REVIEW ARTICLE

Stimuli-Responsive Hydrogels for Controlled Drug Delivery in Oncology: A Comprehensive Review

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Abstract

Advancements in cancer treatment have been significant, but challenges remain with traditional methods such as chemotherapy and radiation, which often suffer from poor specificity, toxicity, and drug resistance. This highlights the need for more targeted drug delivery systems. On-demand, stimuli-responsive hydrogels offer a promising solution, capable of releasing drugs in response to biological signals from the tumor microenvironment. However, clinical challenges such as biocompatibility, scalability, and regulatory constraints still hinder their widespread adoption. This review explores hydrogels that react to pH, temperature, and enzyme activity–key traits of cancerous tissues. These "smart" materials improve drug bioavailability, reduce off-target effects, and enhance patient responses. We also discuss advanced hydrogels with multiple responsive elements, helping counteract drug resistance. While these hydrogels are transforming cancer therapy, challenges such as biocompatibility, scalability, and regulatory hurdles persist. Future directions may leverage emerging technologies such as artificial intelligence to optimize hydrogel design, paving the way for safer, more effective, and personalized treatments.

Key words: Antineoplastic agents, delayed-action preparations, drug delivery systems, hydrogels, neoplasms, polymers

INTRODUCTION

Cancer remains one of the leading global health burdens, being responsible for nearly 10 million deaths in 2020, or approximately one in every six deaths worldwide. It is anticipated that this number will greatly increase to about 28.4 million new cancer cases by 2040.[1] Although conventional therapies such as surgery, chemotherapy, radiotherapy, and immunotherapy have considerably advanced cancer treatment, they are often hindered by critical limitations. These include multidrug resistance (MDR), frequent tumor recurrence, and severe adverse drug reactions, all of which undermine therapeutic efficacy and patient outcomes.[2,3] Chemotherapy, for example, lacks specificity and often damages both cancerous and healthy cells, leading to side effects such as immunosuppression, nausea, organ damage, and hair loss. Immunotherapy, while offering targeted action, can result in systemic inflammation and autoimmune responses that require close management.[4] In addition to these clinical drawbacks, conventional cancer therapies impose a substantial economic burden due to prolonged treatment durations, repeated hospitalizations, and the need for managing severe side effects, making access and affordability significant concerns globally.

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One of the key obstacles to improving treatment response is the complexity of the tumor microenvironment (TME). The TME is a dynamic and heterogeneous network, composed of cancer cells, stromal components, immune cells, extracellular matrix (ECM), and vasculature; it consists of unique property such as density or acidic pH, hypoxia, high interstitial fluid pressure, and elevated levels of cytokines and enzymes. Collectively these features not only aid tumor growth and metastasis but also impede the effect of therapies, often protecting cancer cells and facilitating drug resistance.[5] Consequently, there is a pressing demand for novel therapeutic tactics to develop therapies that can surmount these natural biological hurdles while mitigating the incidence of systemic toxicity.

An encouraging methodology exists within the construct of developing drugs through targeted drug delivery systems that can respond to the distinct characteristics of the TME. Conventional methods of drug delivery (tablets, capsules, injections, etc.) have considerable shortcomings such as reduced bioavailability, limited tumor penetration, and erratic drug concentration, all of which contributes to diminished effectiveness and compliance.[6] In contrast, hydrogel-based delivery platforms have shown great potential in addressing these challenges by enabling sustained release, site-specific targeting, and stimulus-responsive behavior. A comparative overview of conventional therapies and hydrogel systems is presented in Table 1, outlining key distinctions in therapeutic efficiency, toxicity, and control over drug release.

Hydrogels, which were initially introduced for ocular applications in the early 1960s, have evolved into sophisticated smart materials capable of responding to physiological cues such as pH changes, enzymatic activity, and temperature fluctuations.[7,8] These stimuli-responsive hydrogels can be designed to release therapeutic agents specifically at the tumor site, thereby minimizing exposure to healthy tissues and maximizing therapeutic efficacy. Their adaptability makes them ideal candidates for cancer therapy, especially considering the hostile and variable conditions of the TME. Recent advancements in hydrogel technology have led to the creation of dual- and multi-stimuli-responsive systems that are better suited for complex clinical scenarios. For example, thermo/pH-sensitive hydrogels are being developed for oral drug delivery, taking advantage of the changing conditions along the gastrointestinal tract.[9] Additional innovations encompass hydrogel platforms with multifunctionality that can unilaterally deliver multiple therapeutics, integrate biosensing capability for real-time monitoring of drug actions, and surface modifications that provide some functionality for cellular targeting.[2] These features, while supplementing hydrogel use in therapeutic delivery, expand opportunities in regenerative medicine, tissue engineering, and biosensing. Their high water content and adjustable mechanical properties can closely mimic the natural microenvironment of tissues and promote cell growth while providing a biocompatible substance.[10] Their versatility in terms of administration, ranging from injectable formulations to topical and oral delivery – further broadens their clinical potential.

