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# A Review of Adaptive Smart Hydrogel : A New Paradigm for Cancer Therapeutics and Drug Delivery

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**Abstract:** *Cancer remains one of the most challenging diseases to treat due to tumor heterogeneity, multidrug resistance, and non-specific drug distribution. Recent advances in biomaterials have introduced adaptive smart hydrogels as innovative platforms for targeted and controlled drug delivery in cancer therapeutics. These hydrogels possess dynamic, stimuli-responsive properties that enable them to sense and respond to various internal and external physiological cues such as pH, temperature, redox potential, enzymes, light, and magnetic or electric fields. By mimicking the extracellular matrix and exhibiting biocompatibility, injectability, and self-healing characteristics, adaptive hydrogels offer site-specific and sustained release of anticancer agents while minimizing systemic toxicity. Furthermore, their ability to integrate multiple stimuli-responsiveness enhances precision in therapeutic delivery and improves tumor microenvironment modulation. This review highlights recent developments in adaptive smart hydrogel design, classification, mechanisms of responsiveness, and their emerging applications in cancer therapy. It also discusses current challenges, limitations, and future perspectives toward clinical translation, emphasizing the potential of these dynamic systems to revolutionize personalized cancer treatment.*

**Keywords:** Adaptive smart hydrogel, Cancer therapeutics, Stimuli-responsive hydrogel, Controlled release, Tumor targeting

## I. INTRODUCTION

Cancer remains one of the leading causes of death worldwide, with millions of new cases diagnosed each year. In 2022, there were approximately 20 million new cancer cases and 9.7 million deaths worldwide. Without effective intervention, these numbers are projected to rise to about 35 million new cases by 2050 Cancer is a highly heterogeneous disease characterized by uncontrolled cell growth, frequent development of drug resistance, and a complex tumor microenvironment (TME). Conventional treatments (surgery, chemo-, radio- and immunotherapy) often produce systemic toxicity and limited specificity, creating a strong need for platforms that concentrate therapeutics at tumor sites and control release over time.[1]

Hydrogels are three-dimensional (3D) hydrophilic polymer networks capable of absorbing and retaining large amounts of water or biological fluids without dissolving. They are composed of natural, synthetic, or hybrid polymers that are cross linked either physically (through ionic or hydrogen bonding) or chemically (through covalent bonding), allowing the material to maintain its structure while swollen .[2]

**Adaptive smart hydrogel:**

Adaptive smart hydrogels are 3D, water-rich polymer networks whose physical or chemical properties such as swelling, porosity, degradation, cargo release, mechanical stiffness, adhesiveness change in response to internal tumor cues (pH, enzymes, redox, GSH, ROS, glucose) or external triggers (temperature, light, magnetic field, ultrasound, electric field). These property changes are exploited to achieve spatially- and temporally-controlled drug delivery, immune modulation, or mechanical remodeling of the tumor microenvironment.


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**Rationale for adaptive hydrogels in cancer therapy:**

Localized, sustained delivery: in situ-forming hydrogels can be injected/implanted to maintain therapeutic concentrations at the tumor and limit systemic exposure. [3] Stimulus-triggered specificity: tumor features (acidic pH, high glutathione, upregulated enzymes) are exploited for selective release. Combination and theranostics: co-delivery of chemo-, immuno-, gene therapies or imaging/photothermal agents is feasible within a hydrogel matrix.[1]

**Structure and composition of smart hydrogel:**

Smart hydrogels are formed by hydrophilic polymer networks capable of responding to environmental stimuli such as pH, temperature, or redox potential. Their composition can be broadly divided into three categories:

a .Natural Polymers:

Derived from biopolymers such as chitosan, alginate, gelatin, hyaluronic acid, and collagen, these materials provide excellent biocompatibility, biodegradability, and cell adhesion properties. However, they often require blending with synthetic polymers for mechanical strength.[4]

b. Synthetic Polymers

Polymers like poly(N-isopropyl acrylamide) (PNIPAAm), polyethylene glycol (PEG), polyacrylic acid (PAA), and polyvinyl alcohol (PVA) enable tunable mechanical strength, degradation rate, and stimuli sensitivity. Their chemical versatility allows functionalization for targeted drug release.[5]

c. Hybrid (Composite) Hydrogels:

Hybrid hydrogels integrate natural and synthetic polymers or embed nanoparticles (e.g., gold, graphene oxide, silica) to improve mechanical stability, drug-loading capacity, and responsiveness to tumor microenvironment cues.[6]

Structural design of smart hydrogel- The 3D structure of hydrogels determines their drug diffusion rate, swelling behavior, and mechanical integrity.

a. Crosslinking Mechanisms

Hydrogels can be physically, chemically, or dynamically crosslinked:

Physical crosslinking involves ionic or hydrogen bonds—reversible and biocompatible. Chemical crosslinking uses covalent bonds for stability. Dynamic (reversible) bonds (e.g., Schiff base, disulfide linkages) allow self-healing and stimuli-responsiveness.[7]

b. Porosity and Network Density: The pore size and crosslinking density regulate water uptake, nutrient diffusion, and drug-release kinetics. Highly porous hydrogels favor sustained drug diffusion, while dense networks enhance mechanical strength.[2]

c. Functional Group Incorporation: The inclusion of responsive functional moieties (e.g., carboxyl, amine, disulfide, or azobenzene groups) enables pH-, redox-, or photo-responsive behavior. These structural modifications provide on-demand release of anticancer agents in tumor environments.[1]

Importance of polymer composition on properties: Polymer choice and crosslink density determine mechanical strength, porosity, swelling, diffusion, drug-release kinetics, biodegradability, and bioactivity (e.g., HA targeting CD44). Optimizing composition balances stability, release profile, and biocompatibility.

