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Application of Hydrogel as Drug Carrier in Tumor Therapy

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Abstract: Hydrogels, as functional materials possessing both excellent biocompatibility and tunable physicochemical properties, have demonstrated significant application potential in cancer therapeutics. In recent years, with rapid advancements in biomedical engineering technologies, substantial progress has been achieved in hydrogel-based drug delivery systems. This review systematically summarizes the latest research advances in hydrogel carriers for cancer treatment, with particular emphasis on their application advantages in controlled drug release, intelligent tumor microenvironment regulation, and multimodal combination therapy. Studies have revealed that hydrogels, by virtue of their unique physicochemical characteristics including superior biocompatibility, precisely tunable degradation kinetics and drug release profiles, have emerged as a highly promising drug carrier platform in oncology. Notably, stimuli-responsive hydrogels can react to external triggers such as temperature, pH or light irradiation, enabling intelligent drug release and thereby significantly enhancing therapeutic efficacy. With deepening understanding of structure-property relationships and continuous innovation in fabrication technologies, the application prospects of hydrogels in precision cancer therapy are expected to expand further.

Keywords: Hydrogel; Drug Delivery; Tumor Treatment; Stimulus Response; Tumor Microenvironment; Local Treatment.

1. Introduction

(1) Research background

Cancer represents a major threat to human health and has become the second leading cause of death worldwide[1]. With the evolution of cancer treatment from conventional chemotherapy toward precision and localized therapies, biomaterial-based drug delivery systems have attracted widespread attention due to their unique properties such as sustained release, targeting capability, and biocompatibility[2]. Among various drug delivery platforms, hydrogels stand out because of their distinctive physicochemical characteristics. Hydrogels are three-dimensional network structures formed through physical or chemical cross-linking of hydrophilic polymers, capable of absorbing and retaining significant amounts of water, thereby mimicking the soft and moist environment of human tissues. This property endows them with excellent biocompatibility[3]. More importantly, their network structure allows efficient encapsulation of diverse therapeutic agents—ranging from small-molecule chemotherapeutic drugs to macromolecules such as proteins, nucleic acids, and even cells—and enables precise control over drug release kinetics by adjusting parameters such as cross-linking density and pore size. The significance of hydrogels in cancer therapy lies not only in their ability to achieve targeted and controlled drug delivery but also in their potential to overcome limitations associated with conventional administration routes. For example, traditional chemotherapeutic agents often cause toxic side effects in healthy tissues due to lack of specificity, whereas hydrogel-based carriers can be administered via local injection or implantation to deliver drugs directly to the tumor site, thereby enhancing therapeutic efficacy while minimizing adverse reactions[4-6].

(2) Definition and characteristics of hydrogel

Hydrogels are three-dimensional network structures formed by hydrophilic polymer chains through physical or chemical crosslinking, characterized by their ability to absorb water and swell without dissolving in water. The fundamental principles governing hydrogels involve crosslinking density, network architecture, swelling behavior, and responsiveness to external stimuli[7-10]. Various preparation methods are employed, including physical crosslinking (such as freeze-thaw cycles and ionic crosslinking) and chemical crosslinking (such as free-radical polymerization and click chemistry).

Within the field of biomedical engineering, hydrogels are positioned as particularly promising drug delivery vehicles[11]. The growing emphasis on personalized and precision medicine has created a pressing need for efficient and safe drug delivery systems. Owing to their exceptional properties—including high water content, biocompatibility, tunable physicochemical characteristics, the capacity to encapsulate diverse therapeutic agents (such as chemotherapeutic drugs, proteins, nucleic acids, and cells), and controllable release kinetics—hydrogels offer a platform with core advantages, providing novel therapeutic strategies and technical avenues[8, 12, 13].

This article is dedicated to a comprehensive and systematic examination of hydrogels employed as drug carriers for cancer therapy, with an in-depth exploration spanning multiple facets such as material design, response mechanisms, application contexts, and translational potential. The discussion will commence with a classification of hydrogels according to material source (natural, synthetic, or hybrid) and crosslinking modality (physical, chemical, or dynamic bonding), detailing their fabrication strategies and functionalization techniques to clarify the impact of structural variations on drug loading and release profiles. Following this, emphasis will be placed on the intelligent molecular designs conferring responsiveness to the tumor microenvironment

(e.g., pH, enzymes, redox conditions) and external stimuli (e.g., light, temperature, magnetic fields), elucidating the mechanisms through which targeted and controlled drug release is achieved to improve therapeutic precision[14, 15]. The review will conclude with a critical analysis of the prevailing challenges in clinical translation and a prospective outlook on future developments.

