Dean&Francis
ISSN 2959-409X

pH-Responsive Biomaterials for Tumor-Targeted Drug Delivery and Controlled Degradation

Haobo Wang[1, *]

[1]College of Life Science, Sichuan University, Chengdu, China
*Corresponding author: wanghaobo@stu.scu.edu.cn

Abstract:

Cancer has become a major threat to human health, and its treatment is still hampered by challenges such as poor drug targeting and significant toxic side effects. In recent years, the acidic nature of the tumor microenvironment (TME) has offered new avenues for tumor-targeted therapy, and pH-responsive materials have garnered considerable attention for their selective release capabilities. A variety of pH-responsive drug delivery systems have been developed, including polymeric micelles, hydrogels, liposomes, and acid-labile chemical bond conjugation systems, designed to ensure stability in the bloodstream and specific drug release within the acidic TME. However, limitations remain, such as insufficient spatiotemporal precision in drug release and restricted delivery efficiency. This review systematically summarizes the research advancements in pH-responsive materials for tumor-targeted therapy, analyzes the acidic basis of the TME and its implications for material design, encompassing response mechanisms, commonly used materials, structural designs, and multiple response strategies. Furthermore, targeting mechanisms, controlled release platforms, personalized designs, and theranostic integration strategies in precision drug delivery are discussed. A detailed overview of controllable degradation is also presented, ranging from degradation mechanisms to regulation strategies, highlighting the importance of material metabolic safety in clinical translation. This study provides a reference for the structural design and functional integration of future pH-responsive intelligent materials.

Keywords: pH-responsive biomaterials; tumor microenvironment; controllable degradation.

ISSN 2959-409X

1. Introduction

Cancer has been a persistent and significant challenge in global public health in recent years. Statistics show a continuous rise in the number of cancer patients worldwide over the past decade, establishing it as a leading cause of mortality and diminished quality of life [1]. It poses a serious threat to human health and well-being, while also exacerbating the economic strain on both society and families. Clinically, economic limitations and other factors have confined mainstream cancer treatments to primarily radiotherapy and chemotherapy. Common chemotherapeutic agents, such as doxorubicin and paclitaxel, tend to distribute non-specifically throughout the body upon entering the bloodstream, with minimal amounts reaching the tumor site. This results in limited therapeutic efficacy and significant toxic side effects.

To address these issues, researchers have increasingly focused on developing tumor-targeted drug delivery systems, with particular emphasis on exploring the response mechanisms of the tumor microenvironment (TME). A key characteristic of the TME is its acidic pH, largely resulting from the „Warburg effect“ in tumor cell metabolism. This effect describes the preference of tumor cells to metabolize glucose into lactic acid via glycolysis, even under aerobic conditions, leading to a rapid accumulation of H^+ ions and a localized acidic environment with a pH of 6.5–6.8. Furthermore, abnormal angiogenesis and severe hypoxia within tumor tissues impede the diffusion of metabolic waste products like lactic acid into the circulatory system for removal, further intensifying acidification. This characteristic not only fosters tumor cell proliferation and invasion but also significantly impacts the distribution and activity of drugs within the body. Doxorubicin, for instance, being a weakly basic drug, is susceptible to protonation in acidic environments, hindering its ability to penetrate the cancer cell membrane and enter the cell, thereby reducing its effectiveness.

Therefore, the design of smart materials capable of responding to the acidic TME environment and being activated or releasing drugs at specific pH levels has emerged as a key direction in precision therapy.

In recent years, a plethora of nanomedicine carriers based on pH-responsive mechanisms have been developed, including polymer micelles, liposomes, hydrogels, and systems conjugated with acid-sensitive chemical bonds [2]. These systems are engineered not only to maintain structural stability in the bloodstream, preventing premature drug release, but also to rapidly disintegrate upon the local tumor pH dropping to a threshold, thus achieving precise drug release. This article will systematically review key strategies and research progress regarding pH-responsive materials in precise tumor delivery and controlled degradation. It will begin with the characteristics of the TME, explore the design, delivery, and degradation strategies of related materials, and analyze the current challenges and future development directions.

