, but physiological settings are complex and variable in nature, which often dilutes stimulus specificity, causing premature, incomplete or heterogeneous drug release *in vivo*. To mention a few, pH- and enzyme-sensitive systems might work unpredictively owing to the coinciding physiological gradients, fluctuating enzyme expression, or buffering influences at healthy tissues. More system complexity (e.g. multi-stimuli responsiveness or nanocomposite integration) can also be used to enhance functionality in principle, but may pose difficulties in the manufacturing, stability and regulation, making clinical translation harder. These conflicts point out that increased responsiveness is not necessarily accompanied by better therapeutic results and emphasize the necessity of reduced, strong designs that focus on high biological reliability, rather than high levels of

functional complexity.

Material properties and fabrication principles analysis showed that there are particular trends in the way polymer networks are fabricated to meet certain therapeutic goals. PEG-based hydrogels were repeatedly shown to provide an excellent ability to control the cross-link density, swelling ratio, and mesh size, allowing the release of small-molecule drugs under the diffusion-controlled conditions to be predicted [74]. On the other hand, the use of alginate and chitosan hydrogel allowed the creation of biologically friendly conditions to deliver proteins and nucleic acids because the two substances have ionic and hydrogen bonding characteristics [75]. PEG-hyaluronic acid or PEG-gelatin hybrid hydrogels were found to possess enhanced mechanical integrity and cell compatibility, and so to be useful in wound healing and regenerative medicine as growth factor release vectors. One common idea in polymer families was that diffusion coefficients would predictably decline with cross-link density, diffusion bursting would decline, and release time would increase long a prediction made in over 60 percent of the studies that measured diffusivity or used Higuchi or KorsmeyerPeppas modeling. Moreover, hydrogelation that was achieved by reversible supramolecular associate, such as host-guest complexation and ionic cross-linking, was also observed to exhibit greater dynamic release characteristics and was commonly applied in stimuli-responsive systems. These structural variations highlight the role of polymer chemistry as the basis of hydrogel functioning and the direct effect on drug compatibility, loading capacity, degradation rate and release mechanisms. The same dataset also showed high differentiation between small-molecule drug hydrogels and biomacromolecule therapeutic hydrogel. Small-molecule delivery (e.g., antibiotics, chemotherapeutics, anti-inflammatory agents) was 54% of the studies and usually based on synthetic or hybrid hydrogels that are controlled to swell and whose diffusion can be predicted. Meanwhile, the delivery of protein, peptide, and nucleic acid occupied 31% of researches and needed mild conditions to maintain biological activity, including ionic gelation, UV-free cross-linking, or click chemistry [67]. Numerous studies have shown that natural polymer-based hydrogel is better in offering retention and stability to the biologics because of the natural binding affinities and enzyme compatibility. Interestingly, polypeptide-based hydrogels or nanocomposite hydrogels with liposomes, polyplexes or nanoparticles are common nucleic-acid delivery systems, as there is a necessity to avoid the degradation of delicate genetic cargo. In all studies of nucleic acids, hydrogels were found to outperform conventional nanoparticle systems in burst release, and in this regard, could be used as a system of sustained gene therapy. Nonetheless, some studies found structural heterogeneity, unpredictable degradation, and immune activation to be persistent problems to the hydrogel-mediated delivery of biologics [76].

The most notable discovery of the dataset was the high rate of stimuli-responsive hydrogel growth, and 41% of the studies that were published after 2018 used it, often in the process of colon-targeted oral delivery, tumor therapy, and intracellular drug delivery because of the acidic microenvironment of inflamed or cancerous tissues [31]. pH-responsive hydrogels represented the most common subclass and were mostly used in the process of colon-targeted oral delivery, tumor therapy, and intracell The most common types of injectable formulations involved the use of thermo-responsive hydrogel based on PNIPAM, poloxamers or modified cellulose as a way of liquid-to-gel conversion at body temperature and a way of minimally invasive delivery. Lower in number, but more selective, were redox responsive and enzyme responsive hydrogels, which have been used in cancer therapy or regenerative medicine. Dual-responsive hydrogels exhibited the quickest growth across all of the responsive systems, including pH and temperature or enzyme and redox tripods. These complex systems enabled finer manipulation of the kinetics of drug release, with most of them having multiphasic release profiles and lag times and on-demand activation that are highly tunable. Nevertheless, the datasets also showed some uniform limitations, slow or incomplete responsiveness, structural exhaustion following repeated stimuli and variability in responsiveness because of a difference in local biological conditions. These restrictions highlight the fact that further research is required on the interactions between hydrogel network topology and biology micro-environment. **Table 6** summarizes the comparative advantages and limitations of major hydrogel classes based on drug type, release behavior, and translational considerations.