Table 1: Comparative summary of traditional cancer treatments and hydrogel-based drug delivery systems with respect to efficacy, safety, targeting, and responsiveness to TME

Parameter	Traditional cancer treatments	Hydrogel-based drug delivery systems
Drug release profile	Burst release; less controlled	Sustained, controlled, and stimuli-responsive release
Targeting ability	Non-specific; affects both cancerous and healthy cells	Specific targeting through pH, temperature, or enzyme responsiveness
Systemic toxicity	High; causes adverse effects throughout the body	Reduced; localized delivery minimizes side effects
Tumor penetration	Limited; especially for dense tumor tissues	Can be engineered for enhanced tumor penetration
Patient compliance	Often requires frequent dosing; severe side effects reduce adherence	Potential for reduced dosing frequency and better tolerability
Bioavailability	Often low due to degradation or metabolism before reaching target	High; protects the drug and ensures release at the site of action
Drug resistance risk	High due to repeated systemic exposure	Lower; localized delivery can overcome MDR mechanisms
Route of administration	Mostly intravenous or oral	Injectable, implantable, oral, or topical depending on formulation
Responsiveness to TME	Absent; no reaction to TME	Designed to respond to tumor-specific stimuli (e.g., acidic pH, enzymes, and heat)
Side effects	Common and often severe (e.g., nausea, and immune suppression)	Fewer and milder due to localized and controlled drug action
Clinical status	Well-established and widely used	Under active research, some approved systems but many are in preclinical or clinical stages

MDR: Multidrug resistance, TME: Tumor microenvironment

Stimulus-responsive nanomedicines, especially those based on hydrogels, constitute a revolutionary advancement in targeted cancer treatment. Stimulus-responsive nanomedicines act through the selective delivery of drugs on exposure to biological signals present in the TME. Stimulus-responsive nanomedicines provide a way to counter MDR, improve drug bioavailability, and limit off-target toxicity.[11] Research toward the design and operation of these materials is still advancing rapidly, particularly with respect to developing responsive hydrogels with multiple stimuli activated simultaneously, increasing drug loading efficacy, and providing long-term biocompatibility and stability. As the field continues to develop, the application of hydrogels in personalized cancer treatments is becoming increasingly achievable. The current research is focused on addressing some of the lingering challenges, including scalability, clinical implementation, and regulatory barriers. Ultimately, the goal is to develop a hydrogel-based system that can be implemented not only as a better drug delivery carrier but also as an active therapeutic platform that can respond to specific patient and tumor requirements. This description of research into the rationale for design, operation of mechanisms, and applications of stimuli-responsive, biocompatible hydrogels details the intended evolution of hydrogels to transform cancer therapy and provide long-term opportunities in the field of therapeutics for controlled drug delivery.

FUNDAMENTALS OF HYDROGELS AND STIMULI-RESPONSIVENESS

Definition and classification of hydrogels

Hydrogels form three-dimensional (3D) hydrophilic polymer chains that soak and maintain vast quantities of water as well as biological fluids without degrading up to 90% of their initial weight. The high-water absorption ability in hydrogels results from the hydrophilic functional groups (hydroxyl, carboxyl, and amine groups) which exist along the polymer chain backbone. The network receives its mechanical strength through physical (non-covalent) or chemical (covalent) crosslinking of its hydrophilic polymer chains.[9,12] The development of hydrogel suitable for medical applications started in the 1960s with Wichterle and Lím creating poly (2-hydroxyethyl methacrylate) for biomedical use. Today, hydrogels are broadly categorized based on their source, method of crosslinking, and responsiveness to environmental stimuli as shown in Figure 1.[13]

By origin

Natural hydrogels are derived from biopolymers such as chitosan, alginate, gelatin, and hyaluronic acid. They are highly biocompatible and biodegradable, making them well-suited for biomedical applications, though often limited in mechanical stability.[14] Synthetic hydrogels, such as those made from poly(ethylene glycol), poly(N-isopropylacrylamide)

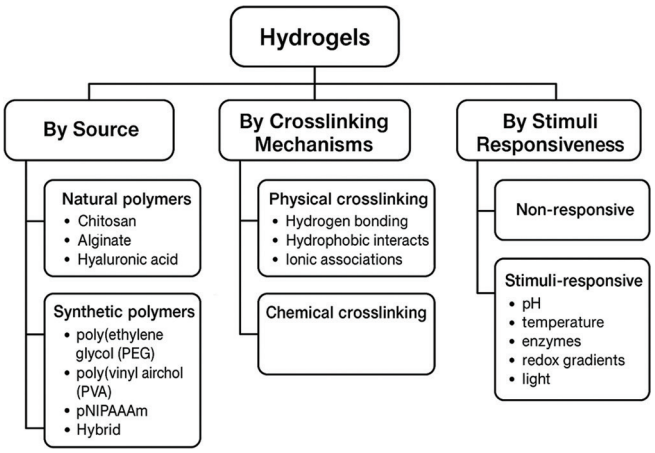

Figure 1: Flowchart of hydrogel classification based on structure and responsiveness

