WWW.IJRPR.COM

International Journal of Research Publication and Reviews

Journal Homepage: www.ijrpr.com ISSN 2582-7421

Stimuli-Responsive Drug Delivery Systems: pH, Temperature and Enzyme Triggered Nanocarriers for Site-Specific Therapy *(A Comprehensive Review Article)*

[1]Dr. Nagaraj, [2]Ms Annu Sharma, [3]Ms Sona Thakur, [4]Mr Sachin Sharma, [5]Mrs Neha Yadav,[5]Ms Swati Sharma

[1]Assistant Professor, Akshaya Institute of Pharmacy, Tumakuru, Karnataka
[2]Assistant Professor, GIP, Geeta University
[3]Assistant Professor, Globus College of Pharmacy, Bhopal
[4]Assistant Professor, ITS College of Pharmacy, Muradnagar, Ghaziabad
[5]Associate Professor, HRIT University, Ghaziabad
[5]Associate Professor, Neelkanth College of Pharmacy, Meerut

ABSTRACT

The biggest limitation of conventional chemotherapeutic and drug delivery approaches is that the drug becomes distributed non-specifically throughout the body, giving rise to problems such as systemic toxicity, a low therapeutic index, and poor patient compliance. Stimuli-responsive drug delivery systems (SRDDS), also known as "smart" or "intelligent" nanocarriers, provide an advanced solution to this problem. These nanocarriers remain stable in healthy tissues and release their therapeutic cargo only after reaching the specific pathological site, in response to a physiological or pathological stimulus (such as pH, temperature, or enzyme concentration). This review paper presents a detailed discussion of nanocarrier systems based on the three most extensively studied endogenous and exogenous stimuli — pH, temperature, and enzymes. pH-responsive systems exploit the acidic pH gradient of the tumor microenvironment, endosomes, and lysosomes, while temperature-responsive systems, such as poly(N-isopropylacrylamide) (PNIPAM), show a sharp phase transition around their lower critical solution temperature (LCST). Enzyme-responsive nanocarriers utilize peptide or ester linkers that are cleaved by overexpressed enzymes such as matrix metalloproteinases (MMPs), cathepsins, and esterases. This paper systematically discusses the design principles, materials, mechanisms of drug release, characterization techniques, dual/multi-stimuli combinations, the current status of clinical translation, and future challenges for all three stimuli. It also covers the practical applications of these nanocarriers for site-specific therapy in cancer therapy, colon-targeted oral delivery, cardiovascular disease, and inflammatory conditions. This review will serve as a comprehensive reference document for researchers, pharmaceutical scientists, and students.

Keywords: *Stimuli-responsive nanocarriers; pH-sensitive drug delivery; Thermoresponsive polymers; Enzyme-triggered release; Tumor microenvironment; Site-specific therapy; Nanomedicine; Controlled drug release*

1. Introduction

Over the past three decades, nanotechnology has brought about a paradigm shift in the field of drug delivery. Traditional drug formulations, whether oral tablets or intravenous injections, generally distribute uniformly throughout the body, so that only a small fraction of the drug reaches the target site while a large amount of the drug is left to expose healthy tissues. This non-specific biodistribution creates a particularly serious problem in cancer chemotherapy, where cytotoxic drugs also damage normal proliferating cells (bone marrow, GI epithelium, hair follicles), causing severe side effects such as myelosuppression, alopecia, and cardiotoxicity.

Nanocarriers — such as liposomes, polymeric nanoparticles, micelles, dendrimers, and mesoporous silica nanoparticles — provided the ability for passive accumulation in tumor tissues through the enhanced permeability and retention (EPR) effect, which made first-generation nanomedicines such as Doxil® (liposomal doxorubicin) and Abraxane® (albumin-bound paclitaxel) clinically successful [1,2]. However, the EPR effect is heterogeneous and is not found to be as consistent in human tumors as it appears in preclinical animal models. Furthermore, passive targeting does not control drug release — once a nanocarrier reaches the tumor, the drug can still leak slowly and uncontrollably, or may remain trapped within the carrier without producing a therapeutic effect.

To overcome this limitation, "stimuli-responsive" or "smart" drug delivery systems have been developed. The design philosophy of these systems is that the carrier remains completely stable in blood circulation and healthy tissues (the "off" state), but as soon as it comes into contact with a specific physicochemical signal of the diseased microenvironment (such as a tumor, inflamed tissue, or infected site), a structural or conformational change occurs

and the drug is rapidly released (the “on” state). These triggers are classified into two broad categories: endogenous (internal) stimuli — such as pH, redox potential, enzyme concentration, and hypoxia; and exogenous (external) stimuli — such as temperature, light, magnetic field, and ultrasound [3–5].

This review focuses on the three most wid

ely-studied and clinically relevant stimuli: (i) pH, which exploits the acidic gradient between the tumor extracellular matrix, endosomes, and lysosomes; (ii) temperature, in which thermoresponsive polymers (such as PNIPAM) show a sharp phase transition around their lower critical solution temperature, which can be triggered by mild hyperthermia or the slightly elevated temperature of a tumor; and (iii) enzymes, in which tumor-associated proteases (matrix metalloproteinases, cathepsins) or specific hydrolases release the drug by cleaving substrate-specific peptide or ester linkers [6,7]. In this paper, we systematically explore the fundamental mechanisms, representative materials, design strategies, characterization approaches, dual-stimuli combinations, and the current status of clinical translation for all three stimuli.

2. Rationale: Tumor Microenvironment and Physiological Stimuli

The scientific foundation of stimuli-responsive drug delivery is that diseased tissues — particularly solid tumors — differ significantly from normal tissues in their physicochemical characteristics. Due to the Warburg effect, tumor cells predominantly derive energy from anaerobic glycolysis, whether or not oxygen is available. This results in excessive production of lactic acid, and because of the tumor's poorly organized vasculature, this acid cannot be efficiently cleared, so the extracellular pH drops from the normal-tissue value of 7.4 to approximately 6.5–7.0 [8,9]. At the cellular level, when a nanocarrier enters a cell through endocytosis, it sequentially passes through the early endosome (pH ~6.0–6.5), the late endosome (pH ~5.0–6.0), and finally the lysosome (pH ~4.5–5.0) — the pH continues to decrease until the carrier reaches the degradative compartment [10].