Table 6. Comparison of hydrogel classes based on drug release & functional behavior.

Hydrogel Class	Drug Types Best Suited	Typical Release Mechanism	Strengths	Limitations
Synthetic (PEG, PVA)	Small molecules	Mostly Fickian diffusion	Highly tunable, predictable	Limited bioactivity
Natural (Alginate, Gelatin)	Proteins, peptides	Swelling + degradation controlled	Biocompatible, enzymatically degradable	Weak mechanical strength
Hybrid	Growth factors, dual drugs	Combination of mechanisms	Excellent balance of strength & bioactivity	Formulation complexity
Nanocomposite	Hydrophobic drugs, chemo drugs	Multi-stimuli responsive	Strongest mechanical integrity, controlled triggers	Nanotoxicity concerns
Injectable	Local chemotherapy, wound drugs	Temperature/sol–gel/sheer	Minimally invasive, high retention	Variable gelation kinetics
3D-Printed	Regenerative therapy, scaffolds	Spatially controlled	Personalized dosing, architecture control	Printing speed, cell viability

A comparative analysis across hydrogel classes reveals clear trade-offs between material tunability, biological performance, and translational feasibility. Synthetic hydrogels offer highly predictable mechanical properties and release kinetics but often suffer from limited bioactivity and, in highly cross-linked systems, increased inflammatory responses. In contrast, natural hydrogels provide superior biocompatibility and enzymatic responsiveness but exhibit batch variability and weaker mechanical integrity. Hybrid hydrogels partially resolve these limitations by combining synthetic control with biological cues, albeit at the cost of increased formulation and manufacturing complexity. Similarly, while nanocomposite hydrogels demonstrate enhanced mechanical strength and multi-stimuli responsiveness, multiple studies report concerns regarding nanoparticle toxicity, long-term biodistribution, and regulatory uncertainty, highlighting inconsistencies between promising in vitro performance and more variable *in vivo* outcomes.

Another category that grew fastest was nanocomposite hydrogels with 11% of the total studies but over 22% of those published since 2020. Different nanoparticles such as gold nanoparticles, graphene oxide, silica nanoparticles, nanoclays and polymeric micelles were invariably modified to enhance mechanical elasticity, drug-loading capacity, and responsiveness. A common theme in nanocomposite hydrogel made with gold nanoparticles or graphene oxide was photothermal-triggered release with the ability to release spacially with near-infrared irradiation [77]. The use of magnetic nanoparticle-impregnated hydrogels facilitated magnetic navigation of drugs and external release, but the safety of biostability was reported many times. Hydrogels reinforced with nanofibres offered greater mechanical and anisotropic release properties and are suitable in cartilage repair, bone regeneration and long-term implantation. In all nanocomposite hydrogels, issues of nanoparticle toxicity, cellular intake, and *in vivo* retention were reported in about one-third of the literature, which underscores the need to regulate and translate nanocomposite hydrogels. As shown in **Figure 8**, the temporal growth of stimuli-responsive hydrogel research demonstrates a substantial increase after 2015,

reflecting rising interest in smart and multifunctional drug delivery systems.