(PNIPAm), and poly(acrylic acid) (PAA), offer greater control over physical properties, degradation rates, and responsiveness, though their biocompatibility may be comparatively lower.[15] Hybrid hydrogels, such as gelatin methacryloyl, combine natural and synthetic features to balance bio-functionality and structural integrity.[16]

By crosslinking mechanism

Physical hydrogels rely on reversible non-covalent interactions such as hydrogen bonding, ionic interactions, and hydrophobic associations. These are often dynamic and suitable for transient applications.[17] Chemical hydrogels form stable covalent bonds, often initiated by light, heat, or chemical agents. They offer long-term durability but may require toxic reagents during synthesis.[18]

By stimuli-responsiveness

Hydrogels can be classified as either passive or stimuli-responsive. Responsive systems are engineered to react to specific environmental signals such as changes in pH, temperature, enzymatic activity, redox conditions, or light exposure. These functionalities are particularly valuable in targeted drug delivery and cancer therapy, where the pathological microenvironment differs significantly from healthy tissue.[19]

Key properties for drug delivery

Several physicochemical and biological properties dictate the performance of hydrogels in controlled drug delivery, particularly in oncology in Table 2.

Mechanisms of stimuli-responsiveness

Stimuli-responsive or "smart" hydrogels undergo physicochemical changes in response to specific environmental cues. These stimuli include variations in pH, temperature,

Table 2: Properties of hydrogels relevant to drug delivery in oncology

Property	Description	Impact on drug delivery	Example
Biocompatibility	Compatibility with cells and tissues	Reduces immune response and inflammation	PEG, Alginate, Hyaluronic Acid
Swelling behavior	Ability to absorb water and expand	Regulates drug diffusion and release profiles	pH-sensitive hydrogels in tumor tissues
Degradability	Breakdown via hydrolysis or enzymatic activity	Allows for programmed release and biodegradation	MMP-sensitive PEG-peptide hydrogels
Mechanical strength	Resistance to deformation	Affects injectability and *in vivo* stability	Crosslinked GelMA, PVA
Porosity	Internal pore structure	Controls molecule diffusion and cell infiltration	Macroporous chitosan hydrogels
Stimuli-responsiveness	Reaction to external/internal stimuli	Enables targeted and site-specific release	Thermo-responsive pNIPAAm, pH-sensitive PAA
Cost-effectiveness	Affordability and ease of large-scale production	Influences scalability and clinical translation potential	Natural polymer-based hydrogels (e.g., alginate and gelatin)

PEG: Poly (ethylene glycol), PAA: Poly (acrylic acid), GelMA: Gelatin methacryloyl

ionic strength, light exposure, electric and magnetic fields, or the presence of specific biomolecules.[20] Mechanisms of responsiveness are typically rooted in the chemistry of the polymer network. For instance:

pH-responsive hydrogels contain ionizable groups such as carboxyl or amine moieties. These undergo protonation or deprotonation, altering hydrogel swelling and solubility.[21] Temperature-sensitive hydrogels exhibit critical solution temperatures lower critical solution temperature/ upper critical solution temperature (LCST/UCST). At these thresholds, polymers transition between swollen and collapsed states. PNIPAm is a classic LCST-responsive polymer.[22] Recent studies also highlight thermo-responsive behavior in copolymers such as poly(N-vinylcaprolactam) (PVCL), which demonstrate improved biocompatibility and tunable LCSTs suitable for drug delivery applications. Light-responsive hydrogels incorporate photochromic agents that change structure under specific wavelengths, affecting crosslinking density and physical properties.[23] Enzyme-sensitive hydrogels are engineered with cleavable peptide sequences. These degrade in the presence of disease-specific enzymes like matrix metalloproteinases (MMPs) commonly overexpressed in cancer and inflamed tissues.[24]

DRUG LOADING AND RELEASE MECHANISMS

Hydrogels accommodate therapeutic agents through: Passive diffusion, where small molecules permeate the pre-formed network post-gelation. Encapsulation during the gelation process allows uniform distribution of drugs, such as the distribution of doxorubicin in the matrix. Reversible bonding, employing covalent or ionic interactions for sensitive biologics such as proteins or RNA, and ensuring stability

