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FORMULATION AND OPTIMIZATION OF PHARMACEUTICAL HYDROGELS: A COMPREHENSIVE OVERVIEW

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ABSTRACT

Pharmaceutical hydrogels have profoundly altered the landscape of contemporary medicine, transforming them from passive, simple materials to bio-responsive, dynamic therapeutic systems. This comprehensive review explores the fundamental characteristics, evolutionary history, and classification of hydrogels, highlighting their unique ability to resemble human tissue as a result of their exceptional water-retention capabilities. The essential formulation and synthesis strategies are discussed, and physical cross-linking techniques, such as freeze-thawing and ionic interactions, are compared to robust chemical methods, such as free radical polymerisation and "click" chemistry. The integration of secondary nanocarriers, such as liposomes, to prevent premature burst release is a comprehensive study that involves the optimisation of release kinetics, which is influenced by diffusion, swelling, and degradation. This is essential for the precise delivery of drugs. Furthermore, the review emphasises the significance of Quality by Design (QbD) principles in the meticulous engineering of these intricate matrices to guarantee clinical safety and pharmacological efficacy. Lastly, we underscore the critical role of stimuli-responsive "smart" hydrogels as biomimetic scaffolds in advanced tissue engineering, particularly for the restoration of the central nervous system and 3D bioprinting, as well as their innovative applications. In summary, this summary provides a fundamental framework for the ongoing clinical translation of hydrogel therapies of the next generation.

KEYWORDS: Pharmaceutical hydrogels, water-retention capabilities, Quality by Design (QbD): stimuli-responsive, hydrogels, tissue engineering.

1. INTRODUCTION TO PHARMACEUTICAL HYDROGELS

Over the past few decades, the biomaterials science domain has undergone a paradigm shift, transitioning from the use of biologically inert structural implants to the deployment of highly dynamic, bio-responsive matrices that are specifically engineered to interact with living tissues. This domain is both extensive and interdisciplinary. Pharmaceutical hydrogels, a class of soft materials that are exceptionally versatile, are at the forefront of this revolution. They have fundamentally altered the landscape of modern pharmacotherapy and controlled drug delivery. Hydrogels are three-dimensional, cross-linked polymeric networks that possess an extraordinary ability to absorb, swell, and retain substantial volumes of water or physiological fluids without dissolution.[1] These hydrogels possess a thermodynamic compatibility and physical flexibility that are remarkably similar to natural extracellular matrix (ECM) architectures and biological tissues, as their high-water content frequently exceeds 90% of their total mass.[2] As a result, these systems exhibit an unparalleled level of biocompatibility, which reduces the immunogenic and inflammatory responses that are frequently associated with conventional macroscopic drug carriers.

Within the pharmaceutical sciences, the advent of hydrogel-based systems has addressed several long-standing challenges in conventional drug delivery methods, including rapid systemic clearance of active pharmaceutical ingredients (APIs): degradation of labile

biomacromolecules (e.g. proteins, peptides and nucleic acids) in harsh physiological environments, and systemic toxicities resulting from non-specific drug distributions.[3] Hydrogels are highly hydrated, porous polymeric meshes that encapsulate therapeutic agents, providing a protective microenvironment for the drug, shielding it from premature enzymatic degradation, and allowing sustained, localised, and mathematically predictable release over extended temporal windows.[4] In addition, the structural and chemical diversity of the constituent polymers allows molecular-level rational design of hydrogels. Using strategic optimising of polymer molecular weights, the addition of specific ionisable functional groups, and precise calibration of cross-linking densities, pharmaceutical scientists can optimise macroscopic properties of the hydrogel such as mechanical stiffness, degradation kinetics, and absolute swelling capacity.[5]

With the evolution of research from basic macroscopic platforms to complex microgels and nanogels, the scope of hydrogels has significantly expanded, allowing for advanced delivery routes such as site-specific intra-tumoral injections, long-lasting ocular formulations, and dynamically responsive oral delivery vehicles.[6] The shift from inert structural scaffolds to dynamic stimuli-responsive "smart" hydrogels is the forefront of pharmaceutical research combining the fields of polymer chemistry, rheology and clinical pharmacology to create the next generation of therapeutic modalities. It is important to study the evolutionary history, structural features, swelling thermodynamics, and strong classification schemes of hydrogels to fully appreciate their wide-ranging usefulness in modern formulation science before going into the complex details of their synthesis and structural optimisation.

1.1. Historical Context and Evolution

The evolution of pharmaceutical hydrogels is an interesting confluence of synthetic polymer chemistry and biomedical engineering with different generational leaps that have progressively improved their therapeutic value. While the conceptual roots of polymeric biomaterials were built in the early part of the 20th century, the contemporary era of biomedical hydrogels was not truly launched until the crucial advances of the mid-20th century. In particular, poly(2-hydroxyethyl methacrylate): commonly known as pHEMA, was first synthesised in 1936 by scientists at DuPont, but its profound implications for human health remained largely unexplored for more than two decades.[7] The critical turning point in the history of hydrogels came in 1960 when the pioneers Wichterle and Lim proved definitively the critical importance of cross-linked pHEMA networks and demonstrated their exceptional suitability for biological use, most famously in the revolutionary development of soft contact lenses.[8, 9] This achievement offered the fundamental proof-of-concept that synthetic, water-swollen polymeric networks might interface safely and effectively with fragile human tissues, and so triggered a worldwide research drive on soft biomaterials.

Since the findings of Wichterle and Lim, the evolution of hydrogels has traditionally been classified into three different generations according to common scientific aims and technological capabilities.[9] The pioneering work on hydrogels, which dominated the literature of the 1970s and early 1980s, was concerned largely with the development of simple macroscopic formulations and chemical modifications designed to achieve high equilibrium swelling ratios while retaining a reasonable degree of physical integrity. These early systems mainly consisted of chemically cross-linked macroscopic networks of relatively straightforward monomers such as HEMA, poly (ethylene glycol) (PEG) and poly(vinyl alcohol) (PVA). They were very successful in superficial and macroscopic applications such as wound dressings and simple space-filling implants, showing excellent biocompatibility, but were often limited by suboptimal mechanical strength and an inability to respond dynamically to the surrounding physiological environment.[1] Moreover, their application in targeted drug delivery was hampered by the tendency for small-molecule medicines to rapidly and uncontrollably diffuse out of their very porous matrices, a phenomenon referred to as "dose dumping" in pharmacokinetics.

The limitations of this first generation of hydrogels lead to the development of a second generation of hydrogels, enabled by developments in polymer science that allowed the synthesis of stimuli-responsive, or "smart", materials.[10] Researchers started to carefully construct the polymer backbones with certain functional groups that might undergo significant physicochemical phase transformations with minor environmental stimuli, like temperature, local pH, and ionic strength. In this age, intelligent systems were developed, which could actively modulate their swelling behaviour and pore diameters, turning hydrogels from passive diffusion matrices into active, triggerable drug delivery devices.[11]

The third generation of hydrogels, which is actively shaping the contemporary landscape, is directed towards architectural complexity, structural hierarchy and exquisite molecular targeting.[9] Third generation hydrogels are often based on the stereo-complexation, supramolecular assembly and hybrid organic-inorganic compositions for the development of multi-functional platforms. These current systems are designed to respond not only to physical and chemical inputs but also to biological triggers such as certain enzyme activity or local antigen expressions. Furthermore, the arrival of microfluidics and nanotechnology has allowed the miniaturisation of hydrogels to injectables microgels and nanogels, greatly extending their pharmacological repertoire.[12] The historical journey from the basic pHEMA lenses of Wichterle and Lim to complex multi-responsive nano-polymeric constructions today shows a

constant, strong effort towards highly personalised, targeted and safe medication.