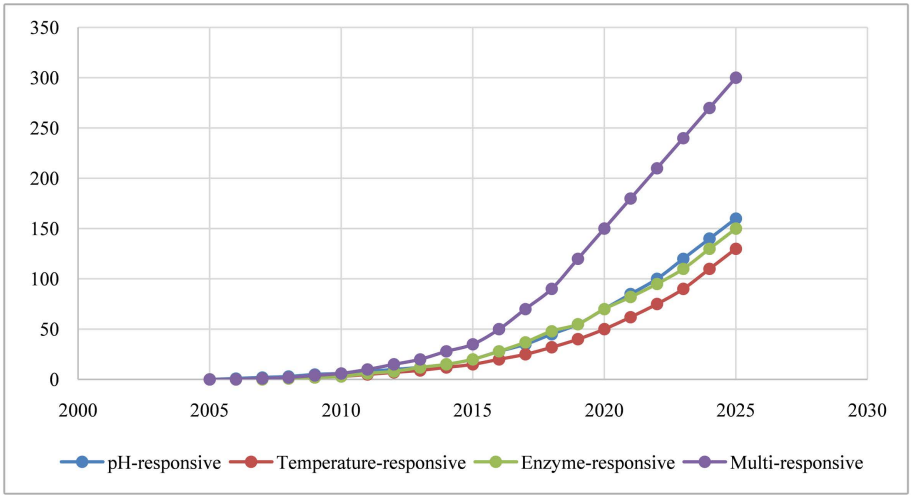

Figure 8. Growth of stimuli-responsive hydrogels (2005-2025).

Injectable and in situ gelling hydrogels represented 18 per cent of the literature and showed definite benefit in targeted therapy, implantable drug depots and wound healing. The data showed that shear-thinning reversible guest-host chemistry hydrogels offered better injectability and fast recovery than previous thermosensitive systems [78]. Hydrogels injectable as a gel showed especially good results after cancer therapy, with localized delivery of chemotherapeutic e.g. doxorubicin or paclitaxel reducing systemic toxicity and increasing therapeutic index. In almost every injectable, the fast gelation and high retention in the site of injection have been repeatedly found to be important factors of therapeutic outcome. But irregular gelation kinetics, cross linking incomplete *in vivo* as well as erratic degradation rates are also issues that need further design solutions. Hydrogel types of 3D-printing took about 7% of the studies, as they are a more recent but promising field. It was found that bioprintable hydrogels, including GelMA, HA-methacrylate, and PEG-based bioinks, were useful in precisely patterning drugs, cells, and structural components, which made them useful in tissue engineering and regenerative medicine [79]. Several experiments showed that printed hydrogels were better in structurally faithful and controlled release behavior in comparison to bulk cast hydrogels. However, mechanical frailty, low printing rate and difficulties in preserving cell health through printing were typical drawbacks that were reported in research. Irrespective of these weaknesses, 3D printing and hydrogel design will keep growing because of its opportunities of personalized therapy and the organ on chip drug screening platforms. As shown in **Figure 9**, the distribution of hydrogel types highlights the dominance of synthetic and natural hydrogels, alongside the growing contribution of hybrid, nanocomposite, injectable, and 3D-printed systems in drug delivery research.

The cross-sectional study of drug release data showed that there are a number of mechanical patterns. In most cases (around 62 percent) Fickian diffusion prevailed especially in highly swollen synthetic hydrogel. Meanwhile, anomalous (non-Fickian) transport was typical of natural or biodegradable hydrogels because swelling, degradation, and polymer relaxation occur simultaneously. Hydrogel systems that were based on growth factors or nucleic acids often exhibited case II transport behavior, which is indicative of strong hydrogel-drug interactions and requires relaxation-based release by the polymer [80]. It is worth noting that nanocomposite hydrogels had more property tunability, allowing a considerable ability to fit a variety of models, including Higuchi, Peppas and Weibull. The burst release was greater in systems with a large pore size or weak drug-matrix interactions but was actually decreased in hybrid and nanocomposite systems. These results highlight the importance of the combined modeling approach, considering degradation, swelling, and structural dynamics, and not by the classical models of diffusion alone. All figures in this review are designed to support specific analytical points by illustrating key mechanisms, comparative be-

haviors, or synthesis outcomes identified across the systematically reviewed studies.