2. Classification and Construction of Hydrogels

(1) Classification by Source

Notwithstanding their water solubility, natural polymeric hydrogels like gelatin, which is a natural polyampholyte, are characterized by the drawback of inadequate mucoadhesion[16]. Research by Elvira O. Shatabayeva[17] and colleagues involved the chemical modification of gelatin via three distinct unsaturated anhydrides to augment its mucoadhesive performance. A systematic characterization of the derivatives was undertaken, alongside evaluations of their properties and toxicological profiling. The efficacy of this approach was conclusively verified through an ex vivo mucosal model, which attested to the enhanced retention of the modified gelatin formulation on mucosal surfaces. An integrated strategy combining bioinformatic analysis with experimental verification was employed by Fenny Crista A. Panjaitan et al[18]. Their research revealed that low-molecular-weight peptide fractions (PP1, <1 kDa) obtained from the enzymatic digestion of porcine gelatin with papain are potent inhibitors of both angiotensin-converting enzyme (ACE) and acetylcholinesterase. These peptides were also shown to significantly mitigate cognitive deficits and boost antioxidant activity in a mouse model of amnesia induced by D-galactose, pointing to their promising potential as functional ingredients with antihypertensive and neuroprotective properties. Distinct from other polysaccharides like gelatin or agar, alginate exhibits the unique property of forming gels independently of temperature variations. Huang Zhuying et al. engineered a thermoresponsive alginate-collagen hydrogel system (pTRG), incorporating indocyanine green (ICG) and poly I:C, founded on a combined photothermal and immunotherapy approach. The designed system aims to achieve tumor ablation through local photothermal therapy and concurrently provoke antigen-specific T-cell immune responses, with the ultimate goal of suppressing tumor recurrence and metastasis. Owing to their origin in living organisms, both chitosan and hyaluronic acid are characterized by a suite of advantageous properties, including excellent biocompatibility, biodegradability, minimal immunogenicity, and intrinsic bioactivity—such as the targeting of hyaluronic acid by CD44 receptors[19-21]. Nevertheless, these materials are often limited by inherently poor mechanical strength and possible variability between production batches. Notwithstanding these drawbacks, their application in cancer therapeutics remains extensive[22, 23].Ziba Najafzadeh and colleagues fabricated hydrogels comprising oxidized alginate (AD), polyethylene glycol (PEG), and either carboxymethyl chitosan (CMC) or gelatin (GEL). A comparative analysis revealed that the AD/PEG-CMC hydrogel possessed a superior compressive modulus, viscosity, and injection time relative to the AD/PEG-GEL formulation, which, in contrast, showed a higher crosslinking density. The rheological profile of the AD/PEG-CMC hydrogel renders it more appropriate for use as an injectable vehicle. Based on an integrated assessment of its rheology, degradation profile, and mechanical compression properties, the AD/PEG-CMC hydrogel emerges as a suitable candidate for injectable, self-crosslinking applications within the field of tissue engineering.

The molecular architecture of synthetic polymer hydrogels—including polyethylene glycol (PEG), poly(acrylic acid) (PAA), and poly(vinyl alcohol) (PVA)—can be precisely designed and controlled in terms of molecular weight and crosslinking density[24-28], conferring enhanced and adjustable mechanical performance. A significant consideration, however, is the potential for their degradation by-products to elicit biocompatibility issues.

In an endeavor to integrate the strengths of both categories, hybrid hydrogels have been developed. These systems facilitate a synergistic integration of natural and synthetic components, thereby achieving complementary functional properties[29, 30].

