EUROPEAN JOURNAL OF SCIENTIFIC RESEARCH AND REVIEWS
2025; 2(3): 130-153
10.5455/EJSRR.20250307022206

WisdomGale

REVIEW ARTICLE

Open Access

Biodegradable peptide hydrogels for precision drug release: Advances and future perspectives

Mubaraq Damilare Yussuf[1], Chukwunonso Augustine Ikedionu[2], Amina Jafaru Ocheinehi[3], Ifeanyi Ugwuanyi[3], Eniola Blessing Olaoye[4], Mariam Damilola Olawuyi[5]

[1]Department of Drug Discovery, University of Lagos, Lagos, Nigeria

[2]Department of Manufacturing Engineering, Georgia Southern University, Statesboro, Georgia, USA

[3]Department of Physical Sciences, Eastern New Mexico University, Portales, Mexico, USA

[4]Department of Naturopathic Medicine, National University of Natural Medicine, Portland, Oregon, USA

[5]Department of Health Promotion, University of Ilorin, Ilorin, Nigeria

ABSTRACT

Biodegradable peptide hydrogels have emerged as a promising platform for precision drug release, offering controlled, sustained, and targeted therapeutic delivery. These hydrogels, formed through the self-assembly of short peptides, exhibit excellent biocompatibility, biodegradability, and tunable mechanical properties, making them ideal carriers for various bioactive molecules. Recent advances in peptide hydrogel design have enabled enhanced drug loading capacity, stimuli-responsive release, and improved stability, addressing key challenges in drug delivery systems. This review explores the molecular design, structural properties, and drug-release mechanisms of biodegradable peptide hydrogels, highlighting their applications in cancer therapy, wound healing, and antimicrobial treatments. Furthermore, we discuss current challenges and future perspectives in optimizing these biomaterials for clinical translation. The continued development of peptide-based hydrogels holds great potential for advancing precision medicine and personalized drug delivery.

ARTICLE HISTORY

Received March 07, 2025
Accepted March 22, 2025
Published March 30, 2025

KEYWORDS

Peptide hydrogels; biodegradable materials; precision drug release; controlled drug delivery; self-assembly; stimuli-responsive hydrogels; biomedical applications; nanomedicine; biocompatibility; therapeutic carriers

Introduction

Overview of peptide hydrogels

Hydrogels made from peptides have emerged as important biomaterials that researchers study extensively because of their exceptional physicochemical behavior and wide biomedical functionality [1]. Hydrogels consist mainly of short peptide sequences that form nanostructured three-dimensional structures that function as high water absorbents [2]. The realistic simulation of extracellular matrix (ECM) structure and biological system binding properties make peptide hydrogels an optimal candidate for medical and pharmaceutical use.

Non-covalent forces between hydrogen bonds and electrostatic bonds and π–π stacking and hydrophobic bonds drive the peptide hydrogel formation process [1]. Biological materials with predetermined mechanical characteristics and specific structural properties as well as external stimulus responsiveness can be achieved through controlling hydrogel interactions.

Definition and basic properties

Hydrogels based on peptides exist as biomaterials that are soft and water-rich because peptides assemble themselves into nanofibrous three-dimensional networks [3]. These hydrogels demonstrate unique attributes that enable their use in biomedical settings for pharmaceutical delivery systems and wound care as well as tissue constructiveness and biological detection elements [4]. The ability of these materials to function and

Contact Mubaraq Damilare Yussuf ✉ Damilareoluwaseun54@gmail.com Department of Drug Discovery, University of Lagos, Lagos, Nigeria.

© The Author(s) 2025. Open Access. This article is licensed under a Creative Commons Attribution 4.0 International License (CC BY). http://creativecommons.org/licenses/by/4.0/.

structurally represent natural ECM enhances biological integration.

The main distinguishing characteristic of peptide hydrogels is their ability to retain and absorb almost 99% of water [5]. Water retention ability in these materials serves as a vital factor for creating conditions that benefit cellular life and advance biochemical network functions. The biological systems react minimally to peptide hydrogels because of their biocompatibility properties thus making them attractive for clinical implementation.

Peptide hydrogels have a natural breakdown capability which produces harmless amino acids that do not accumulate in the body [1]. Controlling hydrogel degradation requires adjustment of peptide sequences for obtaining the needed therapeutic duration. Inject ability together with self-healing ability represent key properties of these materials as reported by Bao et al. [6]. Many peptide hydrogels demonstrate both sol-gel transition abilities that enable them to be useful for minimally invasive medical applications. Clinicians should consider these hydrogels because they reconstruct their network framework after injection resulting in a perfect delivery platform for local treatment [7].

By adjusting peptide sequence modifications and both crosslinking density and the influence of temperature and ionic strength properties hydrogels become mechanically adjustable [1]. Hydrogel peptides possess adjustable properties that enable their use across various biomedical fields including soft tissue regeneration work as well as controlled drug delivery. Hydrogels formed from peptides demonstrate high responsiveness to external stimuli because they can change their structure and function when exposed to pH shifts and enzymes or temperature fluctuations and light exposure [8]. The dynamic nature of these systems permits doctors to achieve exact drug delivery control and precise therapeutic treatment delivery thus improving their clinical benefits.

Peptides transform into hydrogel networks through the forces of hydrogen bonding and electrostatic forces as well as hydrophobic interactions [1]. Peptide sequence variation allows controlling the mechanical response together with degradation pace and biological activity through these forces during gelation. The biomedical applications of peptide hydrogels demonstrate outstanding versatility as well as potential in many fields because of their promising characteristics. The unique attributes comprising biocompatibility together with biodegradability in addition to injectability and property-tunability make peptide hydrogels a critical foundation for developing precision medicine methods and personalized drug delivery systems [9].

Peptide self-assembly in hydrogel formation

The amphiphilic peptides within peptide hydrogels assembly into nanostructures like fibers, micelles, and nanotubes until they create a hydrogel matrix through crosslinking processes [10]. Hydrogel formation results from multiple non-covalent interactions between peptides which include both hydrogen bonds as well as π–π stacking and electrostatic forces combined with hydrophobic effects. Multiple non-covalent interactions together propel peptide aggregation while resulting in the formation of structures of a stable and functional hydrogel network.

Fundamental driving forces of peptide self-assembly

1. Hydrogen bonding: Stabilizes peptide chains and facilitates the formation of ordered nanostructures. The hydrogel stability requires backbone hydrogen bonds between amide groups in peptide sequences for forming β-sheet and helical structures [11].

2. π–π Stacking: The aromatic amino acid residues in peptides create π–π stacking contacts to enhance hydrophobic binding forces while they direct the formation of ordered fibrillary peptide structures. The mentioned effect significantly contributes to strengthening both hydrogel stability and mechanical properties of the system [12].

3. Electrostatic interaction: Compositional electrical charges in the sequence of peptides determine how the material forms gels. Peptide assemblies keep different arrangements because positively and negatively charged peptides either attract or repel one another. A modification in surrounding ionic strength influences the physical interactions and changes both gelation formation speed and the hydrogel creation dynamics [13].

4. Hydrophobic interaction: The amphipathic character of peptides promotes hydrophobic aggregation which results in micelle or fibril arrangement [14]. The separation of hydrophobic from hydrophilic domains through structural peptide assemblies functions as the key requirement for creating gels.

Factors influencing self-assembly and hydrogel formation

The self-assembly behavior of peptides becomes more controllable through specific functional group addition as well as external stimuli manipulation to optimize hydrogel characteristics. These factors include:

1. Peptide sequence composition: The position of hydrophobic as well as charged and aromatic amino acids along peptide sequences directly affects how these molecules assemble on their own, how strongly gels form, and how they react to external conditions [5].

2. pH sensitivity: Many peptide hydrogels become sensitive to pH levels because acidic and basic conditions initiate hydrogel assembly and disassembly [15]. This characteristic enables controlled drug delivery from such systems.

3. Enzymatic triggers: The hydrogel degrades through enzyme-sensitive peptides whose response to biological enzymes controls drug release processes and makes them suitable for physiological needs [16].

4. Temperature dependence: Some peptide hydrogels undergo sol-to-gel transitions in response to temperature changes, providing additional control over their formation and application.

5. Light activation: Certain peptides can be engineered with photo-responsive groups that trigger self-assembly or disassembly when exposed to specific wavelengths of light, enabling remote control over hydrogel properties.

Tailoring self-assembly for biomedical applications

Research teams have demonstrated the capability to adjust both peptide sequence patterns and environmental conditions which allows them to modify hydrogel characteristics for particular biomedical applications. Scientists have discovered three main approaches to enhance peptide hydrogel applications: they added bioactive motifs, strengthened the material structure using covalent crosslinks, and created complex peptide assemblies that serve multiple purposes [17]. This methodology enables developers to create adaptive biomaterials as well as tailored drug delivery systems and tissue engineering scaffolds that respond to physiological changes in their environments.

Types of peptide hydrogels

Different types of peptide hydrogels exist according to their composition as well as their structural formation and functional properties which amount to Asai et al. [5]. The different types of hydrogels exist because each configuration possesses unique properties that match particular application requirements. These hydrogels differ mainly through their molecular design as well as their gelation mechanisms together with their mechanical capabilities and response to environmental signals.

Short-peptide hydrogels

Short-peptide hydrogels construct themselves into nanofibrous networks through non-covalent interactions by employing dipeptides as well as tripeptides or tetrapeptides [1]. The hydrogels maintain basic molecular design which allows their quick transformation into gels when placed under normal physiological environments. The simple synthesis process allows short-peptide hydrogels to form gels efficiently using minimal peptide sequences. These materials present high biocompatibility and degradability characteristics which allows their use in localized medicine delivery and various intervention procedures requiring minimal invasiveness [18]. Hydrogel types other than short-peptides tend to possess superior mechanical strength which restricts their utilization in structural feature-dependent applications.

Peptide-polymer hybrid hydrogels

Short-peptide hydrogels achieve enhanced mechanical stability through their combination with peptide-based structures which unite synthetic or natural polymers [1]. These hybrid hydrogels surpass conventional short-peptide hydrogels in terms of mechanical strength and elasticity since they incorporate polymers for reinforcement.

Hydrogel functional lifespan can be extended through controlled degradation rates which polymers help achieve [19]. Hydrogels can be customized through a selection of polymers with designated properties which enables them to adapt to use in tissue engineering as well as wound healing applications. The use of polymers affects hydrogel biodegradability but this effect can be controlled by selecting appropriate polymer-peptide combinations that strike the right balance between stability and compatibility.

Enzyme-responsive hydrogels

Hydrogels with enzyme-sensitive properties undergo breakage and structural variations when particular enzymes perform enzymatic activities [20]. Controlled drug release occurs because these hydrogels possess peptide sequences that specific enzymes can detect for site-specific degradation. This hydrogel uses a specific degradation method which keeps it intact except during activation with a particular enzyme thus enabling enhanced therapeutic control. While peptide-polymer hybrid hydrogels degrade because of generic hydrolytic activities during normal operation time, enzyme-responsive hydrogels only degrade when purposefully triggered by targeted enzymes [21]. Tumor-associated enzymes initiate the drug release process in these hydrogels which find applications in cancer therapy treatments. Their effectiveness depends on the specificity of target enzymes along with their concentration level but these conditions can differ among various physiological environments.

The classification and comparison of different peptide hydrogel types, including their molecular complexity, mechanical properties, and biodegradability, are presented in Table 1.