1.2. Characteristics and Swelling Behaviour of Pharmaceutical Hydrogels

The physical and thermodynamic features of pharmacological hydrogels, particularly their unusual swelling kinetics and extensive water-retention capacities, are inextricably linked to their functional value. At a molecular scale, hydrogels have a large number of hydrophilic functional groups throughout the polymer backbone such as hydroxyl (-OH): carboxyl (-COOH): amino (-NH2): sulfonate (-SO3H): amide (-CONH2): among others.[13] When a dehydrated hydrogel matrix (sometimes called xerogel) is immersed in an aqueous physiological environment, a complex thermodynamically driven hydration process begins. The swelling process develops basically in three consecutive stages. The water molecules first diffuse rapidly into the polymer network because to the significant osmotic pressure gradient and high thermodynamic attraction of the hydrophilic functional groups for water.[10] The primary bound water is formed in the initial hydration stage, when water molecules are strongly bound to the polar functional groups via strong hydrogen bonding.

The ongoing flux of the fluid after saturation of polar groups causes hydration of the hydrophobic portions of the polymer chains and accumulation of the "secondary bound water. During these first hydration events, the compressed and entangled polymer chains begin to disentangle, loosen, and relax, transforming the network from a glassy state to a highly flexible, rubbery state.[14] Finally, capillary pressures and the ubiquitous osmotic driving force suck a huge amount of "free water" into the interstitial spaces of the growing matrix. And the network grows and sucks in fluid until it reaches an exact thermodynamic equilibrium. This equilibrium swelling condition is a subtle balancing of the osmotic forces that expand and drive water into the gel and the retractile elastic forces of the cross-linked polymer chains that oppose limitless expansion.[11] The macroscopic swelling behaviour, and thus the resultant release kinetics, of any encapsulated pharmacological drugs is dictated mathematically by both diffusion and polymer relaxation mechanisms. Swelling may be generally classified as Fickian (diffusion regulated) or non-Fickian (relaxation controlled).[15] If the water diffusion into the hydrogel is much slower than the polymer chain relaxation, then the swelling is classical Fickian diffusion. Conversely, if the polymer chains relax at a rate similar to or slower than the diffusion rate of water, the swelling profile is controlled by anomalous or non-Fickian transport mechanics. The knowledge of these kinetic parameters is of utmost importance for the rational design of sustained release systems for drug administration as the mesh size of the swelling network directly influences the steric hindrance an eluting drug molecule is being subjected.[16]

The final degree of swelling is inversely proportional to the crosslink density of the polymer network. Highly cross-linked hydrogels have an extremely tight, constrained architectural mesh that physically constrains chain mobility and limits the total volume of water that can be absorbed severely.[17] A high degree of cross-linking gives higher mechanical stiffness and tensile strength but at the same time gives a more brittle structure with lower permeability. Loosely cross-linked hydrogels nevertheless swell more, resulting in extreme softness and high permeability, at the expense of lower mechanical robustness.[18] Thus, the pharmaceutical formulation scientists need to balance the hydrophilic-hydrophobic ratio and the cross-linking density carefully to obtain a hydrogel with sufficient mechanical integrity to withstand physiological stresses, and yet have an optimum porosity for precisely controlled drug elution.

1.3. Classification and Biomedical Applications of Pharmaceutical Hydrogels

Due to the great variety of polymeric materials and fabrication routes, pharmaceutical hydrogels are systematically classified based on different criteria, such as their source, cross-linking type, ionic charge, and response to external environmental stimuli.[5, 19]

Hydrogels are classified into natural, synthetic and semi-synthetic (hybrid) polymers, according on their source. Natural hydrogels are made from naturally occurring polysaccharides and proteins such as alginate, chitosan, hyaluronic acid, cellulose derivatives, collagen and gelatin.[20] These materials are extremely appealing in biomedicine due to their intrinsic biocompatibility, enzymatic biodegradability, low toxicity and natural abundance, therefore making them promising candidates for interacting with living tissues.[21] However, natural hydrogels always possess intrinsic limitations such as large batch-to-batch structural deviation, sensitivity to rapid *in-vivo* breakdown, and weak inherent mechanical characteristics. To overcome these constraints, synthetic hydrogels such as poly(vinyl alcohol) (PVA): poly(ethylene glycol) (PEG): poly(acrylamide) (PAM): and poly(N-isopropylacrylamide) (PNIPAAm) have been extensively produced. Synthetic hydrogels are characterised by excellent repeatability, highly variable mechanical strengths, and precise control over their physicochemical properties, although they can sometimes display inferior biocompatibility or slower disintegration than natural hydrogels.[1] So, new formulations are increasingly based on hybrid hydrogels where natural and synthetic polymers are purposefully combined to synergise biological signalling and degradability of natural materials with the strong structural integrity and tunability of synthetic networks.

Another basic classification is based on the type of the cross-linking processes that link the polymer chains together. Chemical hydrogels (permanent gels) are formed by covalent bonding using chemical cross-linking agents, photopolymerization or enzymatic

processes. Such permanent networks cannot be broken down in aqueous conditions without breaking primary covalent links, giving them great long-term stability and structural durability. Instead, physical hydrogels (reversible gels) are formed by transient non-covalent physicochemical interactions such as ionic complexation, hydrogen bonding, hydrophobic contacts and host-guest supramolecular chemistry.[4] In physical hydrogel systems, the cross-links are generally weak and reversible which makes them highly responsive to changes in the environment and allows them to undergo phase transitions (sol-gel transitions). This is especially beneficial for injectable, *in-situ* forming depot formulations.