Biodegradability and safety considerations: Biodegradable backbones and non-toxic degradation products are essential. Immunogenicity, sterilization, manufacturability, and regulatory hurdles remain central challenges for translation to clinical use.[3]

**Classification :**

1. Classification Based on Type of Stimuli:
   - Internal (Endogenous) Stimuli-Responsive Hydrogels:

1.pH-Responsive Hydrogels.
2.Temperature-Responsive Hydrogels.
3.Redox-Responsive Hydrogels.
4.Enzyme-Responsive Hydrogels.
5.Glucose-Responsive Hydrogels. [1]

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• External (Exogenous) Stimuli-Responsive Hydrogels:
1.Light-Responsive Hydrogels.
2.Magnetic-Responsive Hydrogels.
3.Electric-Field-Responsive Hydrogels. [5]
2. Classification Based on Number of Stimuli:
1.Single stimuli responsive Hydrogels.]
2.Multi-stimuli responsive Hydrogels.[1]
3. Classification Based on Cross-Linking Mechanism:
1. physical cross linking.
2. Chemical cross linking. [8]

**Evaluation parameters of Hydrogel:**

The evaluation of hydrogels is an essential step in determining their suitability for biomedical and pharmaceutical applications. Since hydrogels are designed to interact with biological environments, their physicochemical, mechanical, and biological properties must be thoroughly characterized to ensure functionality, safety, and therapeutic efficacy.[3]

1.Swelling Behavior: Measures hydrogel's water absorption capacity, influencing porosity and drug diffusion. High swelling indicates greater water uptake and faster drug release.[2]

2. Gel Fraction and Crosslinking Density: Indicates the extent of polymer network formation and stability. Higher crosslinking increases strength but decreases swelling.[9]

3. Mechanical Properties: Determines elasticity, injectability, and durability under physiological stress. Evaluated by rheological or compression analysis.[1]

4. Drug Loading and Release Profile: Measures encapsulation efficiency and drug release under tumor-like pH. Controlled release ensures sustained therapeutic effect.[10]

5. Biocompatibility and Cytotoxicity: Tested using cell viability assays (MTT, Live/Dead) to ensure safety.Non-toxic hydrogels promote better tissue integration.[3]

6. Degradation and Stability:

Evaluates hydrogel's breakdown rate and byproduct safety. Biodegradable hydrogels are preferred for cancer therapy applications.[4]

## II. LITERATURE REVIEW

**1.solanki, R. and Bhatia, D.(2024):** Stimulus-responsive hydrogels are designed to release drugs only when they encounter tumor-specific signals such as low pH, high glutathione, or tumor enzymes. these smart hydrogels improve targeting by responding to internal (pH, redox, enzymes) or external (temperature, light) triggers, allowing controlled and localized drug delivery. Multi-stimuli systems further increase precision and reduce side effects. However, challenges such as tumor variability, material safety, and large-scale production still limit their clinical use. Overall, the review shows that stimulus-responsive hydrogels offer a promising strategy for more effective and targeted cancer therapy.

**2. Li et al. (2023):** highlight that hydrogels offer controlled and localized drug delivery due to their biocompatible and tunable structure. They discuss injectable, stimuli-responsive, and nanoparticle-loaded hydrogels that improve drug targeting and reduce side effects in cancer therapy. The review also notes challenges such as tumor penetration limits and the need for stronger clinical evidence

**3. Patkar and Sherje (2025):** summarize recent progress in smart hydrogels designed for targeted cancer drug delivery. They highlight how stimuli-responsive hydrogels—triggered by pH, enzymes, redox or temperature enable controlled, localized drug release and reduce side effects. The authors also note examples like MMP and heparanase-responsive gels and discuss challenges such as biocompatibility and scale-up, concluding that multi-stimuli hydrogels offer strong future potential in cancer therapeutics.

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**4.Wang et al. (2024): r**eview injectable, in situ-forming hydrogels as promising local drug-delivery platforms to prevent postoperative tumor recurrence. They emphasize that these hydrogels can fill irregular surgical cavities, gel in place under physiological triggers (like temperature or pH), and deliver a variety of therapeutic agents chemotherapy drugs, immunomodulators, or phototherapy agents with sustained release and low systemic toxicity. The authors also highlight how these hydrogels support tissue repair and wound healing, while discussing the current translational challenges such as biocompatibility, gelation kinetics, and long-term stability.

**5.Mohammadzadeh et al. (2025):** discuss how injectable, stimuli-responsive hydrogels can revolutionize cancer immunotherapy by delivering Immunomodulatory agents directly into the tumor microenvironment. These hydrogels can sustain the release of cytokines, immune checkpoint inhibitors, or CAR-T cells, reducing systemic toxicity and improving immune cell infiltration. They also explore multifunctional designs, such as combining chemotherapy or phototherapy with immunotherapy, and highlight challenges like biocompatibility, manufacturability, and translation to clinical use.

**6.Lu et al. (2024)** review the wide potential of hydrogels across both cell-based and non-cell therapeutic applications, showing how tunable chemistries and responsive designs (pH, temperature, ROS, light, magnetic/electric) enable improved delivery, protection, and function of cells, drugs, and biologics. They summarize design considerations—mechanical properties, degradation, bioactivity and highlight applications in tissue engineering, tumor immunotherapy, and theranostics, while noting translational hurdles (in vivo variability, manufacturability, sterilization) and calling for integration with advance manufacturing and standardized preclinical pipelines to accelerate clinical translation.

**7.Kasiński et al.:** review synthetic "smart" hydrogels that change their swelling, permeability, and mechanical behavior in response to stimuli like pH, temperature, magnetic fields, or biological signals. These hydrogels can be injected in situ, form depots, and deliver anticancer drugs precisely at the tumor site, thereby reducing systemic toxicity. The authors discuss chemical strategies (e.g., using biodegradable polyesters and phosphazenes) to build responsive networks, as well as challenges in controlling drug release and ensuring biocompatibility.