Similarly, the temperature in tumor tissues can also be slightly higher than in normal tissue (locally up to 38–42°C), especially when external hyperthermia (magnetic, ultrasound, or laser-induced) is applied, which provides a controllable exogenous trigger for selectively activating thermoresponsive nanocarriers [11]. The enzymatic environment is also dramatically altered in tumors: matrix metalloproteinases (MMP-2, MMP-9), cathepsin B, urokinase-type plasminogen activator (uPA), and various esterases/phosphatases play a central role in tumor tissue remodeling, invasion, and angiogenesis, and these enzymes are greatly overexpressed compared to healthy tissue [12,13]. Table 1 summarizes representative pH values of these different physiological and pathological compartments, which are used in nanocarrier design.

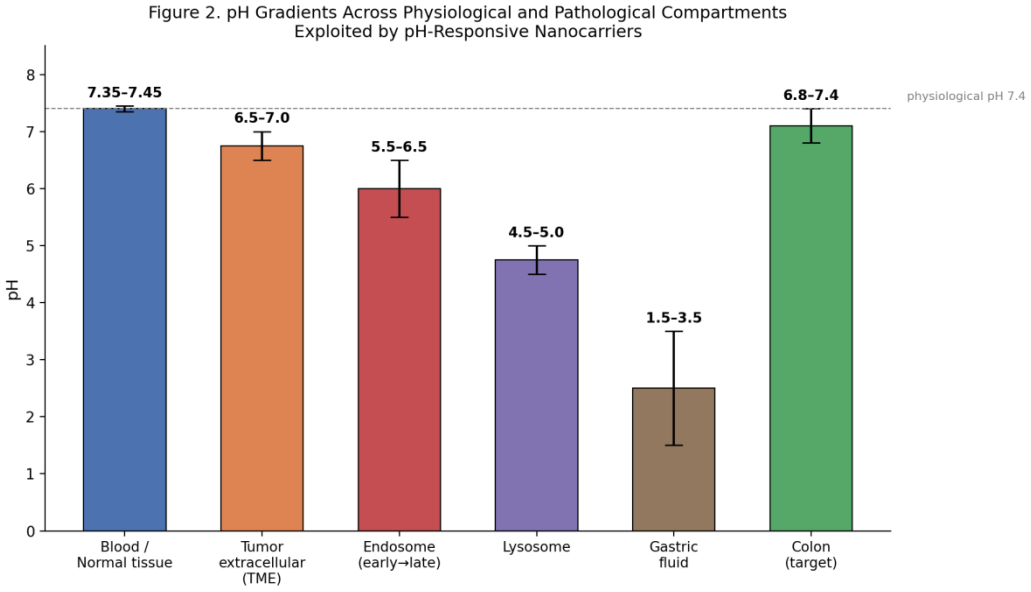


Figure 2. pH gradients in physiological and pathological compartments used in pH-responsive nanocarrier design.

Table 1. Representative pH Values of Different Physiological and Pathological Compartments

Compartment	Typical pH Range	Relevance for Nanocarrier Design
Blood / Normal tissue	7.35 – 7.45	Baseline; carrier must remain stable
Tumor extracellular matrix (TME)	6.5 – 7.0	Primary trigger for extracellular pH-responsive release

Compartment	Typical pH Range	Relevance for Nanocarrier Design
Early / Late Endosome	5.5 – 6.5	Trigger for endosomal escape strategies
Lysosome	4.5 – 5.0	Trigger for acid-labile linker cleavage
Gastric fluid	1.0 – 3.5	Protects drug from acid degradation (enteric coating)
Colon (target region)	6.8 – 7.4	Site of drug release for colon-targeted systems (e.g., Eudragit® S100)

2.1 Classification of Stimuli

Stimuli-responsive nanocarriers are broadly classified into two categories — endogenous (internal) and exogenous (external) stimuli. Endogenous stimuli are naturally present at the disease site, such as pH, redox potential (glutathione concentration), enzyme activity, and hypoxia. Exogenous stimuli are applied from outside, such as temperature (external heating), light (UV/NIR), magnetic field, and ultrasound. Figure 1 schematically illustrates this classification.

Figure 1. Classification of Stimuli-Responsive Nanocarrier Systems

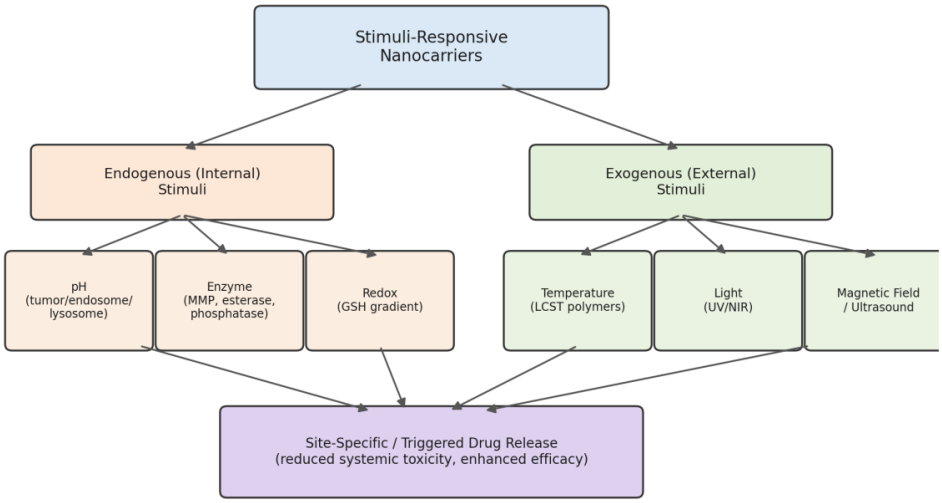


Figure 1. Classification of stimuli-responsive nanocarrier systems based on endogenous and exogenous stimuli.

3. pH-Responsive Nanocarriers

pH-responsive nanocarriers are the most extensively researched category of stimuli-responsive drug delivery, because the pH gradient is a stable and reliable endogenous signal in the body that can be exploited without any external intervention [14,15]. Their design principle is that the physicochemical properties of the material (solubility, charge, conformation, or chemical bond stability) change with pH.

