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Review Article

Thermo-Responsive Hydrogels for Hyperthermia-Triggered Drug Release in Tumors

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ABSTRACT

Thermo-responsive hydrogels represent an innovative class of smart materials showing great promise for heat-triggered drug delivery in cancer treatment. These hydrogels, commonly made from polymers like PNIPAAm, Pluronic F127, and PEG-based copolymers, can shift from a liquid to a gel state at body temperature or slightly above. This unique property enables site-specific and controlled drug release at tumor locations in a minimally invasive manner. Their thermal sensitivity, along with their compatibility with biological systems and protective drug-carrying capacity, makes them valuable tools in targeted cancer therapy. However, certain limitations persist, including low drug-loading capacity, potential instability in the body, toxicity concerns related to synthetic ingredients, and inconsistencies in tumor environments. Future research aims to overcome these issues by incorporating natural polymers like chitosan and alginate and designing systems that can also respond to pH or enzymatic changes. Combining these hydrogels with targeting agents and imaging tools may further improve their clinical

INTRODUCTION

Hydrogels are water-filled polymer networks that combine solid-like elasticity with fluid-like permeability. Their crosslinked structure gives them softness and flexibility, while the high water content allows transparency and transport of molecules. These characteristics enable unique behaviors like swelling and responsiveness, blending the properties of both solids and liquids.[1]Thermo-sensitive hydrogels, such as poly(N-isopropylacrylamide) (pNIPAAM), poloxamer, PEG/PLGA, and chitosan, respond to temperature changes by swelling or shrinking, enabling controlled drug release. These hydrogels

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improve local drug penetration, spatial and temporal control, and bioavailability, making them ideal for drug delivery.[2] Controlled drug delivery is extensively utilized in cancer treatment and tissue regeneration. Among emerging systems, thermosensitive hydrogel-based drug delivery has gained significant attention due to its ability to encapsulate drugs efficiently and enable their controlled release in response to temperature changes, offering a promising approach for targeted and sustained therapeutic effects.[3] Thermosensitive hydrogels are temperature-responsive materials that undergo a reversible sol–gel transition with changes in ambient temperature. When exposed to specific temperature stimuli, temperature-sensitive polymers shift from a dispersed micellar state to a dense, three-dimensional network. This transition, triggered at the critical solution temperature (CST), results from hydrophobic interactions among polymer chains, leading to self-assembly and hydrogel formation in aqueous environments.[4]The sol–gel transition is particularly attractive due to its simplicity in formulation, where drugs or biological molecules are incorporated via straightforward solution mixing. These systems exhibit excellent biocompatibility and can be engineered for biodegradability, ensuring safe degradation into non-toxic byproducts. Their versatility supports applications such as solubilizing poorly water-soluble drugs, achieving sustained or controlled drug release, and delivering sensitive biomacromolecules like proteins and genes. Additionally, they are useful for cell encapsulation and tissue engineering scaffolds.[5] Injectable thermosensitive hydrogels are polymer solutions that remain fluid at room or lower temperatures, allowing easy encapsulation of therapeutic agents or cells through simple mixing. Once injected, they undergo sol–gel transition at body temperature, forming in situ hydrogels that function as drug reservoirs or scaffolds for cell growth. These hydrogels degrade naturally after fulfilling their therapeutic role.[6] A series of enzymatically degradable PEG hydrogels with adjustable degradation rates were developed by varying the ratio of two cross-linkers: a matrix metalloproteinase (MMP)-sensitive degradable peptide and a non-degradable PEG-dithiol[7]. Huang L et al. study about the in situ injectable chitosan/ PEG hydrogel for disc repair and found that fast-forming injectable chitosan/PEG hydrogel (CSMA-PEGDA-L) was developed by combining methacrylated chitosan (CSMA) with aldehyde-terminated PEG (PEGDA) through photo-crosslinking and Schiff base reactions. This dual-crosslinked hydrogel showed superior compressive strength and low cytotoxicity to nucleus pulposus cells. When injected into rat tail IVD defects, it significantly slowed degeneration, as shown by radiological and histological evaluations. This study suggests that the CSMA-PEGDA-L hydrogel could be a promising, minimally invasive therapeutic approach for preventing or reducing IVD degeneration progression.[8]

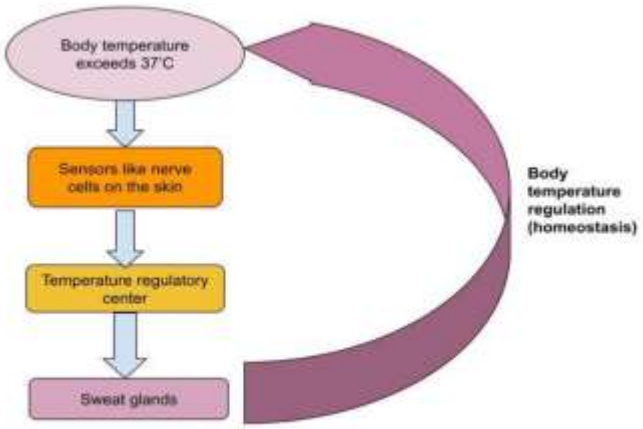

Fig 1:- Homeostasis mechanism of regulation of body temperature through sweating

Body temperature is tightly controlled by the body's homeostatic mechanisms, which maintain a consistent and predictable daily rhythm. Typically, it ranges from a low of about 36 °C in the early morning to a peak near 37.5 °C in the late afternoon. An elevated body temperature can result from various causes. When it occurs due to a failure in the body's ability to regulate heat, it is termed hyperthermia. However, if the temperature increase is part of a controlled physiological response to infection or illness, it is classified as a fever. The distinction between hyperthermia and fever lies in whether the body's internal regulation systems are functioning normally.[9]

