WORLD JOURNAL OF PHARMACY AND PHARMACEUTICAL RESEARCH

Review Article

Coden USA: WJPPCL

2026
Volume: 03
Issue: 06
Page: 92-109

# STIMULI-RESPONSIVE AND FUNCTIONALIZED HYDROGELS AS ADVANCED PLATFORMS FOR CONTROLLED DRUG DELIVERY: MECHANISMS, CATEGORIZATION, AND CLINICAL IMPLICATIONS

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**Received: 21 April 2026** **Revised: 11 May 2026** **Accepted: 31 May 2026**

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**DOI:** https://doi.org/10.5281/zenodo.20483732,

## ABSTRACT

Among the many biomaterial platforms explored for pharmaceutical use, hydrogels occupy a singularly compelling position — they mimic the water-rich architecture of living tissue while offering a programmable scaffold for drug containment and release. This article examines the growing relevance of hydrogel technology in the design of controlled drug delivery systems (CDDS), tracing its intellectual lineage from early polymer chemistry to present-day stimuli-responsive applications. We systematically address how hydrogels are categorised by their composition, network topology, ionic identity, and cross-link chemistry, and how each of these variables shapes the eventual pharmacokinetic behaviour of the formulation. Special attention is given to injectable and in situ-gelling architectures — including shear-flow-responsive gels and thermoset peptide assemblies — as well as to the continuum from macroscopic implants to colloidal nanogel suspensions. The mathematical underpinnings of drug transport through these matrices are presented alongside illustrative clinical correlates. Delivery applications spanning parenteral, enteral, rectal, and cutaneous routes are surveyed, and a curated summary of authorised hydrogel products on the global market is provided. The review concludes with a forward-looking discussion of intelligent hydrogels, three-dimensional bioprinting, and translational bottlenecks that must be addressed before the next generation of hydrogel therapies reaches patients.

**KEYWORDS:** *Hydrogel; Smart Polymer Networks; Controlled-Release Formulations; Injectable Gels; Drug Transport Kinetics; Nanogel; Thermoresponsive Biomaterials; Mucoadhesion; Biocompatible Matrices; Pharmaceutical Drug Delivery.*

## 1. INTRODUCTION

What does it take for a drug carrier to truly serve a patient? Beyond simply ferrying a molecule from a bottle to a biological target, an effective delivery platform must protect the cargo, release it in a manner the body can actually use, and avoid causing harm in the process. Hydrogels — water-swollen, cross-linked polymeric architectures — satisfy these demands with unusual elegance. Their physical resemblance to soft biological tissue, their tolerance for high water content, and their capacity to be chemically engineered for nearly any release profile have positioned them as one of the most versatile families of pharmaceutical excipients in contemporary practice.[1,2]

Historically, the concept of a material capable of absorbing and retaining water within a polymer network was formalised by Van Bemmelen as early as 1894, though practical pharmaceutical interest in hydrogels did not ignite until 1960, when Wichterle and Lim demonstrated that cross-linked poly(2-hydroxyethyl methacrylate) [P(HEMA)] could serve as a functional soft contact lens — a proof-of-concept that immediately suggested far broader biomedical possibilities.[3] The decades that followed saw hydrogel research expand into tissue engineering, regenerative medicine, wound management, agricultural slow-release fertilisers, and biosensing.[4] Within pharmaceutical science specifically, the ability to tune gel porosity, mechanical stiffness, and degradation behaviour has made these materials central to the controlled-release paradigm.[5]

At a molecular level, a hydrogel network owes its hydrophilicity to pendant functional groups — carboxylates, hydroxyls, sulphonates, amides — that form hydrogen bonds with water molecules and maintain a characteristic aqueous interior even as the macroscopic gel retains its shape.[6] Cross-links, whether permanent covalent bonds or transient physical associations, govern how aggressively the network swells and how readily it releases entrapped molecules. The balance between swelling and elastic restoring forces sets the mesh geometry that a diffusing drug molecule must navigate.[7,8] Fully hydrated gels present an internal aqueous environment analogous to the extracellular matrix, which minimises local biological response — a feature that distinguishes them favourably from many synthetic implants and particulate carriers.[9,10]