3.1 Mechanism of pH-Responsiveness

pH-responsive nanocarriers primarily work through three mechanisms:

(a) Protonation/deprotonation of ionizable groups: Polymers containing carboxylic acid (–COOH), amine ($–NH_2$), or imidazole groups change their ionization state as pH changes. For example, polymers such as poly(β-amino ester)s and poly(histidine) remain neutral/hydrophobic at physiological pH but protonate and become hydrophilic at acidic tumor or endosomal pH, destabilizing the micelle or nanoparticle and releasing the drug [16,17].

(b) Hydrolysis of acid-labile chemical bonds: Certain specific bonds — such as hydrazone, acetal, ortho ester, and β-thiopropionate — remain stable at neutral pH but hydrolyze under mildly acidic conditions (pH 5–6.5). These bonds are used to covalently attach the drug to the carrier (such as hydrazone-linked doxorubicin conjugates), which cleave at tumor or endosomal pH to release the free drug [18,19].

(c) Charge-reversal and size-switchable strategies: In recent advanced designs, nanoparticles are engineered to maintain a negative surface charge in blood circulation (reducing non-specific cellular uptake and opsonization), but their surface charge becomes positive at the acidic pH of the tumor, enhancing cellular uptake. Similarly, some systems also show programmable size-shrinkage — larger nanoparticles first accumulate in the tumor through the EPR effect, then disassemble into smaller particles in response to acidic pH to achieve deep tumor penetration [20,21].

3.2 pH-Responsive Materials

Many natural and synthetic polymers are used for pH-responsiveness. Chitosan, a cationic natural polysaccharide, is soluble at acidic pH and also has mucoadhesive properties, making it popular for oral and nasal delivery. In contrast, the methacrylic acid copolymers of the Eudragit® series (Eudragit L100, L100-55, S100) are soluble only at neutral to alkaline pH (above 6.0–7.0), so they are extensively used for enteric coating and colon-targeted delivery [22–27]. Poly(acrylic acid), poly(histidine), poly(β-amino ester)s, and calcium carbonate/calcium phosphate-based inorganic nanoparticles also fall into this category. Mesoporous silica nanoparticles are also made pH-responsive by functionalizing them with acid-cleavable linkers or "gatekeeper" molecules (such as cyclodextrin caps or polymer coatings) [28].

3.3 Applications and Representative Examples

The largest application area for pH-responsive nanocarriers is cancer therapy, where both tumor extracellular acidity and the intracellular endosomal/lysosomal pH gradient are exploited. Chemotherapeutic drugs such as doxorubicin, paclitaxel, and cisplatin have been incorporated into polymeric micelles, liposomes, or mesoporous silica nanoparticles through pH-cleavable linkers, resulting in minimal leakage during systemic circulation but rapid release upon reaching the tumor microenvironment [29,30]. Another major application area is colon-targeted oral drug delivery, where Eudragit S100-coated systems are used for local treatment of ulcerative colitis, Crohn's disease, and colorectal cancer, since they protect the drug from gastric acid while selectively releasing it at the near-neutral pH of the colon [24–27].

4. Temperature-Responsive (Thermoresponsive) Nanocarriers

Temperature-responsive nanocarriers are the most well-established category of exogenous stimuli-responsive systems. Their core principle is based on the lower critical solution temperature (LCST) or upper critical solution temperature (UCST) behavior of thermoresponsive polymers.

4.1 LCST and UCST Behavior

LCST is the critical temperature below which a polymer remains completely soluble in water (hydrophilic, extended coil conformation), but above which the polymer dehydrates and collapses, forming a precipitate/aggregate (hydrophobic, globule conformation) [31,32]. The most widely studied thermoresponsive polymer is poly(N-isopropylacrylamide) (PNIPAM), which has an LCST of approximately 32–33°C — slightly below human body temperature (37°C). This means that PNIPAM in its pure form is already in a collapsed state at body temperature. Therefore, PNIPAM is copolymerized with hydrophilic comonomers (such as acrylamide, hydroxyethyl methacrylate) to shift its LCST into the 37–42°C range, so that the drug delivery vehicle remains stable at normal body temperature but collapses and releases the drug in response to mild hyperthermia (local heating) [33–37].

Figure 3. Coil-to-Globule Phase Transition of a Thermoresponsive Polymer (e.g., PNIPAM) Around Its LCST

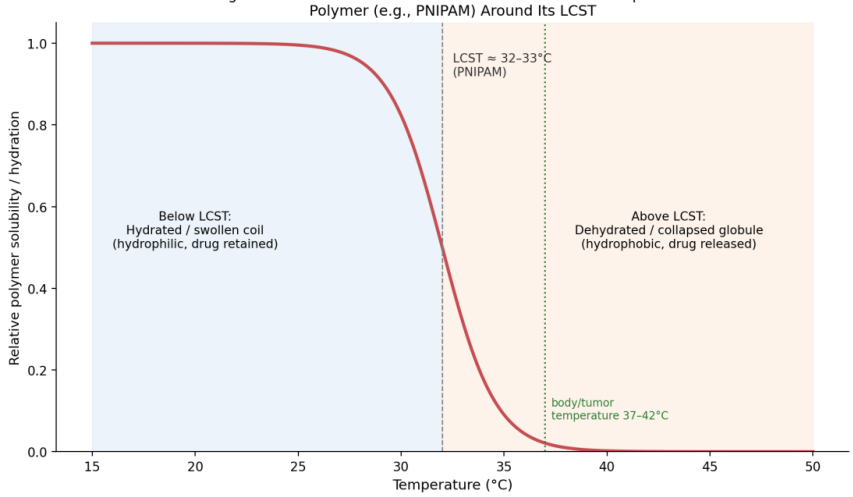


Figure 3. Coil-to-globule phase transition of a thermoresponsive polymer (such as PNIPAM) around its LCST.