**8.Xie et al. (2023):** Hydrogel-based local drug delivery systems have recently gained attention for improving postoperative radiotherapy outcomes. highlight that hydrogels can be applied directly to the surgical site, where they provide sustained and targeted release of radiosensitizers, chemotherapeutic agents, radioisotopes, or immunomodulators. This localized delivery enhances radiation effectiveness, reduces systemic side effects, and helps prevent tumor recurrence. Although highly promising, challenges remain in optimizing hydrogel formulation, controlling release behavior, and translating these systems into clinical practice.

**9.Arsuffi et al. (2024):** developed programmable, multi-responsive nanocellulose-based hydrogels that can perform "embodied logic," meaning they respond only when specific combinations of stimuli occur. The study shows how nanocellulose networks can be engineered to sense pH, temperature, ions, or other triggers and convert them into controlled shape changes or release behaviors. These logic-gated hydrogels improve precision in biomedical applications, enabling more accurate drug delivery and smart therapeutic systems.

**10.Liu and Jin (2025):** highlight significant progress in using 3D-bioprinted cancer models to better mimic tumor architecture, cellular interactions, and the heterogeneous tumor microenvironment. These hydrogel-based bioinks allow precise spatial positioning of cancer cells, stromal cells, and biomolecules, enabling more realistic studies of tumor behavior, drug response, and metastasis. The authors emphasize that such bioprinted models offer strong potential for personalized medicine by allowing patient-specific tumors to be recreated for individualized drug screening. Despite these advances, challenges remain in achieving vascularization, long-term stability, and fully replicating complex in vivo physiology, which continue to limit clinical translation.

**Mechanism of adaptivity :**

Adaptive (stimuli-responsive) hydrogels are polymeric networks that undergo reversible physicochemical changes—such as swelling, contraction, or degradation—in response to internal or external stimuli. These stimuli mimic biological environments, allowing hydrogels to self-regulate drug release or structural behavior dynamically for targeted cancer therapy.

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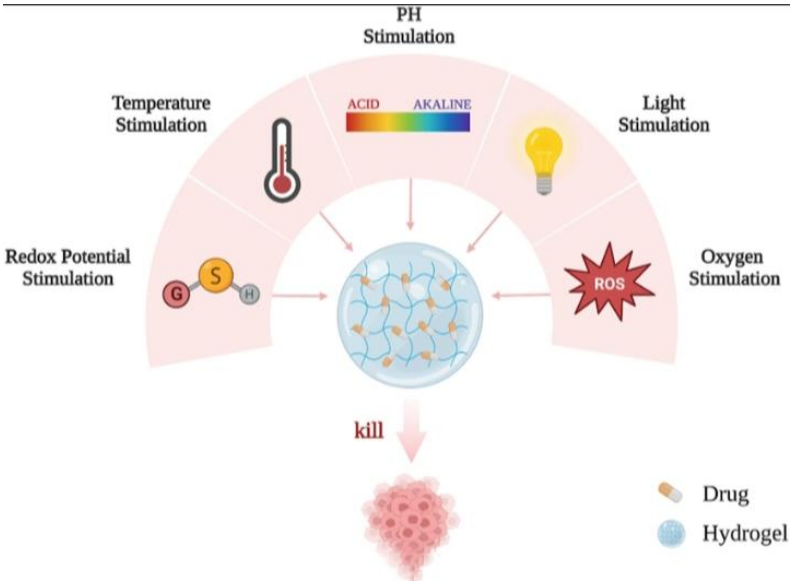


**Fig: stimuli responsive mechanism of smart hydrogel**

**1.pH -responsive hydrogel:**

pH-responsive adaptive smart hydrogels are cross-linked , hydrophilic polymer networks engineered to adapt their structure or surface properties in response to local pH, enabling controlled swelling, degradation, drug release, or surface charge switching in the slightly acidic tumor microenvironment (typically ~pH 6.5–6.9 vs blood pH 7.4). [11] The core mechanism of pH-responsive hydrogels lies in their polymeric structure, which includes ionizable functional groups such as carboxyl, amino, or imidazole groups. At physiological pH (around 7.4), these groups are neutral or less charged, leading to a compact hydrogel structure. However, in the acidic tumor microenvironment (typically pH 5.5–6.5), these groups become protonated or ionized, causing the hydrogel to swell or degrade, thereby releasing the encapsulated drug . [12] In cancerous tissues, the microenvironment is more acidic (pH 6.5–7.2) than in normal tissues or the bloodstream (pH 7.4). This acidity arises because cancer cells produce more lactic acid as a result of increased glycolysis and proton -pump activity. The low pH of tumor tissues thus provides a natural stimulus for the release of drugs from pH-sensitive hydrogels. These hydrogels remain stable in the neutral pH of the bloodstream but swell or degrade in the acidic tumor environment, allowing drugs to be released precisely where they are needed. The release of drugs from pH-responsive hydrogels can occur through several mechanisms, including diffusion-controlled, swelling-controlled, and chemically-controlled processes. [13] These hydrogels contain pH-sensitive functional groups such as acidic or basic residues within their polymer network, allowing them to swell or shrink when exposed to different pH environments. Common polymers used include poly(acrylic acid), poly(ethylene glycol), chitosan, and methacrylic acid, which possess ionizable groups responsible for pH sensitivity. Recent studies have shown that pH-responsive hydrogels can provide sustained release, biocompatibility, and enhanced tumor inhibition, making them promising systems for controlled and targeted drug delivery in cancer treatment.[1]

**2.Temparature -responsive hydrogel :**

Temperature-responsive hydrogels are a class of smart biomaterials that can reversibly change their physical state in response to temperature variations, typically shifting between sol (liquid) and gel (solid-like) forms. These phase transitions occur due to the formation or breaking of cross-linking bonds and temperature - induced conformational changes in the polymer chains. This unique property allows the hydrogel to adapt to