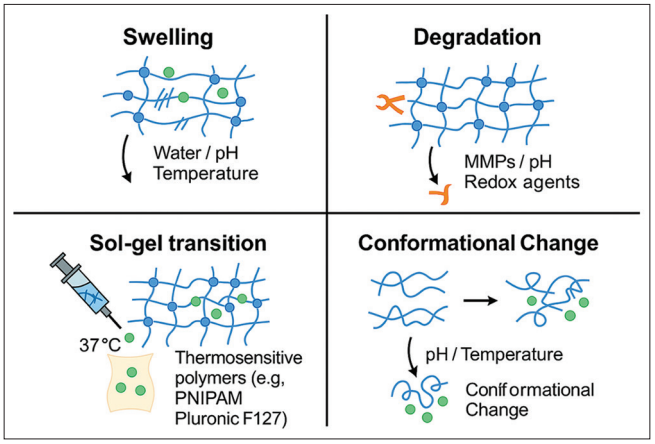

Figure 2: Mechanisms of stimuli-responsive hydrogels

until triggered release.[25] Drug release mechanisms include diffusion-controlled release**,** governed by the mesh size of the network (typically 5–100 nm). For example, 5-fluorouracil diffuses through alginate hydrogels through Fickian mechanisms.[26] Swelling-controlled release, responsive to environmental stimuli such as pH or temperature shifts. PAA hydrogels release paclitaxel in acidic TMEs. Stimuli induced the degradation process, whereas the breakdown of the hydrogel triggers the release of the drug from the matrix. PEG matrices degrade in response to tumor-specific MMP-2 enzymes, offering site-specific delivery, as shown in Figure 2.[27] These controlled release strategies enhance therapeutic efficacy, permit precise dosing, and reduce systemic toxicity.

ADVANTAGES OF HYDROGELS IN ONCOLOGY

Hydrogels provide multiple benefits in cancer therapy:

Localized delivery

Injectable hydrogels (e.g., poly(epsilon-caprolactone) [PELG]-PEG-PELG) can form *in situ* at tumor sites, maintaining cytokine release (e.g., IL-2) over extended periods. Prolonged drug release: Chitosan hydrogels, for instance, extend cisplatin release from hours to over 2 weeks.[28] Minimized systemic toxicity: Drug encapsulation limits off-target exposure, as seen with doxorubicin-loaded silk fibroin hydrogels reducing cardiac side effects.[29] Protection of labile drugs: Nucleic acids and proteins are shielded from enzymatic degradation within hydrogel matrices.[30] Multimodal therapies: Dual-stimuli-responsive hydrogels enable co-delivery of agents such as doxorubicin and anti-PD-1 antibodies for synergistic chemo-immunotherapy.[31]

PH-RESPONSIVE HYDROGELS FOR CANCER THERAPY

The TME exhibits an acidic pH compared to normal physiological pH, which results from abnormal metabolic processes, insufficient blood supply, and accumulation of metabolites, such as lactic acid and carbon dioxide. This acidity leads to extracellular pH values of approximately 6.5–7.0, which is a hallmark of tumors when combined with a normal tissue pH of around 7.4. Acidic conditions enhance in intracellular compartments such as endosomes with a pH range of 5.0–6.0 and lysosomes with a pH range of 4.5–5.0 which serve as destinations for macromolecules and nanoparticles during internalization.[32]

The detection of distinct pH levels between tumors and normal tissues creates an important opportunity for using pH-based delivery systems. Hydrogel structures that alter their composition through swelling or degradation or drug release when exposed to acidic conditions can utilize pH variations to direct therapeutic treatment of tumors while protecting surrounding healthy tissue. Hydrogels with pH-responsive features that recognize TME extracellular acidity in addition to endosomal and lysosomal pH environments have demonstrated dual ability to enhance tumor-specific drug delivery and improve resistance to drugs and improve therapeutic drug uptake by cancer cells.[33] For example, hydrogels that swell and release drug on exposure to the acidic extracellular pH of the TME can be given either systemically or delivered locally. The hydrogels will remain stable until reaching the acidic pH of the tumor, then will dissolve and release drug, improving the drug concentration at the tumor site and enhancing the therapeutic efficacy. Table 3 provides an overview of the pH conditions in tumor versus normal microenvironments and highlights the mechanisms, functional groups, and polymers involved in pH-responsive drug delivery systems. Similarly, hydrogels that respond to acidic pH within endosomes and lysosomes can be used to help deliver drugs intracellularly, thereby improving