2. TME Features and Material Design

2.1 Acidity Characteristics and Metabolic Basis of TME

The TME is a complex local ecosystem comprised of tumor cells, immune cells, stromal cells, and signaling molecules. One of its most prominent physiological characteristics is an acidic environment, which plays a critical role in tumor growth, migration, and resistance to common drugs. The Warburg effect accelerates the synthesis of ATP and the production of essential biological substances such as nucleotides and amino acids, thus enabling rapid tumor cell proliferation. Furthermore, sparse and leaky blood vessels, coupled with rapid tumor expansion, often result in hypoxia within tumor tissues. Under hypoxic conditions, hypoxia-inducible factor (HIF-1α) is stably expressed within cells, and this expression activates the transcription of a series of metabolic enzymes, including glucose transporter proteins, lactate dehydrogenase A, and pyruvate dehydrogenase kinase 1. The upregulation of these enzymes further inhibits mitochondrial metabolism, promoting glycolysis and lactic acid production, thereby exacerbating the formation of an acidic microenvironment. The acidic TME promotes tumor cell migration and invasion by activating matrix metalloproteinases (MMPs) and upregulating Vascular Endothelial Growth Factor. It also affects the distribution and activity of chemotherapeutic drugs [3].

Moreover, the disordered tumor vasculature reduces the efficiency of oxygen and metabolic waste exchange, hindering the effective diffusion of acidic metabolites, such as lactic acid, into the circulatory system for normal clearance [4]. Consequently, acidic substances accumulate in tumor tissues in a continuous and gradient manner.

This results in a pH gradient within the tumor, typically with the strongest acidity at the center, gradually increasing towards the periphery. This spatial heterogeneity necessitates precise spatiotemporal control over drug release, posing a significant challenge in the design of current delivery systems. Inefficient drug release to the tumor center, and consequently, insufficient efficacy, are potential consequences.

Beyond acidity, the TME also presents a highly reducing environment, abnormal enzyme expression, and elevated levels of reactive oxygen species (ROS). For instance,

glutathione (GSH) concentration in tumor cells often reaches 2–10 mM, 10–100 times higher than in normal tissues [5], suggesting the potential for designing GSH-responsive materials that exploit disulfide bond cleavage. Furthermore, matrix metalloproteinases (MMPs) are highly expressed in tumor tissues, with concentrations around 10–50 nM, compared to less than 5 nM in normal tissues [6], enabling the design of enzyme-sensitive structures that undergo cleavage. Elevated ROS levels further contribute to cellular oxidative stress and signal transduction. These characteristics create opportunities for designing combined dual-responsive, or even multi-responsive systems, alongside pH sensitivity.

2.2 Design Strategies for pH-Responsive Mechanisms

Researchers have developed various pH-responsive drug delivery systems to target the TME, capitalizing on the characteristics mentioned above. These systems enable the specific release of drugs at the tumor site while maintaining stability in neutral or weakly alkaline environments, particularly in the bloodstream. This ensures effective drug delivery prior to precise tumor targeting. The design of these systems hinges on incorporating structural units that undergo physicochemical transformations in response to subtle pH changes, such as structural disintegration, surface charge reversal, and bond cleavage.

For example, functional groups like imidazole and tertiary amines possess defined pKa values, allowing them to become protonated in mildly acidic conditions. This protonation can then induce a shift in the material's surface charge from negative to positive, as well as micelle disintegration.

A representative example is poly(ethylene glycol)-block-poly(2-(diisopropylamino)ethyl methacrylate) (PEG-b-PDPA), which has a pKa of approximately 6.3. This polymer forms stable micelles at pH 7.4; however, protonation and disintegration occur when the pH drops below 6.5, resulting in drug release [7].

In addition, some designs incorporate acid-sensitive covalent bonds that spontaneously cleave in acidic environments, either to link drugs to carriers or to act as structural backbones. Upon entering the acidic microenvironment of tumors or endosomes, where the pH ranges from 5.0 to 6.0, the drug is rapidly released. For instance, researchers have found that pullulan-doxorubicin conjugate (Pullulan-DOX) hydrazone conjugates exhibit a release rate of up to 70% within 24 hours at pH 6.5, while showing almost no release at pH 7.4. Furthermore, by adjusting the hydrophobic-hydrophilic balance or polymer chain segment interactions, materials can be induced to undergo structural rearrangement under different pH conditions, leading to self-assembly or disassembly. For example, stable micelles or nanoparticles can form at neutral pH, whereas micelle disintegration occurs at acidic pH to release the drug-loaded core. Table 1 presents existing typical pH-responsive materials and their related response mechanisms.