Furthermore, hydrogels are categorised according to their electrical charge into anionic, cationic, neutral and ampholytic systems that considerably influences their interaction with variously charged medicinal compounds and biological membranes. However, potentially the most clinically impactful classification is between ordinary hydrogels and stimuli-responsive (or "smart") hydrogels.[22] Smart hydrogels are developed to undergo sudden volume phase transitions in response to highly tailored physiological or environmental stimuli. Temperature sensitive hydrogels, especially those with a lower critical solution temperature (LCST) such as PNIPAAm, are liquid at ambient temperature and gel rapidly on exposure to physiological body heat.[23] Similarly, pH responsive hydrogels contain ionisable acidic or basic pendant groups that receive or release protons depending on the ambient pH, leading to rapid swelling or deswelling. This method is often used for targeted drug delivery in oral administration, protecting acid-labile medicines from the harsh stomach environment and initiating fast drug release when entering the alkaline environment of the intestines.[14]

This exceptional combination of these adjustable qualities has opened up a wide range of pharmacological and biological uses. Hydrogels are exceptionally efficient vehicles for preserving and managing the release of a variety of therapeutic agents from low-molecular-weight hydrophobic medicines to huge, fragile, biologic macromolecules and nucleic acids in targeted drug delivery.[24] They are formulated as transdermal patches to avoid first-pass hepatic metabolism, as mucoadhesive oral delivery systems for localised gastrointestinal treatment, and as highly specialised ophthalmic inserts to significantly increase the corneal residence time of drugs as opposed to traditional liquid eye drops.[6] Besides medication delivery, hydrogels are structurally similar to human tissue and are therefore crucial in tissue engineering, where they serve as three-dimensional scaffolds to support cell adhesion, proliferation and differentiation for organ regeneration. Furthermore, owing to the high moisture retention capacity and protective physical barrier qualities, they have been the gold standard for advanced wound dressings, expediting the healing process of severe burns and chronic diabetic ulcers.[25, 26] With the architectural complexity of these systems increasing, pharmaceutical hydrogels are a fundamental component of modern therapeutic design, providing the essential groundwork for the subsequent formulation, synthesis and strict optimisation processes necessary to bring these advanced therapies to the clinical stage.

2. Fundamental Formulation and Synthesis Strategies

The transformation of a hydrogel from a hypothetical polymeric network into a functional medicinal formulation needs a precise and highly regulated synthesis procedure. The design of hydrogels for drug delivery and tissue engineering differs substantially from the synthesis of hydrogels for industrial or agricultural purposes; in the pharmaceutical area, the main issues are total biocompatibility, predictable biodegradation and the maintenance of the structural integrity of the active pharmaceutical ingredient (API).[1] The primary goal of hydrogel formulation is to turn linear or branched hydrophilic polymer chains into a resilient three-dimensional matrix that swells in physiological fluids without dissolving.[19]

At its most rudimentary level, hydrogel formulation is composed of three basic elements: the monomeric or polymeric precursors, the cross-linking agent (or mechanism) and the dispersion medium, which is generally water or a biologically suitable physiological buffer.[18] Pharmaceutical scientists should also carefully consider the toxicological characteristics of unreacted monomers and residual cross-linking agents during the formulation, as these components are often subjected to thorough pharmacological and toxicological evaluation before clinical approval. For example, while certain synthetic precursors can produce hydrogels with very high mechanical resilience, the presence of unreacted toxic monomers can lead to severe local inflammation or tissue necrosis, preventing their use in sensitive *in-vivo* environments such as in mice or in human clinical trials. Thus, the selection of the synthesis strategy directly defines the final therapeutic viability of the formulation.[27] Hydrogel synthesis is traditionally divided into two main approaches according to the type of molecular bonds between the polymer chains: physical cross-linking and chemical cross-linking. Both techniques have specific advantages and disadvantages concerning mechanical strength, degradation kinetics and influence on encapsulated pharmacophores. Such synthesis techniques are often tuned to achieve very specific drug release profiles in modern formulation science, such as minimising the initial "burst release" effect typically seen with highly porous matrices or allowing for the precise spatiotemporal elution of complex biomacromolecules.[28]

2.1. Physical Cross-Linking Techniques

Physically cross-linked hydrogels are also referred to as reversible or transitory hydrogels. In this case, the network is formed by transient, non-covalent

intermolecular forces rather than permanent covalent bonds.[29] The main driving forces of physical gelation are hydrogen bonding, ionic contacts, hydrophobic associations, van der Waals forces and stereo-complexation.[19] From the point of view of a pharmaceutical formulation, physical cross-linking is very advantageous since it avoids the use of potentially cytotoxic chemical cross-linking agents, photo-initiators or organic solvents, thus ensuring excellent biocompatibility and protecting delicate APIs like liposomal vesicles, proteins and live cellular therapeutics from chemical denaturation during the encapsulation process.[18]

- **Ionic Interactions and Polyelectrolyte Complexation**

One of the most often used approaches to manufacture physically cross-linked hydrogels is based on ionic interactions. The process involved is complexation of a polyelectrolyte polymer with multivalent counter-ions of an opposing charge.[30] A classic example in pharmaceutical research is the formulation of alginate hydrogels. Sodium alginate is a naturally occurring anionic polysaccharide found in brown algae that readily forms gels in the presence of divalent cations (Ca^{2+}, Ba^{2+}, or Zn^{2+}, etc). The divalent cations operate as cationic bridges that cooperatively engage with the negatively charged carboxylate groups on the glucuronic acid residues of adjacent alginate chains, resulting in the development of the characteristic “egg-box” structural shape.[31] This method is utilised extensively for the soft, room temperature encapsulation of sensitive biopharmaceuticals and formulation of *in-situ* gelling systems for wound dressings or intra-articular injections. Moreover, the mixing of two oppositely charged polymers (e.g. the anionic alginate and the cationic chitosan) can also lead to the formation of polyelectrolyte complexes (PECs).[31] The ensuing electrostatic coacervation produces a strong hydrogel matrix without requiring low-molecular-weight cross-linkers, giving a highly adjustable platform for sustained, targeted mucosal drug administration.

- **Crystallization and Freeze-Thawing**

Crystallisation is another potent physical formulation method, most commonly performed through repeated freeze-thaw cycles. This physical cross-linking approach is very successful for homo-polymeric systems such as poly(vinyl alcohol) (PVA). By cooling a concentrated aqueous solution of PVA down to cryogenic levels and then thawing at normal temperature, the polymer chains are pressed together as water nucleates form ice crystals. The close closeness permits the creation of dense, localised areas of crystalline microstructures, stabilised by substantial intermolecular hydrogen bonding.[8] These crystalline domains are very strong physical cross-linking junctions. The macroscopic features of the resulting hydrogel, including its mechanical modulus, pore size, and elasticity, may be easily fine-tuned by simply changing the polymer content, the freezing temperature, and the total number of freeze-thaw cycles. Since this technique involves no chemical additives, freeze-thawed PVA hydrogels are very biocompatible and have been actively considered for load-bearing pharmaceutical applications such as synthetic articular cartilage replacements and tough transdermal administration patches.

- **Hydrophobic Associations and Amphiphilic Copolymers**

Advances in polymer chemistry now also allow physical cross-linking to occur by hydrophobic interactions. Polymers that have an amphiphilic nature, that is to say they contain both hydrophilic and hydrophobic parts, spontaneously self-assemble in an aqueous medium so as to minimise the thermodynamic free energy of the system. Hydrophobic domains aggregate to form individual hydrophobic cores or micelles that can be considered transitory cross-linking nodes, whereas hydrophilic segments extend into the aqueous phase to preserve solvation and the macroscopic structure of the network.[32] This method is often employed to generate thermos-reversible hydrogels, e.g. those based on Poloxamers (Pluronics) or poly(N-isopropylacrylamide) (PNIPAM) derivatives. These stimuli-responsive smart formulations are free flowing liquid sols at room temperature which permit uncomplicated drug loading and less invasive delivery using conventional hypodermic needles. However, once in the physiological environment, they achieve their lower critical solution temperature (LCST): where the hydrophobic interactions become dominant, and the *in-situ* sol-gel phase transition occurs rapidly (Ansari et al., 2022; Koland et al., 2022).[32,33] Such a method is extremely desirable for the development of injectable depots for localised, sustained delivery of chemotherapeutics, analgesics, and anti-inflammatory medicines directly to specified tissue areas.