Stimuli-responsive hydrogels

Structural and functional elements within hydrogels respond to outside stimuli including pH fluctuations, changes in temperature, and exposure to light according to the research of Ezike et al. [22]. The main distinction of pH-sensitive hydrogels from enzyme-responsive hydrogels comes from their environmentally activated response instead of biological enzyme-triggered effects. The controlled drug release in gastrointestinal tracts and tumor sites benefits from pH-sensitive hydrogel responsiveness. Thermoresponsive hydrogels have temperature-sensitive characteristics because they change from gel to sol states according to temperature variation thus enabling formulation injection which solidifies in the body. Hydrogels with light-sensitive composition include photo-reactive groups which enable accurate external activation [23]. The high level of control these hydrogels provide comes with particular environmental demands to activate them effectively, limiting their application to environments where external stimuli can be precisely regulated.

Importance in precision drug release

Research shows that peptide hydrogels represent an advanced drug delivery platform since they resolve the problems observed with traditional drug delivery methods [24]. The inherent biocompatibility together with degradability combined with adjustable physical and chemical characteristics enables these materials to deliver drugs safely and precisely and infrequently require additional medication.

Limitations of conventional drug delivery

Traditional drug delivery systems have persistent weaknesses in pharmaceutical science advancement that affect treatment effectiveness together with patient medication compliance [25]. Small molecules and biologics and many other drugs experience limited systemic half-life because these pharmaceutical substances rapidly move through metabolism then leave the body. The resulting need for multiple doses throughout the day produces distress to patients and can lead to them avoiding their medications during long-term illness care.

The main constraint of drug therapy exists from the suboptimal quantity of medications available to the body because of inadequate absorption rates or quick metabolism and degradation processes in

Table 1. Comparison of peptide hydrogel types [Source: Authors].

Feature	Short-peptide hydrogels	Peptide-polymer hybrid hydrogels	Enzyme-responsive hydrogels	Stimuli-responsive hydrogels
Molecular complexity	Low	High	Moderate	Moderate
Gelation mechanism	Non-covalent self-assembly	Peptide-polymer interactions	Enzyme-triggered degradation	pH, temperature, or light triggers
Mechanical strength	Low	High	Moderate	Variable
Biodegradability	High	Variable	High	Variable
Stimuli sensitivity	Limited	Moderate	High (enzyme-dependent)	High (environment-dependent)
Primary application	Injectable drug delivery	Tissue engineering, wound healing	Controlled drug release	Smart therapeutic systems

biological environments [26]. The body diminishes the accessible amount of drugs through substantial liver-mediated metabolism when patients take oral medications. The ability of hydrophilic drugs to penetrate biological membranes is restricted as well as the capability of hydrophobic drugs to dissolve which negatively affects their therapeutic outcome.

The traditional drug delivery methods experience unwanted side effects because drugs spread non-selectively through the body [27]. Drugs that are distributed widely through the bloodstream before reaching their target location raise the possibility of harmful side effects because of improper drug accumulation at the action site. The therapy goals of chemotherapy drugs often fail because these medicines harm healthy tissues along with cancer cells resulting in serious toxic effects.

A problem with current drug delivery systems arises because of their uncontrolled drug release patterns. Drug carriers express a burst release behavior which releases a high percentage of medication rapidly thus generating body therapeutic concentration variability [28]. The unpredictable drug levels reduce both drug effectiveness and increase possible adverse effects. The problem with drug delivery becomes severe when treatments need stable therapeutic drug amounts over prolonged periods during chronic pain and hormone therapy applications.

Advantages of peptide hydrogels for drug delivery

Peptide hydrogels serve as an excellent alternative to conventional dosage forms since they deliver a flexible system for encapsulation along with controlled drug distribution [18]. Drugs within these structures experience gradual release due to their porous framework which provides sustained diffusion for numerous drugs by minimizing quick-release aphasia. These properties require fewer drug dosages which enhances medication adherence thus preserving therapeutic drug levels [29].

Peptide hydrogels offer a crucial benefit through their biodegradable nature which leads to amino acids breaking down into standard components that the body comfortably metabolizes for excretion. Such drug carriers protect patients from toxic effects because they avoid both permanent storage within the body and harmful effects from foreign materials which commonly appear in synthetic polymer drug carriers. Scientists control the speed of biodegradation through peptide sequence changes, crosslinking density, and external conditions adjustment to create specified drug release periods [30].

The delivery of drugs through peptide hydrogels becomes specific due to their ability to incorporate functional elements that aid site-directed accumulation [31]. Scientific hydrogel design that employs peptides to detect and attach to specific cell receptors or tissues enables medicine distribution only to diseased locations for superior therapeutic impacts alongside reduced unintended impacts. The precise delivery strategy proved advantageous for cancer management because it minimizes drug side effects while enhancing medication access to tumors [32].

Drug delivery through peptide hydrogels becomes possible because these materials exhibit external-stimulated release behavior. The hydrogel materials undergo engineering to create responses that detect changes both inside the body and externally, such as pH changes, enzyme activity, temperature fluctuations, or light exposure [33]. For example, pH-sensitive hydrogels can release their drug payload in acidic tumor microenvironments, while enzyme-responsive hydrogels degrade in the presence of disease-associated enzymes, ensuring on-demand drug activation. This smart responsiveness enhances drug bioavailability and therapeutic precision [33].

Peptide hydrogels show minimal immune response which helps their cells interact with biological systems effectively. Energetic responses from immune systems become less likely when using peptide-based materials since they behave similarly to natural ECM components [25]. Peptides are particularly suited for extended therapeutic applications such as regenerative medicine and implantable drug delivery systems because of their desirable properties.

Professional drug delivery methods use peptide hydrogels as an advanced system that conquers major obstacles in traditional drug delivery systems [25]. Peptide hydrogels serve modern therapeutic applications as an optimal platform because they enable specific drug delivery and sustained release as well as targeted drug delivery at a controlled rate alongside biomolecule compatibility and responsiveness changes with environmental signals. Scientists can prepare upcoming drug delivery platforms with improved patient results through the use of peptide hydrogel systems whose properties researchers can tune [34].

Benefits of peptide hydrogels

The combination of advantages of peptide hydrogels establishes them as strong candidates for medical and pharmaceutical needs [35]. The distinctive characteristics of peptide hydrogels which include biocompatible behaviour and adjustable mechanics together with their reaction to environmental triggers make them an adaptable material for pharmaceutical delivery systems and therapeutic field development. The close resemblance of peptide-based hydrogels to the ECM enables them to serve cells optimally for growth and drug delivery control [25].

Biocompatibility and immunogenicity

The biological compatibility of peptide hydrogels provides optimal suitability for biomedical applications that need tissue-hydrogel contact [35]. Hydrogels made of amino acid-based peptides generate degradation products that both the human body tolerates well and break down effortlessly. The tissue accumulation risk remains minimal since these compounds do not stay in the body tissue spaces. The degradation products of peptide hydrogels transform into naturally occurring amino acids which merge perfectly with biological processing systems [35].

Peptide hydrogels demonstrate low immunogenicity because it reduces the chances that the immune system will trigger inflammatory responses [36]. Synthetic implants along with other biomaterials tend to trigger immune responses which cause tissue scarring along with persistent inflammation and implant rejection. Peptide hydrogels demonstrate weak immunogenic potential which makes them suitable for implantations exceeding short periods as in regenerative medicine, sustained therapy, and wound closure applications [37].

These compounds also show great compatibility with cells and are used as effective scaffolds for stem cell delivery and cell-based therapeutic approaches. Due to their three-dimensional structural capability, peptide hydrogels create an excellent cellular environment thus serving as important tissue engineering scaffolds for cell adhesion and growth together with developmental potential [38]. Stem cell therapy utilizes peptide hydrogels to deliver protection against hostile conditions which allows controlled cell dispersion for successful incorporation into tissue areas under repair.

Mechanical strength and tunability

The main benefit of peptide hydrogels derives from their capability to undergo mechanical adaptations suitable for particular needs. Multiple strategies exist to modify the stiffness elasticity and gelation kinetics of these hydrogels which makes them appropriate for multiple biomedical uses [39].

Hydrogel mechanical properties depend mostly on the peptide sequence choice together with the concentration level [39]. Successful addition or alteration of amino acid sequences allows scientists to alter intermolecular connections including hydrogen bonds and π–π stacking and hydrophobic bonds that modify the gel strength and gel formation mechanisms. The mechanical strength and network stability of peptide-based hydrogels increase when concentrations rise which makes them suitable for fighting physical force yet they become softer at reduced concentrations that create suitable formulations for injections [40].

Additional cross-linking procedures strengthen both the mechanical properties of peptide hydrogels. The stability of peptide networks receives enhanced reinforcement from covalent cross-links that create disulfide bonds between cysteine residues [41]. Non-covalent associations like electrostatic supramolecular assemblies together with hydrophobic interactions create resilient hydrogel frameworks that also exhibit self-healing dynamics. These adjustable characteristics specifically support gel applications that need to reform their composition during administration [42].

Hydrogel strength along with mechanical properties receives substantial enhancement through the addition of reinforcing agents. Enhancements in mechanical strength and conductive properties together with stability can be achieved through hydrogel matrix reinforcement with nanoparticles, graphene, and synthetic polymers [43]. ophone devices. Scientists have demonstrated the neural regeneration capability of nanomaterial-reinforced peptide hydrogels since these materials deliver structural reinforcement together with bioelectrical characteristics [43].

The ability to precisely alter peptide hydrogels makes them suitable for different biomedical system requirements. They possess excellent properties for minimally invasive therapies since they strike the right equilibrium between soft tissue characteristics and mechanical durability. Hydrogels that adapt their gelation abilities find application when used as tissue engineering platforms to offer structural

backbone functions and stimulate cell proliferation and tissue regeneration [44]. The rapid gelation characteristics along with adjustable fluidity of peptide hydrogels promote their use as bioinks for three-dimensional bioprinting processes.

The promise of peptide hydrogels as drug delivery platforms intensifies because of their three core benefits which are their biocompatibility together with biodegradability and their capacity for mechanical property adjustments [25]. The stimuli-responsive characteristics and precise drug-release abilities of peptide hydrogels create them as excellent replacement options for traditional drug-delivery methods. Furthermore, their tunable mechanical properties enable their application across diverse fields, from injectable drug formulations to tissue engineering and regenerative medicine [40]. The following sections will delve deeper into their molecular design, drug-loading mechanisms, and the various biomedical applications that are shaping the future of peptide hydrogel technologies.

Molecular Design and Structural Properties

Peptide self-assembly mechanisms

Molecular interactions governing self-assembly

The formation of peptide hydrogels results from multiple non-covalent forces that direct peptides to assemble themselves into a spatial network. The studies of non-covalent interactions enable scientists to establish fundamental aspects about hydrogel stability as well as mechanical properties and biomedical application functionality [45].

The process of peptide self-assembly depends greatly on hydrogen bonding to establish its fundamental structure. The peptide structure gains stability from the formation of β-sheet and α-helix secondary structures that result from hydrogen bonds. Amide groups present in the backbone establish numerous hydrogen bonds which leads to nanostructure formation with increased order [46]. The hydrogel stiffness, viscoelastic behavior, and overall mechanical stability depend heavily on the strength and orientation alongside the density of these particular bonds. The self-assembly process depends on hydrophobic interactions since they drive hydrophobic residues in water to aggregate toward each other. The structural arrangement of nanomaterials occurs due to free energy reduction which attracts peptide molecules into specific geometric forms [47]. The extent of hydrophobic character in peptide sequences controls how quickly and what amount of self-assembly occurs. The hydrogel protects hydrophobic drugs through hydrophobic interactions that also boost both the stability and bioavailability rates of these substances and bioactive molecules.