4.2 Design Strategies and Materials

Thermoresponsive nanocarriers are designed in several formats: (a) Thermosensitive liposomes, in which the phase transition temperature (Tm) of the lipid bilayer is used as the trigger point for drug release — the most famous example is ThermoDox®, a lyso-thermosensitive liposomal doxorubicin that has been tested in clinical trials in combination therapy with radiofrequency ablation [38,39]. (b) PNIPAM-grafted nanoparticles, in which PNIPAM or PNIPAM-copolymer chains are grafted onto the surface of silica, iron oxide, or gold nanoparticles, achieving temperature-controlled pore opening/closing [40–43]. (c) PNIPAM-based hydrogels and nanogels, which can also show dual pH-temperature responsiveness when copolymerized with pH-sensitive comonomers [44,45]. (d) Magnetic nanoparticle-coupled thermoresponsive systems, in which superparamagnetic iron oxide nanoparticles (SPIONs) are locally heated through an alternating magnetic field (AMF) (magnetic fluid hyperthermia), which simultaneously triggers drug release and thermally damages tumor cells [46–52]. This magnetic hyperthermia approach has also been clinically approved in Europe for glioblastoma treatment [47,53].

4.3 Advantages and Challenges

The biggest advantage of temperature-responsive systems is that temperature is a precisely controllable external trigger — clinicians can deliver localized heating at a specific anatomical location through focused ultrasound, radiofrequency, or a magnetic field, achieving both spatial and temporal control. However, there are also challenges: achieving uniform heating is technically difficult in deep-seated tumors, avoiding healthy surrounding tissue is necessary, and precisely tuning the LCST (without formulation-to-formulation variability) is complex [54].

5. Enzyme-Responsive Nanocarriers

Enzyme-responsive drug delivery systems offer the highest level of biological specificity, because enzymes are highly substrate-specific catalytic proteins — a particular enzyme recognizes and cleaves only its specific substrate sequence. This considerably reduces the risk of false-triggering [55,56].

5.1 Mechanism

Enzyme-responsive nanocarriers typically have an enzyme-cleavable linker (a peptide sequence, ester bond, or glycosidic bond) that connects the drug or the stabilizing shell of the nanocarrier (such as PEG or a protective coating) to the core. When the nanocarrier reaches a disease site where a specific enzyme is overexpressed, the enzyme selectively cleaves that linker, removing the protective shell and exposing the naked, drug-loaded core for cellular uptake, or releasing the drug directly [57]. Figure 4 schematically illustrates this process.

Figure 4. Enzyme (Protease)-Triggered Drug Release from a Peptide-Functionalized Nanocarrier

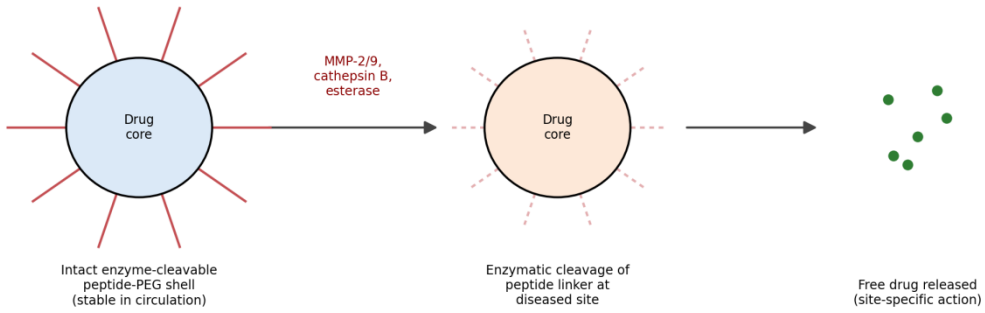


Figure 4. Schematic representation of enzyme (protease)-triggered drug release — free drug release after cleavage from a peptide-functionalized nanocarrier.

5.2 Key Enzymes Exploited in Nanocarrier Design

The most exploited enzymes in cancer and inflammatory diseases are matrix metalloproteinases (MMP-2 and MMP-9), which play a central role in tumor invasion and extracellular matrix remodeling and are significantly overexpressed in multiple cancer types [58–62]. Specific peptide sequences such as PLGLAG, PVGLIG, and GPLGVRG are widely used as MMP substrates. Cathepsin B, a lysosomal cysteine protease, is also overexpressed in tumor cells and is exploited through substrates such as the GFLG (glycine-phenylalanine-leucine-glycine) peptide linker. In addition, esterases and phosphatases

are also used to activate ester-linked prodrugs, while enzymes such as urokinase plasminogen activator (uPA) and β-glucuronidase have also been utilized in specific tumor types [63]. Table 2 summarizes these enzymes and their corresponding applications.

Table 2. Representative Enzyme-Responsive Systems and Their Applications

Enzyme	Typical Cleavable Substrate/Linker	Overexpression Site	Application
Matrix metalloproteinase-2/9 (MMP-2/9)	PLGLAG, GPLGVRG peptide	Tumor stroma, invasive front	Anti-tumor drug release, tumor imaging
Cathepsin B	GFLG peptide	Lysosomes of tumor cells	Intracellular prodrug activation
Urokinase plasminogen activator (uPA)	Specific uPA-cleavable peptide	Tumor invasion margin	Targeted chemotherapy release
Esterases / Phosphatases	Ester / phosphate bonds	Various tissues, inflamed sites	Prodrug activation, controlled release
β-glucuronidase	Glucuronide conjugates	Hypoxic tumor regions, gut microbiota	Colon-targeted / hypoxia-activated prodrugs

5.3 Applications

Enzyme-responsive nanocarriers have also shown promising results in cardiovascular medicine besides cancer therapy. After myocardial infarction (MI), MMP activity increases significantly in injured heart tissue, and MMP-responsive micellar nanoparticles have been designed to exploit this, selectively delivering MMP inhibitors to the infarcted region to help control cardiac remodeling [64–67]. Similarly, plant-based anti-metastatic agents such as veratridine have been delivered for metastatic colorectal cancer through MMP-7-responsive calcium-based nanoparticles [68].

6. Dual and Multi-Stimuli Responsive Systems

Single-stimulus responsive nanocarriers have limitations in specificity and selectivity — sometimes a single stimulus, such as a pH change, can give a false-positive trigger (due to inflammation or normal metabolic variations), or in some tissues that stimulus is not strong enough for reliable drug release. To solve this problem, dual or multi-stimuli responsive systems have been designed, in which drug release occurs only when two or more conditions are simultaneously satisfied (AND-gate logic), further enhancing specificity [69–71].