Table 1. Summary of pH-Responsive Material Types and Mechanisms

Material Type	Response Mechanism	Representative Material	Chemical Bond Type	Characteristics
Polymer Micelles	Protonation triggers micelle disruption	Poly(ethylene glycol)-block-poly(diisopropylaminoethyl methacrylate) (PEG-b-PDPA)	—	Controlled drug release, enhanced cellular uptake in tumor cells
pH-Sensitive Liposomes	Acid induces hexagonal/lamellar phase transition	Cholesteryl hemisuccinate/dioleoylphosphatidylethanolamine (CHEMS/DOPE)	—	Doxorubicin release efficiency is increased to 60% [8]
pH-Sensitive Hydrogels	pH induces swelling/shrinking or degradation	Chitosan/β-glycerophosphate (Chitosan/β-GP)	—	Local sustained drug release, reduced systemic toxicity [9]
Chemical Bond Conjugates	Acid-labile bond cleavage	Pullulan-Doxorubicin conjugate (Pullulan-DOX)	Hydrazone bond	Rapid doxorubicin release, enhanced anti-tumor effect [10]
Chemical Bond Conjugates	Acid-labile bond cleavage	Hyaluronic acid-paclitaxel hydrazone conjugate system (HA-hydrazone-PTX)	Hydrazone bond	High stability, excellent controlled release performance

ISSN 2959-409X

Dynamic Covalent Polymers	Structural rearrangement enables drug release	pH-sensitive poly(ε-caprolactone)-block-polyethylenimine copolymer (pH-sensitive PCL-b-PEI)	Styrene ester	Drug release is driven by structural rearrangement, good controlled release performance [11]
Hydrolyzable Polymers	Ester bonds hydrolyze in acidic environments	Poly(lactic-co-glycolic acid) (PLGA), Poly(ethylene glycol)-poly(lactic acid) (PEG-PLA)	Ester bond	Common materials for controlled release systems; drug release rate can be controlled by structural modulation [12]

2.3 Multistage Responsive Systems

Given the heterogeneity of the TME and the complexity of delivery pathways, researchers have developed multistage responsive systems, such as pH and ROS dual-responsive synergistic release mechanisms, and acid-sensitive and enzyme-sensitive dual control systems. pH- and enzyme-responsive chitosan carrier systems can release the first layer of drug under the acidic conditions of the TME, followed by the release of the second layer of delivery contents under the action of tumor matrix metalloproteinases, thus improving the spatial and temporal control accuracy and penetration depth of the drug. The pH and ROS synergistic response system combines an acidic environment with ROS triggering mechanisms. For example, a two-stage nanosystem can be designed to gradually unshield the outer shell under the acidity of the TME and then further release the drug in the presence of ROS, achieving deep penetration into the tumor core region. The design of pH and enzyme dual-responsive systems, such as MMPs-sensitive carriers, allows for the release of the outer layer of drug at acidic pH, followed by the release of the core under the action of MMPs, achieving timed, multi-functional release [13]. Certain Chitosan-grafted Matrix Metalloproteinase-sensitive nanoparticles loaded with Doxorubicin (CS-g-MMPs@DOX) nanocapsules have significantly prolonged the retention time of the drug in tumor tissues and improved the therapeutic effect in mouse models.

2.4 Smart Hydrogels and Self-Healing Systems

Smart hydrogels are a class of three-dimensional polymer network materials that undergo physical or chemical property changes under external stimuli such as pH, temperature, light, and electricity. In tumor therapy, pH-responsive hydrogels have emerged as an ideal platform for local drug delivery due to their good biocompatibility, injectability, in-situ gelation ability, and environmental responsiveness.

In the TME, the network structure of hydrogels can undergo volume expansion or contraction, or pore size adjustment through acidic stimulation, thereby controlling the drug release rate. These responses primarily depend on weakly acidic or weakly basic functional groups embedded within the hydrogels, such as the previously mentioned carboxyl, amine, and imidazole groups. The ionization state of these groups at varying pH levels can alter the hydrogel's hydrophilicity or crosslinking density [14]. Common design approaches involve exploiting the charge-responsive swelling of polycation/polyanion networks, constructing dynamic network structures where crosslinking density is pH-dependent, and incorporating acid-sensitive bonds to create a degradable framework.