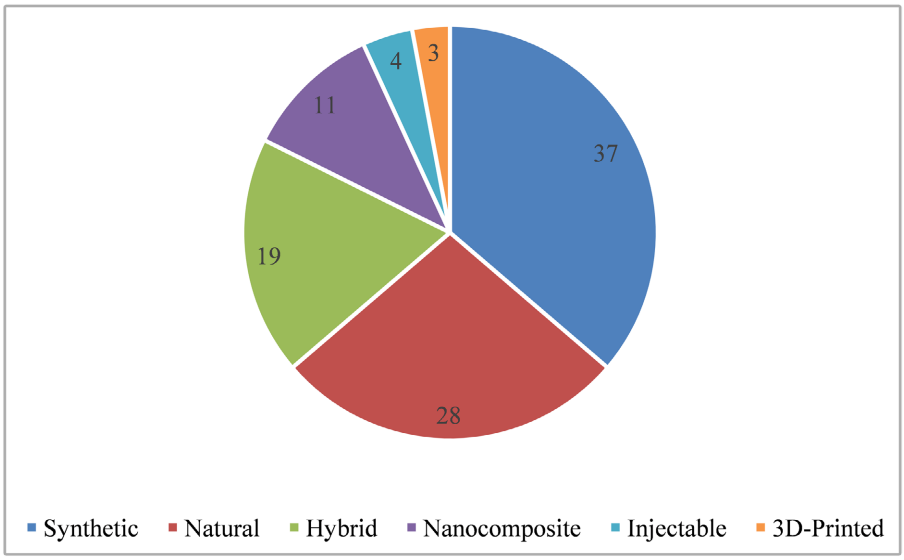

Figure 9. Distribution of hydrogel types in drug delivery research.

The biocompatibility analysis of the full data set showed that natural and hybrid hydrogels had an overwhelmingly positive response, and low cytotoxicity, high cell viability and low inflammatory reaction *in vivo*. High-density synthetic hydrogels have been reported to induce immune or inflammatory responses in certain *in vivo* settings. These responses are typically attributed to a combination of factors, including residual unreacted monomers or crosslinking agents, bioactive or acidic degradation byproducts, and physical properties such as high crosslink density and stiffness mismatch with surrounding tissues, which can promote foreign body reactions and fibrosis. The highest-risk profile was nanocomposite hydrogel, especially those involving the use of metallic or carbon-based nanoparticles; about 30% of these researches reported evidence of oxidative stress, inflammation, or clearance persistence. Nevertheless, numerous *in vivo* experiments of the studies that utilized nanoparticles showed excellent performance at low concentrations or when incorporated into the stable polymer materials that could not leak out. The findings demonstrate that the biocompatibility is not determined by the type of hydrogel used but by the formulation, crosslinking chemistry, as well as degradation byproducts. In general, the results reveal that hydrogel systems can deliver drugs in an extremely versatile and constantly sophisticated manner. The trends observed in the data indicate a vicious migration to multifunctional, responsive, and customized platforms that have the capacity to address the therapeutic needs of contemporary medicine. Nonetheless, other issues such as consistency in biological responsiveness, the issue of nanoparticle integration, imperfect prediction modeling of release properties, and scalable production processes are also highlighted by the discussion. Such observations underscore the need to carry on with interdisciplinary studies to convert hydrogel innovations into clinical drug delivery technologies. Formal meta-analysis was not pursued due to substantial heterogeneity in hydrogel composition, drug classes, experimental conditions, and outcome reporting; however, structured quantitative descriptors were used to preserve systematic rigor.

6. CONCLUSION AND FUTURE DIRECTIONS

In summary of the overall evidence provided in this review, the hydrogel-based drug delivery systems have grown to be one of the multipurpose and fastest developing classes of biomaterials in modern biomedicine. The field has evolved over the last thirty years to progress beyond the basic hydrophilic polymer networks, to extremely engineered multifunctional platforms that are able to respond to complex therapeutic

issues of localized, sustained, and responsive drug release. The systematic review of 432 studies indicated evident tendencies in the innovative use of materials, such as the rising popularity of hybrid polymers, nanocomposites structures, and multi-stimuli-responsive systems, which combine to offer more than ever before to provide tunability in mechanical properties, degradation, and drug release kinetics. Such developments have been especially seen in application to chemotherapeutics, biologics, and nucleic-acid-based agents, using hydrogels to stabilize microenvironments, and to allow spatiotemporal release to be deregulated using a microfluidic platform. Although significant progress has been made, the results also indicate that there are still significant challenges that prevent complete clinical translation. Problems like incomplete responsiveness, structural instability at physiological conditions, unpredictable degradation routes and issues relating to long term biocompatibility particularly in nanocomposites are significant challenges. In addition, issues in scale-up manufacturing, sterilization compatibility and regulatory acceptance are major challenges in transferring the hydrogel technologies of the laboratory models to clinically approved drug delivery devices.