The polymer feedstock may come from natural sources — chitosan, alginate, hyaluronic acid, gelatin, collagen — or from synthetic chemistry — PEG, PAA, PVA, PNIPAAm — or from deliberate combinations of both. Natural polymers tend to excel on biocompatibility and biodegradability, though their batch-to-batch consistency and susceptibility to microbial attack can complicate pharmaceutical development. Synthetic polymers, by contrast, afford precise molecular weight control and straightforward chemistry for functional modification, but may require additional biocompatibility evaluation.[6,7] Hybrid systems seek to harvest the best attributes of each. This review surveys the full landscape of hydrogel-based controlled drug delivery — from classification and fabrication through to release kinetics, macroscopic architecture, clinical applications, and the emerging frontiers that will define the field's next chapter.

## 2. CLASSIFICATION OF HYDROGELS

No single taxonomy captures every dimension of hydrogel chemistry, which is why the literature employs several overlapping classification frameworks simultaneously. Understanding how each framework maps onto formulation behaviour is essential for rational product design.[11–13]

### 2.1 Polymeric Source

The simplest sorting criterion is origin. Natural-source hydrogels draw on biopolymers whose backbone chemistry evolved over millions of years to interact with biological fluids. Anionic members of this group — alginic acid, pectin, hyaluronic acid — carry negatively charged carboxylate and sulphate residues that confer pH sensitivity and the ability to form ionic cross-links with divalent cations. Cationic natural polymers such as chitosan and polylysine carry protonatable amine groups, making them mucoadhesive and particularly valuable for GI delivery. Amphipathic species — collagen, fibrin — contribute structural versatility and are widely used in tissue-mimetic constructs. Neutral polysaccharides like dextran and agarose offer a blank-slate matrix for entrapment without electrostatic drug interactions.[11]

Synthetic hydrogels built on PEG-polyester block architectures (PEG-PLGA-PEG, PEG-PLA-PEG, PEG-PCL-PEG, PLA-PEG-PLA) can be precisely engineered to degrade at predetermined rates, giving formulation scientists direct control over the temporal drug release profile. Hybrid networks — collagen-PEG, alginate-poly(sodium acrylate-co-acrylamide), collagen-g-poly(acrylic acid) — are increasingly favoured because they combine biological recognition with synthetic tunability in a single construct.[12,13]

### 2.2 Polymeric Composition

**Single-component (homopolymeric) networks** are built exclusively from one monomer species. Despite their structural simplicity, they can be functionally sophisticated: PVP/PAA networks formed by radiation-induced cross-linking in deoxygenated aqueous media, for example, incorporate glucose oxidase to create glucose-sensing hydrogels useful in diabetic monitoring and insulin delivery.[14]

**Binary and multi-component (co-polymeric) networks** require at least one hydrophilic co-monomer to drive water uptake, but the second monomer can introduce stimuli responsiveness, mechanical enhancement, or degradable linkages. These matrices underpin a large share of the "smart material" literature, including optical transducers, pH-gated capsules, and pressure-sensitive actuators.[15,16]

**Dual-network (interpenetrating) architectures** entangle two separately cross-linked polymer chains without forming covalent connections between them. The interpenetration imparts mechanical toughness that neither network alone could achieve, while the independent cross-link densities can be tuned to produce near-zero-order drug release profiles — a property exploited, for instance, in chitosan-hydroxyethyl cellulose microspheres cross-linked with glutaraldehyde, which sustained antitubercular isoniazid release for up to 16 hours at 50–66% encapsulation yield.[17]