The peptide sequence incorporates charged amino acid residues that create electrostatic interactions that control both hydrogel formation along with its durability [48]. The structural stability of hydrogels increases because positively and negatively charged residues create ionic bridges between them. Clinical applications benefit from the ability of environmental factors to regulate peptide interactions because these factors control the gelation properties. Electrostatic repulsive forces emerging from residues with identical charges lead to affecting the alignment of fibrils as well as the shape of hydrogels [49].

π–π stacking interactions, primarily mediated by aromatic residues such as phenylalanine, tyrosine, and tryptophan, contribute to peptide self-assembly by reinforcing peptide alignment. The peptide concentration between hydrogel chains through these interactions leads to better structural order while boosting mechanical strength and rigidity [50]. π–π stacking behavior enables electron transport behavior in these peptide hydrogel systems making them applicable for bioelectronics applications. Hydrogel properties regarding strength and frequency of interactions can be manipulated by adjusting the composition of peptide sequences and aromatic amino acid population.

Self-assembled nanostructures in hydrogels

Once peptides self-assemble into hydrogels their formed nanostructures control both mechanical behavior and material compatibility as well as drug delivery properties [51]. The nanostructures serve as critical elements that establish the capabilities of hydrogels used in biomedical applications. The formation of nanofibers occurs as one of the most prevalent structural features within peptide hydrogels. Long-fibred assemblies with high stability and porosity form a cell-friendly framework that boosts cell connection and cell growth as well as cell specialization [52]. Furthermore, these structures interact well with biological tissues because of their large surface area while helping drugs release over extended periods. Nanofiber networks found special use in tissue engineering practice because they provide vital guidance during cellular organization and ECM development. The hydrogel matrix

benefits from the adjustability of mechanical properties which allows for exact control of drug release speed [53].

The self-assembly of amphiphilic peptides leads to the formation of hollow cylindrical nanostructures which are classified as vesicles and nanotubes. Nanoparticle structures serve as excellent carriers that deliver drugs while maintaining control over targeted delivery methods regardless of drug hydrophilicity or hydrophobicity. Nanotubes enable drug loading through their enhanced surface area and healthcare providers can connect targeting ligands to the nanotubes for directed medical treatment [54]. Bioactive molecules inside vesicles receive protection from degradation because they exist inside water-filled compartments. The ability to specify how vesicles function together with membrane transfer properties lets researchers accurately control how drugs are released.

Peptide hydrogels contain micelles as significant self-assembled nanostructures according to research in Mandal et al. [55]. The amphiphilic peptide components of micelles create structures with hydrophobic centers surrounding a hydrophilic outer surface that enhances drug compounds that resist water solutions. The drug-release process from micelles occurs through stimulus-induced activation that responds to pH changes together with temperature fluctuations and enzyme molecular actions [55]. Their behavior toward stimuli helps make these nanostructures optimal candidates for energy-sensitive drug delivery methods. The dual application of micelles extends to nucleic acid protection through drug delivery and assisting cellular uptake of nucleic acids [55].

The modification of nanostructure structures creates opportunities to develop better peptide hydrogels that maintain optimal mechanical properties and achieve therapeutic effects besides controlled degradation rates [56]. Research teams use modifications in peptide sequence patterns together with hydrophobicity controls and charge distribution and incorporation of aromatic groups to design hydrogels suitable for particular biomedical needs such as drug delivery and wound healing and regenerative medicine applications.

The in-depth analysis of peptide self-assembly shows how different molecular forces together with hierarchical nanostructures control hydrogel development. The acquired knowledge stands as a base for creating advanced biomaterials that have defined functional characteristics for therapeutic purposes.

Rheological and mechanical properties

The elastic and viscous properties that characterize peptide hydrogels make them suitable for biomedical uses needing adjustments to changing physiological settings [57]. Their mechanical properties determine their structural integrity, durability, and ability to support cell growth or facilitate controlled drug release. These properties are influenced by factors similar as peptide sequence, cross-linking viscosity, solvent composition, and external stimulants. Understanding the interplay between these factors is pivotal for designing peptide hydrogels with tailored mechanical characteristics for specific biomedical operations.

Elasticity and viscoelastic behavior

The elasticity of peptide hydrogels is a crucial parameter impacting their performance in natural applications, including tissue scaffolding and wound mending. Their viscoelastic nature allows them to distort under stress and recover once the stress is removed, mimicking the mechanical behavior of soft tissues [58]. Several factors contribute to the elasticity and viscoelastic behavior of peptide hydrogels.

Peptide length and sequence play an essential part in defining mechanical properties. Longer peptides, especially those that favor β-sheet formation, tend to produce further rigid and mechanically stable hydrogels. In contrast, shorter peptide sequences allow lesser inflexibility, enabling the hydrogel to conform to irregular tissue shells. The secondary structures within the peptide network, particularly β-sheets and α-helices, influence hydrogel elasticity by affecting intermolecular hydrogen bonding and overall peptide alignment [43].

Cross-linking viscosity directly affects the mechanical strength and adaptability of the hydrogel [59]. An advanced degree of cross-linking increases the hydrogel's resistance to distortion, enhancing its stability and decelerating its declination [59]. However, extreme cross-linking can lead to fineness, reducing the hydrogel's rigidity in dynamic natural surroundings. The nature of cross-linking, whether covalent or non-covalent, also determines the hydrogel's capability to respond to external stimulants.

Solvent composition and environmental conditions significantly impact hydrogel stiffness and mechanical rigidity [60]. Ionic strength influences electrostatic relations between charged peptide residues, altering the network's cohesion and

rigidity. Changes in pH affect peptide charge distribution, modifying self-assembly dynamics and eventually impacting the stiffness of the hydrogel. Temperature oscillations also play a part in hydrogel behavior by altering molecular relations and hydration states.

The interplay of these factors allows peptide hydrogels to exhibit tunable mechanical properties, making them adaptable to different biomedical usages. By fine-tuning peptide sequences, cross-linking viscosity, and environmental conditions, experimenters can manipulate hydrogels with optimal elasticity for specific remedial requirements [61].

Degradation kinetics and stability

The stability and degradation profile of peptide hydrogels is critical for their performance in biomedical operations, particularly for sustained drug release and tissue revitalization. The declination rate must be precisely controlled to match the intended remedial timeline, ensuring that the hydrogel remains functional for the needed duration before being safely resorbed by the body [62].

Enzymatic declination is one of the primary mechanisms controlling hydrogel breakdown in natural surroundings. Proteases similar as matrix metalloproteinases (MMPs) widely stick peptide bonds, leading to controlled hydrogel decomposition. The vulnerability of peptide hydrogels to enzymatic declination depends on their amino acid composition and structural organization. By incorporating protease-sensitive motifs, hydrogels can be designed to degrade in response to specific enzymatic exertion, allowing for targeted drug release or altar resorption at the desired spot [63].

Hydrolytic fractionalization is another factor governing peptide hydrogel declination. The rate of hydrolysis depends on the stability of peptide bonds and the compassing physiological conditions. Certain amino acids are more prone to hydrolytic fractionalization, making their inclusion a crucial parameter in designing hydrogels with tailored declination kinetics. Environmental factors such as pH, temperature, and the presence of metal ions can accelerate or decelerate hydrolytic declination [64].

Cross-linking variations offer an important strategy for controlling hydrogel stability. Covalent cross-links significantly reduce the rate of declination, extending the hydrogel's lifetime and ensuring sustained drug release. Again, incorporating hydrolyzable or enzymatically cleavable cross-links allows for gradational hydrogel breakdown, smoothing dynamic drug delivery and tissue remodeling. The balance between stability and declination must be precisely optimized to ensure that the hydrogel provides structural support while maintaining its capability to disintegrate at the applicable rate [53].

External stimulants such as temperature, mechanical stress, and oxidative conditions can also impact the declination geste of peptide hydrogels [64]. Hydrogels designed with stimulants-responsive linkages can experience controlled declination upon exposure to specific physiological triggers. For example, thermosensitive peptide hydrogels can dissolve at body temperature, releasing wrapped-up remedial agents in a controlled manner. Also, oxidative conditions in inflamed tissues can be exploited to accelerate hydrogel declination for targeted remedial operations.

The combination of these declination mechanisms enables peptide hydrogels to be customized for a wide range of biomedical uses [58]. By precisely tuning enzymatic perceptivity, hydrolytic stability, and cross-linking characteristics, experimenters can develop hydrogels with predictable declination kinetics suitable for precision medicine delivery, tissue engineering, and regenerative drugs. The capability to manipulate hydrogels with controlled mechanical properties and declination biographies paves the way for advanced biomaterials tailored to specific clinical requirements.

Biocompatibility and in vivo behaviour

Biocompatibility is a fundamental demand for peptide hydrogels intended for biomedical operations. These materials must not provoke an adverse vulnerable response, must integrate seamlessly with surrounding tissues, and should degrade into non-toxic by-products that can be safely metabolized by the body. Their *in vivo* geste, including bioadhesion, declination, and interactions with cells and vulnerable factors, determines their fitness for operations similar to drug delivery, wound mending, and tissue engineering [65].

Immune response and cytotoxicity

The vulnerable response to implanted biomaterials plays a critical role in determining their long-term safety and efficacy. Peptide hydrogels are designed to minimize vulnerable activation and cytotoxic effects by capitalizing on their biodegradable and biocompatible nature [66]. One of the crucial factors impacting immunogenicity is the amino acid

composition of the hydrogel. Peptides derived from naturally occurring sequences in the mortal body are less likely to activate an immune response, reducing the threat of inflammation and adverse vulnerable responses. Also, the absence of synthetic supplements or immunogenic cross-linkers further enhances the hydrogel's biocompatibility [66].

As these hydrogels degrade, they break down into amino acids and small peptides that are readily metabolized through natural physiological pathways [67]. Unlike synthetic polymers that may produce potentially dangerous degradation products, peptide-based hydrogels degrade into bioavailable factors that can be employed in normal cellular processes. This eliminates the threat of poisonous accumulation and ensures the material's safety for prolonged remedial operations.

Another pivotal aspect of the vulnerable response is the hydrogel's interaction with macrophages, which play a central part in modulating inflammation and tissue recovery [68]. Hydrogels that activate inordinate macrophage activation may lead to chronic inflammation, fibrosis, or foreign body responses. To forestall this, peptide hydrogels can be maneuverer to exhibit anti-inflammatory properties by incorporating bioactive motifs that modulate vulnerable cell geste. Some peptide sequences can laboriously suppress seditious signaling pathways, promoting a regenerative rather than a fibrotic response [69].

The implicit cytotoxicity of peptide hydrogels is another major consideration. Cell viability assays have demonstrated that duly designed peptide hydrogels support cellular growth and proliferation without converting apoptosis or necrosis. The hydrogels provide a probative medium for reprised cells, allowing them to maintain normal metabolic exertion. Also, peptide hydrogels can be optimized to interact favorably with specific cell types by modifying their chemical composition and structural properties [70].

Bioadhesion and tissue integration

For peptide hydrogels to be effective in biomedical operations, they must interact favorably with natural tissues. The capability of a hydrogel to stick to and integrate with surrounding tissue determines its performance in operations similar as wound mending, scaffold-based tissue engineering, and localized medicine delivery [71]. Several crucial factors impact the bioadhesion and tissue integration of peptide hydrogels.