The future in hydrogel-based drug delivery is likely to be aimed at the enhancement of adaptive, personalized, and digitally enhanced therapeutic systems that are more likely to respond to dynamic biological conditions. A great opportunity is the ability to design multi-responsive hydrogel that is able to simultaneously react to a range of biochemical signals, including pH, enzymatic action, oxidative stress, and mechanical forces. The next-generation systems have a potential of a highly precise on-demand release of drugs that replicates the complexity of disease microenvironments, especially in cancer, inflammation and metabolic diseases. The other crucial frontier is the development of hydrogels with the ability to interface with biosensors, electronic interfaces and microfluidic circuits to form closed-loop drug delivery systems that automatically regulate therapeutic output responses in real-time. This type of system has the potential to revolutionize chronic conditions like diabetes where glucose-responsive hydrogels can be attached to wearable or implanted sensors and automatically release insulin with greater accuracy than ever before. In the same fashion, hydrogel-coated implantable electronics can be used as smart drug-eluting interfaces that can be activated by neural or physiological signals and can increase therapeutic applications in neurology, cardiology, and regenerative medicine.

The future of 3D bioprinting and organ-on-chip technologies is viewed as another promising path because these systems can be used to build complex and tissue-like structure using hydrogels to facilitate both drug delivery and tissue repair. Hydrogels with gradients of drugs, growth factors, or living cells bioprinted are likely to find more and more applications in personalized regenerative therapies, including cartilage, skin, and neural tissue engineering. Furthermore, microphysiological systems made of hydrogel could be used as highly predictive systems of disease models and drug-testing systems in vitro and do not require animal testing to achieve faster drug development. Further studies are required to enhance the printability, structural fidelity and the long-term mechanical stability of bioprinted hydrogel and to guarantee consistency in integration with living tissues.

The future will also be based on nanocomposite hydrogels, as they are characterized by outstanding tunability and multifunctionality. Nevertheless, the following step of investigation should focus on the issues of safety, toxicity, and biodistribution, especially concerning inorganic nanoparticles, including graphene oxide, metal oxides, and gold nanoparticles. The mitigation of the long-term risk can be achieved through the use of the following strategies: the use of biodegradable nanomaterials, the surface functionalization to regulate immune interactions, and the development of self-clearing composites. *In vivo* experiments of chronic implantation, immune profiling and long term pharmacokinetics need to be done in greater detail to construct a regulatory pathway to nanocomposite hydrogel based clinical products. The other new paradigm is that of AI-driven hydrogel design in which machine learning models facilitate polymer interaction predictions, cross-linking chemistry, and drug-matrix dynamics. The capability to integrate computational design tools can dramatically decrease the time spent in the development process and provide a performance that is predictable due to the possibility of optimization in silico prior to experimental validation. The strategy is in line with the bigger trend of data-driven biomaterials studies and will be even more necessary as hydrogel structures become more intricate. Nevertheless, to achieve large-scale use of AI-based materials

design, standard datasets will be needed, enhanced reporting, and research-wide databases will be required.

The rate of clinical translation will be determined by regulatory and manufacturing issues. Achieving batch-to-batch consistency, coming up with scalable and GMP-compliant manufacturing methods, as well as, sterilization methods that do not harm the integrity of the hydrogel, are crucial priorities. Joint programs between the academic scientists, industrial partners, and regulatory agencies will play a very essential role in defining standardized assessment routes of hydrogel-based systems especially those that use biologics or nanostructures. The literature of long-term clinical studies is currently thin, and it will require such research to analyze safety, efficacy, and patient outcomes in detail. Moreover, aspects of sustainability will have increasing relevance in the future development of hydrogel systems. This includes the use of green and water-based solvents during synthesis, the adoption of polymers derived from renewable or bio-based sources, and manufacturing strategies that minimize waste and energy consumption. Such approaches not only reduce environmental impact but also align with regulatory expectations and facilitate scalable, clinically translatable hydrogel production. Altogether, hydrogels can be considered one of the most promising and versatile platforms to promote the development of modern drug delivery, and the possibilities of innovation in this area are massive at the intersection of polymer chemistry, biology, nanotechnology, and digital medicine. The research fraternity is now entering a stage where the objective is not only to maximize the valor of the hydrogel in the controlled laboratory environments but also to develop clinically viable, patient-specific, and technologically enhanced systems that can serve the real-life therapeutic requirements. The future of hydrogels can transform the field of targeted therapy, regenerative medicine, and personalized care by solving the existing scientific, engineering, and regulatory issues and creating a new generation of the technology.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest regarding the publication of this paper.

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