### 2.3 Network Architecture

Polymer chain organisation within the gel introduces a further tier of classification. In an amorphous network, chain segments are randomly coiled with no preferential orientation — a loosely packed structure that swells readily but can release drugs quickly. Semi-crystalline networks contain ordered microdomains that act as physical cross-link junctions, slowing both swelling and drug egress. Hydrogen-bonded networks achieve a well-defined three-dimensional geometry through extensive inter-chain hydrogen bonding, producing materials with predictable pore geometry and mechanically distinct behaviour.[11]

### 2.4 Cross-linking Modality

A gel whose cross-links are covalent — formed by radical polymerisation, gamma irradiation, enzymatic catalysis, or click chemistry — behaves as a permanent elastic solid. It resists dissolution even on prolonged aqueous exposure and retains its drug payload until diffusion or degradation depletes it. In contrast, gels held together by non-covalent forces —

electrostatic attraction, hydrophobic stacking, hydrogen bonding, or stereocomplex formation — are inherently reversible. This reversibility is both a limitation (mechanical weakness under prolonged loading) and a clinical asset: a shear-reversible gel can be injected through a needle and rebuild its structure at the deposition site.[8,18]

### 2.5 Charge Character

The presence, absence, and sign of ionisable groups along the polymer backbone determines how a gel responds to local pH and ionic environment, and how it interacts electrostatically with drug molecules. Non-ionic gels swell uniformly regardless of environmental pH — they are predictable but insensitive. Anionic gels, carrying carboxylate or sulphonate groups, expand dramatically in alkaline conditions as electrostatic repulsion between deprotonated chains drives water ingress — a phenomenon exploited for colon-targeted oral delivery where the luminal pH rises above 6.5. Cationic gels carrying protonated amines behave conversely, swelling in acidic conditions, and their intrinsic positive charge makes them mucoadhesive — a property that extends gastric residence time and improves absorption.[13]

## 3. FABRICATION STRATEGIES

The architecture and performance of a hydrogel-based delivery system are dictated as much by how it is made as by what it is made from. Fabrication routes fall into two broad families depending on whether the cross-links formed are covalent or non-covalent, and each family contains several distinct sub-strategies with markedly different suitability profiles for pharmaceutical use.[11,18]

### 3.1 Covalent Cross-linking Approaches

**Free-radical chain polymerisation:** This workhorse approach initiates polymerisation with redox couples (ammonium persulfate/TEMED) or UV-activated photoinitiators in aqueous monomer solutions. It is extremely versatile — acrylamide, acrylic acid, HEMA, and their derivatives all participate readily — and scale-up is straightforward. Post-synthesis purification to remove residual monomers and initiators is mandatory before pharmaceutical use.

**High-energy irradiation:** Exposure of polymer solutions to electron beams or γ-radiation generates reactive radical species that cross-link chains in situ without any chemical additive. The dual benefit of cross-linking and sterilisation in a single step makes this method

attractive for aseptic manufacturing, and PVA networks prepared by this route are well-characterised.[11]

**Enzyme-catalysed coupling:** Horseradish peroxidase, transglutaminase, and tyrosinase catalyse mild covalent bond formation under physiological conditions, making enzymatic gelation the preferred route when proteins, growth factors, or living cells must be co-encapsulated without denaturation.[18]

**Complementary functional-group reactions:** Michael addition between thiol and vinyl sulphone groups, Schiff base condensation of aldehyde-modified polysaccharides with amine-bearing polymers, and strain-promoted click chemistry all produce injectable formulations that gel in situ within clinically acceptable timeframes. These platforms are especially valued for slow-gelling in situ systems where precise timing of gelation onset matters.[18]

### 3.2 Non-covalent Cross-linking Approaches

**Ionic gelation:** Exposure of aqueous sodium alginate solutions to calcium chloride instantly forms a water-insoluble calcium alginate gel through electrostatic bridging of adjacent carboxylate groups by $Ca^{2+}$ ions. Analogous processes occur in chitosan-tripolyphosphate systems. These formulations are easy to prepare under ambient conditions with no hazardous reagents, though mechanical durability can be modest.