Surface functionalization plays a significant role in enhancing bioadhesion. By incorporating bioactive ligands, similar as cell-adhesion motifs derived from ECM proteins, peptide hydrogels can promote cell attachment and proliferation. Peptides containing sequences similar as arginine-glycine-aspartate (RGD) ease integrin-intermediated cell adhesion, allowing cells to cleave and spread on the hydrogel surface. This biomimetic approach ensures that peptide hydrogels provide a favorable medium for tissue rejuvenescence [72].

Another important aspect of tissue integration is the capability of peptide hydrogels to synopsize and release bioactive motes. These hydrogels can serve as reservoirs for controlled delivery of cytokines, growth factors, and other signaling motes that impact cell geste and tissue shape. By modulating the release kinetics of these factors, peptide hydrogels can provide sustained remedial effects, guiding processes similar as angiogenesis, ECM remodeling, and cell segregation. Hydrogels loaded with vascular endothelial growth factor (VEGF), for illustration, have been shown to promote neovascularization in ischemic tissues, demonstrating their eventuality in regenerative drugs [73].

The structural properties of peptide hydrogels, including porosity and network configuration, are also pivotal for successful tissue integration. Hydrogels with tunable porosity enable effective nutrient and oxygen prolixity, creating a probative medium for cell survival and function [72]. The aperture size and interconnectivity influence cell migration and tissue ingrowth, allowing host cells to insinuate and revise the hydrogel into functional tissue. By conforming peptide sequence composition and assembly conditions, hydrogels can be designed with optimized porosity to suit specific biomedical operations [71].

Another consideration in tissue integration is the hydrogel's mechanical compatibility with the native tissue. Hydrogels that nearly match the mechanical properties of the target tissue reduce the threat of stress-induced damage and ameliorate long-term functionality. Soft hydrogels may be ideal for operations involving neural or cardiac tissue, while stiffer hydrogels are more suited for haul-bearing tissues similar as cartilage and bone. By fine-tuning mechanical properties through peptide design and cross-linking strategies, peptide hydrogels can be customized to seamlessly integrate with a variety of tissue types.

One of the crucial challenges in hydrogel-based tissue engineering is achieving long-term stability

while allowing for controlled declination. Peptide hydrogels must remain complete long enough to support cell growth and tissue health but should eventually degrade without leaving behind residual materials [74]. The balance between stability and biodegradability is essential to ensure that the hydrogel provides temporary structural support before being completely resorbed. Incorporating enzyme-sensitive declination motifs can allow for hydrogel decomposition in response to specific natural cues, enabling precise control over the duration of hydrogel function. The interplay between bioadhesion, structural properties, and degradation kinetics determines the overall *in vivo* geste of peptide hydrogels [75]. By precisely designing these properties, experimenters can develop hydrogels that give both mechanical support and bioactive signaling, easing their use in different biomedical operations similar as wound mending, regenerative drug, and localized medicine delivery.

Drug Loading and Release Mechanisms

Strategies for drug encapsulation

Peptide hydrogels provide a protean platform for medicine encapsulation, allowing controlled and sustained medicine release. Various techniques are used to incorporate medicines within these hydrogels, ensuring optimal remedial effects while minimizing side effects. The choice of encapsulation strategy influences medicine stability, release kinetics, and bioavailability, making it essential to choose an applicable system based on the remedial target and hydrogel properties [76]. Various drug encapsulation strategies employed in peptide hydrogels are summarized in Table 2, highlighting their mechanisms and therapeutic applications.

Physical entrapment within the hydrogel network

Physical ruse is one of the simplest techniques for medicine loading, where the medicine motes are dispersed within the hydrogel matrix during its conformation. This strategy relies on the permeable structure of the hydrogel, which retains the medicine and allows step-by-step diffusion over time. The release rate is influenced by factors similar as hydrogel mesh size, medicine solubility, and prolixity coefficients [77].

Also, the degree of crosslinking within the hydrogel network plays a pivotal role in modulating medicine release. An advanced crosslinking viscosity results in lower pore sizes, decelerating medicine prolixity and extending release, whereas a lower crosslinking viscosity allows for faster diffusion and further immediate medicine action. This system is particularly favorable for hydrophilic small motes and proteins that demand unresisting diffusion over an extended period.

Covalent bonding for sustained release

In this approach, medicine motes are chemically conjugated to the peptide backbone via cleavable bonds, similar as ester, amide, or disulphide liaison [78]. The hydrogel degrades under physiological conditions, leading to a controlled and lengthened release of the medicine. This system is particularly useful for delivering small motes and bio macromolecules with short half-lives.

Covalent medicine conjugation provides high stability and reduces the threat of unseasonable medicine leakage before reaching the target point. By incorporating enzyme-sensitive or pH-responsive bonds, the hydrogel can achieve stimulants-responsive release, where medicinal emancipation is activated by specific environmental conditions similar as the acidic growth medium or enzymatic exertion in diseased tissues [64]. This strategy is extensively used in cancer remedy, regenerative drug, and the delivery of growth factors.

Affinity-based drug binding

Affinity-based medicine loading involves the interaction between the medicine and specific peptide motifs within the hydrogel. Electrostatic interactions, hydrophobic forces, and hydrogen adhesion can be employed to enhance medicine retention and modulate release kinetics. This approach is generally used for proteins, antibodies, and nucleic acid-based rectifiers [79].

The advantage of affinity-based binding lies in its capability to give largely tunable release kinetics by conforming the strength of molecular relations between the hydrogel and the medicine. For example, appreciatively charged peptides within the hydrogel can interact with negatively charged nucleic acids, ensuring step-by-step and sustained gene delivery. Also, hydrophobic areas within peptide hydrogels can trap lipophilic medicines, decelerating their release while enhancing solubility and stability. In addition, peptide sequences can be designed to mimic natural ligand-receptor interactions, enabling targeted medicine retention and release at specific natural locations. This strategy has been considerably explored for the controlled

delivery of cytokines, monoclonal antibodies, and remedial peptides in precision drug operations [80].

Stimuli-responsive drug release

Peptide hydrogels can be maneuverer to release drugs in response to specific environmental stimulants, ensuring place-specific and time-controlled medicine delivery. These stimulants-responsive hydrogels ameliorate remedial effectiveness while reducing systemic toxins by ensuring that the medicine is only released when and where it is demanded. The primary stimulants used for controlled medicine release include pH changes, enzymatic exertion, temperature oscillations, and external light exposure [81].

pH-triggered release

Hydrogels designed for pH-sensitive medicine release respond to changes in pH by altering their network structure. This property is particularly useful for targeting acidic surroundings, similar as neoplasm tissues or inflamed spots, where pH levels are lower than those in normal physiological conditions. Peptides containing acid-labile linkers degrade under low pH conditions, activating medicine release.

The mechanism behind pH-sensitive medicine release frequently involves protonation or deprotonation of specific functional groups within the hydrogel matrix, leading to swelling or declination [82]. For illustration, hydrogels incorporating histidine-rich peptides display pH-dependent solubility, enhancing their felicity for targeted cancer remedy and seditious disease treatment. Also, polymer-peptide crossbreed hydrogels incorporating ionizable groups, similar as carboxyl and amine groups, further enhance pH-responsive geste for tailored release kinetics.

Enzyme-sensitive drug release

Peptide hydrogels can be programmed to degrade in the presence of specific enzymes overexpressed in diseased tissues. For illustration, MMPs are largely expressed in cancerous and kindled tissues. Incorporating MMP-cleavable peptide sequences into the hydrogel ensures selective medicine release at the target point [83].

Beyond MMPs, other enzyme-responsive systems include hydrogels designed to respond to proteases, phosphatases, and lipases. These hydrogels degrade in response to complaint-specific enzymatic exertion, leading to precise remedial action with minimum off-target effects. Enzyme-cleavable hydrogels are particularly profitable for regenerative drug and localized cancer remedy, as they allow for largely selective medicine administration in response to pathological enzyme exertion [84].

Thermo-Responsive and Light-Activated Systems

Thermo-responsive hydrogels experience gel-sol transitions at physiological temperatures, facilitating controlled medicine release. These hydrogels contain temperature-sensitive peptide sequences that experience conformational changes when exposed to temperature variations. Generally, thermo-responsive hydrogels show lower critical result temperature behavior, meaning they remain in a gel state at body temperature and transition into a sol state when exposed to advanced temperatures, allowing medicine diffusion [85].

Light-activated hydrogels use near-infrared (NIR) light to activate structural changes, enabling precise spatiotemporal control of medicine release. Photocleavable peptide linkers within these hydrogels enable rapid-fire medicine emancipation upon exposure to external light stimulants. This approach is particularly profitable in ophthalmology, localized neoplasm remedy, and wound mending operations, where external light sources can be used to control medicine administration precisely.

Further advancements in light-responsive hydrogels involve the integration of up-conversion nanoparticles that convert NIR light into ultravioletor visible light, setting off hydrogel declination and medicine release with deeper tissue penetration [54]. These crossbreed systems enhance the connection of light-responsive hydrogels for *in vivo* remedial operations.

Controlled and targeted drug delivery

Controlled medicine release from peptide hydrogels prevents burst release and ensures a harmonious remedial effect over extended periods. By modifying hydrogel properties, experimenters can design medicine delivery systems adjusted to specific operations. The capability to control medicine prolixity, declination kinetics, and targeting capabilities allows for optimized remedial issues in various medical operations, including cancer treatment, tissue renewal, and infection control [86].

Sustained release profiles

The rate of medicine release is governed by hydrogel mesh size, cross-linking viscosity, and declination rate. Hydrogels with slower declination profiles give lengthened medicine release, reducing dosing prevalence and enhancing patient compliance. By confirming the molecular composition and cross-linking of peptide hydrogels, experimenters can fine-tune medicine release kinetics to match the desired remedial window.

Diffusion-controlled, swelling-controlled, and declination-controlled release mechanisms can be employed collectively or in combination to achieve sustained medicine delivery [87]. For example, hydrogels with a largely cross-linked structure produce slower prolixity rates, resulting in extended-release durations. Also, incorporating biodegradable linkers sensitive to physiological enzymes ensures controlled hydrogel declination and posterior medicine emancipation over time. This strategy is particularly valuable for habitual disease regulation, where long-term medicine administration is needed.

Ligand-functionalized peptide hydrogels

Functionalization with targeting ligands, similar as antibodies, peptides, or aptamers, enhances the particularity of peptide hydrogels. Ligand-functionalized hydrogels ensure that medicine motes accumulate preferentially at diseased tissues, enhancing remedial efficacy while minimizing systemic side effects.

Targeting ligands can be incorporated through covalent attachment or affinity relations, allowing for precise control over medicine release at specific natural spots [88]. For illustration, peptide hydrogels functionalized with growth-targeting ligands, similar as RGD sequences, promote selective binding to cancer cells, easing localized chemotherapy with reduced toxin. Also, hydrogels conjugated with antimicrobial peptides can enhance infection point targeting, perfecting remedial effectiveness against bacterial biofilms. Different stimuli-responsive peptide hydrogels and their mechanisms of drug release are outlined in Table 3, demonstrating their adaptability for precision drug delivery.