Homeostasis is maintained through a regulatory reflex loop involving five components: sensor, setpoint, error detector, controller, and effector. A sensor detects changes in a regulated variable (e.g., blood glucose), while controlled variables (e.g., gluconeogenesis) adjust to maintain balance. The controller (often endocrine cells or neurons) interprets the error signal and activates effectors to restore balance. Negative feedback systems counter deviations by producing opposite responses, while anticipatory (feedforward) controls act before changes occur. Positive feedback, though less common, reinforces stimuli, as seen during labor when oxytocin release increases contractions until delivery. Together, these mechanisms maintain physiological stability and respond to internal changes.[10] Hyperthermia, raising tumor tissue temperature to 40–43 °C, is used alongside radiotherapy and chemotherapy to enhance treatment outcomes. Advances in modeling and planning systems have improved in vivo power distribution control, enabling the development of multiantenna applicators and advanced temperature/E-field monitoring tools like MR thermometry and electro-optical sensors. Phase III clinical trials have shown hyperthermia's benefits in improving local control and survival in cancers such as breast, cervical, and glioblastoma. Emerging research highlights its role in enhancing gene and immunotherapy. However, precise spatial and temporal temperature control, especially in deep tissues, is essential to fully realize its clinical potential.[11] May JP et al. found that targeted drug delivery is advanced by temperature-sensitive liposomes (TSLs), which protect drugs in circulation and release them at heated tumor sites (~41 °C). ThermoDox® enhances release and uptake in tumors, while combining TSLs with MR-guided focused ultrasound enables precise, localized chemotherapy with real-time monitoring of drug release.[12] Norouzi M, et al. found that Injectable biodegradable hydrogels provide an

effective alternative to traditional chemotherapy by enabling localized and sustained release of anticancer drugs directly at the tumor site, thereby minimizing damage to healthy tissues and reducing systemic side effects. Various types of hydrogels—including thermosensitive, pH-sensitive, photosensitive, dual-sensitive, and targeted systems—have demonstrated improved therapeutic outcomes in cancer treatment. These advanced hydrogel-based drug delivery systems offer greater precision and efficacy, making them a significant advancement over conventional systemic chemotherapy in modern oncology.[13]

Thermosensitive hydrogel

Controlled drug delivery systems are extensively used in cancer treatment and tissue regeneration. Thermosensitive hydrogels have emerged as a promising platform in this field, offering the ability to encapsulate drugs and release them in response to temperature changes. This temperature-triggered release enhances targeted delivery and therapeutic effectiveness.[14] Thermosensitive hydrogels are temperature-responsive materials that undergo a physical state transition with changes in ambient temperature, shifting between sol and gel phases. When exposed to specific temperatures, temperature-sensitive polymers transform from a dispersed micellar state into a dense three-dimensional network. This transition, known as phase separation, occurs above or below a critical solution temperature (CST) and is primarily driven by hydrophobic interactions between polymer chains. As a result, the polymers self-assemble and aggregate in aqueous environments to form a stable hydrogel structure.[15]

Mechanism

Thermogelation in aqueous polymer solutions occurs through various mechanisms, some of which remain under investigation. A common explanation involves the reduction in polymer solubility due to changes in hydrophilicity with temperature. In water, three key interactions influence behavior: polymer–polymer, polymer–water, and water–water. For polymers with a lower critical solution temperature (LCST), an increase in temperature leads to a decrease in system free energy (ΔG), making polymer–water interactions unfavorable. This thermodynamic shift is explained by the relation $\Delta G = \Delta H - T\Delta S$, where the rise in entropy (ΔS)—primarily from enhanced water–water interactions—outweighs the enthalpy change (ΔH), resulting in the hydrophobic effect. Structural transitions such as micelle packing and coil-to-helix formation contribute to polymer network formation at the critical temperature. These conformational changes drive reversible physical crosslinking, allowing the gel to revert back to solution once the thermal stimulus is removed.[16]

Polymers used for thermosensitive hydrogel:-

Table 1:- different polymers and there characteristics used in thermosensitive hydrogel preaperation

Source	Name	Characteristic	Reference
Natural Polymers	Cellulose	it lacks inherent thermosensitive properties. Therefore, to impart temperature-responsive behavior, cellulose-based formulations often require the addition of thermosensitive agents or chemical modifications.	[17]
	Chitosan	Second most abundant natural polymer and is highly suitable for biomedical applications. However, it exhibits very low or negligible inherent thermosensitive properties, often requiring the	[18]