**Amphiphilic block-copolymer self-assembly:** PEG-polyester (Pluronic, poloxamer) and other amphiphilic co-polymers organise into micellar aggregates above a critical concentration and temperature, producing physical networks that are liquid at refrigerator temperatures and solid at body temperature. This thermogelatability makes them ideal for depot-injection applications.

**Crystallisation-driven gelation:** Repeated freeze-thaw cycling of PVA solutions creates microcrystalline domains that serve as physical cross-link junctions, yielding tough, resilient gels without any chemical reagents. Stereocomplexation between enantiomeric PLA chains achieves an analogous result through helical co-assembly.[18]

Regardless of the cross-linking route, the general manufacturing workflow follows a common thread: dissolve the polymer in a compatible solvent, induce cross-linking, purify by extensive washing, allow equilibration in aqueous medium, load the therapeutic agent either

during synthesis or by post-equilibration soaking, and then dry or formulate for the chosen delivery route.

## 4. MECHANISMS GOVERNING DRUG RELEASE

How a drug escapes from a hydrogel matrix is rarely a simple story, and in many systems two or more mechanisms operate simultaneously. Broadly, release from hydrogel platforms is governed by concentration-gradient-driven molecular transport, by the dynamics of matrix hydration and expansion, or by chemical reactions that liberate drug from covalent or physical tethering within the network.[19]

### 4.1 Gradient-Driven Molecular Transport

Where the gel is already fully swollen and no network transformations are occurring, the dominant release mechanism is passive molecular transport down a concentration gradient. The driving force is the difference in drug chemical potential between the gel interior and the surrounding medium. For small molecules navigating an aqueous polymeric mesh, this transport is well described by Fickian theory, and the rate can be expressed concisely as:

$$J_i = -D_{ip} \times (\partial C_i / \partial x)$$

Here, $J_i$ is the mass flux of the drug per unit cross-sectional area, $C_i$ is the local drug concentration, and $D_{ip}$ is the apparent transport coefficient within the swollen polymer matrix — a quantity that is substantially lower than the free-water value and depends sensitively on mesh geometry, cross-link density, polymer-drug interactions, and the hydrodynamic radius of the drug molecule itself.[20,21] Reservoir-type architectures, in which a drug-loaded core is enclosed within a rate-controlling gel membrane, give near-constant release rates governed by this membrane; matrix-type architectures, in which drug is uniformly embedded throughout the network, give declining release rates as the surface concentration depletes.

### 4.2 Matrix Hydration-Controlled Release

When a drug is dispersed within a glassy polymer that must first hydrate before it can swell and permit molecular motion, the gel-front velocity — not the intrinsic drug transport — becomes the rate-governing parameter. Water penetrates the outer surface of the dry tablet or film, converting the brittle glassy polymer to a rubbery, mobile state. Only once a given polymer segment has transitioned through this glassy-to-rubbery relaxation can drug molecules begin to diffuse outward. The rate at which the hydration boundary advances into the matrix therefore determines how quickly drug is made available.[20,22]

The interplay between molecular-transport kinetics and polymer-chain relaxation kinetics is captured by the Deborah number ($D_e$), defined as:

$D_e = \lambda / t = \lambda D / \delta(t)^2$

where λ is the characteristic polymer relaxation time, t is the characteristic drug transport time, D is the drug transport coefficient, and δ(t) is the instantaneous thickness of the hydrated layer. When $D_e >> 1$, chain mobility cannot keep pace with water ingress and matrix expansion controls release; when $D_e << 1$, conventional Fickian transport governs. Most commercial HPMC and methyl cellulose oral matrix tablets operate in the intermediate regime, blending both mechanisms.[21]