Although physically cross-linked hydrogels have great safety profiles, they have major structural restrictions. Physical hydrogels are very prone to premature dissolution or mechanical disintegration when exposed to physiological shear forces or dramatic changes in local environmental conditions such as pH or ionic strength, because the intermolecular forces that bind the network are weak and reversible.[19] Such structural instability can lead to unpredictable degradation kinetics, and rapid and uncontrolled release of encapsulated drug payload which can be problematic for formulations that require precise zero-order release kinetics over an extended period.

2.2. Chemical Cross-Linking Techniques

Pharmaceutical scientists typically use chemical cross-linking to overcome the mechanical fragility and fast disintegration of physical network. Chemical hydrogels are formed by the formation of permanent and irreversible covalent connections between the constituent polymer chains, which gives rise to a highly stable, rigid and structurally resilient three-dimensional structure.[18] The substantial structural integrity facilitates the precise

mathematical optimisation of the hydrogel's degradation profile and drug release kinetics, enabling the design of formulations for therapeutic durations ranging from a few days to many years. However, the formulation process has to be strictly managed to thoroughly eliminate any unreacted chemical agents, harmful catalysts or leftover monomers before the material interfaces with biological systems.

- **Free Radical Polymerization**

Free radical polymerisation is still one of the most versatile and widely used methods for the bulk synthesis of synthetic chemical hydrogels, especially those based on acrylate and methacrylate monomers, such as poly(2-hydroxyethyl methacrylate) (pHEMA) or poly(acrylamide) (PAM).[8] The synthesis basically has three kinetic steps, namely initiation, propagation and termination. The method usually starts with the dissolving of the hydrophilic monomers and a multifunctional cross-linking agent (eg N,N′-methylenebisacrylamide) in an aqueous solvent. Then an initiator system is added to generate highly reactive free radicals. They can be activated by thermal energy (thermal initiators) or by reduction-oxidation reactions (redox initiators). These main radicals aggressively attack the double bonds of the monomers, thereby starting a rapid chain-growth polymerisation process that quickly propagates into a vast, highly cross-linked macroscopic network.[1] Free radical polymerisation is a highly efficient and scalable approach for industrial pharmaceutical manufacture. Nevertheless, this approach sometimes produces a large quantity of exothermic heat that can readily denature heat-sensitive biological medicines enclosed during the gelation phase.

- **Photopolymerization**

Due to these constraints of thermal polymerisation, photopolymerization has become a deeply essential formulation approach, especially for tissue engineering and bio-fabrication of complicated drug-eluting matrices. This technique involves the use of polymerisable macromers such as methacrylated gelatin (GelMA) or poly(ethylene glycol) diacrylate (PEGDA) along with a very specialised photo-initiator. Upon exposure to ultraviolet (UV) or particular wavelengths of visible light, photo-initiator quickly degrades to form free radicals that facilitate near-instantaneous covalent cross-linking.[8] Photopolymerization provides exceptional spatiotemporal control; the reaction occurs only when and where the light is delivered, which enables the fabrication of sophisticated, micro-patterned hydrogel frameworks or very complicated 3D-bioprinted scaffolds. Moreover, the rapid reaction at physiological temperatures makes it suitable for *in-situ* encapsulation of sensitive cells and thermolabile biologics.[28] Regarding modern formulation optimisation, there is a strong push towards subbing high energy UV light with milder, visible light activated photo-initiating systems (e.g. Eosin Y, ruthenium-based complexes) that can completely circumvent the risk for UV-induced cytotoxicity or DNA damage to encapsulated cellular cargo.

- **"Click" Chemistry Approaches**

One of the key recent advances in chemical synthesis of medicinal hydrogels is the inclusion of "click" chemistry. Coined by K. Barry Sharpless, click chemistry is a family of extremely efficient, fast and stereospecific reactions that occur under mild, physiologically relevant conditions with almost no hazardous consequences.[34] The copper-catalyzed azide-alkyne cycloaddition (CuAAC) is the most notable example. However, because to the high toxicity of residual copper, pharmaceutical formulation experts have quickly shifted to copper-free versions such as strain-promoted azide-alkyne cycloaddition (SPAAC) or thiol-ene Michael addition processes.[35] Hydrogels can be synthesised with remarkable molecular accuracy using click chemistry. They allow the formulator to obtain well defined and very homogenous polymeric networks with mechanical properties and mathematical predictability far superior to the chaotic networks obtained with ordinary free radical polymerisation.[34] Furthermore, the high specificity of click reactions allows the post-fabrication functionalisation of the hydrogel surface with targeting ligands, therapeutic peptides or specifically tuned degradation sequences, thus enabling the creation of highly advanced, bio-instructive matrices for targeted drug delivery.[35]

- **Enzymatic Cross-Linking**

Enzymatic cross-linking is an elegant hybrid technique taking advantage of the specificity of biological catalysts to form persistent covalent connections. In this approach, specialised enzymes, such as horseradish peroxidase (HRP): transglutaminase or tyrosinase are used to catalyse the crosslinking of polymer chains functionalised with certain chemical moieties (e.g. phenol or amine groups). The enzymatic synthesis is performed under mild, aqueous, physiological conditions (pH 7.4, 37°C) only, therefore eliminating the cytotoxicity risks of typical chemical initiators or high light exposure. This formulation approach is highly favoured for the development of injectable, *in-situ* forming hydrogels used for localised tissue repair and fragile protein delivery. The biological nature of the cross-linking ensures maximum preservation of the structural conformation and bioactivity of the encapsulated therapeutic payload.[1, 19]

2.3. Structural Modifications and Interpenetrating Networks

With the increasing complexity of the requirements of modern pharmacotherapy, researchers often find that simple single-network hydrogels cannot meet the contradictory requirements of high mechanical toughness, rapid stimuli responsiveness, and precise-controlled drug elution at the same time.[30] This has caused the development of synthesis methodologies to include multi-component structures. A good example is

the development of Interpenetrating Polymer Networks (IPNs).

IPN is a very sophisticated composite formulation and is characterised as a combination of two or more different cross-linked polymer networks that are physically entangled at the molecular scale but do not have covalent bonds bringing the different networks together. These networks are synthesised either sequentially (in which a pre-formed primary hydrogel is swollen in a secondary monomer solution which is then polymerised) or simultaneously (where both distinct polymer precursors and their respective, non-interfering cross-linking agents are mixed and polymerised concurrently).[36] IPNs offer an unparalleled synergistic benefit, merging the enhanced biocompatibility and bioactivity of natural polymers (such as hyaluronic acid or pullulan) with the elevated structural integrity and stimuli-responsiveness of synthetic networks (such as polyacrylamide).[36]

Standard IPNs, as well as Semi-Interpenetrating Polymer Networks (semi-IPNs) where one polymer network is cross-linked and the other remains as a linear, uncross-linked chain physically entangled within the mesh, increase the elasticity of the network and dramatically change the pore-size distribution. These architectural optimisations are key for tailoring diffusion pathways of encapsulated therapeutics, thus equipping pharmaceutical formulation scientists with a highly versatile toolbox to achieve complex multiphasic drug release profiles necessary for next generation individualised medicine.[37,38] The ability to seamlessly blend biological compatibility with synthetic structural robustness underscores the fast-paced maturation of hydrogel formulation science, leading to the rigorous optimisation procedures necessary to translate these intricate biomaterials from the laboratory bench to the clinical setting.