		incorporation of thermoresponsive agents or chemical modification to enable its use in temperature-sensitive drug delivery systems or hydrogel formulations.	
	Hyaluronic Acid	excellent biocompatibility and biodegradability. it exhibits good thermosensitive properties, making it highly suitable for temperature-responsive hydrogel formulations	[19]
	Gelatin	it exhibits poor intrinsic thermosensitive properties. Due to its limited temperature responsiveness, it often requires chemical modification or blending with thermosensitive polymers to enhance its performance in temperature-triggered drug delivery and biomedical applications.	[20]
	Collagen	exhibits poor intrinsic thermosensitivity. Its limited response to temperature changes restricts its standalone use in thermoresponsive applications, often necessitating combination with other thermosensitive materials to improve its functionality in temperature-triggered drug delivery or tissue engineering systems.	[21]
	Agrose	exhibits poor thermosensitivity under physiological conditions. Its gelation and melting temperatures are typically too high for responsive behavior in the human body, limiting its effectiveness in thermoresponsive drug delivery without modification or blending with other thermosensitive polymers.	[22]
Synthetics	Pluronic	exhibits good thermosensitivity, making it suitable for temperature-responsive applications. However, it has low mechanical strength and is non-degradable, which limits its long-term use in biomedical applications without structural reinforcement or chemical modification.	[23]
	Poly(N-isopropylacrylamide) PNIPAAM	demonstrates excellent thermosensitivity, undergoing a sharp phase transition near body temperature.	[24]
	Polylactide-polyethylene glycol-Polylactide (PEGPLA-PEG)	thermosensitive and biodegradable copolymer.	[25]
	Poly(oligo(ethylene glycol) methacrylate) (POEGMA)	biocompatible and biodegradable polymer that exhibits good thermosensitive properties, making it a promising candidate for temperature-responsive drug delivery and biomedical applications.	[26]
	Polyphosphazene	biocompatible and biodegradable polymers with non-toxic degradation products, making them emerging candidates for anti-cancer drug delivery applications.	[27]

Intelligent polymer hydrogels that alter their structure and volume in response to external stimuli offer exciting opportunities in advanced technologies and medical applications. Natural polymer-based hydrogels are particularly attractive due to their eco-friendliness, abundance, and excellent biocompatibility. Depending on the type of stimulus, these hydrogels are categorized into temperature-, pH-, light-, electric-, redox-, enzyme-, magnetic-, and multi-responsive types.[28] Unlike traditional controlled-release forms, intelligent systems use stimuli-responsive polymers to sense changes and trigger reversible release. [29] Chitosan-based thermosensitive hydrogels for wound healing and a deeper understanding of their underlying mechanisms. With advancements in tissue engineering and regenerative medicine, enhancing the wound microenvironment has become essential. Chitosan-based thermosensitive hydrogels are gaining attention due to their temperature-responsive gelation, biocompatibility, and adjustable degradability.[30]Phan VG et al. study presents a robust, injectable, and 3D-printable hydrogel formed by incorporating cellulose nanocrystals (CNCs) into amphiphilic poly(ε-caprolactone-co-lactide)-b-poly(ethylene glycol)-b-poly(ε-caprolactone-co-lactide) (PCLA) copolymers. CNCs enhanced mechanical strength by bridging PCLA micelles, enabling a transition from flowable sols to stable hydrogels at physiological temperature. These hydrogels effectively encapsulated both hydrophobic doxorubicin and hydrophilic lysozyme via hydrophobic and hydrogen bonding interactions, providing controlled release.[31]

Chen JP et al. study and investigated thermosensitive hydrogels for intravesical cisplatin delivery to the bladder. Poly(N-isopropylacrylamide) (PNIPAM) was grafted onto hyaluronic acid (HA) to form HPN, and further modified with gelatin to produce HPNG. These copolymers exhibited gelation at lower concentrations (3%) compared to PNIPAM (8%). Structural and drug delivery properties were examined using SEM, LCST, hydration ratio, and in vitro release studies. Incorporating HA and gelatin modified the hydrogel's microstructure, with gelatin enhancing fibrous structure. LCST values for PNIPAM, HPN, and HPNG were 32.3°C, 32.0°C, and 30.7°C, respectively. HPN and HPNG showed significantly higher hydration than PNIPAM. Drug release was slower from hydrogels, with HPNG releasing only 52% of cisplatin over 8 hours. In vivo rat studies revealed enhanced bladder drug concentration with PNIPAM and HPNG after 6 hours, without tissue toxicity. These findings suggest that HPNG hydrogels are promising carriers for safe, localized, and sustained cisplatin delivery in bladder cancer therapy.[32]

Gelatin-based pH- and temperature-responsive magnetic hydrogels (MH-1 and MH-2) were developed for targeted cancer chemo/hyperthermia therapy. Gelatin was functionalized and copolymerized with DMAEMA, magnetic nanoparticles, and crosslinked using TEGDMA. A thermosensitive polymer, PNIPAAm-SH, was grafted via thiol-ene chemistry. The hydrogels demonstrated porous structures and strong hydrogen bonding, allowing high doxorubicin loading (72–77%). Drug release was effectively triggered by pH and heat. In vitro studies confirmed their cytotoxic effect, especially under combined chemotherapy and hyperthermia, showing enhanced anticancer efficacy. These results indicate that the hydrogels are promising candidates for smart, stimuli-responsive drug delivery in cancer treatment.[33]

Integration with Cancer Hyperthermia Therapies

Hyperthermia (≥39°C) enhances cancer therapy by disrupting DNA repair, inducing apoptosis, and modulating heat shock proteins. It boosts immune responses, especially when combined with immunotherapy. Mild hyperthermia activates immune cells, while higher temperatures release tumor antigens. Photothermal nanoparticles enable targeted heating, making hyperthermia a promising, cost-effective adjuvant treatment.[34] Chemotherapy is widely used in cancer treatment but faces challenges like side effects and drug resistance. Hyperthermia offers fewer side effects but lacks precise control. Combining both using natural and stimuli-responsive hydrogels and nanomaterials enhances drug delivery, reduces toxicity, and improves therapeutic outcomes through synergistic chemo/hyperthermia cancer treatment strategies[35].