### 4.3 Reaction-Mediated Release

The third major paradigm encompasses systems where drug escape is coupled to a chemical transformation within the matrix. In erosion-based systems, hydrolytic or enzymatic scission of backbone ester or amide bonds gradually reduces polymer molecular weight, fragments the network, and releases encapsulated drug as the matrix physically disintegrates. PLA-PEG, PLGA, and polycaprolactone-based hydrogels exemplify this approach and are particularly valued for depot applications where surgical retrieval of the spent matrix is undesirable. In pendant-chain systems, the drug itself is covalently attached to the network via a labile linkage — an ester, a disulphide, or a pH-sensitive Schiff base — and liberation requires breakage of that bond. The rate of bond hydrolysis or enzymatic cleavage then sets the pharmacokinetic profile, potentially yielding near-zero-order kinetics over extended periods.[23]

## 5. ARCHITECTURAL FORMATS FOR DRUG DELIVERY

One of the less-appreciated advantages of hydrogels over rigid particulate carriers is their geometric flexibility. A hydrogel can be cast, moulded, extruded, or printed into essentially any shape — from centimetre-scale implants to sub-micrometre colloidal particles. The size and morphology of the final construct profoundly influence biodistribution, administration route, and release kinetics.[24]

### 5.1 Bulk (Macroscopic) Hydrogel Implants and Injectables

Full-sized hydrogel constructs — ranging from a few millimetres to several centimetres — are surgically placed or endoscopically deposited at the intended site. Infuse®, a type I collagen gel carrying recombinant human bone morphogenetic protein-2, exemplifies the

clinical viability of this approach: surgically implanted to bridge bone defects and promote spinal fusion, it has accumulated a substantial record of safety and efficacy.[25] Three injectable macrogel architectures have attracted particular pharmaceutical interest:

### *5.1.1 Macro-Porous Cryogels*

Rather than a dense homogeneous matrix, these gels possess a sponge-like network of interconnected macropores. When loaded into a syringe, pore water is expelled by the applied pressure and the gel compresses dramatically; once extruded and the mechanical constraint lifted, it rebounds to its original three-dimensional form within seconds. The ability to sustain compressive strains approaching 90% without permanent structural damage makes these materials uniquely injectable through standard-gauge needles.[26] In oncological settings, subcutaneous implantation of alginate-gelatin cryogels loaded with immune checkpoint modulators triggered measurable regression of established tumours in murine models, demonstrating the immunotherapeutic applicability of this platform.[27] Macro-porous architectures are manufactured by freeze-drying, gas-foaming with sodium bicarbonate or $CO_2$, or microemulsion templating.

### *5.1.2 Flow-Responsive Gels*

Certain physically cross-linked hydrogels liquefy under the mechanical shear generated within a syringe and needle, allowing injection without chemical modification, and then spontaneously rebuild their network once flow ceases. The reversibility of this process arises from dynamic non-covalent interactions — hydrophobic contacts, aromatic π-stacking, hydrogen bonds, electrostatic pairing — which are reversibly disrupted by the shear field and restored within milliseconds at the injection site.[28] Designer β-hairpin peptides known as MAX peptides offer a well-characterised example: alternating hydrophobic and charged residue blocks fold into hairpin structures that assemble into extended fibrillar networks under physiological salt conditions. These networks are robust under static loading but flow readily under shear, and they can be tuned by varying hydrophobic content and peptide concentration.[29,30]

### *5.1.3 In Situ-Forming Gels*

The concept here is disarmingly simple: inject a polymer solution that is liquid at the point of administration and watch it solidify precisely where it is needed. The clinical appeal — avoidance of invasive surgery, conformation to irregular tissue geometries, and localised drug

exposure — drives sustained research into the triggers that can initiate gelation reliably within the physiological environment.[31]