The most common combination is pH + temperature, where copolymers such as PNIPAm-co-acrylic acid respond to both stimuli simultaneously — acidic pH modulates swelling through protonation while temperature controls LCST-based collapse [72,73]. pH + enzyme combinations are also common, where the nanocarrier enhances cellular uptake through charge-reversal at acidic tumor pH, after which an intracellular enzyme (such as cathepsin B) releases the drug. Temperature + magnetic field combinations, such as magnetic hyperthermia-coupled thermoresponsive liposomes, combine both external control and internal targeting.

Table 3. Comparison of Single- and Dual-Stimuli Responsive Nanocarrier Approaches

Parameter	Single-Stimulus System	Dual/Multi-Stimuli System
Specificity	Moderate; false triggers possible	High; AND-gate logic reduces off-target release
Design complexity	Relatively simple synthesis	Complex; requires precise co-tuning of two responsive units
Clinical translation status	Several in clinical trials (e.g., ThermoDox)	Mostly preclinical; limited clinical data
Representative example	PNIPAM homopolymer (temperature only)	PNIPAM-co-acrylic acid (pH + temperature)

Parameter	Single-Stimulus System	Dual/Multi-Stimuli System
Main advantage	Simplicity, established manufacturing	Enhanced site-specificity and reduced systemic leakage

7. Characterization Techniques

Thorough physicochemical characterization of stimuli-responsive nanocarriers is essential to ensure their quality, safety, and efficacy. Particle size and size distribution are measured by dynamic light scattering (DLS), while morphology is visualized by transmission electron microscopy (TEM) and scanning electron microscopy (SEM). Surface charge (zeta potential) measurement is particularly critical for pH-responsive charge-reversal systems. Drug loading and entrapment efficiency are quantified through UV-visible spectrophotometry or HPLC [74,75].

Specialized techniques are used to specifically evaluate stimulus-responsiveness: in vitro drug release studies are performed in different pH buffers (such as pH 7.4, 6.5, 5.0) to compare release kinetics; for thermoresponsive systems, LCST is determined using turbidimetry and DLS through temperature-dependent particle size/turbidity change; and to confirm enzyme-responsiveness, the release profile is monitored by incubating nanocarriers with the relevant recombinant enzyme (such as MMP-2) [76,77]. Microfluidic platforms have also recently been developed that simulate gastrointestinal or tumor conditions with controlled pH, temperature, and residence time, enabling more standardized and reproducible evaluation [78].

8. Applications in Site-Specific Therapy

8.1 Oncology

Cancer therapy is the most dominant application area for stimuli-responsive nanocarriers. pH-, temperature-, and enzyme-responsive systems, alone or in combination, have been used to selectively deliver chemotherapeutic agents (doxorubicin, paclitaxel, cisplatin, methotrexate), photosensitizers, and immunotherapeutic agents to the tumor site, reducing systemic toxicity and improving the therapeutic index [79,80].

8.2 Gastrointestinal and Colon-Targeted Delivery

pH-responsive enteric coatings (Eudragit series) have been used in oral drug delivery for decades, particularly to protect acid-labile drugs from gastric degradation and to achieve colon-specific release for the local treatment of ulcerative colitis and Crohn's disease [22–27].

8.3 Cardiovascular Disease

As discussed in Section 5.3, enzyme-responsive nanoparticles can exploit locally upregulated MMP activity after myocardial infarction to deliver anti-remodeling agents to the infarcted myocardium, helping to reduce adverse cardiac remodeling [64–67].

8.4 Inflammatory and Infectious Diseases

Inflamed tissues also show acidic pH and elevated protease activity (such as in rheumatoid arthritis), which can be exploited for anti-inflammatory drug delivery. Similarly, local pH changes and bacteria-secreted enzymes (such as lipases and toxins) in bacterial infections have also been used in the design of antibiotic-loaded stimuli-responsive nanocarriers [81,82].

9. Clinical Translation and Challenges

Despite a large number of preclinical studies, the clinical translation of stimuli-responsive nanocarriers is still limited. The most advanced example is ThermoDox® (lyso-thermosensitive liposomal doxorubicin), which has been evaluated in multiple Phase III trials in combination with radiofrequency ablation for hepatocellular carcinoma, although primary endpoints have not always been consistently met [38,39]. Magnetic fluid hyperthermia (NanoTherm®) is already approved in Europe for glioblastoma treatment [47]. Table 4 summarizes some representative clinically approved or advanced clinical-stage nanomedicines.

Table 4. Representative Clinically Approved / Advanced Clinical-Stage Nanomedicines Related to Stimuli-Responsive Concepts

Product	Type	Stimulus/Mechanism	Status
Doxil® / Caelyx®	PEGylated liposomal doxorubicin	Passive EPR-based (baseline nanomedicine)	FDA/EMA approved
ThermoDox®	Lyso-thermosensitive liposomal doxorubicin	Temperature (mild hyperthermia, ~40–42°C)	Phase III clinical trials
NanoTherm®	Aminosilane-coated iron oxide nanoparticles	Magnetic hyperthermia	Approved in Europe (glioblastoma)
Abraxane®	Albumin-bound paclitaxel	Passive EPR-based / albumin receptor	FDA approved
Eudragit®-coated oral systems	pH-sensitive enteric polymer coating	pH (colon targeting)	Marketed pharmaceutical excipients

Clinical translation faces several significant challenges: (i) achieving large-scale, reproducible, and GMP-compliant manufacturing is technically complex; (ii) inter-patient variability — tumor pH, enzyme expression levels, and vascularity differ from patient to patient, making it difficult to predict a consistent therapeutic response; (iii) the regulatory pathway is complex and time-consuming because these products can be treated as combination products (device + drug); and (iv) long-term safety and biodegradability data are needed, particularly for inorganic nanocarriers (such as mesoporous silica, iron oxide) [83–85].