3. Optimization of Drug Delivery and Controlled Release Kinetics

The next and possibly the most important stage of pharmaceutical research is the thorough optimisation of the hydrogel, to attain accurate drug delivery and controlled release kinetics, which may be mathematically predicted, after a stable polymeric network is successfully synthesised. The main goal of this optimisation process is to design a therapeutic system that keeps drug concentrations within the optimal therapeutic window for a specific period of time, thus achieving maximum clinical efficacy and reducing systemic toxicity and the frequency of administration.[39] In an effort to do this, formulation scientists need to engineer the physicochemical properties of the hydrogel matrix, to manage the key mechanisms of drug elution, diffusion, swelling and polymer degradation.

In diffusion-controlled systems, the release of active pharmaceutical ingredient (API) is basically controlled by the concentration gradient between the drug loaded hydrogel and the surrounding physiological environment.[40] In the case of macroscopic hydrogels with pore size much greater than the hydrodynamic radius of the drug molecule to be encapsulated, diffusion proceeds fast in the water filled interstitial spaces. This process is well defined by Fick's laws of diffusion where the rate of drug release is directly proportional to the concentration gradient and inversely proportional to the diffusion distance.[41] However, when the steric barrier of the polymer chains is close to the size of the drug molecule, the release kinetics will not follow the ideal Fickian behaviour. Formulators often use the Korsmeyer-Peppas empirical model to analyse the release data for optimisation of these systems. The diffusional exponent (n) can be calculated by plotting log of cumulative drug release against log of time which provides profound insight into whether the release is governed by pure diffusion, polymer chain relaxation (swelling): or a complex amalgamation of both processes known as anomalous transport.[42,43]

The swelling-controlled release mechanisms are mostly used in formulations containing glassy hydrophilic polymers that undergo a substantial volume expansion upon hydration. In these dynamic systems the medication is successfully immobilised within the collapsed xerogel matrix until physiological fluids penetrate the structure. The polymer chains relax and extend as a glass to rubber transition occurs when the hydration front moves inward, thus forming aqueous channels for the diffusion of the medication.[44] Fine-tuning of swelling-controlled hydrogels demands the precise adjustment of the polymer's cross-linking density and the introduction of particular ionisable functional groups. The structure-activity relationship (SAR) of the resultant matrix can be greatly affected by deliberately changing the structure of the polymer backbone so as to adjust the thermodynamic affinity of the hydrogel for particular biological settings. For instance, the rate of penetration of the hydration front into the matrix can be tuned finely by adjusting the ratio of the hydrophobic to the hydrophilic monomers, leading to a consistent, zero-order release profile that is highly sought in advanced pharmacotherapy.[45]

In contrast, degradation regulated hydrogels are prepared to provide the therapeutic payload as the polymeric network degrades in a controlled manner physiochemically *in-vivo*. This degradation can occur by bulk erosion, where the entire matrix degrades simultaneously, or surface erosion, when degradation is restricted to the external contact of the hydrogel.[46] Surface eroding hydrogels are very useful to optimise since the release rate of the medication is exactly proportional to the degradation rate of the polymer, allowing for highly predictable zero-order elution kinetics. In this paradigm, optimisation entails the strategic incorporation of enzymatically cleavable peptide sequences or hydrolytically labile links (e.g., esters or anhydrides) in the polymer backbone.[47] By carefully tuning the molecular weight and chemical

reactivity of these degradable linkages, formulation scientists may optimise the degradation rate of the hydrogel to the desired therapeutic duration of the encapsulated drug, ensuring that the carrier is safely dissolved and eliminated from the body once the pharmacological intervention is complete.