Advancements in ligand-functionalized hydrogels also include binary targeting approaches, where multiple ligands are incorporated to ameliorate particularity and binding affinity [89]. For example, combining folic acid and transferrin ligands can enhance hydrogel-intermediated medicine delivery to cancer cells that overexpress corresponding receptors. Also, stimulants-responsive ligand-functionalized hydrogels further improve medicine release kinetics, ensuring optimal medicine bioavailability in response to pathological conditions similar as inflammation or hypoxia. These targeted hydrogel systems have significant capability in precision drug, enabling substantiated curatives conditioned to individual cases based on complaint biomarkers and receptor expression profiles [90].

Peptide hydrogels offer diverse and adaptable platforms for drug delivery, integrating responsive mechanisms for precision medicine. By refining these systems, researchers can further optimize drug loading, release kinetics, and targeting capabilities to enhance clinical applications.

Table 2. Drug encapsulation strategies and their applications [Source: Authors].

Encapsulation strategy	Mechanism	Advantages	Applications
Physical entrapment	Drug diffuses within hydrogel pores	Simple preparation, suitable for various drugs	Small molecule drugs, hydrophilic compounds
Covalent bonding	Drug conjugated via cleavable bonds	Prolonged release, prevents premature degradation	Peptide drugs, proteins, antibodies
Affinity-based binding	Drug interacts with hydrogel matrix	High drug loading efficiency, controlled release	Protein-based drugs, nucleic acids

Table 3. Stimuli-responsive peptide hydrogels [Source: Authors].

Stimulus	Mechanism	Application
pH-responsive	Hydrogel degrades under acidic conditions	Tumor-targeted drug delivery, gastric drug release
Enzyme-sensitive	Cleaved by disease-associated enzymes	Cancer therapy, inflammatory diseases
Thermo-responsive	Temperature-induced gel-sol transition	Injectable drug delivery, wound healing
Light-activated	Photo-induced structural change	On-demand drug release, localized therapy

Biomedical Applications of Biodegradable Peptide Hydrogels

Peptide hydrogels have arose as a protean platform for biomedical operations, offering unique advantages similar as biocompatibility, tunable declination rates, and stimulants-responsive geste. These properties make them ideal for medicine delivery, tissue engineering, wound mending, and antimicrobial operations.

Cancer therapy

Peptide hydrogels have surfaced as a promising tool in cancer remedy by enabling localized, controlled medicine release and reducing the systemic toxin generally associated with conventional chemotherapy. Their unique properties similar as tunable declination rates, responsiveness to neoplasm ambient cues, and ease of functionalization allow them to be doctored for specific remedial requirements [71]. In cancer treatment, peptide hydrogels are employed not only for localized chemotherapy delivery but also for advanced immunotherapy and gene remedy operations.

Localized chemotherapy delivery

Traditional chemotherapy is frequently hampered by non-specific medicine distribution, which leads to significant off-target toxins and adverse side effects. Peptide hydrogels address these limitations by delivering a localized medicine depot that gradually releases chemotherapeutic agents directly at the neoplasm point. This targeted approach enhances medicine bioavailability within the lump while sparing healthy tissues.

i. Localized chemotherapy delivery using peptide hydrogels involves several crucial design rudiments.
ii. Encapsulation of chemotherapeutic agents medicines similar as doxorubicin, paclitaxel, and cisplatin can be physically entrapped or covalently bonded within the hydrogel network [80]. The matrix's fissure size and cross-linking viscosity are precisely contrived to achieve a sustained release profile that matches the remedial window needed for effective lump repression.
iii. Tumor-targeting strategies functionalization of the hydrogel with lump-targeting ligands similar as RGD peptides further enhances medicine retention at the neoplasm point. These ligands promote specific binding to receptors overexpressed on cancer cells, ensuring advanced original medicine attention.
iv. Stimuli-responsive release of numerous peptide hydrogels are designed to be enzyme-responsive. For example, the incorporation of MMP-cleavable sequences allows the hydrogel to degrade in response to the high MMP exertion set up in numerous neoplasms [91]. This results in precise, point-specific medicine release.
v. Improved patient compliance the sustained release of chemotherapeutic agents minimizes the need for frequent dosing, thereby reducing patient discomfort and enhancing overall treatment adherence. Table 4 presents notable examples of chemotherapeutic agents successfully delivered via peptide hydrogels, showcasing their potential for targeted cancer therapy.

These strategies collectively contribute to a more effective and safer chemotherapeutic regimen, as evidenced by improved tumor regression and lower systemic side effects in preclinical studies.

Immunotherapy and gene therapy applications

In addition to chemotherapy, peptide hydrogels serve as robust platforms for immunotherapy and gene remedy, which are fleetly gaining height in the fight against cancer.

i. Immunotherapy delivery immunotherapy relies on modulating the patient's vulnerable system to honor and destroy cancer cells [92]. Hydrogel-based delivery systems for immunotherapeutic agents similar as checkpoint inhibitors (anti-PD-1,anti-CTLA-4 antibodies) offer several advantages. By handing a controlled and localized release, peptide hydrogels help maintain remedial levels of these agents at the lump point while minimizing systemic vulnerable-affiliated adverse events. This localized approach enhances the antitumor-vulnerable response

Table 4. Examples of chemotherapeutic delivery via peptide hydrogels [Source: Authors].

	Encapsulation method	Targeting strategy	Observed benefits
Doxorubicin	Physical entrapment	RGD peptide functionalization	Enhanced tumor retention; reduced toxicity
Paclitaxel	Covalent bonding	pH-sensitive release	Sustained release; improved bioavailability
Cisplatin	Enzyme-responsive system	MMP-cleavable linkers	Targeted release in high MMP environments

by ensuring that vulnerable cells are triggered directly within the neoplasm medium.

ii. Gene therapy applications and gene remedy holds great pledges for treating cancer by targeting inheritable anomalies within neoplasm cells. Peptide hydrogels have been contrived to deliver a variety of inheritable materials, including small interfering RNA(siRNA), messenger RNA (mRNA), and CRISPR/Cas9 factors. The hydrogel matrix protects these sensitive biomolecules from declination by nucleases, while its sustained release profile allows for extended remedial action. Cationic peptide sequences incorporated into the hydrogel ease the binding and effective cellular uptake of negatively charged nucleic acids. This enhances gene silencing or editing effectiveness, leading to enhanced remedial effects [93].

iii. Synergistic therapies, especially, peptide hydrogels have been explored for combination curatives where immunotherapeutic agents and gene remedy vectors are co-delivered. This multimodal approach can concurrently modulate the vulnerable system and correct or silence oncogenic drivers, providing a synergistic attack on cancer cells.

The applications of peptide hydrogels in immunotherapy and gene therapy, including their roles in localized immune activation and gene silencing, are summarized in Table 5.

Wound healing and tissue engineering

Peptide hydrogels are uniquely suited for wound mending and tissue renewal due to their capability to mimic the natural ECM. Their high water content, previous structure, and biocompatibility produce an ideal terrain for cell adhesion, proliferation, and isolation. In addition, the essential bioactivity of peptide hydrogels can be further enhanced by incorporating growth factors, antimicrobial agents, and other bioactive motes, all of which contribute to accelerated tissue health and renewal [94].

Peptide hydrogels for skin regeneration

Chronic injuries, including diabetic ulcers and pressure blisters, present a significant clinical challenge due to their prolonged mending times and vulnerability to infection. Peptide hydrogels offer an innovative result by acting as advanced wound dressings that maintain a damp terrain—a critical factor for optimal wound mending. This damp terrain facilitates gas exchange and waste disposal while forestalling tissue desiccation, thereby promoting faster re-epithelialization. Table 6 highlights key bioactive components in peptide hydrogels that contribute to accelerated wound healing and skin regeneration.

One of the primary advantages of peptide hydrogels in skin regeneration is their capability to deliver bioactive motes directly to the wound point. For illustration, the incorporation of epidermal growth factor (EGF) and transubstantiating growth factor-beta (TGF-β) into the hydrogel matrix has been shown to stimulate fibroblast proliferation and collagen conflation. These growth factors not only enhance the structural integrity of the regenerating tissue but also expedite the conformation of new blood vessels (angiogenesis), which is essential for sustained tissue health [95].

In addition to growth factors, antimicrobial peptide (AMP) loaded hydrogels serve a binary purpose. They help bacterial colonization and posterior infection while concurrently promoting mending. Some phrasings combine AMPs with spare agents similar as silverware nanoparticles or chitosan derivations, which give fresh antimicrobial efficacy. These multifunctional hydrogels have been demonstrated to reduce infection rates in open injuries and ameliorate overall mending issues.

These advanced skin regeneration strategies using peptide hydrogels have shown promise in preclinical studies and are paving the way for more effective, patient-friendly wound care solutions.

Table 5. Immunotherapy and gene therapy applications using peptide hydrogels [Source: Authors].

Therapeutic Modality	Agent/component	Mechanism	Key benefits
Immunotherapy	Anti-PD-1/anti-CTLA-4	Localized checkpoint inhibition	Reduced systemic toxicity; enhanced local immune activation
Gene therapy	siRNA/mRNA	Gene silencing/editing via sustained release	Protection from degradation; improved cellular uptake
Combination therapy	CRISPR/Cas9 + antibodies	Concurrent gene editing and immune modulation	Synergistic antitumor effects; multi-target approach

Table 6. Key components and benefits of peptide hydrogels in skin regeneration [Source: Authors].

Component	Function/Mechanism	Key Benefits
EGF	Stimulates fibroblast proliferation and re-epithelialization	Accelerated wound closure
TGF-β	Promotes collagen synthesis and ECM remodeling	Enhanced structural integrity
AMPs	Disrupt bacterial membranes	Reduced infection risk
Silver nanoparticles/chitosan	Additional antimicrobial action	Synergistic infection control

Bone and cartilage regeneration

In orthopedic operations, peptide hydrogels have been abused to support the health and regeneration of bone and cartilage tissues. The crucial challenge in bone and cartilage health lies in recreating a scaffold that not only provides mechanical support but also encourages the isolation of cells into osteoblasts (bone-forming cells) or chondrocytes (cartilage-forming cells) [96].

Mineralized peptide hydrogels, which are loaded with inorganic factors similar as calcium phosphate or hydroxyapatite, have surfaced as promising materials for bone renewal. These mineral complements mimic the natural mineral content of bone, thereby promoting osteoblast isolation and accelerating new bone conformation. The previous network of the hydrogel facilitates nutrient prolixity and waste disposal, while its biodegradability allows for gradual relief by aboriginal tissue [96].

For cartilage renewal, the focus is on creating a terrain conducive to the growth and conservation of chondrocytes or mesenchymal stem cells (MSCs). Hydrogels that synopsize these cells give a three-dimensional scaffold that mimics the cartilage ECM, thereby supporting cell viability and function. Also, injectable peptide hydrogels offer a minimally invasive option for delivering these regenerative curatives. Upon injection, these hydrogels experience *in situ* gelation, conforming to the shape of the disfigurement and filling irregular tissue gaps, which is critical for effective cartilage repair. Table 7 summarizes strategies for utilizing peptide hydrogels in bone and cartilage regeneration, including their role in osteoblast differentiation and defect filling.

The use of peptide hydrogels in bone and cartilage regeneration demonstrates their versatility as both a structural support and a delivery vehicle for bioactive molecules and cells. These hydrogels facilitate a controlled healing environment that is critical for the successful repair of musculoskeletal tissues.

Antimicrobial and antiviral applications

Peptide hydrogels demonstrate potent antimicrobial and antiviral properties, making them high-end tools for infection control and remedial interventions [97]. By combining the essential bioactivity of peptides with the controlled release capabilities of hydrogels, these materials offer a multifaceted approach to combat bacterial and viral infections while concurrently supporting tissue renewal.