Zheng Y and there colleague studied an injectable, temperature-sensitive hydrogel based on chitosan (CS) was developed for safe and effective colon cancer treatment through combined hyperthermia and chemotherapy. In the presence of β-glycerophosphate (β-GP), the hydrogel forms in situ at body temperature after injection. It encapsulates doxorubicin (DOX) and MoS_2/Bi_2S_3-PEG (MBP) nanosheets, enabling localized photothermal therapy while minimizing systemic drug exposure and toxicity. The CS/MBP/DOX (CMD) hydrogel achieved notable photothermal efficiencies of 22.18% and 31.42% under NIR I and NIR II irradiation, respectively, even at low MBP concentrations. DOX release was temperature-sensitive and controlled by laser stimulation. The hydrogel also exhibited antibacterial activity, offering a multifunctional platform for targeted, efficient cancer therapy.[36]Huang S et al. study introduces an injectable, thermosensitive hydrogel (DAML/H) for treating multidrug-resistant (MDR) hepatocellular carcinoma (HCC). Incorporating doxorubicin (DOX) and gold–manganese oxide (Au–MnO) nanoparticles in liposome micelles, the hydrogel enables on-demand, NIR-triggered drug release and real-time MRI monitoring. DAML/H offers sustained therapeutic delivery for 14 days, strong photothermal effects, and prolonged tumor retention. In vivo results confirmed its synergistic chemo–photothermal efficacy and modulation of resistance-related proteins, making it a promising long-acting platform for targeted cancer therapy.[37] Pang X et al. presents a smart, injectable hydrogel system (GDMH) designed for synergistic tumor therapy by co-delivering a chemotherapeutic drug (docetaxel, DTX) and a protein-based immunotherapeutic agent (granzyme B, GrB). The hydrogel is both thermo- and pH-responsive, allowing it to gel at body temperature and degrade in the tumor microenvironment. It enables sustained release of pH-sensitive mini micelles that deeply penetrate tumors and escape lysosomes for efficient drug delivery. The combination of GrB and DTX at an optimal ratio showed enhanced antitumor activity in vitro and in vivo, including prevention of post-surgical tumor recurrence, making GDMH a promising cancer therapy platform.[38]

Radiotherapy has advanced significantly since the discovery of X-rays, offering precise tumor targeting while sparing healthy tissue. Supported by strong clinical evidence, it improves survival, preserves organs, and reduces costs. Recent innovations, like particle beam therapy and computer-guided systems, have enhanced its effectiveness in multidisciplinary cancer treatment approaches.[39] Radiotherapy treats around 50% of cancer patients but may cause long-term side effects, especially cardiac issues. Hyperthermia enhances radiation effectiveness by disrupting protein function and DNA repair. It sensitizes tumor cells without harming normal tissue and, when combined with gene therapy, improves treatment precision, tumor targeting, and overall therapeutic outcomes. [40]Radiotherapy

resistance in solid tumors is often caused by hypoxia and glutathione (GSH) overexpression. To address this,Wang Z and there colleague studied sorafenib-loaded PLGA hydrogel (SPH) was developed and combined with microwave (MW) hyperthermia. Upon intratumoral injection, MW heating enhances oxygen delivery and induces SPH disintegration, enabling sorafenib release. This dual strategy enhances radiotherapy (RT) efficacy by overcoming hypoxia ("first layer" sensitization) and inhibiting GSH synthesis to elevate reactive oxygen species (ROS) ("second layer" sensitization). Both in vitro and in vivo studies demonstrated that SPH combined with MW hyperthermia achieves synergistic RT sensitization and tumor suppression, offering a promising approach for effective cancer treatment.[41] Li T et al. developed thermosensitive hydrogel (Au-DOX-Gel) using Pluronic® F127 was developed to deliver gold nanoparticles (AuNPs) and doxorubicin (DOX) for enhanced cancer chemoradiotherapy. AuNPs acted as radiosensitizers while DOX served as a chemotherapeutic agent. This formulation enabled sustained intratumoral release. In vitro and in vivo studies showed effective tumor suppression under radiation, with reduced tumor growth, inhibited cancer cell proliferation, and confirmed safety in mice. The combined treatment significantly enhanced therapeutic outcomes, suggesting Au-DOX-Gel as a promising and safe strategy for improving targeted chemoradiotherapy in cancer treatment.[42]