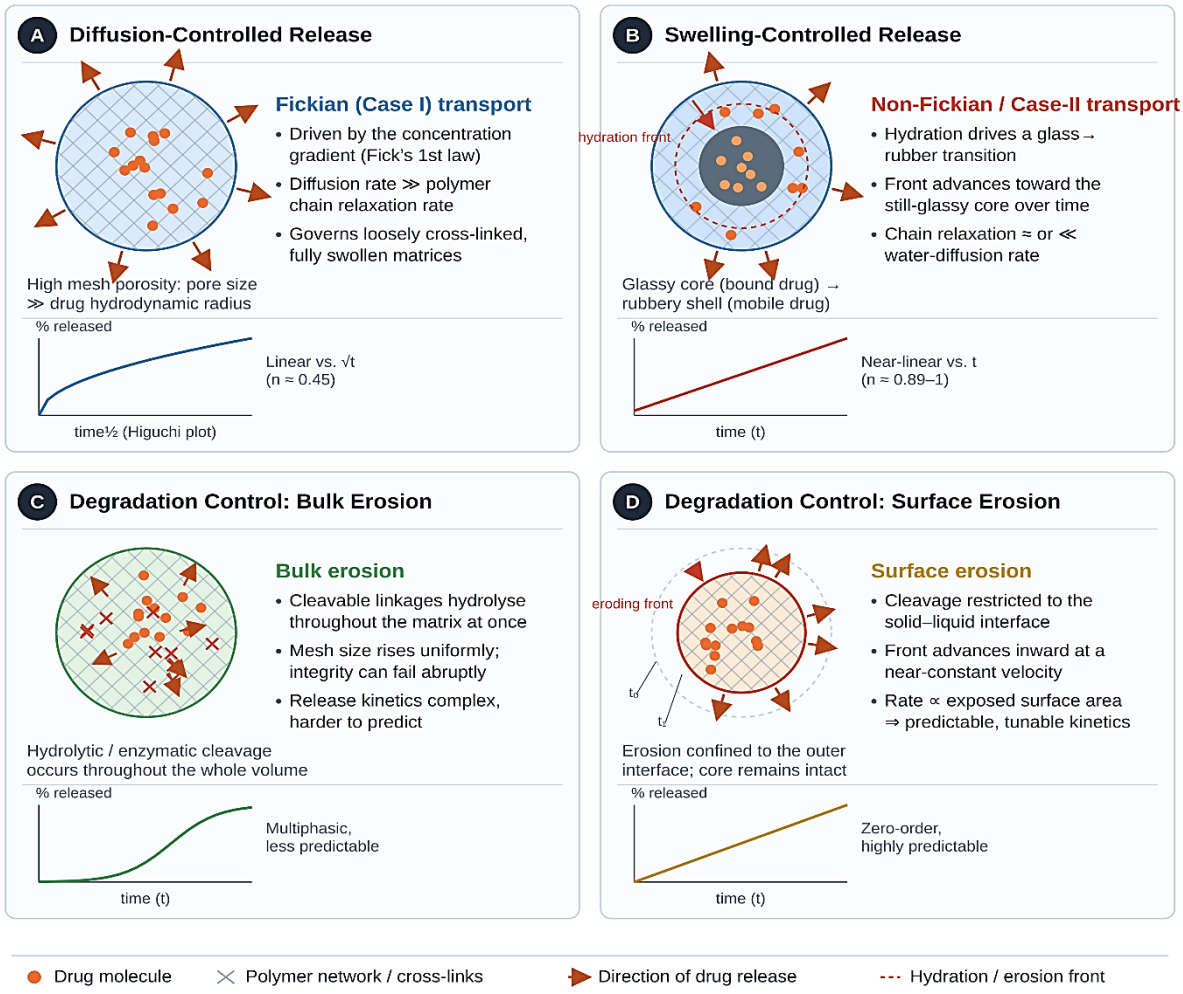


Figure 1: Mechanisms governing drug release from pharmaceutical hydrogels. (A) Diffusion-controlled (Fickian, Case I) release: in loosely cross-linked, fully swollen matrices, drug efflux is governed by the concentration gradient between gel and medium (Fick's Ist law): giving cumulative release that is linear with the square root of time (Higuchi relationship; diffusional exponent n ≈ 0.45). **(B) Swelling-controlled (non-Fickian/Case-II) release:** hydration drives a glass-to-rubber transition, and the hydration front advances from the swollen outer shell toward the still-glassy, drug-laden core; because chain relaxation approaches or exceeds the rate of water diffusion, release rises near-linearly with time (n ≈ 0.89-1). **(C) Degradation-controlled release by bulk erosion:** cleavable linkages hydrolyse simultaneously throughout the matrix, producing a multiphasic, comparatively unpredictable release profile. **(D) Degradation-controlled release by surface erosion:** cleavage is confined to the outer solid–liquid interface, which advances inward at a near-constant velocity while the core remains intact; because the release rate is proportional to the exposed surface area, this mode yields highly predictable, near zero-order release kinetics.

3.1. Advanced Nanocarrier Integration and Pharmacological Screening

While progress has been made in regulating crosslinking densities in conventional macroscopic hydrogels, they usually exhibit an initial "burst release" behaviour. This phenomenon is due to highly soluble un-entrapped drug molecules at or near the surface of the hydrogel rapidly diffusing into the surrounding media upon initial contact with biological fluids.[48] Such a burst effect can cause local toxicity and rapid depletion of the drug depot, thus seriously compromising the desired sustained release profile. To surpass such a crucial limitation, sophisticated optimisation efforts have been increasingly focused on the development of composite or hierarchical delivery systems, in particular by the incorporation of secondary nanocarriers into the primary hydrogel matrix.[49]

Incorporation of liposomes into hydrogel networks is one of the most complex optimisation strategies in modern formulation science. Liposomes are spherical vesicles consisting of concentric phospholipid bilayers and have a great potential to encapsulate both hydrophilic

pharmaceuticals (in the aqueous core) and hydrophobic medications (in the lipid bilayers).[50] However, unbound liposomes are generally promptly removed from the systemic circulation by the mononuclear phagocyte system and have poor structural stability. Formulators incorporate liposomes into a strongly cross-linked hydrogel, creating a "dual-barrier" delivery mechanism.[51] For this composite design, the medication must first partition out of the liposomal lipid bilayer, and then diffuse through the sterically restricting mesh of the hydrogel before reaching the physiological target. This ordered diffusion mechanism efficiently prevents the burst release effect and allows for a very long, almost continuous elution profile. In addition, the hydrogel serves as a protective mechanical scaffold to protect the delicate liposomes from premature degradation and physiological shear stresses, while the liposomes inhibit the quick leaching of small-molecule medicines from the highly porous hydrogel matrix.

To translate these highly optimised and structurally changed composite hydrogels from bench to clinic, thorough preclinical investigation is needed. A comprehensive pharmacological and toxicological assessment of these systems is required before they can be considered suitable for human trials.[52] This step of optimisation depends primarily on the application of standardised *in-vivo* murine models. Murine models (mice and rats) are vital in pharmaceutical studies due to their well-characterized physiological and genetic similarity to humans, allowing for precise assessment of the hydrogel biocompatibility, biodegradation kinetics, and systemic pharmacokinetics.[53] After obtaining rigorous ethical approvals from the institutional animal ethics committees, the researchers then implant or inject the optimised hydrogel formulations in the murine subjects to monitor the localised inflammatory response, systemic toxicity and the real-time pharmacokinetic release profile of the encapsulated drug.

In these mouse models, it is of utmost importance to evaluate the structural activity relationship (SAR) of the hydrogel matrix. Minor changes in the structure of the polymer, such as the extent of functionalisation or the length of the cross-linking spacer arms, can have dramatic effect on recognition and interaction of the implanted material with the immune system.[54] These structural changes can be systematically correlated with observed pharmacological efficacy and safety profiles *in-vivo*, to iteratively enhance the formulation.

4. Quality by Design (QbD) in Hydrogel Engineering and Optimization Matrices

Traditionally, the pharmaceutical industry has followed an empirical trial and error strategy for formulation development, sometimes referred to as Quality by Testing (QbT). In this retrospective paradigm, the quality of a hydrogel formulation was largely assessed by testing the final product against pre-specified criteria, providing limited mechanistic insight into how formulation variables affected the end therapeutic effect.[55] However, the very complexity of advanced hydrogels, especially composite systems containing nanocarriers or stimuli-responsive polymers, requires a far more rigorous, science-based approach. This has resulted in the global regulatory bodies demanding Quality by Design (QbD).[56] The International Council for Harmonisation (ICH) has taken the lead in this area with its Q8(R2) guidelines. QbD is a methodical, proactive strategy for pharmaceutical development, starting with established objectives and focusing on a thorough comprehension of the product and process, based on strong research and quality risk management.

The fundamental principle of QbD in hydrogel engineering is that the quality should be intentionally and thoroughly designed into the product right from the start of the formulation process, and not just tested into the product.[57] The QbD workflow starts with the definition of a Quality Target Product Profile (QTPP): which is a brief statement of the target quality attributes of the hydrogel required to achieve its intended clinical safety and pharmacological efficacy. For a pharmaceutical hydrogel, the QTPP might be the targeted mode of administration (e.g., intra-articular injection): the exact therapeutic indication, the needed drug release period, and the required stability during storage. The formulators obtain the Critical Quality Attributes (CQAs) from the QTPP The critical quality attributes (CQAs) are the precise physical, chemical, biological or microbiological qualities of the hydrogel that have to be within an appropriate limit, range or distribution to achieve the required product quality.[58] Typical CQAs for an advanced hydrogel formulation are gelation duration, mechanical strength (rheological moduli): equilibrium swelling ratio, absolute porosity, drug entrapment efficiency and the specific kinetic parameters of drug release.