10. Future Perspectives

Stimuli-responsive nanocarrier research is moving forward in several directions in the coming years. First, multi-stimuli and "AND-gate" logic-based systems are being developed for more precise and personalized therapy, in which drug release occurs only when multiple disease-specific conditions are simultaneously present. Second, the use of artificial intelligence and machine learning is increasing in carrier design optimization, drug release kinetics prediction, and the development of patient-specific dosing regimens [86,87]. Third, focus is increasing on biodegradable and biocompatible natural polymers (such as hyaluronic acid, chitosan, alginate) to reduce long-term toxicity concerns. Fourth, theranostic nanoplatforms — which simultaneously provide both imaging and therapy — are becoming an important tool for personalized medicine, enabling clinicians to monitor treatment response in real time. Finally, the development of regulatory frameworks and standardized characterization protocols is also necessary so that laboratory-scale innovations can be safely and efficiently translated into clinical practice.

11. Conclusion

Stimuli-responsive drug delivery systems, particularly pH-, temperature-, and enzyme-triggered nanocarriers, have shown significant progress in the field of site-specific therapy. These systems effectively address the limitations of traditional non-specific drug delivery — systemic toxicity, low bioavailability, and poor targeting — by keeping the carrier stable in healthy tissues and selectively releasing the drug in the diseased microenvironment. pH-responsive systems exploit tumor and endosomal/lysosomal acidity; temperature-responsive systems offer precise external control through LCST-based phase transitions; and enzyme-responsive systems provide the highest degree of biological specificity through substrate-specific cleavage. Dual and multi-stimuli approaches combine these individual strengths to achieve even more precise, AND-gate logic-based release. Although clinical translation remains challenging — due to manufacturing complexity, inter-patient variability, and regulatory hurdles — examples such as ThermoDox® and NanoTherm® show that the concept is clinically viable. Continued interdisciplinary research — with collaboration between materials science, pharmaceutics, biology, and clinical medicine — will help make these smart nanocarriers part of mainstream clinical practice in the coming years, ultimately leading to significant improvement in patient outcomes.

References

1. Barenholz Y. Doxil® – the first FDA-approved nano-drug: lessons learned. Journal of Controlled Release. 2012;160(2):117–134.

2. Matsumura Y, Maeda H. A new concept for macromolecular therapeutics in cancer chemotherapy: mechanism of tumoritropic accumulation of proteins and the antitumor agent smancs. Cancer Research. 1986;46(12 Pt 1):6387–6392.

3. Mura S, Nicolas J, Couvreur P. Stimuli-responsive nanocarriers for drug delivery. Nature Materials. 2013;12(11):991–1003.

4. Karimi M, Ghasemi A, Sahandi Zangabad P, et al. Smart micro/nanoparticles in stimulus-responsive drug/gene delivery systems. Chemical Society Reviews. 2016;45(5):1457–1501.

5. Torchilin VP. Multifunctional, stimuli-sensitive nanoparticulate systems for drug delivery. Nature Reviews Drug Discovery. 2014;13(11):813–827.

6. Ganta S, Devalapally H, Shahiwala A, Amiji M. A review of stimuli-responsive nanocarriers for drug and gene delivery. Journal of Controlled Release. 2008;126(3):187–204.

7. Li Y, et al. Enzyme-Responsive Nanoparticles for Anti-tumor Drug Delivery. Frontiers in Chemistry. 2020.

8. Gerweck LE, Seetharaman K. Cellular pH gradient in tumor versus normal tissue: potential exploitation for the treatment of cancer. Cancer Research. 1996;56(6):1194–1198.

9. Wang Y, et al. Endogenous pH-responsive nanoparticles with programmable size changes for targeted tumor therapy and imaging applications. Theranostics. 2018;8(11):3038–3058.

10. Deirram N, Zhang C, Kermaniyan SS, Johnston APR, Such GK. pH-responsive polymer nanoparticles for drug delivery. Macromolecular Rapid Communications. 2019;40:1800917.

11. Du J, Lane LA, Nie S. Stimuli-responsive nanoparticles for targeting the tumor microenvironment. Journal of Controlled Release. 2015;219:205–214.

12. Almeida B, et al. Tumor Microenvironment-Stimuli Responsive Nanoparticles for Anticancer Therapy. Frontiers in Molecular Biosciences. 2020.

13. Olson ES, et al. Enzyme-Responsive Nanoparticles for the Targeted Delivery of an MMP Inhibitor to the Heart post Myocardial Infarction. bioRxiv. 2022.

14. Egeblad M, Werb Z. New functions for the matrix metalloproteinases in cancer progression. Nature Reviews Cancer. 2002;2(3):161–174.

15. Al-Ahmady Z, et al. pH-Responsive Nanocarriers in Cancer Therapy. Polymers. 2022;14(5):936.

16. Cai H, et al. A critical review on the dissemination of pH and stimuli-responsive polymeric nanoparticular systems to improve drug delivery in cancer therapy. Journal of Drug Delivery Science and Technology. 2023.

17. Nori A, et al. Advancements in pH-responsive nanocarriers: enhancing drug delivery for tumor therapy. Expert Opinion on Drug Delivery. 2023;20(11).

18. Sancenon F, et al. pH-Responsive Mesoporous Silica and Carbon Nanoparticles for Drug Delivery. Materials. 2017.

19. Zhang L, et al. Breaking barriers with pH-responsive nanocarriers: a new frontier in precision oncology. International Journal of Pharmaceutics. 2025.

20. Gimenez V, et al. Fast and reliable analysis of pH-responsive nanocarriers for drug delivery using microfluidic tools. International Journal of Pharmaceutics. 2023.

21. Fan M, et al. Stimuli-responsive nanocarriers for drug delivery, tumor imaging, therapy and theranostics. Theranostics. 2020;10(11):4863–4884.

22. Elzoghby AO, et al. Charge-reversal and size-switchable nanoparticles for enhanced tumor penetration. Journal of Controlled Release. 2019.

23. Peralta ME, et al. Design and evaluation of magnetic mesoporous silica nanoparticles with thermoresponsive polymer for regulated drug delivery. Journal of Colloid and Interface Science. 2019.

24. Vashist A, et al. Poly(N-isopropylacrylamide)-Based Hydrogels for Biomedical Applications: A Review of the State-of-the-Art. Gels. 2022;8(7):437.

