Review on Stimuli-Responsive Drug Delivery Systems (SRDDS): An Advanced Overview of Triggered and Precision-Controlled Therapeutics

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Abstract : Stimuli-responsive drug delivery systems (SRDDS) represent an advanced class of engineered therapeutic platforms capable of modifying their physicochemical behavior in response to specific internal or external triggers. These systems offer enhanced spatial and temporal control over drug release, significantly improving therapeutic efficacy while minimizing off-target toxicity. SRDDS are designed to exploit biological cues such as pH gradients, enzymatic concentrations, redox imbalances, and reactive oxygen species, or externally applied stimuli such as heat, magnetic fields, light, or ultrasound to achieve highly selective and controlled drug activation. Their integration with nanotechnology and biomaterials has expanded their applicability in oncology, inflammation, neurological disorders, and targeted delivery to complex microenvironments. This review provides a comprehensive evaluation of their mechanisms, structural designs, stimulus-specific behavior, therapeutic potential, and existing limitations, highlighting their transformative role in modern precision medicine.

Keywords
Stimuli-responsive delivery; triggered release; nanocarriers; precision therapeutics; pH-sensitive systems; targeted drug delivery

1. Introduction

Conventional drug delivery approaches—such as oral tablets, capsules, and systemic injections—are often associated with limited bioavailability, rapid clearance, and undesirable systemic toxicity. These limitations significantly restrict therapeutic outcomes, particularly in diseases that require targeted delivery and controlled exposure. Recent advances in materials science, polymer chemistry, and nanotechnology have enabled the development of stimuli-responsive drug delivery systems (SRDDS), which represent a major technological shift towards precision-controlled therapeutics (1,3).

SRDDS are engineered to undergo structural or functional transformations in response to specific stimuli present in the biological environment or applied externally. Tumors, inflamed tissues, and hypoxic microenvironments naturally provide distinct physicochemical signatures such as acidic pH, elevated glutathione (GSH) levels, and high reactive oxygen species (ROS), which can be exploited for selective drug activation (10,33). Likewise, externally applied triggers—such as near-infrared (NIR) light, magnetic fields, temperature modulation, or ultrasound—enable on-demand drug release at precise anatomical locations (12,13,15).

The integration of smart polymers, nanocarriers, hydrogels, micelles, and inorganic platforms into SRDDS has further expanded their versatility. These systems are capable of improving drug solubility, enhancing tumor accumulation through the enhanced permeability and retention (EPR) effect, and enabling controlled, minimally invasive therapeutic interventions (28,29). Given their adaptability and clinical potential, SRDDS have become a focal point in modern pharmaceutics and interdisciplinary biomedical research.

Overall, SRDDS offer profound opportunities for advancing personalized medicine by delivering therapeutics at the right site, right time, and right dose (1,3).

2. Types of Stimuli

Stimuli-responsive drug delivery systems are broadly classified based on whether activation is driven by endogenous (internal) biological cues or exogenous (external) applied triggers. Each stimulus influences the physicochemical properties—such as solubility, charge, conformation, or degradation—of the carrier system, thus enabling controlled and site-specific drug release (3,6,18).

2.1 Endogenous Stimuli

pH-responsive SRDDS exploit variations in acidity between normal tissues, tumor sites, inflammatory regions, and intracellular compartments. Carriers incorporating acid-labile linkages such as hydrazone, imine, or acetal bonds undergo selective cleavage under acidic conditions, enabling targeted release (1,5,33).

Redox-responsive nanocarriers detect intracellular glutathione (GSH) gradients, which are significantly elevated in tumor cells. Disulfide, diselenide, and thioketal linkers cleave rapidly in reductive environments, enabling cytosolic release (4,7,41).

Diseased tissues overexpress enzymes such as MMPs, phospholipases, and cathepsins. Carriers containing enzyme-cleavable peptide sequences or substrates undergo selective degradation, improving specificity (7,42).

Reactive oxygen species (ROS) levels are elevated in cancer and inflammation. ROS-cleavable motifs such as boronic esters and thioketals rapidly degrade in response, enabling triggered release (8,43).

2.2 Exogenous Stimuli

Thermosensitive polymers such as PNIPAM exhibit LCST-based transitions, expelling drugs upon heating and enabling mild hyperthermia-triggered release (14).

Light-triggered systems exploit photocleavable linkers or photothermal agents such as gold nanorods to induce spatially controlled release under NIR irradiation (12,13,45).

Magnetic nanoparticles can be activated using alternating magnetic fields, generating localized heat or mechanical effects that trigger release (15).

Ultrasound induces cavitation, mechanical perturbation, or thermal effects that disrupt carrier structure, promoting controlled release (16).