Antimicrobial peptide-loaded hydrogels

Bacterial infections remain a significant challenge in wound operation and implant-associated complications. To address this, AMP-functionalized hydrogels have been developed. These systems incorporate naturally occurring AMPs similar as LL-37, defensins, and magainins, which are known for their broad-spectrum antimicrobial exertion.

AMPs act primarily by interacting with and dismembering bacterial cell membranes, leading to severance conformation and eventual cell lysis. Within a hydrogel matrix, these peptides can be incorporated either by physical ruse or covalent conjugation. The hydrogel not only serves as a reservoir for sustained AMP release but also provides a physical hedge that limits bacterial colonization. The controlled and gradual release of

Table 7. Strategies for bone and cartilage regeneration with peptide hydrogels [Source: Author].

Regenerative target	Strategy	Key benefits
Bone regeneration	Mineralized hydrogels with calcium phosphate/ hydroxyapatite	Promotes osteoblast differentiation; accelerates bone formation
Cartilage regeneration	Encapsulation of chondrocytes or MSCs	Provides 3D scaffold; supports cell viability and ECM synthesis
Injectable formulations	In situ gelation for defect filling	Minimally invasive delivery; conforms to defect shape

AMPs maintains remedial attention at the wound or implant point, minimizing the threat of infection and reducing the liability of bacterial resistance development [98].

Advanced phrasings may combine AMPs with fresh antimicrobial agents similar as silverware nanoparticles or chitosan derivations to further enhance antibacterial efficacy. Similarly, binary-function hydrogels that also retain anti-inflammatory properties have been explored to contemporaneously address infection and the seditious response that frequently complicates chronic injuries.

Peptide hydrogels for antiviral remedy

In the realm of antiviral remedies, peptide hydrogels have been delved as platforms for the controlled delivery of antiviral peptides and small-patch impediments targeting pathogens similar as HIV, influenza, and SARS-CoV-2. Encapsulation within the hydrogel matrix protects these sensitive antiviral agents from enzymatic declination and enhances their bioavailability.

The sustained release profile of peptide hydrogels ensures that antiviral agents remain at effective attention over prolonged periods, which is critical for suppressing viral replication [99]. In addition, these hydrogels can be formulated as mucoadhesive systems, making them particularly useful for treating infections in mucosal tissues. For example, in respiratory or gastrointestinal tracts, the mucoadhesive properties of the hydrogel help localize the medicine, enhancing its efficacy and reducing systemic exposure. A summary of peptide hydrogels' antimicrobial and antiviral applications, including their role in infection control, is provided in Table 8.

By enabling localized and extended delivery, peptide hydrogels not only enhance the stability of antiviral medicines but also allow for combination curatives. Co-delivery of multiple antiviral agents may affect in synergistic effects, further enhancing treatment issues and reducing the threat of medicine resistance.

In summary, the integration of antimicrobial and antiviral agents into peptide hydrogels represents a powerful strategy for addressing infectious challenges in clinical settings. These systems provide controlled and localized drug delivery while simultaneously creating a conducive environment for tissue repair. Their versatility makes them particularly promising for applications ranging from chronic wound management to the targeted treatment of viral infections.

Ophthalmic drug delivery

Peptide hydrogels have shown great pledges in optical medicine delivery due to their essential biocompatibility, optic clarity, and sustained release properties [100]. The delicate nature of optical tissues requires materials that not only deliver medicines effectively over extended ages but also maintain the comfort and physiological function of the eye. Peptide hydrogels address these requirements by forming a soft, transparent matrix that conforms to the eye's surface while ensuring controlled medicine release.

The unique network structure of peptide hydrogels enables them to act as budgets for various ophthalmic medicines, minimizing the rapid-fire concurrence that is typical of conventional eye drops. This sustained release improves medicine retention time on the optical surface, which is critical for treating habitual eye conditions similar as uveitis, dry eye complaint, and retinal diseases. Also, these hydrogels can be contrived to be mucoadhesive, ensuring intimate contact with optical tissues and farther enhancing medicine bioavailability [95].

Table 8. Summary of antimicrobial and antiviral applications using peptide hydrogels [Source: Authors].

Application type	Key agents/components	Mechanism of action	Benefits
Antimicrobial therapy	LL-37, defensins, magainins	Membrane disruption, pore formation	Broad-spectrum activity; sustained release
Dual-function hydrogels	AMPs + anti-inflammatory agents	Infection control and inflammation reduction	Enhanced wound healing; reduced resistance risk
Antiviral therapy	Antiviral peptides, inhibitors	Inhibition of viral replication/ entry	Improved stability; localized, sustained delivery
Mucoadhesive systems	Hydrogels with mucoadhesive polymers	Adherence to mucosal tissues, localized release	Targeted delivery; enhanced bioavailability

Hydrogel-based contact lenses for sustained medicine release

One of the most innovative operations in ophthalmology involves the integration of peptide hydrogels into contact lenses. These hydrogel-based contact lenses are designed to lodge anti-inflammatory and anti-glaucoma specifics, among other rectifiers, to deliver prolonged medicine release compared to traditional eye drops. The sustained release medium is achieved by the slow prolixity of the medicine from the hydrogel matrix, which is impacted by the cross-linking viscosity and severance size of the hydrogel.

In this operation, the hydrogels must maintain high levels of translucency and oxygen permeability to ensure that vision is not compromised and that corneal health is saved. Medicines similar as corticosteroids, cyclosporine, and anti-vascular endothelial growth factor (anti-VEGF) agents can be incorporated into the hydrogel matrix. These agents are particularly useful for managing seditious conditions, vulnerable mediated optical conditions, and retinal diseases. The extended medicine release delivered by these lenses not only reduces the need for frequent administration but also improves patient adherence, eventually enhancing remedial issues. The potential of hydrogel-based contact lenses for sustained ophthalmic drug release is outlined in Table 9.

Neural tissue engineering and regeneration

Neural tissue engineering aims to restore or replace damaged neural tissues by supplying a probative medium for neuronal growth, isolation, and repair. Peptide hydrogels are particularly well-suited for this operation due to their capability to mimic the natural ECM of neural tissues. Their soft, doused nature provides an optimal scaffold that supports cell adhesion and facilitates the prolixity of nutrients and signaling motes.

The design of peptide hydrogels for neural operations frequently involves acclimatizing the material's mechanical properties to nearly match those of the native neural tissue. This harmony is essential to avoid driving glial scar conformation and to promote the survival and integration of bedded cells. In addition, these hydrogels can be functionalized with bioactive peptides and growth factors that encourage neurite outgrowth, synapse conformation, and overall neural connectivity.

Hydrogel scaffolds for spinal cord repair

Spinal cord injuries (SCIs) present a redoubtable challenge due to the limited regenerative capacity of central nervous system tissues. Peptide hydrogels offer a promising strategy for SCI repair by acting as injectable platforms that fill the injury depression and give a conducive terrain for axonal rejuvenescence. Upon injection, these hydrogels experience *in situ* gelation, conforming to the irregular figures of the injury point and establishing a physical ground for regenerating axons.

A critical aspect of spinal cord repair involves the incorporation of neurotrophic factors similar as brain-derived neurotrophic factor (BDNF) and nerve growth factor (NGF). These factors support neuronal survival, promote axonal growth, and enhance synaptic connectivity. By bedding similar neurotrophic agents within the hydrogel altar, a sustained and localized delivery can be achieved, ensuring that the regenerating neurons admit nonstop support during the critical phases of form. The strategies employed in peptide hydrogel scaffolds for neural tissue engineering, particularly in spinal cord repair, are detailed in Table 10.

Hydrogel platforms for spinal cord repair can be designed to give directional cues that guide axonal extension. Micro-patterning ways or grade-based delivery systems within the hydrogel matrix can encourage the alignment of regenerating fibers, which is essential for the restoration of functional neural circuits.

Table 9. Below summarizes key features and benefits of hydrogel-based contact lenses for ophthalmic drug delivery [Source: Authors].

Feature	Description	Key benefits
Transparency and comfort	High optical clarity and soft mechanical properties	Maintains vision quality; increases comfort
Sustained drug release	Controlled diffusion of embedded drugs	Prolonged therapeutic effect; reduced dosing frequency
Mucoadhesive properties	Enhanced adherence to the ocular surface	Improved bioavailability and retention time
Oxygen permeability	Engineered to allow sufficient oxygen transmission	Supports corneal health and prevents hypoxia

Together, these approaches highlight the potential of peptide hydrogels to transform neural tissue engineering and spinal cord repair. Their capacity to deliver bioactive molecules in a controlled manner, combined with their structural and functional compatibility with neural tissues, makes them a powerful tool for regenerative medicine.

Cardiovascular applications

Peptide hydrogels are utilized in cardiovascular therapies, including myocardial infarction repair and vascular graft coatings.

Injectable hydrogels for myocardial infarction repair

Injectable peptide hydrogels are designed to support cardiac tissue regeneration post-myocardial infarction. These hydrogels provide a protective niche for cardiac cells, reducing inflammation and enhancing angiogenesis. Incorporating angiogenic factors such as VEGF further promotes new blood vessel formation [80].

Anti-thrombogenic peptide hydrogels

Hydrogels functionalized with heparin or nitric oxide-releasing peptides prevent thrombus formation in vascular grafts and stents. The sustained release of anti-coagulants reduces the risk of post-surgical complications. Table 11 provides an overview of the diverse biomedical applications of peptide hydrogels, ranging from cancer therapy to cardiovascular interventions.

Peptide hydrogels have demonstrated immense potential in various biomedical applications. Their adaptability, tunability, and biocompatibility position them as promising candidates for next-generation therapeutic platforms. Future research will continue to refine their functionality, improving their clinical translation and efficacy in diverse medical fields.

Future Perspectives and Conclusions

The rapid evolution of peptide hydrogel technology has opened new avenues for precision drug delivery and regenerative medicine. Despite impressive advances in design, functionality, and application, several challenges remain that must be addressed before these materials can be widely adopted in clinical settings. Future research is expected to build upon current successes by overcoming these limitations, integrating cutting-edge technologies, and expanding the range of biomedical applications.

Current challenges and limitations

A critical aspect of future development is understanding and addressing the existing challenges in peptide hydrogel research. One major issue is the scalability of peptide synthesis and hydrogel production. Although many peptide hydrogels are synthesized using well-established methods, ensuring

Table 10. Summarizes the key strategies employed in designing peptide hydrogel scaffolds for neural tissue engineering, particularly for spinal cord repair [Source: Authors].

Strategy	Mechanism	Key benefits
In situ gelation	Injectable hydrogels solidify at the injury site	Conforms to irregular injury shapes; minimally invasive
Neurotrophic factor delivery	Incorporation of BDNF, NGF, etc.	Promotes neuronal survival and axonal growth
ECM mimicry	Tailored mechanical and biochemical properties	Supports cell adhesion and neurite outgrowth
Directional cues	Micro-patterned or gradient hydrogels	Guides axonal alignment for functional connectivity

Table 11. Biomedical applications of peptide hydrogels [Source: Authors].