Temperature-triggered gelation exploits polymers with a lower critical gelation threshold near 37°C (body temperature). Below this temperature the polymer chains are hydrated and mobile; above it, hydrophobic associations overcome entropic penalties and a macroscopic gel precipitates. Poloxamers, PNIPAAm copolymers, and PEG-polyester triblocks all follow this thermodynamic logic.[32] Growth factor delivery from in situ-gelling heparin-peptide matrices leverages the high affinity of heparin for heparin-binding domains on VEGF and FGF, protecting these labile proteins from proteolytic degradation while releasing them gradually as heparin-peptide bonds dissociate.[33] Self-assembling RADA16-I ionic peptide hydrogels loaded with the plant-derived antineoplastic emodin gel spontaneously at physiological ionic strength, confining cytotoxic drug to the tumour microenvironment and substantially reducing systemic exposure-related toxicity in animal experiments.[34]

### 5.2 Micro- and Nanoscale Hydrogel Particles

Reducing the hydrogel to colloidal dimensions introduces a new set of pharmacokinetic possibilities. Microgels (roughly 1–1000 μm) and nanoscale gels (1–100 nm) retain all the intrinsic properties of their macroscopic counterparts — water uptake, stimuli responsiveness, drug encapsulation — but add injectable convenience, high surface-to-volume ratios for ligand conjugation, and size-dependent biodistribution.[35]

Size is particularly consequential for systemic delivery. Particles above approximately 5 μm are rapidly captured by pulmonary capillaries or phagocytic cells in the spleen and liver; those below 200 nm can extravasate through the fenestrated vasculature of tumour tissue via the enhanced permeation and retention (EPR) effect; particles below 8–10 nm are cleared renally with relatively short plasma half-lives.[36] This size landscape has guided the development of tumour-targeted nanogels in the 20–100 nm window, which accumulate at tumour sites while being small enough to eventually clear the body. Cationic nanoscale gels assembled from poly(ethylenimine) and poly(ethylene oxide) have demonstrated an intriguing capacity to ferry oligonucleotides across both the gastrointestinal mucosa and the blood-brain barrier, opening avenues for nucleic acid therapy in neurological disease.[37] Microgels are typically manufactured by microfluidic flow-focusing and micro-moulding; nanogels by inverse miniemulsionpolymerisation, nanoprecipitation, or template-assisted nanomoulding.[38]

## 6. CLINICAL AND PHARMACEUTICAL APPLICATIONS

Hydrogels have found productive footing across virtually every major drug delivery route, each presenting a distinct biological environment that exploits different aspects of gel chemistry.[39]

### 6.1 Parenteral Subcutaneous Delivery

The richly vascularised subcutaneous compartment is a natural home for hydrogel depots: implanted or injected gels interface with tissue macrophages and fibroblasts, and their aqueous surface chemistry attenuates foreign body encapsulation relative to harder synthetic implants. Polyethylene-based hydrogels remain inflammation-free for at least 60 days post-injection in rodent models. Alginate, pectin, and gelatin networks give comparable results; chitosan is particularly prized because its inherent cationic character suppresses macrophage activation and prevents fibrous encapsulation from developing around the implant.[40] PEG-grafted chitosan platforms have been investigated for subcutaneous depot delivery of cyclosporine A, achieving sustained therapeutic plasma levels over multi-week intervals.

### 6.2 Oral Administration

Oral delivery asks more of a hydrogel than perhaps any other route: the formulation must survive the acid assault of the gastric lumen (pH ~1.2), release drug appropriately in the duodenum and jejunum (pH 5–7), and resist rapid luminal clearance long enough for adequate absorption — all without causing local mucosal damage.[41] pH-switchable gels based on chitosan, whose amino groups are protonated and the gel contracts in acid, then swells at intestinal pH, enable targeted colon delivery. The mucoadhesive profile of these formulations is further enhanced by thiol-functionalised (thiomer) polysaccharide derivatives, which form disulphide bridges with mucin glycoproteins, dramatically extending mucosal contact time and thereby improving bioavailability.[42] Practical limitations include poor epithelial permeability for hydrophilic macromolecules and the variable transit environment of the upper versus lower gut.[43]