Immunotherapy is a key cancer treatment, but immune resistance limits its success. Autophagy, a stress-response mechanism, supports tumor survival and affects immune function. Its modulation can either hinder or enhance immunotherapy. Targeting autophagy offers a promising strategy to overcome immune resistance and boost antitumor immune responses[43]Yang A, et al perform a hydrogel/nanoparticle-mediated strategy was developed to enhance cancer immunotherapy by combining antiangiogenic treatment with immune modulation. This system enables the sustained release of apatinib, anti-CD47 antibody (aCD47), and CpG oligonucleotides, maximizing therapeutic synergy. Apatinib normalizes tumor vasculature, improving immune cell infiltration, while aCD47 enhances macrophage-mediated phagocytosis by blocking tumor immune evasion. CpG acts as an immune adjuvant, boosting dendritic cell activation and antigen presentation. The combination therapy significantly increases effector immune cells ($CD4^+$, $CD8^+$ T cells, NK cells, active DCs) and decreases immunosuppressive cells (MDSCs, M2 macrophages), effectively shrinking tumors and preventing metastasis. This approach shows strong potential for improved, long-term cancer immunotherapy.[44] Meng Z et al. Immunomodulatory therapy for melanoma faces challenges like low immune cell infiltration and reduced tumor immunogenicity, leading to limited responses. To address this, a combined treatment strategy with low toxicity and strong immune activation is needed. In this study, insoluble immune adjuvant imiquimod (R837) was formulated into nanocrystals, coated with polydopamine (PDA), and embedded in a chitosan hydrogel (CGP) to create R837@PDA@CGP (RPC). RPC induced immunogenic cell death (ICD) and increased cytotoxic T cell infiltration, transforming the tumor into an in situ vaccine. This enhanced the cancer-immunity cycle, suppressing melanoma growth, metastasis, and recurrence.[45]

Recent Advances and Case Studies

Hyperthermia enhances radiotherapy and chemotherapy by heating tumors to 40–43 °C. Accurate treatment planning improves outcomes by optimizing energy absorption and temperature

distribution. Advances in imaging, thermal and biological modeling have made hyperthermia planning clinically viable, aiding in applicator selection, heat evaluation, and real-time guidance for improved cancer treatment.[46] Polymeric nanocarriers are tiny particles used to deliver medicines, proteins, or genes to specific parts of the body. They are popular in cancer treatment because they can release their contents when triggered by certain conditions like heat, pH, light, or magnetic fields. These smart carriers help control when and where the drug is released, making treatment more effective and reducing side effects. Some of them can also be used for imaging, helping doctors see where the medicine goes. These nanocarriers are safe, water-soluble, and can be easily changed for different uses, making them very useful in modern medicine and diagnostics.[47]

Hybrid hydrogels have emerged as promising materials for applications in drug delivery and tissue repair. In this study, an injectable polyethylene glycol (PEG)-based hydrogel was developed using thiol-maleimide crosslinking. It included temperature-sensitive liposomes (TSLs) and peptides that respond to enzymes found in the body. The hydrogel was mechanically strong and adaptable, with the ability to release drugs when exposed to heat or enzymes. Doxorubicin, a common chemotherapy drug, was loaded into TSLs with high efficiency and released in response to heat. The system was also biocompatible, making it a useful tool for targeted, controlled cancer treatment.[48]

Diseased tissues often show distinct traits—such as altered pH, enzyme activity, redox balance, glucose levels, and temperature—compared to healthy ones. Autonomous drug release systems (ADRS) are designed to sense these internal changes and respond by releasing medication in a controlled, timely, and site-specific manner. There work explores how these biological cues act as internal triggers for smart drug delivery, highlighting the latest innovations, ongoing challenges, and emerging possibilities in creating responsive therapies that adapt to the dynamic environment of diseased tissues.[49]

Thermal magnetic resonance (ThermalMR) is a new technique that combines heating, temperature tracking, imaging, and molecule detection using an MRI scanner. This study tested if ThermalMR could control the release of a sample drug from special heat-sensitive nanogels. Using a 7.0-tesla MRI, researchers released a model drug (BSA-FITC) by gently heating the gel. The results matched those from regular water-bath heating. ThermalMR can safely heat and track drug release inside the body, making it a promising tool for personalized, image-guided cancer treatments in the future.[50]

Conventional chemotherapies have limited safety due to narrow therapeutic windows. To address this, a theranostic core@shell system was developed using electrohydrodynamic methods. The pH-responsive Eudragit L100 shell with SPIONs encased a thermo-responsive PNIPAM/ethyl cellulose core carrying carmofur. Adjusting polymer ratios changed particle shapes. Fibers showed thermo-responsive drug release, while particles did not. All forms protected SPIONs in acidic pH and showed MRI-visible, pH-dependent relaxivity. A linear relationship between MRI signals and drug release enables real-time, image-guided monitoring of therapeutic delivery.[51]

Block copolymers (BCPs) have been widely studied for their ability to self-assemble in solution into a variety of nanostructures, including spheres, cylinders, vesicles, and more complex or hierarchical forms. With advances in synthetic chemistry, researchers can now design BCPs with diverse architectures and chemical compositions, leading to unique structural and functional properties. These self-assembled nanostructures

have found promising applications in nanotechnology, materials science, and biomedicine. The review explores recent developments, emerging trends, and application-driven innovations in BCP self-assembly, showcasing their potential in creating advanced, functional materials for a broad range of scientific and industrial uses.[52]

In recent years, hybrid platforms combining transition metal complexes (TMCs) and gold nanoparticles (AuNPs) have emerged as powerful tools for precision cancer theranostics. TMCs—especially those based on platinum, ruthenium, and iridium—offer unique photochemical properties, including singlet oxygen generation for photodynamic therapy and intrinsic imaging capabilities. When paired with AuNPs, known for their excellent biocompatibility and heat-generating thermoplasmonic effects, these hybrids enable targeted, light-activated treatment with minimal side effects. This mini-review explores how these smart, light-responsive nanoconstructs can be activated with visible to near-infrared (Vis–NIR) light to achieve spatially and temporally controlled, dual-action cancer therapies with enhanced efficacy.[53]