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physiological conditions, enabling in situ gelation that can fill irregular tissue cavities accurately. When injected into the body, the hydrogel remains in a liquid form at room temperature and rapidly transforms into a gel at body temperature. This gel provides mechanical support to the damaged tissues, facilitates cell attachment and migration, and allows localized, sustained release of therapeutic agents such as drugs or cytokines, thereby enhancing the effectiveness of cancer therapy.[14] sol-gel transition (liquid → gel) at a certain temperature (LCST = Lower Critical Solution Temperature, or occasionally UCST). Below that temp they are more fluid; above it (or when heated) they become gel or shrink/contract. Can be injected as liquid (sol) and form a gel in situ once they reach body temperature (≈ 37 °C). This helps localization of the drug at the tumor site.[15] Hydrogels often include photothermal agents (e.g., metallic nanoparticles, polydopamine) that convert external stimulus (such as NIR light) into heat. That locally raises temperature, triggering gel temperature response and/or direct tumor cell damage. The elevated heat can also increase local blood flow, increase cell membrane permeability, inhibit repair processes in tumor cells, etc., which helps increase efficacy of chemotherapeutic agents loaded in the hydrogel.[16]

**3.Redox-responsive hydrogel:**

Redox-responsive hydrogels are stimuli-sensitive biomaterials designed to respond to changes in the redox environment, such as variations in glutathione (GSH) or reactive oxygen species (ROS) levels. In cancer tissues, the intracellular concentration of GSH (2–10 mM) is significantly higher than in normal tissues (~2–20 μM), and ROS levels are also elevated. These redox imbalances provide a unique microenvironmental trigger for selective drug release from redox-responsive hydrogels.[2] Glutathione-responsive hydrogels are emerging as an effective strategy for localized and controlled drug delivery in cancer therapy. These hydrogels exploit the abnormally high concentration of glutathione (GSH) in tumor cells often several times higher than that in normal cells to achieve selective drug release within cancerous tissues. The hydrogel matrix is typically engineered with glutathione-reactive linkages, such as disulfide (-S–S-) or diselenide (-Se–Se-) bonds, which act as redox-sensitive cross-links. Upon entering the tumor microenvironment, the abundant intracellular GSH donates electrons from its thiol (-SH) groups, reducing and cleaving these disulfide bonds. This cleavage leads to the degradation or swelling of the hydrogel network, triggering the release of encapsulated chemotherapeutic agents directly at the tumor site. Such redox- responsive degradation minimizes premature drug leakage and systemic toxicity while enhancing therapeutic efficacy . 8, the modular design of these hydrogels allows for integration with other stimuli responsive systems improving spatiotemporal control over drug release and optimizing cancer treatment outcomes. [17]

**4.Enzyme responsive Hydrogel:**

Enzyme-responsive hydrogels are polymer networks engineered to degrade or change properties when cleaved by tumor proteases such as matrix metalloproteinase, MMPs. They enable site- selective drug release, prodrug activation, or exposure of cell-targeting motifs in the tumor microenvironment, improving local efficacy while limiting systemic toxicity. [18] Matrix metalloproteinase (MMPs) are overexpressed in many tumor types and are among the most extensively exploited enzymatic triggers for activating smart drug delivery systems [17] Mechanism: Peptide-cleavable cross linkers: hydrogel crosslinks include short peptide sequences that specific enzymes (e.g., MMP-2, MMP-9) cleave causing gel degradation and drug release. [19] Enzyme-triggered prodrug activation / catalysis: enzymes in tumors can convert an inactive payload inside/at the gel into an active drug locally. [20] Multistage systems: enzyme cleavage can change particle size or surface properties to improve tumor penetration after initial enzyme action. [21]

**5.Glucose -responsive hydrogel:**

Glucose-responsive hydrogels are special gel-like materials that can “sense” the amount of glucose present around them. When the glucose level increases in the tumor area, these hydrogels start to change their shape or break down, which helps in releasing the loaded medicine directly at the cancer site.[22]

Main glucose-sensing/response mechanisms used in hydrogels

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1.Phenylboronic acid (PBA) / boronate ester chemistry-PBA reversibly binds cis-diol-containing sugars (glucose), changing polymer crosslinking/hydrophilicity and causing swelling/deswelling or gel disassembly for cargo release. Widely used because it's reagent less and reversible.[23]

2.Glucose oxidase based enzymatic response-Glucose oxidase enzyme reacts with glucose to produce gluconic acid and hydrogen peroxide ($H_2O_2$).The formation of these products lowers the pH and produces reactive oxygen species (ROS), which not only help release the drug but can also directly kill cancer cells.[24]

3. Lectin / Concanavalin A (ConA) binding-Lectins that bind glucose/mannose can be used as reversible cross linkers; competitive displacement by free glucose results in network loosening and release. Less commonly used clinically due to immunogenicity concerns but useful in designs. [22]

4. Tumor Starvation and ROS Generation-Cancer cells need a lot of glucose to grow. When GOx in the hydrogel uses up the glucose, the cancer cells are starved of energy. At the same time, the reaction creates ROS (Reactive Oxygen Species) such as hydrogen peroxide ($H_2O_2$) and hydroxyl radicals (•OH).These ROS damage the cancer cells' DNA and proteins, leading to their death.[1]Drug Release Controlled by Glucose and ROS-When glucose is high, or ROS are produced, the structure of the hydrogel becomes loose.This allows the drug stored inside to come out slowly and act only where it is needed mainly in the tumor area. This helps reduce side effects and increases treatment safety.[6]