Application area	Function	Key benefits
Cancer therapy	Chemotherapy & immunotherapy delivery	Targeted drug release, reduced toxicity
Wound healing	Skin & bone regeneration	Moist wound healing, accelerated tissue repair
Antimicrobial therapy	Bacterial & viral infections	Prolonged antimicrobial action, reduced resistance risk
Ophthalmology	Sustained ocular drug release	Prolonged retention, improved bioavailability
Neural regeneration	Spinal cord & neural repair	Axonal growth, neuroprotection
Cardiovascular therapy	Myocardial repair & vascular grafts	Angiogenesis, thrombosis prevention

batch-to-batch reproducibility and cost-effectiveness for large-scale manufacturing remains a significant hurdle.

Another challenge lies in the long-term stability and controlled biodegradation of these hydrogels. While the inherent biodegradability of peptides is an advantage, achieving a degradation profile that precisely matches therapeutic timelines is complex. This requires a delicate balance between maintaining structural integrity for sustained drug release and ensuring complete resorption without adverse effects.

Furthermore, the clinical translation of peptide hydrogels is hindered by regulatory challenges. Safety, efficacy, and quality control standards must be rigorously demonstrated through preclinical and clinical studies. Immune compatibility and potential inflammatory responses also need a thorough evaluation to prevent complications after implantation.

Emerging trends and innovations

Recent advancements in biomaterials research are driving innovative approaches to overcome these limitations. Integration with nanotechnology is enhancing the functionality of peptide hydrogels by enabling multi-modal drug delivery systems and improved targeting. For example, incorporating nanoparticles into hydrogel matrices can facilitate simultaneous imaging, diagnostics, and therapy.

Another promising trend is the use of stimuli-responsive and smart hydrogel systems. Advances in photo-responsive, thermo-responsive, and enzyme-sensitive designs are enabling hydrogels that release drugs precisely in response to environmental cues. This fine-tuning not only improves therapeutic efficacy but also minimizes off-target effects. Artificial intelligence and machine learning are beginning to play a role in hydrogel design, allowing researchers to predict and optimize peptide sequences for desired mechanical and biological properties. This computational approach accelerates the development of customized, patient-specific hydrogels that could revolutionize personalized medicine.

Clinical translation and regulatory considerations

The path to clinical application requires addressing both scientific and regulatory challenges. In the coming years, standardized protocols for the characterization, testing, and quality control of peptide hydrogels will be critical. Collaborative efforts between researchers, clinicians, and regulatory agencies are needed to develop clear guidelines for safety and efficacy evaluations.

Pilot clinical trials are beginning to shed light on the performance of peptide hydrogels in various applications, from localized chemotherapy to tissue engineering. These early studies will inform future regulatory frameworks and help identify optimal design parameters for clinical success. Moreover, long-term *in vivo* studies are essential to assess the biodegradation, immune response, and overall therapeutic outcomes in human subjects.

Future research directions

Looking forward, several research avenues are poised to further enhance the capabilities of peptide hydrogels. One key direction is the development of multi-functional hydrogels that can deliver combinations of drugs, genes, or growth factors simultaneously. This could be particularly valuable in complex diseases like cancer, where combination therapies are often more effective.

Another important area is the refinement of stimuli-responsive systems. By incorporating multiple triggers—such as pH, temperature, and enzymatic activity—researchers aim to create hydrogels with ultra-precise control over drug release. The design of such smart systems will benefit from advances in material science and computational modeling.

There is also a growing interest in exploring the potential of peptide hydrogels in emerging fields such as bioelectronics and 3D bioprinting. The ability to tailor mechanical and electrical properties opens up possibilities for constructing neural interfaces and customized tissue scaffolds that closely mimic native tissue architecture.

Conclusions

Peptide hydrogels have established themselves as a transformative platform for precision drug delivery and regenerative medicine. Their biocompatibility, tunable properties, and capacity for stimuli-responsive behavior make them ideal candidates for a wide range of biomedical applications. Although challenges related to scalability, stability, and regulatory approval persist, emerging innovations and interdisciplinary collaborations are rapidly advancing the field.

In conclusion, the future of peptide hydrogel technology is exceptionally promising. Continued research aimed at refining their design, improving manufacturing processes, and establishing robust clinical protocols will pave the way for their

widespread clinical adoption. Ultimately, these advances hold the potential to revolutionize personalized medicine and offer new hope for the treatment of complex diseases.

References

1. Agiba AM, Arreola-Ramírez JL, Carbajal V, Segura-Medina P. Light-responsive and dual-targeting liposomes: from mechanisms to targeting strategies. Molecules 2024; 29(3):636.
2. Ahmad A, Imran M, Sharma N. Precision nanotoxicology in drug development: current trends and challenges in safety and toxicity implications of customized multifunctional nanocarriers for drug-delivery applications. Pharmaceutics 2022; 14(11):2463. Ajdary R, Tardy BL, Mattos BD, Bai L, Rojas OJ. Plant nanomaterials and inspiration from nature: water interactions and hierarchically structured hydrogels. Adv Mater 2021; 33(28):2001085.
3. Am Ende MT, Hariharan D, Peppas NA. Factors influencing drug and protein transport and release from ionic hydrogels. React Polym 1995; 25(2–3):127–37.
4. Asai D, Kanamoto T, Takenaga M, Nakashima H. *In situ* depot formation of anti-HIV fusion-inhibitor peptide in recombinant protein polymer hydrogel. Acta Biomater 2017; 64:116–25.
5. Azman M, Sabri AH, Anjani QK, Mustaffa MF, Hamid KA. Intestinal absorption study: challenges and absorption enhancement strategies in improving oral drug delivery. Pharmaceuticals 2022; 15(8):975.
6. Bao Z, Xian C, Yuan Q, Liu G, Wu J. Natural polymer-based hydrogels with enhanced mechanical performances: preparation, structure, and property. Adv Healthc Mater 2019; 8(17):1900670.
7. Baryakova TH, Pogostin BH, Langer R, McHugh KJ. Overcoming barriers to patient adherence: the case for developing innovative drug delivery systems. Nat Rev Drug Discov 2023; 22(5):387–409. Chai Q, Jiao Y, Yu X. Hydrogels for biomedical applications: their characteristics and the mechanisms behind them. Gels 2017; 3(1):6.
8. Beheshtizadeh N, Gharibshahian M, Bayati M, Maleki R, Strachan H, Doughty S, et al. Vascular endothelial growth factor (VEGF) delivery approaches in regenerative medicine. Biomed Pharmacother 2023; 166:115301.
9. Bertsch P, Diba M, Mooney DJ, Leeuwenburgh SC. Self-healing injectable hydrogels for tissue regeneration. Chem Rev 2022; 123(2):834–73.
10. Bhattacharjee S. Understanding the burst release phenomenon: toward designing effective nanoparticulate drug-delivery systems. Ther Deliv 2021; 12(1):21–36.
11. Branco MC, Schneider JP. Self-assembling materials for therapeutic delivery. Acta Biomater 2009; 5(3):817–31.
12. Caliari SR, Burdick JA. A practical guide to hydrogels for cell culture. Nat Methods 2016; 13(5):405–14.
13. Chandrawati R. Enzyme-responsive polymer hydrogels for therapeutic delivery. Exp Biol Med 2016; 241(9):972–9.
14. Chen W, Zhou Z, Chen D, Li Y, Zhang Q, Su J. Bone regeneration using MMP-cleavable peptides-based hydrogels. Gels 2021; 7(4):199.
15. Collins MN, Ren G, Young K, Pina S, Reis RL, Oliveira JM. Scaffold fabrication technologies and structure/function properties in bone tissue engineering. Adv Funct Mater 2021; 31(21):2010609.
16. Dasgupta A, Mondal JH, Das D. Peptide hydrogels. RSC Adv 2013; 3(24):9117–49.
17. Dehsorkhi A, Castelletto V, Hamley IW. Self-assembling amphiphilic peptides. J Pept Sci 2014; 20(7):453–67.
18. Deshmukh R, Sethi P, Singh B, Shiekmydeen J, Salave S, Patel RJ, et al. Recent review on biological barriers and host–material interfaces in precision drug delivery: advancement in biomaterial engineering for better treatment therapies. Pharmaceutics 2024; 16(8):1076.
19. de Sousa Victor R, Marcelo da Cunha Santos A, Viana de Sousa B, de Araújo Neves G, Navarro de Lima Santana L, Rodrigues Menezes R. A review on Chitosan's uses as biomaterial: tissue engineering, drug delivery systems and cancer treatment. Materials 2020; 13(21):4995.
20. Ding Q, Wu Z, Tao K, Wei Y, Wang W, Yang BR, et al. Environment tolerant, adaptable and stretchable organohydrogels: preparation, optimization, and applications. Mater Horiz 2022; 9(5):1356–86.
21. Dou XQ, Feng CL. Amino acids and peptide-based supramolecular hydrogels for three-dimensional cell culture. Adv Mater 2017; 29(16):1604062.
22. Durán-Lobato M, Niu Z, Alonso MJ. Oral delivery of biologics for precision medicine. Adv Mater 2020; 32(13):1901935.
23. Du X, Zhou J, Shi J, Xu B. Supramolecular hydrogelators and hydrogels: from soft matter to molecular biomaterials. Chem Rev 2015; 115(24):13165–307.
24. Ezike TC, Okpala US, Onoja UL, Nwike CP, Ezeako EC, Okpara OJ, et al. Advances in drug delivery systems, challenges and future directions. Heliyon 2023; 9(6):e17488.
25. Fan T, Yu X, Shen B, Sun L. Peptide self-assembled nanostructures for drug delivery applications. J Nanomater 2017; 2017(1):4562474.
26. Fass D, Thorpe C. Chemistry and enzymology of disulfide cross-linking in proteins. Chem Rev 2018; 118(3):1169–98.
27. Fichman G, Gazit E. Self-assembly of short peptides to form hydrogels: design of building blocks,