Liposomes are versatile, non-toxic nanocarriers capable of encapsulating both water-soluble and fat-soluble drugs, making them highly valuable in cancer therapy. Recent advancements have led to the development of smart, stimuli-responsive liposomes that offer superior drug loading, stability, and targeted delivery compared to traditional formulations. These liposomes can release their therapeutic payload in response to specific internal or external triggers, such as pH, temperature, or light, enabling precise site-specific drug delivery. This targeted approach enhances treatment effectiveness, reduces damage to healthy tissues, and helps prevent metastasis. They shows recent innovations in smart liposome systems for controlled anticancer drug delivery.[54]

Previous research on magnetic nanoparticle-based hyperthermia mainly focused on heat generation using monometallic or metal oxide nanocomposites. However, recent advancements show that these nanoparticles can also trigger localized drug release, expanding the role of hyperthermia beyond thermal therapy. There study highlights the potential of combining magnetically induced heating with controlled drug delivery, particularly using core-shell nanostructures. Such systems enable targeted, on-demand treatment, paving the way for more effective and personalized medical applications in cancer therapy and beyond.[55]

There study developed heat-sensitive microspheres for cancer treatment and imaging. Researchers created nanoparticles called layered double hydroxides (LDH) loaded with chemotherapy drugs like methotrexate (MTX) and 5-fluorouracil (5FU). These were combined with magnetic nanoparticles (SPIONs) that work as MRI contrast agents, and all were encapsulated into polymer microspheres using spray drying. The microspheres, observed as concave-shaped particles, showed even distribution of contents and released drugs more quickly at higher temperatures. Magnetic properties also changed with temperature, making them useful for MRI-guided therapy. Lab tests on cancer cells showed effective treatment using a combination of heat and chemotherapy, proving strong potential for future cancer theranostics.[56]

Hyperthermia can destroy cancer cells by raising body temperature, but targeting tumors without harming nearby healthy tissue remains difficult. Combining nanotechnology with hyperthermia improves precision by enabling better nanoparticle penetration into tumors, allowing localized heat treatment. Unlike radiotherapy, hyperthermia uses non-ionizing radiation, making it a safer therapeutic option which highlights current research on using nanoparticles in hyperthermia-

based cancer therapy, focusing on how these particles induce cytotoxic effects and enhance treatment effectiveness in targeted cancer treatment approaches.[57]

Mild photothermal therapy (mPTT, 42–45°C) is gaining attention in cancer treatment due to its lower side effects and ability to improve tumor environments by enhancing blood flow and reducing tissue density. Although less intense than traditional PTT, mPTT alone may not fully eliminate tumors. Recent research focuses on boosting its effectiveness by overcoming cellular defenses or combining it with other therapies for stronger results. They discussed advancements in nanoplatforms for mPTT, their imaging potential, current limitations, and future research directions to enhance therapeutic outcomes.[58]

Cancer remains one of the leading causes of death worldwide and is often linked to oxidative stress caused by metabolic changes and harmful reactive species. While antioxidants show promise in treating cancer, their clinical use is limited due to poor bioavailability, weak targeting, and side effects. To overcome these challenges, advanced drug delivery systems are being developed. These include lipid-based carriers, polymers, nanoemulsions, cyclodextrins, and smart liposomes, which help improve the solubility, stability, and effectiveness of poorly water-soluble drugs. A specific case study highlights the use of such systems in managing oral cancer and reducing related dental problems.[59]

Catalytic therapy enhances treatment effectiveness and reduces side effects by converting non-toxic substances in the body into toxic reactive species that destroy diseased cells. Advances in material science and nanotechnology have led to the development of catalytic biomaterials and nanomedicines designed to trigger or enhance these reactions. They summarizes recent progress in using such materials for biomedical applications, focusing on activation by internal signals or external stimuli like light, heat, ultrasound, or magnetic fields. It also discusses the safety, compatibility, and current challenges of these therapies, along with future opportunities to advance their clinical use in treating various diseases.[60]

They review and explains how near-infrared (NIR)-responsive smart carriers are used in medicine, especially for drug delivery and cancer treatment using heat. These carriers can release medicine in response to body conditions like pH or heat and can target tumors directly. NIR light can go deep into the body and create heat, making it useful for controlled drug release. Recent research has focused on safe, NIR-absorbing materials that can carry drugs. They also looks at current progress and future goals to make these treatments more effective and safer.[61]

Over the past decade, photothermal therapy (PTT) has emerged as a promising treatment method due to its non-invasive approach, strong antibacterial action, and reduced side effects compared to traditional drugs. It not only suppresses bacterial growth but also encourages cell growth and speeds up wound healing. Graphene-based hydrogels, known for their strong NIR responsiveness and photothermal abilities, are leading materials for such treatments. There study explores recent innovations in these hydrogels, emphasizing their potential in advancing PTT-based therapies and broader biomedical applications.[62]