Table 3: pH conditions in tumor versus normal microenvironments

Aspect	Description	Examples
Tumor microenvironment (TME) pH characteristics	Acidic extracellular pH (6.5–7.0); intracellular compartments like endosomes (pH 5.0–6.0) and lysosomes (pH 4.5–5.0)	Normal tissue: pH~7.4
Mechanism of action	Hydrogels respond to acidic pH by swelling, degrading, or releasing drugs	Enables targeted delivery
Functional groups	Ionizable groups like - COOH (carboxylic acid) and -NH2 (amine) respond to pH changes	- COOH swells at high pH; -NH2 swells at low pH
Common polymers used	- Polyacrylic acid (PAA) - synthetic, pH-responsive at basic pH - Chitosan - natural, pH-responsive at acidic pH	PAA: carboxylic groups Chitosan: Amine groups
Crosslinking methods	- Chemical: Covalent bonds - Physical: Hydrogen bonds, electrostatic interactions	Determines strength, degradation, and responsiveness
Drug delivery applications	Extracellular and intracellular pH-triggered release	Improves targeting and reduces side effects
Therapeutic examples	- Doxorubicin-loaded PAA hydrogels for breast cancer - Cisplatin-loaded hydrogels for lung cancer targeting CD44	Both use acidic pH for triggered release
Advantages	- Increased tumor specificity - Lower systemic toxicity - Potential to overcome drug resistance	EPR effect enhances tumor targeting

EPR: Enhanced permeability and retention

bioavailability for drugs designed for intracellular processes such as DNA replication or protein synthesis.[34]

DESIGN AND SYNTHESIS OF PH-RESPONSIVE HYDROGELS

Hydrogels that are pH responsive are often produced by embedding ionizable groups (from now interchanged with "functional groups"), such as carboxylic groups and amines that will protonate or deprotonate depending on the pH around them. These functional groups define the hydrogels both in terms of charge (positive or negative) and hydrophilicity, which will affect the swelling and degradation of the hydrogel.[35] For acidic pH (low pH), carboxylic groups (-COOH) protonate to become neutral, while amine (-NH2) groups protonate to carry a positive charge. For alkaline pH (high pH), carboxylics will deprotonate to carry a negative electric charge, while amine (-NH2) groups will lose their proton to become neutral. The protonation and deprotonation of these functional groups depending on the pH leads to a notable change in the structure, especially in regards to swelling. For example, hydrogels with carboxylic acid functional groups will generally swell more under high pH as the negatively charged carboxylate functional groups repel one another. Conversely, hydrogels with amine functional groups will swell more at low pH, as the positively charged ammonium functional groups repel each other electrostatically.[36]

COMMON PH-RESPONSIVE POLYMERS

Several common polymers are employed to design these responsive hydrogels: Polyacrylic acid (PAA): A synthetic polymer with carboxylate groups that show enhanced swelling in basic pH.[37] Chitosan: A natural polysaccharide containing amine groups that respond by swelling in acidic conditions.[38] These polymers can be used alone or in combination to create hydrogels with customizable properties tailored for specific applications, such as drug delivery in cancer therapy.

CROSSLINKING STRATEGIES

The synthesis of pH-responsive hydrogels involves either chemical or physical crosslinking methods, which create a three-dimensional network of polymer chains. The chemical crosslinking method forms covalent bonds, yet physical crosslinking depends on hydrogen bonding and electrostatic interactions instead of covalent bonds. Hydrogel crosslinking approaches choose from available methods based on target mechanical needs and degradation requirements and the need for stimulus response.[39]

Applications in targeted cancer drug delivery

Research on pH-responsive hydrogels for targeted cancer drug delivery has intensified because they show exclusive drug-release capabilities in acidic TMEs. The controlled drug release mechanism helps achieve higher drug levels within tumors while lowering standard chemotherapy-related toxicity throughout the body.[23] Figure 3 illustrates this process of pH-responsive hydrogel drug release in cancer therapy, highlighting how these hydrogels enhance drug concentration at the tumor site and improve therapeutic efficacy.

Hydrogel systems use pH variations between cancerous tissue and healthy tissue to deliver medicine only to tumor cells without harming regular tissues.[14]

DRUG ENCAPSULATION AND RELEASE MECHANISMS

Hydrogel drugs utilized for chemotherapeutic delivery incorporate doxorubicin and cisplatin substances inside their structure. The acidic pH conditions of tumors activate these hydrogels to release therapeutic substances (such as doxorubicin that PAA-based hydrogels carry). The hydrogels function as a pH-responsive drug deliverer mechanism inside the acidic tumor environment.[40] The released drug can then exert its cytotoxic effects on the cancer cells, inducing tumor regression. Beyond hydrogels that are extracellularly pH-sensitive, there are other systems that may target intracellular compartments, such as endosomes and lysosomes. For example, hydrogels may be taken up by a cancer cell through endocytosis and once inside the acidic endosome/lysosome, the cargo is released intracellularly. Intracellularly released drug can be of advantage for targeting subcellular processes, such as DNA replication and protein synthesis, important for tumor cell growth, and proliferation.[14]