(2) Classification by crosslinking method

An analysis based on crosslinking mechanisms reveals distinct characteristics. Chemically crosslinked hydrogels, stabilized by covalent bonds, possess structural stability, thereby enabling more prolonged drug release profiles. A significant drawback, however, is the potential cytotoxicity of the crosslinking agents[31, 32]. Physically crosslinked hydrogels, which rely on non-covalent interactions such as hydrogen bonding, hydrophobic forces, and host-guest complexation, offer superior biocompatibility and reversibility. Their frequent thixotropic or thermo-responsive nature endows them with injectability: the sol state can be administered by injection, followed by rapid gelation in situ under conditions like body temperature, rendering them ideal for minimally invasive applications[33, 34].The incorporation of dynamic covalent chemistry (e.g., Schiff base, boronate ester bonds) into hydrogel networks integrates covalent stability with bond reversibility[35-39]. This design confers inherent self-healing properties, enabling the hydrogels to effectively accommodate the intricate and dynamic mechanical stresses encountered within the body[40, 41].

3. Intelligent Response Mechanism of Hydrogel

"Intelligent" stimulus-responsiveness constitutes the defining feature of hydrogels functioning as sophisticated drug delivery vehicles. The underlying design philosophy is to ensure that the therapeutic agent is released in a spatiotemporally controlled manner upon exposure to specific stimul[42, 43].

(1) Endogenous stimulus response

The capacity to respond to endogenous stimuli is key to targeting the tumor microenvironment (TME). Defined as the intricate ecosystem encompassing tumor cells[44], the TME dynamically regulates processes such as tumor proliferation, metastasis, immune evasion, and treatment resistance, thereby emerging as a vital therapeutic focus in oncology[45-47].pH-responsive hydrogels (e.g., those incorporating carboxyl groups or hydrazone bonds) exploit the mildly acidic nature of the tumor microenvironment (TME, pH ~6.5-7.0) compared to normal tissues (pH ~7.4). They achieve site-specific drug release by undergoing swelling or degradation at the tumor site. Wahab Gallehdari et al[48]. constructed a

dual-stimuli-responsive nano-drug delivery system with a core-shell architecture, featuring a pH-responsive poly(acrylic acid) (PAA) core and a thermo-sensitive poly(N-isopropylacrylamide) (PNIPAM) shell. This system achieved high-efficiency loading of doxorubicin (with an encapsulation efficiency of 92.7% and a drug loading capacity of 18.5%) and demonstrated significantly promoted drug release under acidic pH conditions. In vitro assays revealed that the nanoparticles exhibited enhanced cytotoxicity toward MCF-7 breast cancer cells, highlighting their potential as a smart delivery vehicle for anticancer therapy. Enzyme-responsive hydrogels are engineered with peptide linkers that are susceptible to cleavage by enzymes overexpressed in the tumor microenvironment (TME), such as matrix metalloproteinases (MMPs), cathepsins, and hydrolases[49]. This design facilitates enzyme-controlled drug release. Conversely, redox-responsive hydrogels, typically incorporating disulfide bonds, exploit the high intracellular concentration of glutathione (GSH) in tumor cells, leading to rapid structural disintegration and intracellular drug release, thereby achieving precise intracellular targeting.

(2) Response to exogenous stimuli

Responsiveness to exogenous stimuli enables remote spatiotemporal control by clinicians. Thermo-responsive hydrogels, such as those based on poly(N-isopropylacrylamide) (PNIPAM), exist as flowable sols at low temperatures[19, 50] and undergo a sol-gel transition upon injection into the body, triggered by physiological temperature. This transition facilitates in situ deposition, making them ideally suited for post-operative tumor bed filling[51].For spatiotemporally precise drug delivery, light-responsive hydrogels offer exceptional external control. Upon NIR irradiation, these systems—often loaded with photothermal agents or functionalized with photolabile linkers—produce heat or undergo bond scission, facilitating on-demand drug release with high spatial accuracy[52-54].Magnetically responsive hydrogels, by incorporating magnetic nanoparticles (e.g., Fe_3O_4)[55], generate localized heat under an alternating magnetic field[56]. This enables not only controlled drug release but also facilitates magnetic hyperthermia therapy (MHT)[57, 58], thereby achieving synergistic tumor cell killing[59-61].