physical properties and technological applications. Acta Biomater 2014; 10(4):1671–82.
28. Ganji F, Vasheghani FE. Hydrogels in controlled drug delivery systems. Iran Polym J 2009; 18(1):63–88.
29. Ghatak S, Maytin EV, Mack JA, Hascall VC, Atanelishvili I, Moreno Rodriguez R, et al. Roles of proteoglycans and glycosaminoglycans in wound healing and fibrosis. Int J Cell Biol 2015; 2015(1):834893.
30. Guan T, Li J, Chen C, Liu Y. Self-assembling peptide-based hydrogels for wound tissue repair. Adv Sci 2022; 9(10):2104165.
31. Habibi N, Kamaly N, Memic A, Shafiee H. Self-assembled peptide-based nanostructures: smart nanomaterials toward targeted drug delivery. Nano Today 2016; 11(1):41–60.
32. Hager S, Fittler FJ, Wagner E, Bros M. Nucleic acid-based approaches for tumor therapy. Cells 2020; 9(9):2061.
33. Huang G, Li F, Zhao X, Ma Y, Li Y, Lin M, et al. Functional and biomimetic materials for engineering of the three-dimensional cell microenvironment. Chem Rev 2017; 117(20):12764–850.
34. Hu Q, Katti PS, Gu Z. Enzyme-responsive nanomaterials for controlled drug delivery. Nanoscale 2014; 6(21):12273–86.
35. Jonker AM, Löwik DW, Van Hest JC. Peptide-and protein-based hydrogels. Chem Mater 2012; 24(5):759–73.
36. Kailasa SK, Joshi DJ, Kateshiya MR, Koduru JR, Malek NI. Review on the biomedical and sensing applications of nanomaterial-incorporated hydrogels. Mater Today Chem 2022; 23:100746.
37. Kamaly N, Yameen B, Wu J, Farokhzad OC. Degradable controlled-release polymers and polymeric nanoparticles: mechanisms of controlling drug release. Chem Rev 2016; 116(4):2602–63.
38. Kar A, Ahamad N, Dewani M, Awasthi L, Patil R, Banerjee R. Wearable and implantable devices for drug delivery: applications and challenges. Biomaterials 2022; 283:121435.
39. Karavasili C, Fatouros DG. Self-assembling peptides as vectors for local drug delivery and tissue engineering applications. Adv Drug Deliv Rev 2021; 174:387–405.
40. Kharaziha M, Baidya A, Annabi N. Rational design of immunomodulatory hydrogels for chronic wound healing. Adv Mater 2021; 33(39):2100176.
41. Kharkar PM, Kiick KL, Kloxin AM. Designing degradable hydrogels for orthogonal control of cell microenvironments. Chem Soc Rev 2013; 42(17):7335–72.
42. Klinger D, Landfester K. Stimuli-responsive microgels for the loading and release of functional compounds: fundamental concepts and applications. Polymer 2012; 53(23):5209–31.
43. Kondiah PJ, Choonara YE, Kondiah PP, Marimuthu T, Kumar P, Du Toit LC, et al. A review of injectable polymeric hydrogel systems for application in bone tissue engineering. Molecules 2016; 21(11):1580.
44. Koury J, Lucero M, Cato C, Chang L, Geiger J, Henry D, et al. Immunotherapies: exploiting the immune system for cancer treatment. J Immunol Res 2018; 2018(1):9585614.
45. Lai HJ, Kuan CH, Wu HC, Tsai JC, Chen TM, Hsieh DJ, et al. Tailored design of electrospun composite nanofibers with staged release of multiple angiogenic growth factors for chronic wound healing. Acta Biomater 2014; 10(10):4156–66.
46. Lazaridou M, Bikiaris DN, Lamprou DA. 3D bioprinted chitosan-based hydrogel scaffolds in tissue engineering and localised drug delivery. Pharmaceutics 2022; 14(9):1978.
47. Lee SC, Gillispie G, Prim P, Lee SJ. Physical and chemical factors influencing the printability of hydrogel-based extrusion bioinks. Chem Rev 2020; 120(19):10834–86.
48. Lei L, Huang D, Gao H, He B, Cao J, Peppas NA. Hydrogel-guided strategies to stimulate an effective immune response for vaccine-based cancer immunotherapy. Sci Adv 2022; 8(47):eadc8738.
49. Li J, Mooney DJ. Designing hydrogels for controlled drug delivery. Nat Rev Mater 2016; 1(12):1–7.
50. Li L, Zheng R, Sun R. Hierarchical self-assembly of short peptides: nanostructure formation, function tailoring, and applications. Macromol Biosci 2025; 2400523.
51. Lim HL, Hwang Y, Kar M, Varghese S. Smart hydrogels as functional biomimetic systems. Biomater Sci 2014; 2(5):603–18.
52. Lin M, Qi X. Advances and challenges of stimuli-responsive nucleic acids delivery system in gene therapy. Pharmaceutics 2023; 15(5):1450.
53. Liu X, Gao M, Chen J, Guo S, Zhu W, Bai L, et al. Recent advances in stimuli-responsive shape-morphing hydrogels. Adv Funct Mater 2022; 32(39):2203323.
54. Li Z, Zhu Y, Matson JB. pH-responsive self-assembling peptide-based biomaterials: designs and applications. ACS Appl Bio Mater 2022; 5(10):4635–51.
55. Lu P, Ruan D, Huang M, Tian M, Zhu K, Gan Z, et al. Harnessing the potential of hydrogels for advanced therapeutic applications: current achievements and future directions. Signal Transduct Target Ther 2024; 9(1):166.
56. Maghsoudnia N, Eftekhari RB, Sohi AN, Zamzami A, Dorkoosh FA. Application of nano-based systems for drug delivery and targeting: a review. J Nanoparticle Res 2020; 22:1–41.
57. Mandal D, Shirazi AN, Parang K. Self-assembly of peptides to nanostructures. Org Biomol Chem 2014; 12(22):3544–61.
58. Manzari MT, Shamay Y, Kiguchi H, Rosen N, Scaltriti M, Heller DA. Targeted drug delivery strategies for precision medicines. Nat Rev Mater 2021; 6(4):351–70.

59. Martin N, Youssef G. Dynamic properties of hydrogels and fiber-reinforced hydrogels. J Mech Behav Biomed Mater 2018; 85:194–200.
60. Mabey W, Mill T. Critical review of hydrolysis of organic compounds in water under environmental conditions. J Phys Chem Ref Data 1978; 7(2):383–415.
61. McCombs JR, Owen SC. Antibody drug conjugates: design and selection of linker, payload and conjugation chemistry. AAPS J 2015; 17:339–51.
62. Mehra NK, Palakurthi S. Interactions between carbon nanotubes and bioactives: a drug delivery perspective. Drug Discov Today 2016; 21(4):585–97.
63. Merino S, Martín C, Kostarelos K, Prato M, Vázquez E. Nanocomposite hydrogels: 3D polymer–nanoparticle synergies for on-demand drug delivery. ACS Nano 2015; 9(5):4686–97.
64. Mondal S, Das S, Nandi AK. A review on recent advances in polymer and peptide hydrogels. Soft Matter 2020; 16(6):1404–54.
65. Muro S. Challenges in design and characterization of ligand-targeted drug delivery systems. J Contr Release 2012; 164(2):125–37.
66. Panseri S, Russo A, Cunha C, Bondi A, Di Martino A, Patella S, et al. Osteochondral tissue engineering approaches for articular cartilage and subchondral bone regeneration. Knee Surg Sports Traumatol Arthrosc 2012; 20:1182–91.
67. Peppas NA, Sahlin JJ. Hydrogels as mucoadhesive and bioadhesive materials: a review. Biomaterials 1996; 17(16):1553–61.
68. Raza A, Rasheed T, Nabeel F, Hayat U, Bilal M, Iqbal HM. Endogenous and exogenous stimuli-responsive drug delivery systems for programmed site-specific release. Molecules 2019; 24(6):1117.
69. Raza F, Zafar H, Zhu Y, Ren Y, Ullah A, Khan AU, et al. A review on recent advances in stabilizing peptides/proteins upon fabrication in hydrogels from biodegradable polymers. Pharmaceutics 2018; 10(1):16.
70. Rizzo F, Kehr NS. Recent advances in injectable hydrogels for controlled and local drug delivery. Adv Healthc Mater 2021; 10(1):2001341.
71. Rodriguez LM, Hemar Y, Cornish J, Brimble MA. Structure–mechanical property correlations of hydrogel forming β-sheet peptides. Chem Soc Rev 2016; 45(17):4797–824.
72. Sedighi M, Shrestha N, Mahmoudi Z, Khademi Z, Ghasempour A, Dehghan H, et al. Multifunctional self-assembled peptide hydrogels for biomedical applications. Polymers 2023; 15(5):1160.
73. Shafiq M, Rafique M, Cui Y, Pan L, Do CW, Ho EA. An insight on ophthalmic drug delivery systems: focus on polymeric biomaterials-based carriers. J Contr Release 2023; 362:446–67.
74. Shah A, Malik MS, Khan GS, Nosheen E, Iftikhar FJ, Khan FA, et al. Stimuli-responsive peptide-based biomaterials as drug delivery systems. Chem Eng J 2018; 353:559–83.
75. Sharma P, Pal VK, Roy S. An overview of latest advances in exploring bioactive peptide hydrogels for neural tissue engineering. Biomater Sci 2021; 9(11):3911–38.
76. Singh J, Nayak P. pH-responsive polymers for drug delivery: trends and opportunities. J Polym Sci 2023; 61(22):2828–50.
77. Sobczak M. Enzyme-responsive hydrogels as potential drug delivery systems—state of knowledge and future prospects. Int J Mol Sci 2022; 23(8):4421.
78. Tayler IM, Stowers RS. Engineering hydrogels for personalized disease modeling and regenerative medicine. Acta Biomater 2021; 132:4–22.
79. Taylor MJ, Tomlins P, Sahota TS. Thermoresponsive gels. Gels 2017; 3(1):4.
80. van Gent ME, Ali M, Nibbering PH, Kłodzińska SN. Current advances in lipid and polymeric antimicrobial peptide delivery systems and coatings for the prevention and treatment of bacterial infections. Pharmaceutics 2021; 13(11):1840.
81. Varma MV, Kaushal AM, Garg A, Garg S. Factors affecting mechanism and kinetics of drug release from matrix-based oral controlled drug delivery systems. Am J Adv Drug Deliv 2004; 2:43–57.
82. Vermonden T, Censi R, Hennink WE. Hydrogels for protein delivery. Chem Rev 2012; 112(5):2853–88.
83. Wang M, Gao B, Wang X, Li W, Feng Y. Enzyme-responsive strategy as a prospective cue to construct intelligent biomaterials for disease diagnosis and therapy. Biomater Sci 2022; 10(8):1883–903.
84. Wang Y, Zhang W, Gong C, Liu B, Li Y, Wang L, et al. Recent advances in the fabrication, functionalization, and bioapplications of peptide hydrogels. Soft Matter 2020; 16(44):10029–45.
85. Wei G, Su Z, Reynolds NP, Arosio P, Hamley IW, Gazit E, et al. Self-assembling peptide and protein amyloids: from structure to tailored function in nanotechnology. Chem Soc Rev 2017; 46(15):4661–708.
86. Xu F, Dawson C, Lamb M, Mueller E, Stefanek E, Akbari M, et al. Hydrogels for tissue engineering: addressing key design needs toward clinical translation. Front Bioeng Biotechnol 2022; 10:849831.
87. Yang K, Han Q, Chen B, Zheng Y, Zhang K, Li Q, et al. Antimicrobial hydrogels: promising materials for medical application. Int J Nanomed 2018; 13:2217–63.
88. Yousefiasl S, Zare I, Ghovvati M, Ghomi M. Enzyme-responsive materials: properties, design, and applications. In Stimuli-responsive materials for biomedical applications, American Chemical Society, Washington, DC, pp 203–29, 2023.
89. Yuan C, Ji W, Xing R, Li J, Gazit E, Yan X. Hierarchically oriented organization in supramolecular peptide crystals. Nat Rev Chem 2019; 3(10):567–88.
90. Zeinali R, Del Valle LJ, Torras J, Puiggali J. Recent progress on biodegradable tissue engineering

scaffolds prepared by thermally-induced phase separation (Tips). Int J Mol Sci 2021; 22(7):3504.
91. Zhang C, Jiang G, Gao X. Matrix metalloproteinase-responsive drug delivery systems. Bioconjugate Chem 2023; 34(8):1349–65.
92. Zhang DW, Zhao X, Hou JL, Li ZT. Aromatic amide foldamers: structures, properties, and functions. Chem Rev 2012; 112(10):5271–316.
93. Zhang K, Feng Q, Fang Z, Gu L, Bian L. Structurally dynamic hydrogels for biomedical applications: pursuing a fine balance between macroscopic stability and microscopic dynamics. Chem Rev 2021; 121(18):11149–93.
94. Zhang Z, Ai S, Yang Z, Li X. Peptide-based supramolecular hydrogels for local drug delivery. Adv Drug Deliv Rev 2021; 174:482–503.
95. Zhu L, Qiu J, Sakai E, Ito K. Rapid recovery double cross-linking hydrogel with stable mechanical properties and high resilience triggered by visible light. ACS Appl Mater Interfaces 2017; 9(15):13593–601.