25. Nori A, et al. Thermo-Responsive Polymer-Based Nanoparticles. Macromolecular Rapid Communications. 2024/2025.

26. Somaratne WV, et al. pH and Thermoresponsive PNIPAm-co-Polyacrylamide Hydrogel for Dual Stimuli-Responsive Controlled Drug Delivery. Gels. 2023;9(1).

27. Kowalczuk A, et al. Thermoresponsive Graft Copolymers of N-Isopropylacrylamide and Hyperbranched Polyglycerol as Thermally Induced Drug Delivery and Release Nanoformulation Systems for Curcumin. Biomacromolecules / ACS journal. 2025.

28. Kavya D, Jadhav KR, Bhadane SM, Jadhav SA, Kumar M, Nangude MS, Yakin J, Nikam VK, Kumar AKS. Design and Evaluation of Thermo-Responsive Poly(N-isopropylacrylamide)-Based Polymeric Nanoparticles for Temperature-Triggered Intratumoral Release of Doxorubicin in Solid Tumors. ACS Applied Electronic Materials. 2024;6(5):3216–3226.

29. Maleki R, et al. PNIPAM/Hexakis as a thermosensitive drug delivery system for biomedical and pharmaceutical applications. Scientific Reports. 2022;12:16245.

30. Somaratne WV, et al. pNIPAm-Based pH and Thermoresponsive Copolymer Hydrogel for Hydrophobic and Hydrophilic Drug Delivery. Gels. 2024.

31. Tan A, et al. Self-Assembled Thermoresponsive Nanogel from Grafted Hyaluronic Acid as a Biocompatible Delivery Platform for Curcumin. Molecules. 2021;26(2):297.

32. Needham D, Anyarambhatla G, Kong G, Dewhirst MW. A new temperature-sensitive liposome for use with mild hyperthermia: characterization and testing in a human tumor xenograft model. Cancer Research. 2000;60(5):1197–1201.

33. Poon RTP, Borys N. Lyso-thermosensitive liposomal doxorubicin: a novel approach to enhance efficacy of thermal ablation of liver cancer. Expert Opinion on Pharmacotherapy. 2009;10(2):333–343.

34. Kim J, et al. Temperature-responsive polymer-modified silica nanoparticles for pH and temperature stimuli-controlled drug delivery of anticancer drugs. ACS Applied Materials & Interfaces. 2020.

35. Asadi H, et al. Dual pH-temperature responsive nanocarriers for controlled anticancer drug delivery. Journal of Biomaterials Science. 2021.

36. Lucaciu CM. Magnetic Nanomaterials for Hyperthermia-Based Therapy, Imaging, and Drug Delivery. Pharmaceutics. 2024;16(2):263.

37. Chen J, et al. Imaging-guided precision hyperthermia with magnetic nanoparticles. Nature Reviews Bioengineering (or related journal). 2025.

38. Assis RIS, et al. Paclitaxel-Loaded Lipid-Coated Magnetic Nanoparticles for Dual Chemo-Magnetic Hyperthermia Therapy of Melanoma. International Journal of Nanomedicine. 2023.

39. Ahmed M, et al. In Vitro and In Vivo Delivery of Magnetic Nanoparticle Hyperthermia Using a Custom-Built Delivery System. International Journal of Hyperthermia. 2024.

40. Beola L, et al. In vivo magnetic nanoparticle hyperthermia: a review on preclinical studies, low-field nano-heaters, noninvasive thermometry and computer simulations for treatment planning. International Journal of Hyperthermia. 2020;37(2).

41. Sadauskas E, et al. Application of Nanoparticles for Magnetic Hyperthermia for Cancer Treatment — The Current State of Knowledge. Pharmaceutics. 2024;16(4).

42. Andhariya JV, et al. Pharmaceutical Quality by Design Approach to Develop High-Performance Nanoparticles for Magnetic Hyperthermia. Molecular Pharmaceutics. 2024.

43. Zhao Y, et al. Magnetic nanomaterials for hyperthermia-based therapy and controlled drug delivery. Bioactive Materials. 2025.

44. Bhutta MU, et al. Enzyme-Responsive Nanoparticles for the Targeted Delivery of an MMP Inhibitor to Acute Myocardial Infarction. Biomacromolecules. 2023.

45. Chen X, et al. Enzyme-Responsive Nanoparticles for Anti-tumor Drug Delivery. Colloids and Surfaces B: Biointerfaces. 2020.

46. Kalimuthu K, et al. Matrix Metalloproteinase-Responsive Mesoporous Silica Nanoparticles Cloaked with Cleavable Protein for "Self-Actuating" On-Demand Controlled Drug Delivery for Cancer Therapy. ACS Applied Bio Materials. 2020;3(11):8194–8204.

47. Du J, et al. Enzyme Responsive Magnetic Nanoparticles for Targeted Drug Delivery and Precision Medicine. Drug Development Research. 2025.

48. Yu Q, et al. Liver-Specific Nanoparticle-Mediated Delivery and MMP-Triggered Release of Veratridine to Effectively Target Metastatic Colorectal Cancer. International Journal of Nanomedicine. 2025.

49. Sigma-Aldrich (Merck). Stimuli-Responsive Materials as Intelligent Drug Delivery Systems. Technical Article, Materials Science and Engineering. Accessed 2026.

50. Vinogradov SV, et al. Tumor Microenvironment-Based Stimuli-Responsive Nanoparticles for Controlled Release of Drugs in Cancer Therapy. International Journal of Molecular Sciences. 2022;23(20).

51. Wang H, et al. Full article: Advances in Multiple Stimuli-Responsive Drug-Delivery Systems for Cancer Therapy. International Journal of Nanomedicine. 2021;16:2803–2822.

52. Rodriguez A, et al. Bridging the gap in nanomedicine: Translational challenges and innovations in stimuli-responsive nanocarriers. Journal of Drug Delivery Science and Technology. 2026.

53. Lin W, et al. Full article: Tumor Microenvironment-Responsive Nanomedicine: Monitoring and Modulating the Tumor Microenvironment for Precision Cancer Therapy. International Journal of Nanomedicine. 2026.