Non-healing wounds are a growing concern, placing strain on patients and healthcare systems. Traditional dressings often fall short due to the complex healing process. Magneto-responsive biocomposites offer a promising alternative, with features like biocompatibility, remote control, and precise drug release. The researcher explores advances in magnetic wound dressings, covering healing stages, material design, and effects such as magnetic alignment and stimulation. It also highlights how these materials regulate cells,

enhance signals, and support tissue repair, while discussing future challenges and clinical potential.[63]

There review study discusses the promising role of stimuli-responsive nanoparticles in cancer treatment and diagnosis. These smart nanocarriers can react to internal triggers like oxidative stress, acidic pH, high temperatures, and enzyme levels, as well as external stimuli such as light and magnetic fields. The study focuses on nanocarriers functionalized with the Arg-Gly-Asp (RGD) peptide, which targets integrin receptors often overexpressed in tumors. It highlights recent advancements in using these targeted, responsive systems to improve drug delivery, reduce resistance, and enhance the effectiveness of cancer therapies.[64]

The study presents a novel approach for breast cancer treatment using quercetin-loaded magneto-liposomes (Que-MLs) for combined chemotherapy and magnetic hyperthermia (chemo-HT). $CoFe_2O_4$ magnetic nanoparticles were integrated with liposomes and loaded with the anticancer agent quercetin. The resulting Que-MLs showed a high encapsulation efficiency of 69% and a particle size of 38 nm. In vitro studies on MCF-7 breast cancer cells revealed significant cytotoxic effects, inducing both early and late apoptosis. Cellular uptake and internalization were confirmed through fluorescence imaging and TEM. Overall, Que-MLs demonstrated strong potential as an effective, targeted, and multi-modal therapeutic system for breast cancer therapy.[65]

Cancer remains a major global health challenge with limited treatment effectiveness and high unmet needs. Magnetic nanovesicles (MNVs), created by combining nanovesicles with magnetic nanoparticles, offer a promising solution by enabling both targeted therapy and diagnostic capabilities. These multifunctional systems can be guided to tumor sites using external magnetic fields and monitored in real time. MNVs also support magnetic hyperthermia, producing localized heat to kill cancer cells or trigger controlled drug release. They highlights their unique potential in cancer diagnosis and treatment, while addressing key considerations like safety, delivery efficiency, and future prospects for clinical applications.[66]

Photothermal therapy promotes tumor antigen release but often fails to fully activate anticancer immunity. To overcome this, a novel NIR-triggered in situ vaccine (FCDs-A/C@HGs) was developed, combining Fe-doped carbon dots, AIPH, and cyclophosphamide in a thermosensitive hydrogel. Upon NIR exposure, localized heating and alkyl radical release trigger immunogenic cell death. This system inhibits regulatory T cells, promotes dendritic cell maturation, and enhances CD8+ cytotoxic and memory T cell responses, offering a powerful platform for tumor suppression and long-term immune activation.[67]

Cancer continues to pose a major challenge due to incomplete tumor elimination and frequent relapse from drug resistance. To address this, smart nanocarriers have emerged as promising tools in cancer therapy. These carriers enhance drug bioavailability, ensure precise tumor targeting, minimize damage to healthy tissues, and allow controlled drug release at the disease site. Additionally, they protect therapeutic agents from degradation and respond to tumor-specific conditions. They explores a range of smart nanoencapsulation strategies, including organic, inorganic, hybrid materials, and biomembrane-based systems, discussing their advantages, drawbacks, and future potential in advancing targeted and efficient cancer treatment.[68]

Photothermal therapy (PTT) using nanomaterials has emerged as a promising strategy for cancer treatment by converting light energy into heat to destroy tumors and stimulate immune responses. However, PTT alone may not prevent cancer recurrence or metastasis. Combining PTT with

immunotherapy enhances its effectiveness. This chapter reviews recent developments in inorganic nanomaterials for PTT, focusing on their light-to-heat conversion mechanisms. It also covers commonly used inorganic materials such as noble metals, semiconductors, and carbon-based nanostructures. Furthermore, the mechanisms behind nanomaterial-based PTT, recent progress in photothermal immunotherapy, and the challenges and future prospects of this combined approach are discussed.[69]

Challenges and Limitations in Clinical Applications

Although hydrogels show significant promise for cancer therapy, their clinical application remains limited due to several critical challenges. Poor biodistribution reduces their ability to localize effectively at target sites, while insufficient biocompatibility may trigger unwanted biological responses. Moreover, weak tumor penetration diminishes their therapeutic potential. Thermosensitive hydrogels, in particular, face difficulties transitioning from lab-scale success to clinical use. Tumor architecture hinders their deep infiltration, and they often exhibit low drug loading efficiency—especially for hydrophobic drugs—and lack sustained release capabilities. Synthetic polymers offer structural flexibility but may lack ideal biodegradability and safety. Additionally, tumor heterogeneity necessitates personalized treatment strategies, complicating hydrogel design and optimization.[70][71]

Where Rostamipoor M et al. found that Chitosan-based temperature-sensitive hydrogels have emerged as promising carriers in controlled drug delivery due to their excellent biocompatibility, gelation at body temperature, and versatile functionality. They are widely applied in ocular and nasal drug delivery, nutrient encapsulation, wound healing, and tissue regeneration, offering precise and effective therapeutic transport across biomedical applications.[72]Wang Z and there colleague found that PEG-based hydrogels have gained significant attention as drug delivery systems in cancer therapy due to their biocompatibility, easy modification, and high drug-loading efficiency. They explores innovative PEG hydrogel designs, focusing on controlled drug release through both stimuli-responsive (pH, enzyme, light, magnetic, temperature) and non-responsive mechanisms. PEG hydrogels offer precise drug release at tumor sites, enhancing therapeutic outcomes. Their commercial potential is promising, but challenges remain in clinical translation, requiring further research to improve stability, targeting accuracy, and large-scale applicability.[73]