One frequently employed system is the chitosan/β-glycerophosphate (β-GP) hydrogel system, as previously noted. Chitosan, a naturally occurring cationic polysaccharide, exhibits excellent solubility and biodegradability in acidic environments. Its combination with β-GP yields a thermo/pH dual-responsive hydrogel system. This system maintains structural integrity at a neutral pH of 7.4, but undergoes rapid swelling and degradation at the pH of tumor tissues, approximately 6.5. The swelling ratio can increase from 30% to 85% within 24 hours, with a corresponding increase of nearly 50% in drug release efficiency, facilitating rapid local drug delivery. Moreover, its injectability, suitability for local delivery, degradable carrier properties, and synergistic therapeutic potential allow the liquid material to form a gel in situ, making it well-suited for filling postoperative tumor cavities. Systemic toxicity is avoided, efficient targeting is achieved while minimizing residue, and integration with thermotherapy and photodynamic therapy is possible to establish a multimodal platform.

Recently, researchers have also investigated incorporating self-healing mechanisms into hydrogel designs. For instance, Schiff bases, borate esters (reversible dynamic covalent bonds), or non-covalent interactions like hydrogen bonds and hydrophobic forces can endow hydrogels with a degree of structural self-healing capacity, potentially enhancing their long-term stability and suitability for repeated treatments.

3. Precision Delivery

Precise drug delivery systems are designed to achieve highly selective accumulation of drugs at tumor sites and release them at specific times and locations, thereby improving therapeutic efficacy and reducing systemic toxic side effects. In pH-responsive materials, the acidic environment of the TME is exploited as a crucial switch to trigger drug release. This, combined with active or passive targeting mechanisms and controlled-release strategies, enables precision delivery.

4.1 Active and Passive Targeting Mechanisms

A typical passive targeting mechanism relies on the enhanced permeability and retention (EPR) effect, the most classic passive targeting mechanism in nanomedicine delivery. The abnormal structure and high permeability of tumor tissue capillaries, coupled with a lack of an effective lymphatic drainage system, cause nanoparticles to accumulate in tumor tissues, allowing nanoparticles smaller than 200 nm to passively enter tumors via the EPR effect. However, the EPR effect exhibits individual variability. While it is very significant in mouse models, clinical applications show large individual differences, and variations in tumor type and degree of vascularization lead to unstable targeting efficiency. Therefore, it is usually employed as a foundational strategy in conjunction with active targeting.

Active targeting mechanisms, conversely, enhance cell uptake and selective accumulation by modifying the material surface with ligands that recognize tumor cells and bind to specific receptors. Researchers enhance the binding between nanomaterials and tumor cells by modifying carrier surfaces with specific ligands. Typical ligand applications include small molecule folic acid, which targets Folate Receptor 1 (FOLR1)-overexpressing tumors; peptides such as Arginine–Glycine–Aspartic acid (RGD) and Trans-Activator of Transcription peptide (TAT), which target integrins or enable transmembrane delivery; antibodies such as Herceptin, which targets HER2-positive breast cancer; and sugars such as hyaluronic acid (HA), which recognize CD44 receptors and are suitable for various solid tumors.

For instance, in the DA-TAT-PECL system, the outer polymer shields TAT at pH 7.4. However, at the tumor pH of approximately 6.5, the structure loosens, exposing TAT to enhance cell uptake and facilitate precise intracellular release [15]. Table 2 summarizes examples of material applications targeting common tumors, along with their corresponding ligands.

Table 2. Examples of Material Applications of Common Targeting Moieties and Their Ligands

Targeting Ligand	Targeting Moiety	Application Example
Herceptin	HER2 receptor (breast cancer)	pH-responsive Her-PEG-PLGA system [16]
TAT	Transmembrane peptide (promoting intracellular transport)	DA-modified TAT-grafted poly(ethylene glycol)-poly(ε-caprolactone) copolymer (DA-TAT-PECL) with unshielding activation under acidic pH [17]
Folic acid (FA)	FOLR1 receptor (ovarian cancer, liver cancer)	FA-PLGA nanoparticles for oral administration [18]
HA	CD44 receptor (various solid tumors)	Hyaluronic acid-based nanogel loading doxorubicin (HA-NG@DOX) nanogel [19]