**6.Light-responsive Hydrogel:**

"Light-responsive hydrogels" are hydrogel systems designed such that exposure to light typically visible or near-infrared (NIR) triggers a change in their physical or chemical behavior for example gel→sol transition, drug release, structural contraction/expansion, photo thermal heating, etc. Light provides spatial and temporal control of stimulus (i.e., you can target the tumor region and trigger at the desired time)[ 25] Hydrogels allow local delivery and retention of therapeutics (drugs, nanoparticles, photothermal agents) at tumor sites, reducing systemic toxicity .[1] Photosensitive moieties are added to the polymeric structures of hydrogels to create light-responsive hydrogels. Three main mechanisms photoisomerization, photochemical reaction, and photothermal reaction can be used to achieve drug release.[26]Light-responsive hydrogels are engineered by embedding NIR-absorbing photothermal agents such as gold nanorods, graphene oxide, $Mos_2$ nanosheets, or indocyanine green (ICG).These materials efficiently absorb NIR light and convert it into heat through photothermal conversion.[27]When the hydrogel at the tumor site is exposed to NIR laser (808 nm or 1064 nm), the photothermal agent absorbs photons and releases localized heat via non-radiative relaxation. The temperature of the hydrogel microenvironment can rise to 45–55 °C, enough to induce tumor cell apoptosis[28]The localized heat causes structural changes in thermo-sensitive polymer networks such as PNIPAM, PEG, or agarose. These polymers exhibit a lower critical solution temperature (LCST); above LCST, the hydrogel shrinks or changes phase (gel → sol).This transition opens the polymeric network and increases diffusion pathways for drug molecules.[29]Heat from NIR irradiation triggers controlled drug release through: Hydrogel network expansion or collapse (increasing porosity).Cleavage of thermo-labile or photo-cleavable linkers (e.g., o-nitrobenzyl groups).Accelerated diffusion of drugs (DOX, cisplatin, paclitaxel, etc.) from the matrix.[1]

**7. Magnetic responsive Hydrogel:**

Magnetic hydrogels are polymeric 3-D networks that incorporate magnetic nanoparticles (typically iron-oxide, $Fe_3O_4$ / $\gamma$-$Fe_2O_3$) either dispersed in the gel matrix or chemically bound to the polymer. The magnetic component gives the hydrogel remote responsiveness to static or alternating magnetic fields.[30]

Mechanism: Magnetic hyperthermia: alternating magnetic fields (AMF) cause magnetic NPs to dissipate heat (Néel / Brownian relaxation), locally raising temperature (41–46 °C) to kill tumor cells and sensitize them to chemo/radiation.

Magnetically controlled drug release / on-demand dosing: AMF or gradient fields change polymer network (thermal swelling/deswelling or mechanical disruption) and trigger pulse or enhanced release of loaded drugs (e.g., doxorubicin).

Magnetic guidance / positioning: external static magnetic gradients concentrate the hydrogel/nanoparticles at the tumor site for localized therapy.[31] Embedding chemotherapeutics (DOX, etc.) inside magnetic hydrogels enables synergistic therapy: hyperthermia increases tumor uptake/sensitivity while triggered release raises local drug concentration —

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improving efficacy and reducing systemic toxicity. Multiple in vivo studies show better tumor control for combined treatment than either alone.[32] Localized drug release is crucial for cancer treatment in order to reduce systemic side effects. Chemotherapy medications can be administered directly to the tumor site using magnetic hydrogels, which release the chemicals when activated magnetically. By limiting exposure to healthy tissues and enabling larger drug concentrations to reach the tumor, this focused strategy enhances therapeutic results and minimizes side effects.[33]

**8. Electric field responsive Hydrogel:**

Electricity-sensitive hydrogels respond to electric fields by swelling, shrinking, bending, or eroding.[18] They can be made from synthetic polymers like polyaniline, polypyrrole, and PVA, or natural ones like chitosan, alginate, and hyaluronic acid. Drug release from ERHs is governed by the balance of polymer–polymer affinity, ionic pressure, and elasticity (osmotic pressure). Applying an electric field disturbs this balance by causing ion migration ($H^+$, $OH^-$), creating osmotic pressure differences that drive drug release.[5] They are typically made from conductive polymers (e.g., polyaniline, polyacrylamide), conductive nanomaterials (e.g., graphene, carbon nanotubes), or polyelectrolytes. Conductive polymers can alter their redox state under electrical signals, leading to changes in charge distribution, shape, and drug release. Incorporating conductive nanomaterials enhances both mechanical strength and electrical responsiveness.[18] Thus, for cancer-therapy applications, by embedding anti-cancer drugs in such hydrogels and applying an electric stimulus, one can achieve on-demand release of the drug at the tumor site (or locally).[4]

**9.Ultrasound responsive Hydrogel:**

Ultrasound-responsive hydrogels are smart polymeric networks that undergo physical or chemical changes such as swelling, degradation, or drug release when exposed to an external ultrasound stimulus . These hydrogels are designed to respond to ultrasound's mechanical (cavitation, shear) or thermal (localized heating) effects, enabling controlled, site-specific, and non-invasive drug delivery for cancer therapy.[34] Gas-forming droplets, microbubbles, piezoelectric nanoparticles, phase-change agents, mechanophore units are the ultrasound sensitive components added in hydrogel [35]Ultrasound triggers hydrogel-based drug release via several overlapping physical and chemical mechanisms: Mechanical effects / cavitation: US waves generate acoustic pressure, microbubble formation and collapse, shear forces or microstreaming within the gel network, which can disrupt crosslinks or open pores. [36]Thermal effects: Absorption of ultrasound energy generates localized heating, which can soften or collapse hydrogel networks (especially thermoresponsive ones), increasing diffusion or causing release. [37]Phase-change effects: Some hydrogels incorporate ultrasound-sensitive inclusions (e.g., perfluorocarbon droplets) that undergo liquid-to-gas transitions under US, expanding and mechanically perturbing the network. [4]Mechanochemical cleavage: Ultrasound can generate sufficient stress to cleave mechanosensitive bonds (mechanophores) embedded in hydrogels, triggering cargo release or hydrogel degradation. [18]Enhanced transport / permeability: Ultrasound increases diffusion and convection within the hydrogel and into adjacent tissue via microstreaming and increased permeation, thereby enhancing drug flux. [38]

**10.Multi-stimuli responsive Hydrogels:**

Multi-stimuli-responsive hydrogels are polymer networks engineered to change their properties (swelling, porosity, degradation, mechanical stiffness, drug release rate) in response to two or more triggers found in the tumor microenvironment (TME) or applied externally. Combining stimuli increases selectivity and control over payload release versus single-trigger systems.