Once the CQAs are clearly established, the following step in the QbD approach is rigorous risk assessment. This stage aims to discover and rank the possible effect of various raw material qualities and production techniques on the detected CQAs.[59] Using structured risk management tools such as Ishikawa (fishbone) diagrams and Failure Mode and Effects Analysis (FMEA): scientists systematically evaluate the relationship between Critical Material Attributes (CMAs) like polymer molecular weight, cross-linker concentration, and nanocarrier lipid composition and Critical Process Parameters (CPPs) such as polymerisation temperature, stirring speed and pH. This risk assessment serves as a strategic filter, which allows the formulators to identify the high-risk factors that have the maximum effect on the quality of the hydrogel and further experimental work may be carried out efficiently and economically.[60] The empirical core of the QbD paradigm is the execution of highly organised, statistically powerful experimental designs that are aimed at optimisation of the identified high-risk factors.

This is done through Design of Experiments (DoE): a branch of applied statistics that assesses the correlations between many input variables (factors) and important output variables (responses) simultaneously.[58] Compared to traditional "one-factor-at-a-time" (OFAT) research, which does not account for synergistic or antagonistic interactions between factors, DoE enables the production of sophisticated, multidimensional liposomal optimisation data matrices. These matrices of mathematics give us an overall, holistic view of the formulation landscape.

The CMAs (e.g. polymer concentration, cross-linker ratio) and CPPs can be changed in a systematic manner within a defined experimental domain using particular experimental frameworks such as Full Factorial designs, Box-Behnken designs or Central Composite Designs (CCD).[61] The resultant data produced by such highly structured trials are then analysed by powerful multivariate statistical tools to provide polynomial mathematical equations and complex three-dimensional response surface visualisations. The optimisation data matrices enable the scientists to theoretically forecast the exact combination of ingredients and processing conditions to obtain the exact desired CQAs (e.g. exact zero-order release profile with optimum mechanical stiffness).

The outcome of the DoE and the creation of these matrices of optimisation data is the definition of the Design Space. According to ICH Q8 principles, Design Space is the multidimensional combination and interaction of input variables and process factors that have been proved to provide assurance of quality.[56] Working within this specified Design Space within the framework of hydrogel engineering will guarantee that the formulated hydrogel will always be compliant with the pre-determined clinical standards. Importantly, any formulation or process changes within the approved Design Space do not require any additional regulatory approval or review, from a regulatory perspective, thus providing pharmaceutical manufacturers unprecedented flexibility and tight control over post-approval manufacturing changes.[55]

5. Smart Hydrogels in Responsive Pharmacotherapy

The evolution of pharmaceutical hydrogels has experienced a striking transformation from static, passive drug carriers to highly dynamic therapeutic systems actively contributing. The paradigm change is represented by the creation of "smart" or stimuli-responsive hydrogels. Unlike traditional macroscopic matrices, where drug release occurs through simple, continuous diffusion and defined degradation, smart hydrogels are precisely engineered to undergo sharp, reversible and predictable physicochemical changes in response to specific environmental triggers.[62] These triggers are generally classified as endogenous physiological stimuli such as localised temperature, pH, and enzymatic activity, and exogenous clinical stimuli such as magnetic field, ultrasound, and targeted photothermal irradiation.[63] By coupling drug release to these very same spatiotemporal cues, formulation scientists can realise pulsatile or on-demand release kinetics, such that the active pharmaceutical ingredient is delivered only when and where it is needed, thereby dramatically amplifying therapeutic efficacy while minimising off-target systemic toxicity.[64]

Thermo-responsive hydrogels are one of the most investigated and clinically validated classes of this responsive paradigm. The basis of the working principle of these systems is the subtle thermodynamic equilibrium of polymer-water interactions at different temperatures. The most common subset of thermo-responsive polymers is those with a Lower Critical Solution Temperature (LCST). Below the LCST, the polymer chains are highly hydrated by strong hydrogen bonding with water molecules, resulting in a swollen, soluble, and flexible hydrophilic state.[65] However, an increase in ambient temperature above the LCST threshold soon breaks the hydrogen bonds and hydrophobic interactions start to dominate aggressively. This thermodynamic change causes the polymer chain collapse, dehydration and aggregation leading to an instant macroscopic phase transition from a liquid sol to a solid gel.[66]

Poly (N-isopropylacrylamide) (PNIPAAm) is the prototype LCST polymer with an intrinsic transition temperature of approximately 32°C which can be cleverly tuned by co-polymerization to the typical physiological body temperature (37°C).[67] This behaviour is extremely useful in pharmaceutical formulations, for the production of injectable depots. The PNIPAAm formulation loaded with the drug can be administered easily through a standard hypodermic needle as a free-flowing liquid at room temperature. Once in the biological milieu and in equilibrium with body heat, it rapidly forms a localised, highly cross-linked semi-solid depot that offers sustained, zero-order release of the encapsulated medicinal drug over a prolonged period.[68]

Alongside thermo-responsiveness, pH-sensitive hydrogels are of essential importance in targeted pharmacotherapy, particularly in the highly variable environments of the gastrointestinal (GI) tract and the specific microenvironments of diseased tissues. The functional design of pH-responsive hydrogels is based on the inclusion of ionisable acidic (e.g., carboxylic acid) or basic (e.g., primary amine) pendant groups along the polymer backbone.[69] The swelling behaviour of these matrices is governed by the pH of the medium in relation to the acid dissociation constant (pKa) or base dissociation constant (pKb) of the functional groups.[70] For example, anionic hydrogels of poly(methacrylic acid) are fully protonated, neutral and firmly compacted in the highly acidic environment of the stomach (pH 1.2-2.0): which successfully protects acid-labile biopharmaceuticals such as insulin from premature

breakdown in the stomach. As it enters the more alkaline environment of the small intestine (pH 6.8-7.4) the carboxylic acid groups ionise quickly.[71] This leads to the formation of large amounts of negative charges along the polymer chains, triggering a massive electrostatic repulsion that causes the expansion, swelling and release of its therapeutic payload at precisely the right spot for systemic uptake.[72]

Beyond the level of basic physical triggers, the ultimate in responsive pharmacotherapy is represented by bio-responsive hydrogels developed to respond to complex biological macromolecules, most notably particular enzymes that are increased during pathological conditions. Enzyme-responsive hydrogels are formed by crosslinking polymer chains with highly specific enzymatically cleavable peptide sequences.[73] Under normal physiological conditions, the hydrogel is intact and the medicine is safely entrapped. However, the cross-links can be selectively recognised and catalytically cleaved by the presence of high concentrations of certain disease-associated enzymes, such as matrix metalloproteinases (MMPs) in aggressive tumour microenvironments or excess elastase in chronic inflammatory conditions.[74,75] This catalytic degradation breaks down the hydrogel network, allowing for a highly localised, pathology-driven release of the chemotherapeutic or anti-inflammatory medication at the lesion site.[76]. This xquisitely precise targeting marks a quantum leap in formulation science, bridging the gap between passive structural biomaterials and highly active, intelligent medicinal agents.