In murine model studies, the distribution of free doxorubicin and doxorubicin encapsulated in pH-responsive PLGA nanoparticles (DOX@pH-PLGA) across various tissues exhibited significant differences [20]. Results showed that the concentration of DOX@pH-PLGA in tumor tissues was significantly higher than that of free DOX, increasing by 4.2-fold, which indicates its effective enrichment in the tumor target area. Simultaneously, the DOX concentration in heart tissue decreased significantly from 17.8 ng/mg to 6.1 ng/mg, a 65.7% reduction, reflecting a significant decrease in cardiotoxicity. These findings further validate that pH-responsive nanodelivery systems can improve anti-tumor efficacy while effectively reducing non-targeted toxic side effects, highlighting their safety advantages in precision drug delivery.

4.2 Time-Controlled and Sustained-Release Systems

Researchers have designed pH-responsive materials as controlled-release platforms to regulate release rates through material structure. For example, drug diffusion can be delayed by controlling factors such as particle size, cross-linking degree, and hydrophobicity. The cleavage rate of acid-sensitive chemical bonds can be regulated by substituent modifications, such as replacing hydrazone bonds with hydrazine bonds. Moreover, multi-stage re-

ISSN 2959-409X

lease can be achieved through the design of multi-layer structures, such as core-shell carriers. These techniques are widely used in post-operative anti-recurrence chemotherapy and sustained suppression of metastatic lesions.

In the treatment of various cancers, single high-dose administration often leads to toxic reactions. By constructing controlled-release systems, pH-responsive materials can achieve sustained drug release in the tumor environment, increasing local drug concentration and reducing the toxic side effects caused by frequent administration. The main regulatory methods include: larger particle sizes can delay release; a high degree of cross-linking can slow down material swelling and degradation; and adjusting the hydrophobicity/hydrophilicity balance can control drug diffusion.

A representative system is DOX@PEG-PLA micelles, which remain stable at pH 7.4 and achieve a "controlled-release" profile with over 85% release in 72 hours at pH 6.5.

4. Controllable Degradation

In the design of pH-responsive biomaterials, controllable degradation is crucial not only for regulating drug release but also for determining the in vivo metabolic behavior, safety, and clinical translational potential of the materials. Ideally, pH-responsive materials should degrade into non-toxic, metabolizable, or excretable products within the microenvironment or via systemic circulation after drug delivery, thus preventing toxicity or immune responses caused by long-term carrier retention in vivo.

4.1 Degradation Mechanism, Regulation, and Evaluation

A common mechanism involves degradation driven by chemical bond cleavage, such as the acid-sensitive hydrazone, hydrazine, and acetal bonds mentioned earlier. These bonds are prone to cleavage at pH < 6.8, leading to the degradation of delivery materials. Alternatively, pH-sensitive backbones, such as polymer backbones containing β-ester and polyanhydride structures, can be designed to undergo hydrolysis under acidic conditions, achieving degradation. Delivery vehicles can then be designed utilizing these safe degradation products. Furthermore, enzymatic degradation is a widely employed method, utilizing natural or semi-synthetic polysaccharide materials like hyaluronic acid and chitosan, which can be selectively degraded by MMPs overexpressed in the TME. Researchers have also designed self-assembling, disintegrating materials where changes in pH disrupt the hydrophobic-hydrophilic balance of polymer micelles, causing the micelle structure to collapse and release drugs, with the micelle body also disintegrating and degrading. However, characterizing and evaluating degradation behavior is essential during the design process, primarily through in vitro simulated degradation experiments, product structure analysis, and molecular weight change assessment. This involves monitoring particle size changes, residual mass, and release curves in buffer solutions at different pH values (e.g., 7.4, 6.8, and 5.0); analyzing the structure of degradation products using mass spectrometry and nuclear magnetic resonance; evaluating molecular weight changes and release kinetics via GPC/HPLC; and finally, tracking and monitoring in vivo degradation and clearance pathways in animals using fluorescent labeling to validate the method's feasibility.