Common stimulus combinations: pH + redox (GSH): exploits acidic extracellular pH and high intracellular glutathione in tumors to achieve extracellular stability and intracellular burst release. [1]

pH + temperature: uses mild hyperthermia or thermosensitive sol–gel transitions for local injection and on-demand release.[39]

Light (NIR) + photothermal/photodynamic + chemo: NIR triggers local heating or ROS generation to release drugs and/or enhance cell kill synergistically.

Magnetic + heat / ultrasound + mechanical cavitation: external fields permit remote, repeatable triggering and imaging guidance.[1]

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**Design and fabrication approches :**

Smart hydrogels are engineered polymer networks that respond to biological or external stimuli to enable controlled, localized delivery of therapeutics in cancer treatment. Effective design integrates polymer choice, crosslinking strategy, stimuli-responsiveness, payload compatibility, and manufacturability.[3]

1.Polymer Selection

Natural polymers (chitosan, hyaluronic acid, gelatin): biocompatible and bioactive; useful for receptor-mediated targeting (e.g., HA–CD44).

Synthetic polymers (PEG, PNIPAAm, PAA, PVA): tunable mechanics and functionalization sites.

Hybrid systems combine both for optimal performance. [2]

2.Crosslinking Strategies

Physical crosslinking: ionic interactions, hydrogen bonding, hydrophobic assembly — reversible and injectable.

Chemical crosslinking: covalent bonds (click chemistry, radical polymerization) — stable networks.

Dynamic covalent & supramolecular bonds: Schiff-base, disulfide, host–guest enable self-healing and stimuli-triggered disassembly.[9]

3.Incorporation of Stimuli-Responsive Moieties

pH-sensitive groups (carboxyl, tertiary amines) for acidic tumor microenvironments.

Redox-sensitive linkers (disulfide bonds) cleavable by intracellular glutathione.

Thermo-responsive polymers (PNIPAAm) for sol–gel transitions at body temperature.

Photo-responsive units (azobenzene, o-nitrobenzyl) for light-controlled release.[1]

4.Drug Loading Strategies

-Physical entrapment during gelation for small molecules and proteins. Chemical conjugation via cleavable linkers for prodrug strategies. Encapsulation of nanoparticles or liposomes to protect and co-deliver multiple agents (chemo + immunomodulators).[6]

5. Fabrication Techniques:

In situ gelation (injectable): precursor solutions that gel at physiological conditions for minimally invasive delivery.

Photo-crosslinking: spatial and temporal control using light-activated chemistries.

Click chemistry: bio-orthogonal reactions for reproducible network formation.

Freeze–thaw cycling: physical method (e.g., PVA gels) to create physically crosslinked networks.

3D bioprinting and extrusion printing: produce shape-defined hydrogels and scaffolds with controlled architecture.

Microfluidic/emulsion templating: generate uniform hydrogel particles (micro gels) for injectable delivery.[8]

6. Nanocomposite and Hybrid Approaches

Embedding inorganic nanoparticles (gold, iron oxide) imparts photothermal or magnetic responsiveness and can modulate mechanical strength and release profiles.[7]

7. Surface Functionalization and Targeting

Conjugation of targeting ligands (peptides, antibodies, aptamers) enables active tumor targeting. Surface charge and hydrophilicity tuning improve circulation and tissue penetration.[2]

8. Sterilization and Stability Considerations

Choose sterilization methods (gamma, ethylene oxide, filtration) compatible with payload stability. Assess long-term storage strategies (lyophilization, cold storage) and reconstitution behavior. [3]

9. Characterization and Quality Control

Physicochemical tests: swelling ratio, gel fraction, porosity, mechanical testing (rheology). Release kinetics: in vitro studies under simulated physiological and tumor conditions. Biological: cytotoxicity, hemocompatibility, in vivo efficacy and bio distribution. [9]

10. Scale-up and Manufacturing

Adapt fabrication (continuous mixing, flow reactors, photopolymerization rigs) for reproducibility and monitor batch-to-batch consistency in GMP-compliant processes. [1]

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11. Regulatory and Translational Considerations
Address biocompatibility, degradation product safety, sterilization validation, and regulatory pathway for combination products (drug-device). Early engagement with regulators accelerates translation.[6]

**Role of smart hydrogel in cancer therapy:**

1.Localized and Sustained Drug Delivery
Smart hydrogels enable in-situ formation or implantation at tumor sites, maintaining high local drug concentrations and prolonged release. This reduces systemic exposure and improves the therapeutic index compared with systemic chemotherapy.[2]

2. Stimulus-Triggered Targeting and Release
Hydrogels engineered with pH-, redox-, enzyme-, temperature-, or light-responsive moieties selectively release payloads in the tumor microenvironment (TME), exploiting tumor acidity, high glutathione, or overexpressed enzymes for site-specific drug delivery and reduced off-target toxicity.[1]

3.Combination and Multimodal Therapy
Hydrogels can co-deliver chemotherapeutic drugs, immunomodulators, nucleic acids, photosensitizers, or nanoparticles. This enables synergistic approaches (chemo-photothermal, chemo-immuno, gene + drug) that improve tumor kill and overcome resistance.[6]

4.Reduced Dosing Frequency & Improved Patient Compliance
Sustained-release hydrogel systems lower dosing frequency and blunt peak plasma levels, improving adherence and reducing side effects from high bolus dosing. This is particularly valuable for cytotoxic agents with narrow therapeutic windows.[3]

5.Tumor Microenvironment (TME) Modulation
Hydrogels can be used to modulate the TME — delivering cytokines, immune checkpoint inhibitors, or enzymes that remodel extracellular matrix — thereby improving immune cell infiltration and drug penetration. This supports immunotherapy and combination regimens.[8]