### 6.3 Rectal Route

Rectal delivery via hydrogel suppositories or enema formulations avoids hepatic first-pass metabolism, requires no patient swallowing ability, and provides direct access to the distal colonic mucosa — a strategically important target in inflammatory bowel disease. Catechol-functionalised chitosan gels, applied rectally in a murine colitis model, maintained full biocompatibility over 10 days with no evidence of local erosion or systemic toxicity.[44]

Mucoadhesive metronidazole-loaded gels have entered commercial development for localised treatment of rectal infections, exploiting the mucoadhesive surface chemistry to prolong drug-mucosal contact beyond what conventional suppositories can achieve.

### 6.4 Topical and Transdermal Routes

Applied to intact or compromised skin, hydrogels benefit from their high water activity, which hydrates the stratum corneum and potentiates drug penetration, as well as from patient-friendly aesthetics — they feel cool, non-greasy, and comfortable.[45] Transdermal gels are particularly well matched to drugs with low oral bioavailability or narrow therapeutic windows, since the skin acts as a rate-limiting membrane that smooths out plasma concentration fluctuations. Berberine alkaloid delivered transdermally through chitosan gels achieved therapeutic skin concentrations in ex vivo rat skin studies, demonstrating feasibility for a compound otherwise limited by first-pass metabolism.[46] Contemporary research has shown that nanoparticulate cargo — quantum dots, liposomes, polymeric nanoparticles — can be embedded within hydrogel matrices and delivered across intact skin, with penetration depth and extent tunable through particle size, charge, and surface chemistry.[40]

## 7. REPRESENTATIVE HYDROGEL-DRUG SYSTEMS: A SUMMARY

**Table 1: Selected polymer-drug combinations and therapeutic application profiles in hydrogel-based delivery.**

| Polymer Network | Encapsulated Drug | Target Route | Notable Attribute |
|---|---|---|---|
| Chitosan–alginate blend | Bevacizumab | Ocular | Mucoadhesive; pH-gated release |
| Polyacrylic acid / gelatin | Vancomycin HCl + Gentamycin sulphate | Local wound | Dual-antibiotic prolonged release |
| PEG-grafted chitosan | Cyclosporine A | Subcutaneous | Extended immunosuppressant depot |
| Quaternised chitosan + PEG | Insulin | Nasal mucosal | Non-invasive peptide delivery |
| P(MAA-g-EG) copolymer | Anti-TNF-α biologic | Transmucosal | Biologic macromolecule protection |
| Phthaloyl chitosan-g-PEG | Ciprofloxacin | Pulmonary | Aerosolisable hydrogel particle |
| RADA16-I self-assembling peptide | Emodin | Intratumoural | In situ peptide gelation; localised toxicity |
| PNIPAAm-co-acrylic acid | Doxorubicin | Intratumoural | Thermo- and pH-dual-responsive release |

## 8. COMMERCIALLY AUTHORISED HYDROGEL DRUG PRODUCTS

**Table 2: Examples of hydrogel-based drug products currently available on the pharmaceutical market.**

| Brand Name | Manufacturer | Gel Composition | Therapeutic Use | Key Technical Detail |
|---|---|---|---|---|
| SQZ Gel Oral Release System | Macromed, USA | Chitosan + PEG matrix | Hypertension (diltiazem) | pH-responsive; once-daily dosing |
| Hycore-V™ / Hycore-R™ | CeNeS Drug Delivery, UK | Proprietary polymer base | Vaginal / rectal infection | Localised metronidazole delivery |
| Cervidil® Vaginal Insert | Forest Pharmaceuticals, USA | PEO-urethane copolymer | Cervical ripening | 10 mg dinoprostone; controlled 0.3 mg/h release |
| Smart-C Hydrogel | MedLogi Global, UK | PAA + oxypropylene glycol | Ophthalmic / nasal / transdermal | Temperature-triggered mucoadhesive gel |
| Aquamere™ | Hydromer Inc., USA | PVP-urethane graft copolymer | Topical / oral | High-loading capacity soft-coat formulation |