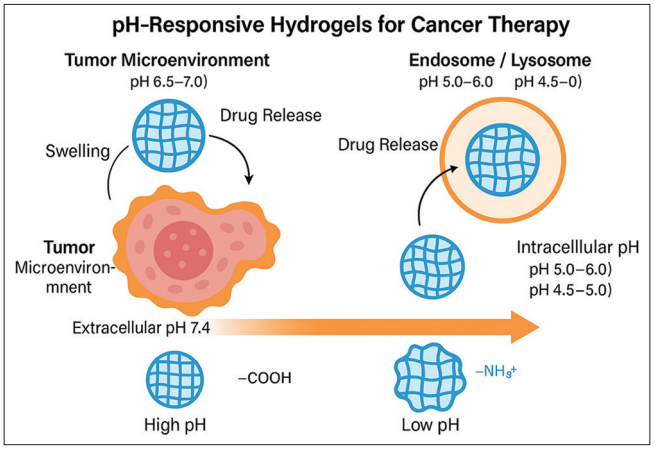

Figure 3: Schematic of pH-responsive hydrogel drug release in cancer therapy

CASE STUDIES AND SPECIFIC APPLICATIONS

The capabilities of pH-sensitive hydrogels in cancer treatment have been demonstrated through numerous successful case studies. For instance, injectable poly (acrylic acid) hydrogels loaded with doxorubicin have been shown to effectively treat breast cancer by releasing doxorubicin in areas of low pH. This case uses the "enhanced permeability and retention" effect that has been demonstrated in the cancer therapeutic field, by allowing the hydrogels to accumulate in the TME and encourage accumulation and selective killing of tumoral tissue.[41] Hydrogels have also been developed that target lung cancer cells to deliver cisplatin by utilizing the overexpression of the CD44 receptor on cancer tissue. Once internalized, the acidotic environment of endosomes leads to release of cisplatin which enhances cytotoxicity and improves therapeutic outcomes.[42]

TEMPERATURE-RESPONSIVE HYDROGELS

Temperature-responsive hydrogels are a class of intelligent polymeric systems that exhibit sol-gel phase transitions in response to temperature changes. These hydrogels are particularly suitable for targeted drug delivery in cancer therapy due to their responsiveness to physiological and pathological temperature variations, especially within the TME.

THERMO-SENSITIVITY IN TUMOR ENVIRONMENT

On average, tumor tissues have a slightly elevated temperature (40–42°C) compared to healthy tissues (~37°C). This is due to the increase in metabolic rates, poor vascularization and inflammation. Localized hyperthermia can also be achieved externally through different means, such as laser irradiation, radiofrequency ablation, or ultrasound. The increase in temperature improves the permeability of tumor cell membranes and vascular networks, resulting in enhanced uptake of anticancer drugs.[43] For example, moderate hyperthermia (~43°C) has been shown to enhance the delivery of cisplatin by modifying copper transporter 1 (Ctr1) expression. Temperature-sensitive hydrogels take advantage of this observation.[44] They are designed to undergo a sol-gel transition at physiological temperatures or hyperthermic temperatures, therefore creating a localized depot of drug delivery. An example of a temperature-sensitive gel is Pluronic F127, a triblock copolymer that experiences gelation at 37°C, which allows for minimally invasive injection and sustained delivery of drugs at the tumor location while reducing systemic toxicity. In one study, *in vitro* release of paclitaxel from a pluronic F127-based hydrogel demonstrated a sustained release profile over 26 days, highlighting its potential for prolonged local drug delivery with reduced dosing frequency.[45]

MATERIALS AND DESIGN

Temperature-sensitive hydrogels are categorized based on their critical solution temperatures: LCST: Hydrogels become insoluble and form gels above this temperature. UCST: Hydrogels dissolve above this threshold; less common in biomedical applications.[46] Table 4 summarizes commonly studied thermo-responsive polymers and their specific properties relevant to drug delivery in cancer therapy.

Hybrid systems

Dual-responsive systems, such as pH- and temperature-sensitive hydrogels, improve tumor targeting. For example, chitosan-g- PVCL gels at 37°C and swells in acidic environments, enhancing doxorubicin delivery to tumors.[9]

Mechanism of drug release

Drug release from thermo-responsive hydrogels is triggered by structural and phase changes induced by temperature: Sol-Gel transition: Injectable precursors, such as PNIPAM solutions, form gels *in situ* on reaching body temperature, encapsulating drugs within the network. Micelle aggregation: Systems like Pluronic F127 form micelles above their LCST, with release governed by micelle degradation and polymer erosion. Structural Collapse: Heating above LCST collapses the polymer network, squeezing out the drug. For instance,