Farasati Far B give us the review offers a valuable foundation for researchers aiming to optimize hydrogel encapsulation in drug delivery and regenerative medicine researchers focused on drug and cell delivery, offering protection to therapeutic agents from harsh physiological conditions and enhancing their efficacy and bioavailability. Despite this, researchers have yet to reach consensus on the optimal hydrogel type, encapsulation strategy, or clinical application. In this systematic review of studies published between 2008 and 2023, nine were selected based on defined inclusion criteria. The findings highlight that physicochemical properties—such as porosity, swelling behavior, and degradation rate—play crucial roles in encapsulation efficiency. The chosen encapsulation technique—physical, chemical, or biological—directly influences therapeutic stability and bioavailability. However, challenges remain for researchers, including inadequate control of release profiles, limited shelf stability, and possible immune responses.[74] Binaymotlagh R et al. highlights recent advances and remaining challenges in developing liposome–hydrogel systems for improved cancer treatment outcomes.

Thermosensitive hydrogels and liposomes have shown great promise due to their biocompatibility, biodegradability, and ability to respond to physiological stimuli. Thermosensitive hydrogels, in particular, offer localized, sustained drug release ideal for cancer therapy. However, their clinical translation remains limited due to challenges such as poor tumor penetration, low drug loading efficiency—especially for hydrophobic drugs—unsatisfactory mechanical strength, and potential immune responses. Integrating liposomes with thermosensitive hydrogels presents a multifunctional platform that may overcome these limitations.[75]

Future Perspectives in Cancer Treatment

Thermosensitive hydrogels hold future potential for targeted drug delivery, especially in cancer treatment. They offer biocompatibility, protect drugs from degradation, and minimize side effects through localized release. Advancing these systems may improve drug stability, release control, and clinical outcomes, making them ideal candidates for future personalized therapies.[76] Wang QQ et al study shows that Gastrointestinal cancers, especially colorectal cancer, remain a leading cause of cancer-related deaths. Future cancer treatment aims to integrate hydrogel-based technologies with precision medicine to improve therapeutic outcomes. Hydrogels offer targeted drug delivery and support for precise interventions like endoscopic resection, minimizing side effects and enhancing treatment efficacy. These biomaterials hold great promise for personalized cancer therapies. Despite advancements, challenges in clinical translation remain. Future efforts must focus on interdisciplinary innovation to optimize hydrogel systems for broader, more effective application in cancer care.[77] Targeted drug delivery systems, especially those using self-assembled nanocarriers, offer promising therapeutic outcomes by directing treatments to tumor-specific receptors or antigens. Injectable hydrogels (IHs) are a key component but present challenges, including compatibility with sensitive biomolecules, avoiding cytotoxicity, and ensuring controlled release. Issues like gelation kinetics, injection viscosity, mechanical strength, and degradation timing must be addressed. Future IHs should be designed with precise application-specific features that respond to disease conditions while maintaining biological safety and therapeutic efficacy for improved cancer treatment outcomes.[78] Future directions in cancer research highlight the promising role of thermodynamic approaches in improving diagnosis, staging, and treatment. Early detection can be significantly enhanced using advanced biosensors engineered through thermodynamic optimization to achieve high sensitivity and selectivity. Cancer staging may benefit from analyzing entropy changes or using thermodynamically driven nanoparticles for imaging and biomarker detection. For therapy, strategies like thermosensitive hydrogel-based delivery systems and photothermal-thermodynamic combinations show strong potential. Advancing these approaches through deeper understanding and innovation could lead to more accurate, efficient, and personalized cancer treatments in the years to come.[79]

CONCLUSION

Thermo-responsive hydrogels represent an innovative and adaptable platform for hyperthermia-triggered drug release in cancer therapy. Polymers such as poly(N-isopropylacrylamide) (PNIPAAm), Pluronic F127, and poly(ethylene glycol) (PEG)-based copolymers exhibit unique sol–gel transitions near physiological temperatures, allowing for localized, controlled, and minimally invasive delivery of chemotherapeutics directly to tumor

sites. These hydrogels offer advantages such as high biocompatibility, protection of encapsulated drugs from degradation, and the potential for tailored drug release in response to thermal stimuli, making them highly relevant in personalized medicine. However, several limitations restrict their widespread clinical application. These include poor loading efficiency for hydrophobic drugs, in vivo instability due to inconsistent gelation or degradation kinetics, and potential cytotoxicity of certain synthetic polymers. The tumor microenvironment's heterogeneity and varying responses to thermal triggers also pose significant barriers to therapeutic consistency. Looking forward, future advancements are expected to address these challenges through the development of hybrid hydrogels that combine synthetic and natural polymers like chitosan and alginate, enhancing both functionality and biocompatibility. Dual-responsive systems sensitive to both temperature and biological cues (e.g., pH, enzymes) offer improved control over drug release. Integration with diagnostic tools and real-time imaging could further enhance the precision and efficacy of cancer treatment using thermo-responsive hydrogels.

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