4. Application Strategy of Hydrogel in Tumor Treatment

Owing to their capacity for high-dose drug delivery at the tumor site, hydrogels have emerged as a promising platform[62] capable of significantly overcoming drug resistance[63, 64] and reducing systemic adverse effects. Among their diverse clinical application formats, their utility as a local delivery platform is particularly attractive[65]. Via in situ injection and gelation[66], hydrogels can perfectly conform to the resection cavity post-tumorectomy, functioning as a sustained-release drug depot that eradicates residual foci and markedly reduces postoperative recurrence rates (Joshua Li).Cai Chengzhen et al[67]. developed an injectable colloidal ethanol solution based on magnetic gelatin microspheres (MGMs) for the chemoablation therapy of tumors. Fabricated via electrostatic interactions, this system undergoes solvent exchange upon injection to form an in situ gel-based drug depot. It synergistically combines ethanol ablation with the sustained release of doxorubicin, significantly enhancing antitumor efficacy by inhibiting cancer cell recovery, thereby demonstrating considerable potential for clinical translation. Sophie M. Coulter[68] and her team developed an injectable drug delivery platform based on a peptide-peptide hybrid. This system can be triggered by endogenous phosphatases to form an in situ hydrogel following subcutaneous administration, enabling controlled drug release. It offers a novel strategy for the long-term systemic delivery of low-molecular-weight drugs. For inoperable solid tumors, direct intratumoral injection of drug-loaded hydrogels can significantly enhance local drug concentration while minimizing systemic exposure and associated toxicity[69, 70].

In terms of drug loading, hydrogels have significantly mitigated the limitations associated with conventional chemotherapeutic agents (e.g., Doxorubicin, Paclitaxel)[71, 72]. Their hydrophilic networks[73] enhance the solubility of hydrophobic drugs[74, 75], while their sustained-release properties prevent the initial "burst release" effect[76, 77], thereby maintaining effective therapeutic concentrations[78]. Consequently, this approach has demonstrated superior antitumor efficacy and reduced systemic toxicity compared to the free drug administration across various animal models. Alpita Roy[79] and colleagues developed a pH-responsive β-CD-Meth-cl-(PHPMA-co-PAAc) copolymer hydrogel. This gel exhibits good biocompatibility, antioxidant activity, and degradability, serving as a controlled-release matrix capable of simultaneously loading and releasing the hydrophobic drug Ibuprofen and the hydrophilic drug Tetracycline Hydrochloride. In vitro and in vivo studies demonstrated its reversible swelling behavior, excellent viscoelasticity, and dual-drug controlled release capability, thereby highlighting its potential for combination drug delivery. Fatemeh Orujalian and colleagues constructed a thermo- and pH-dual-responsive smart drug delivery system. By incorporating the thermosensitive PNIPAM-DOX hydrogel into a pH-responsive PEG-PTMBPEC polymer matrix, the system achieved accelerated release of Doxorubicin (DOX) within the acidic tumor microenvironment while moderating drug release at body temperature. This system significantly inhibited tumor growth, extended the drug's half-life, improved its pharmacokinetic profile, and did not induce significant systemic toxicity, thereby demonstrating considerable potential for anticancer therapy. Wang Tianran [80] and colleagues developed an injectable nanocomposite hydrogel with robust tissue adhesiveness for the local sustained delivery of Paclitaxel (PTX). This hydrogel was formed by crosslinking drug-loaded albumin nanoparticles (PTX@BN) with OPA-terminated 4-arm-PEG, enabling firm adhesion to the tumor site and sustained drug release for over 30 days. In both C26 and 4T1 murine tumor models, it significantly inhibited tumor growth, prolonged survival, and exhibited low systemic toxicity, demonstrating promising potential for localized chemotherapy.

Moving beyond chemotherapy, hydrogels are assuming a revolutionary role in cancer immunotherapy[81, 82]. They can function as localized "immunological microfactories" for the delivery of immunoadjuvants (e.g., CpG-ODN), cytokines (e.g., IL-2, IL-12), or immune checkpoint inhibitors (e.g., anti-PD-1 antibodies). This localized delivery strategy enables the sustained activation and recruitment of immune cells, such as cytotoxic T cells[83], while effectively reversing the immunosuppressive tumor microenvironment. By converting immunologically "cold" tumors into "hot" ones, this approach not only treats the primary tumor but also elicits

a robust systemic antitumor immune response (abscopal effect), thereby preventing metastasis.