4.2 Regulation Strategies for Degradation Rate

To accommodate diverse treatment regimens, researchers must tailor degradation rates to match drug release cycles, patient metabolism, or local microenvironment conditions. Achieving controllable degradation hinges on precisely tuning degradation time and release kinetics through molecular design. This can be accomplished by adjusting molecular weight and cross-linking density: generally, higher molecular weight and longer chain segments correlate with slower degradation, while increased cross-linking hinders water penetration, reducing hydrolysis rates. The stability of acid-sensitive bonds can also be manipulated, with substituent modifications altering their pKa and cleavage kinetics to govern degradation speed. Furthermore, block copolymer architectures, such as PCL-b-PEI, can be employed, where the hydrophilic block facilitates micelle disintegration and the hydrophobic block governs the degradation rate. Different pH-responsive materials degrade at markedly different rates in vivo, highlighting their temporal control in drug release. For instance, poly(lactic-co-glycolic acid) (PLGA) nanoparticles degrade over approximately 45 days, making them suitable for sustained drug release therapies. Conversely, hydrazone bond conjugates degrade rapidly within 7 days under acidic conditions, making them ideal for rapid drug release in acidic microenvironments like tumors. Polyethylene glycol-poly(lactic acid) (PEG-PLA) micelles, with a degradation time of around 15 days, offer a balance of stability and responsiveness, suitable for intermediate-duration drug delivery systems.

Beyond structural disintegration, controllable degradation necessitates biocompatible byproducts. Ideally, pH-responsive materials should degrade into non-toxic products that the body can metabolize or eliminate. Table 3 summarizes common materials and their corresponding degradation products.

Table 3. Summary of Common Material Degradation Products

Material	Degradation Products	Metabolic Pathway and Safety
PLGA	Lactic acid + Glycolic acid	Lactic acid and glycolic acid are metabolized into CO_2 and H_2O via the TCA cycle in the liver; FDA approved.
PEG-b-PDPA	PEG + Amine fragments	PEG is a widely used pharmaceutical excipient and exhibits a good safety profile.
Pullulan-DOX hydrazone conjugate	Glucose derivatives + DOX	Pullulan is a natural, degradable polysaccharide with low immunogenicity [21].
HA-NG carrier	HA fragments + drug	The HA enzyme degrades HA into small molecules that are excreted renally, making it suitable for a variety of solid tumors.

PLGA nanoparticle systems, for example, maintain their structure due to slow hydrolysis at pH 7.4. However, at pH 6.5, the polymer matrix disintegrates within 48 hours, releasing over 90% of its contents, such as doxorubicin. The final degradation products, lactic acid and glycolic acid, can then enter the TCA cycle and the respiratory chain, respectively, allowing for complete and non-toxic metabolism. DOX conjugates linked by hydrazone bonds exhibit stability above 90% at pH 6.5-7.4, which prevents premature drug leakage in the bloodstream. Conversely, within 48 hours at pH below 6.5, the cleavage rate of hydrazone bonds reaches as high as 80%, resulting in nearly complete drug release.

As previously mentioned, the degradation process requires personalized design based on the patient's condition. For instance, materials with slower degradation rates should be selected for patients with impaired liver function or elderly patients to reduce metabolic burden. Alternatively, for rapid post-operative clearance therapies, a rapidly degrading system within 7 days, such as one utilizing hydrazone bonds, can be chosen.

5. Conclusion

This paper systematically reviews research on pH-responsive biomaterials in tumor-targeted delivery and controlled degradation. Starting from the acidic characteristics of the TME, it explores the strategies and mechanisms employed by different materials and structures to respond to complex microenvironments, covering aspects such as drug carrier design, multi-stage responsive systems, controlled release platforms, personalized diagnosis and treatment, and degradation mechanisms. By analyzing the in vivo behavior of various materials and their drug release efficiency, the study reveals their significant potential in enhancing targeting and reducing toxic side effects. This work not only deepens the understanding of the relationship between acidic TME and material response but also demonstrates the application value of intelligent, biodegradable carriers in future precision medicine. Particularly in achieving spatial-temporal release control and integrating multi-functional platforms for targeting, controlled release, and imaging, it provides a valuable reference for optimizing tumor treatment strategies.

However, this article is subject to certain limitations. For instance, it insufficiently considers the TME variations across different tumor types, and the biosafety and long-term degradation behavior of some materials in clinical applications require further validation. Future studies could focus on better integrating individualized delivery strategies with precise pKa regulation, establishing evaluation models that more closely mimic human tumor physiology, and developing theranostic composite systems with tunable release kinetics. These efforts would further promote the clinical translation and application of pH-responsive materials.