54. Zhu Y, et al. Frontiers: Stimuli-Responsive Polymeric Nanoplatforms for Cancer Therapy. Frontiers in Bioengineering and Biotechnology. 2021;9:707319.

55. Huang P, et al. Polymeric nanoparticles—Promising carriers for cancer therapy. Frontiers in Bioengineering and Biotechnology. 2022;10:1024143.

56. Ahmad A, et al. Nanocarriers in Drug Delivery Systems: An Overview. ResearchGate preprint / review. 2025.

57. Sharma P, et al. Advances in nanoparticles in targeted drug delivery — A review. Journal of Drug Delivery Science and Technology. 2025.

58. Mitchell MJ, Billingsley MM, Haley RM, Wenzel MT, Riley RS, Langer R. Engineering precision nanoparticles for drug delivery. Nature Reviews Drug Discovery. 2021;20:101–124.

59. Patra JK, et al. Targeted therapy in chronic diseases using nanomaterial-based drug delivery vehicles. Signal Transduction and Targeted Therapy. 2019;4:33.

60. Cavalu S, et al. Encapsulation for Cancer Therapy. Molecules. 2020;25(8).

61. Norouzi M, et al. Nanomedicine and versatile therapies for cancer treatment. MedComm. 2022.

62. Awad NS, et al. Photo-Induced Drug Release from Polymeric Micelles and Liposomes: Phototriggering Mechanisms in Drug Delivery Systems. Pharmaceutics. 2021;13(9):1489.

63. Rong X, et al. Redox-manipulating nanocarriers for anticancer drug delivery: a systematic review. Journal of Nanobiotechnology. 2024;22:589.

64. Cheng R, Feng F, Meng F, Deng C, Feijen J, Zhong Z. Advances in redox-responsive drug delivery systems of tumor microenvironment. Journal of Nanobiotechnology. 2018;16:74.

65. Wu J, et al. Tumor microenvironment–responsive nanoformulations for breast cancer. Discover Nano. 2024.

66. Zhou Q, et al. Tumor microenvironment responsive drug delivery systems. Asian Journal of Pharmaceutical Sciences. 2020;15(5):605–618.

67. Wilkinson RN, et al. Gastrointestinal pH-dependent colon targeted oral drug delivery system using methacrylic acid copolymers. I. Manipulation of drug release using Eudragit L100-55 and Eudragit S100 combinations. International Journal of Pharmaceutics. 1999;185(1):17–27.

68. Ibekwe VC, et al. A pH-dependent colon-targeted oral drug delivery system using methacrylic acid copolymers. II. Manipulation of drug release using Eudragit L100 and Eudragit S100 combinations. Journal of Drug Targeting. 2000.

69. Khan MZI, et al. Development of Novel pH-Sensitive Eudragit Coated Beads Containing Curcumin-Mesalamine Combination for Colon-Specific Drug Delivery. Pharmaceutics. 2023;15(4).

70. Ali MS, et al. Fabrication, Evaluation, In Vivo Pharmacokinetic and Toxicological Analysis of pH-Sensitive Eudragit S-100-Coated Hydrogel Beads: a Promising Strategy for Colon Targeting. AAPS PharmSciTech. 2021.

71. Elmowafy E, et al. Preparation, Characterization and In Vitro Evaluation of Eudragit S100-Coated Bile Salt-Containing Liposomes for Oral Colonic Delivery of Budesonide. Pharmaceutics. 2022;14(6).

72. Zhang J, et al. Optimizing pH-sensitive and time-dependent polymer formula of colonic pH-responsive pellets to achieve precise drug release. Asian Journal of Pharmaceutical Sciences. 2020;15(2):230–241.

73. Duncan R. The dawning era of polymer therapeutics. Nature Reviews Drug Discovery. 2003;2(5):347–360.

74. Hoffman AS. Stimuli-responsive polymers: Biomedical applications and challenges for clinical translation. Advanced Drug Delivery Reviews. 2013;65(1):10–16.

75. Rejinold NS, et al. Biomedical applications of stimuli responsive nanocarriers. Journal of Materials Chemistry B. 2018.

76. Kim JO, Kabanov AV. Stimuli-sensitive polymer therapeutics. Advanced Materials Interfaces. 2017.

77. Wong PT, Choi SK. Mechanisms of drug release in nanotherapeutic delivery systems. Chemical Reviews. 2015;115(9):3388–3432.

78. Vhora I, et al. Recent advances in characterization techniques for stimuli-responsive nanoparticles. Journal of Pharmaceutical Analysis. 2022.

79. Sun Q, et al. Analytical strategies for evaluating enzyme-responsive drug release from nanocarriers. Analytical Chemistry Reviews. 2021.

80. Fernandez M, et al. Fast and reliable analysis of pH-responsive nanocarriers for drug delivery using microfluidic tools. International Journal of Pharmaceutics. 2023;641:123073.

81. Sanchis J, et al. Polymer-drug conjugates for tumor-targeted combination therapy. Nanomedicine. 2010.

82. Danhier F, Feron O, Preat V. To exploit the tumor microenvironment: passive and active tumor targeting of nanocarriers for anti-cancer drug delivery. Journal of Controlled Release. 2010;148(2):135–146.

83. Wang J, et al. Stimuli-responsive nanocarriers for anti-inflammatory drug delivery. Advanced Healthcare Materials. 2022.

84. Xiong MH, et al. Bacteria-responsive multifunctional nanogel for targeted antibiotic delivery. Advanced Materials. 2012.

85. Anselmo AC, Mitragotri S. Nanoparticles in the clinic: An update. Bioengineering & Translational Medicine. 2019;4(3):e10143.

86. Hare JI, et al. Challenges and strategies in anti-cancer nanomedicine development: An industry perspective. Advanced Drug Delivery Reviews. 2017;108:25–38.

87. Metselaar JM, Lammers T. Challenges in nanomedicine clinical translation. Drug Delivery and Translational Research. 2020;10:721–725.

88. Adir O, et al. Integrating Artificial Intelligence and Nanotechnology for Precision Cancer Medicine. Advanced Materials. 2020.

89. Ho D, et al. Artificial Intelligence in Nanomedicine. Nanoscale Horizons. 2019.