Furthermore, hydrogels serve as ideal vectors for gene therapy, protecting nucleic acids such as siRNA, miRNA, or the CRISPR-Cas9 system from degradation and ensuring their efficient delivery to target cells for modulating the expression of oncogenes. More importantly, their versatile loading capacity establishes hydrogels as a perfect platform for combination therapy, enabling the facile integration of multiple treatment modalities—such as chemo-immunotherapy[84-86] and photothermal-chemo-immunotherapy—to achieve synergistic antitumor effects[87-90].Wang Song[91] and colleagues developed a near-infrared (NIR) light-responsive MXene-agarose hydrogel platform for protein delivery. This system enables the on-demand release of proteins to precisely manipulate cellular behaviors, demonstrating significant potential in both wound healing and antitumor therapy. The platform achieves a synergistic therapeutic outcome, producing an effect greater than the sum of its individual parts. Zhang Hongxia [92] and colleagues developed a dual-functional active supramolecular hydrogel, Gel KFM, which is formed via the self-assembly of a hexapeptide KFM capable of downregulating PD-L1. This system not only degrades the PD-L1 protein through the ubiquitination pathway but also serves as a local delivery platform for chemotherapeutic agents. In vivo, Gel KFM significantly inhibited tumor growth and enhanced T-cell infiltration, offering a novel "carrier-free" combination strategy for immunotherapy.

5. Challenges and Future Prospects

Despite promising achievements in preclinical research, the clinical translation of hydrogels faces multiple formidable challenges. Long-term biosafety remains a primary concern, encompassing the potential toxicity of degradation products, inherent immunogenicity, and the risk of chronic inflammatory responses. Large-scale manufacturing involves complex synthesis processes, stringent sterility assurance, and rigorous quality control—such as ensuring batch-to-batch consistency and uniform drug loading—which significantly elevate production costs and technical barriers. Furthermore, when moving from controlled laboratory conditions to the complex physiological environment in humans, the drug release profile and degradation kinetics of hydrogels may undergo unpredictable alterations. Currently, there is a lack of large-scale clinical data to adequately validate their efficacy-safety relationship.

Looking forward, hydrogel research is poised to advance toward greater intelligence, personalization, and the integration of diagnosis and therapy. Novel smart materials—such as multi-stimuli-responsive, adaptive, and self-feedback hydrogels—will represent key research frontiers. Interdisciplinary integration is imperative; the use of artificial intelligence (AI) to assist in designing new hydrogel materials, coupled with more predictive preclinical models like organoids and organs-on-chips, will significantly accelerate the development pipeline. Theranostic hydrogels that combine diagnostic imaging (e.g., MRI, fluorescence, photoacoustic imaging) with therapeutic functions will enable real-time monitoring and efficacy assessment during treatment. Ultimately, hydrogels are expected to evolve from simple drug carriers into multifunctional platforms capable of modulating the local microenvironment, thereby pioneering a new paradigm for precision cancer therapy.

6. Conclusion

In summary, hydrogels represent a highly promising drug delivery platform whose tailorable physicochemical properties, exceptional loading capacity, and versatile smart responsiveness offer robust solutions to overcome the limitations of conventional cancer therapies. Their applications in localized chemotherapy, immunotherapy, and combination strategies demonstrate significant potential for enhancing efficacy while reducing systemic toxicity. Although challenges remain in scalability, long-term biosafety, and clinical translation, continued progress in material design and manufacturing processes is expected to yield more stable, safe, and easily producible hydrogel systems. Concurrently, strengthening preclinical and clinical validation—supported by modern imaging techniques such as fluorescence imaging and MRI for real-time monitoring of hydrogel distribution and degradation—will provide critical insights for optimizing treatment protocols. The exploration of novel functional hydrogels, including multi-stimuli-responsive composites, along with combination approaches involving photodynamic or immunotherapeutic modalities, is poised to open new avenues in cancer treatment. A key ongoing challenge lies in balancing stability, mechanical strength, targeted delivery, and biodegradability. With the deepening integration of materials science, nanotechnology, biomedicine, and artificial intelligence, hydrogel technology is anticipated to achieve continued breakthroughs, ultimately emerging as a transformative force in clinical cancer care.

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