6.Minimally Invasive & Postoperative Local Therapies
Injectable, thermoresponsive or pH-sensitive precursors allow minimally invasive delivery that gels in situ. Hydrogels applied to surgical margins can deliver adjuvant therapy locally to reduce recurrence and promote wound healing.[1]

7.Theranostics and Image-Guided Therapy
By incorporating imaging contrast agents (MRI, CT, fluorescent probes) or responsive nanoparticles, hydrogels enable combined therapy + diagnostics (theranostics), allowing visualization of delivery and monitoring of therapeutic response.[7]

8.Reduction of Systemic Side Effects
Localized, stimulus-triggered release reduces systemic drug distribution and toxicity (e.g., myelosuppression, gastrointestinal toxicity), enabling higher local drug exposure with fewer adverse events.[2]

9.Enhanced Tumor Accumulation: EPR and Active Targeting
Hydrogel-based carriers and encapsulated nanoparticles exploit the enhanced permeability and retention (EPR) effect and can be functionalized with ligands (antibodies, peptides) for receptor-mediated tumor uptake, increasing local accumulation.[5]

10. Overcoming Drug Resistance & Controlled Intracellular Release
Redox- or enzyme-responsive hydrogels can release payloads intracellularly (e.g., upon disulfide cleavage in high-GSH tumor cells), delivering drugs directly into resistant cancer cells or co-delivering sensitizers to overcome resistance mechanisms.

11. Support for Local Immunotherapy
Hydrogels can present antigens, cytokines, or adjuvants locally to activate antitumor immune responses with lower systemic cytokine exposure, improving safety of immunotherapies.[6]

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12. Versatility for Personalized and Combination Approaches
Because composition and responsiveness are highly tunable, hydrogels can be tailored to tumor type, treatment regimen, and patient-specific needs supporting precision oncology strategies.[3]

**Recent advances of adaptive smart hydrogel:**

**1.Multi/Dual stimuli responsive or programmable Hydrogel :**
Recent designs integrate more than one trigger for instance, pH + redox, or enzyme + temperature or embed logic-based or programmable responses that ensure the gel releases the therapeutic payload only when multiple tumor-specific conditions are simultaneously satisfied. This enhances targeting specificity and significantly reduces off-target drug leakage. For example, nanocellulose /PNIPAM composite hydrogels have been engineered to exhibit logic-gate-like behavior, responding to dual stimuli to control drug release in a highly selective manner[40]

**2. Immunomodulatory & vaccine-style hydrogels:**
Hydrogels are now engineered to deliver checkpoint inhibitors, cytokines, adjuvants, or antigen payloads locally to the resection bed or tumor to boost anti-tumor T cell responses and form tertiary lymphoid structures (TLSs). Hydrogel vaccine platforms (slow release + immune cell recruitment) are an active and growing application.[41]

**3. In situ-forming, injectable hydrogels for locoregional therapy:**
Injectable gels that form at the tumor/resection site enable minimally invasive delivery of chemo, immunomodulators, or combined therapeutics with sustained local exposure useful after tumor resection to reduce local recurrence. Recent reviews and preclinical papers emphasize in situ gels as a translationally attractive format. [42]

**4. Hybrid multifunctional systems (therapy + imaging/theranostics)**
Integration of photothermal agents, radiosensitizers, or imaging contrast into hydrogels supports combined PTT/chemotherapy or image-guided local therapy. Several 2024–2025 reports show improved tumor ablation when combining PTT and controlled chemo release from hydrogels[6]

**5. Injectable and self healing hydrogel:**
Injectable, self-healing adaptive hydrogels are delivered minimally invasively as a liquid and form a depot in situ, autonomously repair their network after mechanical disruption (self-healing), and respond to tumor-relevant stimuli (pH, redox, enzymes, ROS, temperature, light, magnetic fields) to release payloads or change properties. The combination enables prolonged, localized drug exposure, repeated mechanical resilience in vivo, and on-demand/triggered therapy with reduced systemic toxicity.[8]

**Application of adaptive smart hydrogel:**

**1.Localized chemotherapy:** sustained DOX (doxorubicin) or paclitaxel release to maximize tumor exposure and minimize systemic toxicity (multiple preclinical reports). [43]

**2.Post-surgical adjuvant therapy:** implants or in situ gels placed in resection cavities that slowly release immunotherapies or chemo to suppress recurrence.[42]

**3.Cancer vaccines & local immunotherapy:** hydrogels delivering antigens + adjuvants or checkpoint inhibitors to concentrate immune activation at the tumor site.[41]

**4.Combination regimens:** chemo + PTT (photothermal agents in gel), chemo + immunotherapy, and enzyme-activatable prodrugs released from gels — these multimodal strategies show synergistic tumor killing in animal models. [6]

**5.Tumor microenvironment (TME) remodeling:** gels that scavange ROS, release enzymes or modulators to normalize the ECM and improve immune or nanoparticle penetration. [44]

**6.Gene and Nuclic acid delivery:** Hydrogels can encapsulate siRNA, mRNA, or CRISPR-Cas9 complexes and protect them from degradation. They release genetic material in response to intracellular triggers like GSH or ROS. Reference pdf for this[45]

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**Challenges and Limitations:**

1. Biocompatibility, immunogenicity and local toxicity

Smart materials (polymers, cross linkers, nanoparticles) can cause unexpected local inflammation or immune activation; degradation products may be toxic. Careful in-vivo testing is required because in vitro cell assays often under-predict inflammation. [2]

2. Unpredictable in-vivo stimulus responsiveness

pH, ROS, enzymes, temperature or external triggers inside patients vary spatially and temporally. A hydrogel designed to respond at a single stimulus threshold may fail or release drug prematurely or not at all in clinical tumors. [46]

3. Tumor heterogeneity and penetration (limited distribution within solid tumors)Dense extracellular matrix, high interstitial pressure, and variable vasculature hinder hydrogel infiltration and even local drug diffusion limiting efficacy against heterogeneous or poorly perfused tumor regions.[47]