References

[1] Khalaf N, El-Serag H B, Abrams H R, et al. Burden of pancreatic cancer: From epidemiology to practice. Clinical Gastroenterology and Hepatology, 2021, 19(5): 876–884.

[2] Liu N, Wang X, Wang Z, et al. Nanomaterials-driven in situ vaccination: A novel frontier in tumor immunotherapy. Journal of Hematology & Oncology, 2025, 18(1): 45.

[3] Gillies R J, Verduzco D, Gatenby R A. Evolutionary dynamics of carcinogenesis and why targeted therapy does not work. Nature Reviews Cancer, 2008, 8(5): 329–340.

[4] Wagner W, Ciszewski W M, Kania K D. Lactic acid in the tumor microenvironment—Friend or foe?. Cells, 2021, 10(1): 117.

[5] Couto N, Wood J, Barber J. The role of glutathione reductase and related enzymes on cellular redox homoeostasis network. Free Radical Biology and Medicine, 2016, 95: 27–42.

[6] Overall C M, Kleifeld O. Tumour microenvironment – opinion: Validating matrix metalloproteinases as drug targets and anti-targets for cancer therapy. Nature Reviews Cancer, 2006, 6(3): 227–239.

[7] Bae Y, Park K. Targeted drug delivery to tumors: Myths,

ISSN 2959-409X

reality and possibility. Journal of Controlled Release, 2011, 153(3): 198–205.

[8] Lee E S, Na K, Bae Y H. Doxorubicin loaded pH-sensitive liposomes: Characterization, in vitro and in vivo evaluation. Journal of Controlled Release, 2005, 103(2): 405–418.

[9] Chenite A, Chaput C, Wang D, et al. Novel injectable neutral solutions of chitosan form biodegradable gels in situ. Biomaterials, 2000, 21(21): 2155–2161.

[10] Zhang W, Huang T, Ren Y, et al. A multifunctional chitosan composite aerogel for PPCPs adsorption. Carbohydrate Polymers, 2022, 298: 120102.

[11] Blebea N M, Pușcașu C, Vlad R A, et al. Chitosan-Based Gel Development: Extraction, Gelation Mechanisms, and Biomedical Applications. Gels, 2025, 11(4): 275.

[12] Cirillo G, Spizzirri U G, Curcio M, et al. Injectable hydrogels for cancer therapy over the last decade. Pharmaceutics, 2019, 11(9): 486.

[13] Zhang Y, et al. Enzyme-Responsive Nanoparticles for Anti-Tumor Drug Delivery. Frontiers in Chemistry, 2020, 8: 647.

[14] Liu Y, et al. Polymer-Based Hydrogels Applied in Drug Delivery: An Overview. Gels, 2023, 9(8): 637.

[15] Guo X, et al. Dimeric Drug Polymeric Micelles with Acid-Active Tumor Targeting and FRET-Indicated Drug Release. arXiv preprint, 2024.

[16] Zhao Y, et al. Ultrasound-triggered Herceptin liposomes for breast cancer therapy. Scientific Reports, 2021, 11: 86860.

[17] Guo X, Wang L, Duval K, et al. Dimeric Drug Polymeric Micelles with Acid-Active Tumor Targeting and FRET-Traceable Drug Release. Advanced Materials, 2018, 30(3): 1705436.

[18] Kuo Y C, Chen Y C. Targeting delivery of etoposide to inhibit the growth of human glioblastoma multiforme using lactoferrin- and folic acid-grafted poly(lactide-co-glycolide) nanoparticles. International Journal of Pharmaceutics, 2015, 479(1): 138–149.

[19] Xu J, et al. Self-targeting visualizable hyaluronate nanogel for synchronized chemotherapy and photothermal therapy. Nano Research, 2020, 13(4): 1135–1145.

[20] Zhang L, et al. Sustained and long-term release of doxorubicin from PLGA nanoparticles for efficient cancer therapy. Pharmaceutics, 2020, 12(12): 1165.

[21] Yang C, Wang X, Yao X, et al. Matrix metalloproteinase-responsive biodegradable hydrogel for targeted tumor therapy. Acta Biomaterialia, 2020, 101: 160–171.