6. Advanced Tissue Engineering and Biomimetic Scaffolds

With pharmaceutical research and regenerative medicine becoming more and more interrelated, hydrogels have evolved from pharmaceutical delivery systems to key structural and instructive scaffolds in sophisticated tissue engineering. The essential concept behind tissue engineering is that the function of tissue can be restored, maintained or enhanced by combining living biological cells with a very specific supporting matrix.[77] In this regard, hydrogels are certainly the most biomimetic materials, owing to their high-water content, adjustable porosity and viscoelastic mechanical properties that closely match the original extracellular matrix (ECM) of the mammalian tissues.[78] Hydrogels are of great importance as artificial ECM for mechanical support of cell attachment, guidance of three-dimensional cellular proliferation and for the necessary diffusion of oxygen, nutrients and metabolic waste products for cellular survival and differentiation.[79]

The central nervous system (CNS) is one of the most challenging and significant frontiers in hydrogel mediated tissue engineering, especially in developing tailored neuroprotective methods for severe neurological damage and degenerative disorders. The CNS is notoriously refractory to regeneration after injuries such as ischaemic stroke, traumatic brain injury, or severe spinal cord lesions.[80] A major barrier to brain healing is the rapid activation of extremely damaging neuroinflammatory pathways. After localised tissue injury, a vigorous inflammatory cascade is triggered, with activation of resident microglia to a pro-inflammatory (M1) phenotype and fast influx of peripheral macrophages. This hostile neuroinflammatory microenvironment not only promotes secondary neurotoxicity and extensive cellular apoptosis, but also causes the formation of a dense, impenetrable glial scar, which physically and chemically prevents neurite outgrowth and axonal regeneration.[81,82]

To counteract these cascading pathological events, pharmaceutical researchers are designing sophisticated, multi-functional hydrogel scaffolds to directly modulate these aggressive neuroinflammatory pathways and provide a permissive environment for neural repair. Through the introduction of very specific structural changes to the polymeric backbone, formulators can tune the hydrogel to serve as a localised, implantable depot for the prolonged release of potent neuroprotective drugs and immunomodulatory cytokines.[83] Encapsulation of therapeutic proteins, such as Brain-Derived Neurotrophic Factor (BDNF) or Glial Cell Line-Derived Neurotrophic Factor (GDNF): within a biodegradable hydrogel matrix avoids the rapid enzymatic degradation that is typically observed *in-vivo*.[84] The hydrogel enables localised, zero-order delivery of these substances directly to the lesion cavity, therefore maintaining therapeutic levels across critical weeks to months.

Importantly, these optimised hydrogel scaffolds can be intentionally tailored to alter the polarisation of local microglia away from the destructive proinflammatory M1 phenotype toward the tissue-reparative anti-inflammatory M2 phenotype.[85] This switch in immunomodulation successfully dampens the hostile neuroinflammatory response, avoiding the dense creation of the suppressive glial scar. Simultaneously, the physical presence of the soft hydrogel matrix provides a highly permissive, 3D-topographic guidance cue that supports infiltration of endogenous neural stem cells, promotes elongation of regenerating axons, and facilitates functional synaptic reconnections.[86] Hence, the hydrogel is not simply a passive carrier within the framework of CNS repair but an active, structural therapeutic agent that profoundly reprograms the diseased milieu to foster substantial tissue regeneration.

The development of 3D bioprinting technologies has greatly increased the architectural complexity necessary for these advanced applications. Traditional hydrogel casting methods typically generate homogeneous, bulk structures that do not possess the complex, spatially graded microarchitecture of native tissues, such as the stratified layers of articular cartilage or the highly branched networks of the vascular system.[87] This constraint is overcome by 3D bioprinting, which allows

precise layer-by-layer deposition of cell-laden hydrogel formulations, known as "bioinks", under highly regulated computer-aided design (CAD) supervision.[88] The development of an optimal bioink requires the artful balancing of rheological properties: the hydrogel precursor must display distinct shear-thinning behaviour to flow smoothly through the printing nozzle without inflicting fatal shear stress on the encapsulated cells, but it must rapidly undergo physical or chemical cross-linking after deposition to preserve its structural fidelity and geometric resolution.[89]

Moreover, the multi-material bioprinting of several hydrogel formulations in a single construct allows the spatial patterning of different cell types and the formation of finely defined gradients of growth factors. This ability is essential for solving the long-term problem of neovascularisation in large-volume tissue constructs.[90] By bioprinting sacrificial hydrogel networks in a primary structural matrix, researchers can create perfusable microvascular channels after fabrication by dissolving sacrificial templates. These intricate pathways can then be seeded with endothelial cells, thus creating a functional capillary network that nourishes the deep core of the artificial tissue, similar to the native angiogenesis. Hydrogels have emerged as the quintessential platform for modern tissue engineering, seamlessly integrating responsive chemical architectures, immunomodulatory therapeutic payloads, and sophisticated bioprinting fabrication techniques, promising to redefine the clinical boundaries of regenerative medicine and personalised pharmacotherapy.

CONCLUSION

The transition of pharmaceutical hydrogels from primitive physiologically inactive implants to extremely complex therapeutics, which actively participate in the treatment process, is one of the most impressive advances of the current biomedical research. This comprehensive review reveals that the extraordinary structural plasticity, thermodynamic compatibility and adaptable swelling behaviour of hydrogels renders them invaluable instruments for overcoming the established constraints of conventional drug delivery. By effectively selecting among a range of formulation methods, spanning from gentle physical cross-linking methods that preserve the stability of labile biopharmaceuticals to robust chemical polymerisation methods that confer long-term stability, the experimental team can optimise these matrices to address very specialised clinical needs.

Moreover, the precise optimisation of these systems is crucial for their clinical effectiveness. Diffusion, swelling, and degradation processes can be used to modulate drug release kinetics to provide predictable, continuous elution of therapeutic medicines. The technique is greatly improved by the integration of secondary nanocarriers, such as liposomes, to prevent premature burst release and safeguard sensitive active medicinal ingredients. Further modernisation of the area has been achieved by the adoption of Quality by Design (QbD) paradigms that replace empirical trial and error with systematic, statistically powered engineering that assures product quality and regulatory compliance from the very start of formulation.

The frontier of hydrogel research is undoubtedly the dynamic responsiveness and regenerating capacities for the future. The emergence of "smart," stimuli-responsive hydrogels enable on-demand, targeted medication that responds in real-time to physiological or external signals, maximising efficacy with minimised systemic toxicity. At the same time, the use of hydrogels as biomimetic scaffolds in advanced tissue engineering especially through advances like 3D bioprinting and immunomodulatory matrix design presents unprecedented hope for healing complex, resistant tissues such as the central nervous system.

To summarise, pharma hydrogels are not just passive carriers anymore, but highly engineered active interventions that are bridging the gap between polymer chemistry and individualised medicine. To translate these next-generation soft biomaterials from bench to bedside, sustained interdisciplinary collaboration, rigorous preclinical optimisation using models such as murine subjects, and adherence to robust design principles will be required to ultimately reshape the future of global healthcare.

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The authors confirm their contributions to the paper as follows. SP and SKSK were responsible for concept design and writing. M contributed conceptualisation and editing. NK contributed to the methodology and visualization. All authors reviewed the results and approved the final version of the manuscript.

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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