## 9. EMERGING FRONTIERS AND FUTURE DIRECTIONS

The last ten years have seen hydrogel science shift from incremental optimisation toward conceptual reinvention. Three converging developments — programmable molecular self-assembly, precision nanomaterial integration, and digital biofabrication — are reshaping what a hydrogel can do and, critically, how it can be made.[47]

Self-healing formulations represent a particularly intriguing frontier. These gels can autonomously repair mechanical damage — a crack, a puncture, a shear-induced fracture — by re-forming non-covalent cross-links within seconds of injury. Dipeptide-based supramolecular gels exhibiting instantaneous self-healing have been demonstrated as sustained drug delivery matrices, combining mechanical resilience with programmable release profiles [30]. The concept of theranostic hydrogels — constructs that simultaneously deliver a therapeutic payload and report on the local disease environment through an embedded sensor — is advancing rapidly, with fluorescent nanoclusters, MRI contrast agents, and electrochemical reporters all incorporated into gel matrices for real-time treatment monitoring.[47]

Nanogel oncology platforms continue to mature, though translating laboratory EPR-dependent accumulation into reliable clinical benefit remains elusive. Tumour heterogeneity, variable vascular permeability, and unpredictable interstitial pressure all attenuate EPR-

driven accumulation in practice. Active targeting approaches — conjugating nanogel surfaces with antibody fragments, aptamers, transferrin, or folate — are being pursued to override passive accumulation limitations, and early clinical data from a handful of targeted nanomedicine products are informing rational redesign of these platforms.[36]

Perhaps the most transformative near-term technology is bioprinted hydrogel scaffolds. Direct-write extrusion and stereolithographic bioprinting can now produce patient-specific, spatially graded hydrogel implants in which drug concentration, cross-link density, and pore architecture vary continuously across the construct — effectively encoding a customised pharmacokinetic programme into the material geometry. GelMA, methacrylated hyaluronic acid, and alginate-based bioinks are currently the most printable and clinically translatable substrates.[47] Achieving sufficient regulatory clarity, reproducible print quality at clinical scale, and long-term stability of bioprinted constructs will be the defining challenges of the coming decade.

## 10. CONCLUSION

Hydrogels have earned their standing as one of pharmaceutical science's most productive material platforms not through a single defining property but through a productive convergence of many: tissue-like mechanical behaviour, exceptional water compatibility, programmable degradation, and responsiveness to the very biological signals that mark disease. The classification frameworks reviewed here — spanning source, composition, topology, cross-link chemistry, and ionic character — are not merely academic taxonomy; each axis represents a real formulation lever that the scientist can pull to modulate swelling kinetics, drug transport, and biocompatibility. The mathematical models underpinning Fickian transport, matrix-relaxation-controlled release, and erosion kinetics provide the quantitative framework that transforms empirical screening into rational design.

What is perhaps most exciting about the current moment in hydrogel science is the breadth of clinical problems that seem genuinely tractable with these materials — from the local immunotherapy of solid tumours via cryogel depots, to nucleic acid delivery across the blood-brain barrier via cationic nanogels, to precision drug release from patient-specific bioprinted implants. Translating this promise into approved therapies will require not only continued materials innovation but also rigorous scale-up methodology, standardisedcharacterisation frameworks, and clear regulatory pathways for the more complex intelligent constructs. The foundation, however, is robust, and hydrogel-based

controlled delivery is well-positioned to become even more central to how medicines are designed and administered in the coming decades.

## ACKNOWLEDGEMENT

The authors express their gratitude to [Institute/University Name] for providing the academic resources necessary to complete this work. No financial support from external sponsors was received for this review article.

## CONFLICT OF INTEREST STATEMENT

All authors declare that they have no financial or personal relationships with any individual or organisation that could have inappropriately influenced the content of this article.

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