Table 4: Common thermo-responsive polymers used in oncology

Polymer	Type	LCST/UCST	Application
PNIPAM	LCST (~32°C)	Gelation at body temperature when modified; widely studied	Paclitaxel, DOX delivery
Pluronic F127	LCST (~20–30°C)	FDA-approved, gels at 37°C	*IL-2, DOX*, gene therapy
PEG-PLA copolymers	LCST	Tunable transition with PEG/PLA ratio	Localized delivery
Poly (acrylamide-co-acrylic acid)	UCST	Gel stable at lower temperatures	Experimental applications

PEG: Poly (ethylene glycol), PNIPAM: Poly (N-isopropylacrylamide), LCST: Lower critical solution temperature, UCST: Upper critical solution temperature

PNIPAM hydrogels released 90% of paclitaxel within 24 h at 42°C.[47]

Applications for oncology

Injectable localized therapy: These hydrogels offer a platform for localized, sustained drug release. Pluronic F127 has been used to co-deliver IL-2 and doxorubicin in melanoma, sustaining release over 26 days.[48] PELG-PEG-PELG hydrogels enable dual-delivery of chemotherapy and immunotherapy, suppressing glioblastoma growth by 70%.[49] Silk fibroin hydrogels minimize doxorubicin-induced cardiotoxicity in mice while retaining antitumor efficacy.[50] PNIPAM-based systems are undergoing clinical trials (e.g., NCT04815429) for use in photothermal-chemotherapy.[51]

ENZYME-RESPONSIVE HYDROGELS

Enzyme-responsive hydrogels utilize the specific upregulation of select enzymes in the TME including MMPs, cathepsins, and hyaluronidases, to enable responsive and active drug delivery and therapeutic activity. Altered balance of ECM component levels characterizes the TME due to overproduction of functionally active enzymes such as MMPs or cathepsins. These enzymes are important contributors to tumor invasion or metastasis by breaking down the ECM, which is a network of proteins and polysaccharides providing structural support to cells in contact with neighboring cells and tissues.[2] The upregulation of these enzymes in the TME allows hydrogels to be designed to degrade and release a therapeutic agent while remaining stable during hydrogel preparation and physiological delivery of drug encapsulated by the hydrogel, thus providing drug delivery directly on tumor. Enzyme-triggered degradation of the deliverable hydrogels can result in selective therapeutic delivery that limits systemic side effects and allows for localized treatment effect.[24]

Design strategies

Enzyme-responsive hydrogels that contain enzyme sensitive linkers or backbones that may be cleaved by overexpressed TME enzymes comprise a significant design approach. A well-known strategy is the incorporation of peptide sequences as crosslink agents in the hydrogel network that are designed to be cleaved by the target enzyme, such as MMP or hyaluronidases.[52] The hydrogels are retained intact until they are transported to the tumor site and degraded only by overexposed enzymes. There are two fundamental design elements that these systems can fall under:

1. Degradable systems, which physically degrade in the substrate of target enzymes and subsequently releases the therapeutic payload.[53]
2. Non-degradable systems, where hydrogel physical properties (e.g., swelling or structural) change in a reversible nature after enzymes cleave the linker which allows drug release. The specificity of enzymatically cleavable linkers is fundamental for case multiple selectivity of the system in the TME and shoe that it would have minimal degradation in healthy tissue. Achieving the determined hydrogel design for rate of degradation and drug release profile for improved treatment outcome is vital.

CONTROLLED RELEASE MECHANISM

Hydrogels that respond to enzymes are based on enzymatic cleavage of tethered linkers, which can lead to the controlled release of an encapsulated drug. In this case, the hydrogel will degrade or swell on interacting with overexpressed tumor enzymes. This disturbs the hydrogel network arrangement and allows for sustained release of the therapeutics. Moreover, drug release is controlled mainly at the tumor site, maximizing drug concentration to the tumor cancer cells rather than normal tissues.[54] Furthermore, the drug release rate can be controlled by adjusting a variety of factors that impact the rate of hydrogel and decomposition by the enzyme, including concentration of enzyme-sensitive linkers, the activity of enzyme, and the physical characteristics of the hydrogel. These constructs ensure that drug released from the hydrogel network is delivered in a sustained fashion, with improved efficacy while limiting systemic exposure. In addition, hydrogel physical properties will respond to enzyme activity, enhancing swelling or structural change based on changes in enzymatic activity. This controllable dynamic behavior provides the hydrogel an improved ability to deliver the drug in response to the state of the TME.[55] In practical applications, enzyme-responsive hydrogels have shown impressive potential in delivering anticancer drugs specifically to tumor sites. MMP-responsive hydrogels, for instance, degrade in response to high MMP concentrations in the TME, enabling localized release of anticancer agents.[56] Similarly, hydrogels designed to respond to hyaluronidase can target tumors by degrading hyaluronic acid, a key ECM component. Preclinical studies have demonstrated the effectiveness of such hydrogels in delivering therapeutic agents and inhibiting tumor growth. These studies underline the advantages of minimizing systemic toxicity while maximizing localized efficacy. The combination of targeted delivery, controllable release, and reduced off-target effects signifies a major step forward in cancer treatment. Ongoing and future clinical trials will further evaluate the safety and therapeutic potential of these hydrogel-based systems, with the aim of enhancing patient outcomes in oncology.[52]

COMPARATIVE ANALYSIS OF STIMULI-RESPONSIVE HYDROGELS

This section provides a comparative evaluation of the major types of stimuli-responsive hydrogels, as shown in

Table 5, explores synergistic dual/multi-stimuli systems, and outlines essential design considerations for their clinical translation.