4.Stability and premature degradation / clearance

Enzymatic degradation, hydrolysis, or mechanical stress can degrade the gel earlier than intended, reducing local residence time and therapeutic window. Conversely, overly persistent gels risk chronic foreign-body reactions. [48]

5. Scale-up, manufacturing complexity and quality control

Many "smart" hydrogels rely on multi-component chemistries, nanoparticles or biological cargoes producing them reproducibly at GMP scale (sterility, batch-to-batch consistency, defined crosslinking) is nontrivial and raises costs. [49]

6. Regulatory and translational hurdles

Combination products (device + drug, or polymer + biologic) face complex regulatory pathways. Lack of long-term safety data and standard assays for stimulus-responsiveness complicate approval.[50]

7.Imaging, monitoring and dosimetry in patients

It's hard to noninvasively measure in-body gel location, integrity, and real-time release. Without reliable imaging/BIOMARKERS, clinical dose titration and patient selection are difficult. [51]

8. Interactions with the tumor microenvironment (TME) — unintended effects

Hydrogels can alter local oxygenation, pH or immune cell recruitment in ways that reduce efficacy or promote resistance—especially problematic when combined with immunotherapies or radiotherapy.[11]

9. Payload stability (proteins, nucleic acids, cells)

Encapsulated biologics (antibodies, cytokines, mRNA/siRNA, cells) can be denatured, lose activity or be released inactivated if the hydrogel chemistry or manufacturing conditions are not optimized.[6]

**Future perspective:**

1.Clinical integration with immunotherapy (locoregional immune modulation).

Adaptive hydrogels that locally release checkpoint inhibitors, cytokines, or tumor vaccines on demand will be a major route to boost antitumor immunity while reducing systemic immune-related adverse events. Expect hydrogel-based locoregional immunotherapy to move from preclinical validation toward early clinical testing. [52]

2.Precision & personalized hydrogels (patient-matched formulations).

Combining patient tumor profiling (biomarkers, proteomics, metabolomics) with modular hydrogel chemistries will enable personalized trigger thresholds (pH/GSH/enzymes) and drug cocktails tailored to each patient's tumor biology. Integration with ex-vivo tumor models will shorten the path to individualized formulation selection.[53]

3.Theranostic & image-guided adaptive systems.

Embedding imaging reporters or MRI/US/optical contrast agents into responsive hydrogels will permit real-time readout of activation and drug release (closed-loop therapy), improving dose control and enabling theranostic clinical workflows.[11]

4. Better in vitro co-clinical testing using hydrogel tumor models.

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Hydrogels used as 3D tumor models / organoids will not only serve research but will act as companion diagnostic platforms to predict a patient's response to a given hydrogel therapy prior to implantation. This can reduce animal use and de-risk translational steps. [54]

5. Data-driven design and AI acceleration.

Machine learning and physics-informed models will speed optimization of polymer composition, degradation kinetics, and trigger sensitivity — shrinking experimental cycles and enabling multi-parameter optimization of release profiles for complex payloads. (Emerging reviews highlight computational/engineering approaches as a key next step.) 6. Modular "plug-and-play" platforms for rapid payload swapping.

Standardized hydrogel backbones with interchangeable payload modules (small molecules, biologics, cells) and validated release-triggers will permit faster preclinical pipelines and make regulatory filings more modular and efficient.

7. New biologically relevant triggers and multisensoring.

Beyond pH/GSH/ROS/temperature, future hydrogels will sense enzymatic signatures, metabolite gradients, and bioelectric fields — and combine multiple sensors to reduce false positives from tumor heterogeneity.

8. Long-term safety, biodegradation profiling, and immunogenicity studies.

As more candidates approach human studies, comprehensive profiling of degradation pathways, metabolite toxicity, and immune responses (acute and chronic) will be essential to satisfy safety regulators and clinicians. [10]

9. Clinical trial designs & locoregional endpoints.

Early clinical studies will focus on locoregional endpoints (local recurrence, wound bed clearance, drug concentration at resection margins) rather than systemic survival alone — enabling clearer early signals for efficacy. Adaptive trial designs and companion diagnostics will further de-risk development.[6]

10. Convergence with cell therapies and regenerative approaches.

Hydrogels that co-deliver engineered immune cells (e.g., CAR-T/NK) or support local tissue repair while releasing immunomodulators will open hybrid regenerative-oncology approaches for complex resection sites. [51]

11. Ethical, economic, and access considerations.

To avoid inequities, developers must consider cost, supply chain, and cold-chain needs. Simpler, room-temperature-stable hydrogel systems and off-the-shelf modular kits will be important for global access.

5. Combination multimodal therapy as the norm (chemo + PTT/PDT + immuno).

Smart hydrogels will increasingly host synergistic multimodal payloads (chemotherapeutics, photothermal agents, photosensitizers, immunomodulators) with staged, stimulus-programmed release to exploit temporal synergies between modalities.

## III. CONCLUSION:

Adaptive smart hydrogels have emerged as a transformative platform in the field of cancer therapeutics and drug delivery, offering precise, responsive, and patient-tailored treatment strategies. Their capacity to dynamically respond to multiple physiological and external stimuli enables localized, sustained, and controlled release of anticancer agents, thereby improving therapeutic efficacy while minimizing side effects. By combining properties such as biocompatibility, biodegradability, injectability, and self-healing behavior, these hydrogels bridge the gap between conventional drug delivery systems and next-generation intelligent biomaterials. Despite remarkable progress, challenges such as large-scale fabrication, long-term stability, and clinical validation remain key barriers to translation. Future research should focus on integrating nanotechnology, gene delivery, and bioengineering approaches to design multifunctional and programmable hydrogels capable of real-time monitoring and adaptive response within the tumor microenvironment. Overall, adaptive smart hydrogels hold immense potential to redefine precision oncology by enabling safer, more effective, and personalized cancer treatments.

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