CHALLENGES AND FUTURE PERSPECTIVES

The successful clinical translation of stimuli-responsive hydrogels requires overcoming several key challenges. Ensuring biocompatibility and mechanical suitability is essential, as the hydrogel must match the physical properties of the target tissue while minimizing immune responses. For instance, brain-targeted hydrogels require a softness of approximately 0.1–0.3 kPa, and natural polymers such as chitosan and hyaluronic acid are preferred due to their low immunogenicity, reducing the risk of adverse immune activation[62] Scalability and long-term stability are also critical; hydrogel production must be standardized for consistent quality, and formulation strategies such as lyophilization are necessary to preserve function during storage, particularly for thermo-responsive systems.[63] Regulatory challenges persist, including the need to demonstrate reproducible drug release profiles and address delivery-specific barriers such as transport across the blood-brain barrier for neurological applications. Looking forward, artificial intelligence, and machine learning offer powerful tools for the personalized development of multi-stimuli-responsive hydrogels. In particular, machine learning models can be trained on polymer chemistry and environmental variables to predict and optimize hydrogel degradation rates, enabling more precise control over drug release kinetics. This predictive capability could accelerate design iterations, reduce experimental burden, and enhance therapeutic outcomes. In addition, the integration of hydrogels with immunotherapeutics, such as anti-PD-1-loaded systems, may expand their clinical relevance in cancer therapy.[64]

Table 5: Comparative analysis of single and dual/multi-stimuli-responsive hydrogels in cancer therapy

Type of hydrogel	Advantages	Limitations	Representative example	References
pH-responsive	- Targets acidic tumor microenvironment (pH 6.5–7.2) - Reduces systemic toxicity - High biocompatibility with natural polymers	- Heterogeneous intratumoral pH reduces reliability - Risk of off-target release in acidic normal tissues (e.g., stomach)	Alginate hydrogel releasing~80% paclitaxel at pH 5.5	[57]
Temperature-responsive	- Injectable formulations gel at body temperature - Sustained release over weeks - Suitable for localized therapies	- Sensitive to fluctuating body temperatures - Risk of inflammation due to external heat sources (e.g., NIR light)	Pluronic F127 hydrogel with 26-day IL-2 release in melanoma models	[58]
Enzyme-responsive	- High specificity to tumor-associated enzymes (e.g., MMP-2) - Reduces off-target effects	- Variable enzyme expression among tumor types - Slow degradation may delay drug release	MMP-sensitive PEG-peptide hydrogels for tumor-specific degradation	[56]
pH/temperature dual-responsive	- Combines gelation at body temperature with pH-sensitive swelling - Improved localization and drug targeting	- Complex synthesis - Potential interference between stimuli responses	Chitosan-g-poly (N-vinylcaprolactam) hydrogel for doxorubicin delivery	[59]
Enzyme/redox dual-responsive	- Targets enzyme-rich and redox-active TME - Enhanced control and minimized systemic exposure	- Difficult to tune degradation rates for both stimuli simultaneously - Challenging to predict tumor-specific redox profiles	MMP-2/ glutathione-responsive hydrogel enabling targeted degradation in tumor environments	[60]
Light/magnetic dual-responsive	- Enables photothermal-chemotherapy synergy - Combines drug targeting with hyperthermia	- Requires external triggering systems (e.g., NIR, magnetic field) - Safety and depth of penetration concerns light-based activation	Gold nanorod/iron oxide composite hydrogel for NIR/ magnetic-responsive cancer treatment	[61]

PEG: Poly (ethylene glycol)

CONCLUSION

Stimuli-responsive hydrogels hold great promise for improving cancer therapy by enabling precise, localized drug delivery while minimizing systemic side effects. Their ability to respond to pH, temperature, and enzymatic triggers allows for greater treatment control and personalization. However, translating these innovations into clinical practice requires more than just scientific progress – it demands close collaboration between material scientists, clinicians, and regulatory experts. Such interdisciplinary efforts will be essential to address challenges related to biocompatibility, large-scale manufacturing, and regulatory approval. With continued research and cooperative development, these smart hydrogels may soon become an integral part of personalized cancer treatment.

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