Electroresponsive polymers undergo changes in permeability or conformation when exposed to electric fields, allowing pulsatile release (17).

2.3 Multi-Stimuli Responsive Systems

Dual- and multi-responsive systems integrate synergistic triggers such as pH + redox or light + heat to enhance precision and robustness in complex biological environments (9,41).

3. Mechanisms of Action

Stimuli-responsive release can occur via multiple mechanisms, including cleavage of responsive linkers, swelling transitions, structural destabilization, membrane poration, and intracellular activation (4,5,7).

3.1 Cleavage of Stimuli-Sensitive LinkagesSRDDS often rely on the cleavage of specific chemical bonds in response to stimuli such as acidity (hydrazone), redox state (disulfide), enzymes (peptide sequences), or light (photolabile groups). Bond cleavage initiates rapid drug liberation (4,5,7).

3.2 Swelling, Deswelling, and Phase Transitions

Stimuli induce physical transitions in responsive polymers and hydrogels—such as swelling, shrinking, or sol–gel conversion. These transitions alter mesh size and permeability, modulating drug diffusion (18,20).

3.3 Carrier Destabilization and Disassembly

Micelles, liposomes, and polymeric nanoparticles undergo stimuli-triggered disruption of their core–shell architecture. pH or redox signals can break hydrophobic interactions or ionic cross-links, causing rapid drug discharge (6,33).

3.4 Membrane Poration and Cavitation

Ultrasound and photothermal effects generate transient pores in biological or carrier membranes, enhancing intracellular uptake or release kinetics (13,16).

3.5 Intracellular Triggering

Once internalized, carriers respond to endosomal acidity, lysosomal enzymes, or high cytosolic GSH levels, ensuring selective intracellular release and reduced premature drug leakage (4,7,10).

4. Materials and Platform Architectures

The selection of materials for stimuli-responsive drug delivery systems plays a decisive role in determining biocompatibility, responsiveness, degradation behavior, and overall therapeutic performance. Major carrier classes include polymers, hydrogels, liposomes, micelles, inorganic nanoparticles, and hybrid multifunctional nanoplatforms (18,21,28).

4.1 Polymeric Systems

Polymeric materials represent the most versatile class of SRDDS due to their tunable physicochemical profiles, structural stability, and ability to incorporate diverse responsive linkers. Natural polymers such as chitosan, alginate, and gelatin offer excellent biocompatibility and biodegradability, making them suitable for sustained release applications. Synthetic polymers such as PEG, PLGA, poly(β-amino esters), and PNIPAM allow precise control over molecular weight, degradation kinetics, and incorporation of functional groups for pH, redox, or thermal responsivity (21,33).

4.2 Hydrogels and Nanogels

Hydrogels are three-dimensional cross-linked polymer networks capable of absorbing large amounts of water, enabling exceptional swelling and deswelling behavior in response to stimuli such as pH, temperature, ROS, and enzymes (19,20). Their soft tissue-like properties make them suitable for localized therapy, wound healing, and injectable depot formulations. Nanogels further improve tissue penetration and intracellular uptake, offering faster responsiveness and enhanced retention in tumor microenvironments (28,43).

4.3 Liposomes and Polymeric Micelles

Liposomes remain one of the most clinically established nanocarriers due to their biocompatibility, biodegradability, and ability to encapsulate both hydrophilic and hydrophobic agents. Thermo- and light-responsive liposomes undergo membrane disruption under mild heating. Polymeric micelles, formed via self-assembly of amphiphilic block copolymers, can dissociate in response to acidic pH or reductive cytosolic environments, releasing drugs directly into tumor cells (6,33).

4.4 Inorganic and Hybrid NanoparticlesInorganic nanoplatforms such as gold nanoparticles, mesoporous silica nanoparticles, and magnetic iron oxide nanoparticles are widely applied in stimuli-responsive systems due to their optical, thermal, and magnetic properties. Gold nanostructures can convert NIR light into heat (photothermal effect),

enabling controlled drug release in photothermal therapy (13,45). MSNs provide high surface area and tunable pore structures suitable for pH-, enzyme-, or redox-responsive gating (28). Hybrid systems combine organic polymers with inorganic cores to enhance structural stability and multifunctionality, often enabling simultaneous imaging, therapy, and triggered release (30,38).

4.5 Targeting Ligands and Surface Functionalization

Surface modification enhances the specificity of nanocarriers toward diseased tissues. Common ligands include folic acid, RGD peptides, antibodies, aptamers, and transferrin, which facilitate receptor-mediated endocytosis and improve tumor localization (24,26). PEGylation remains essential for extending circulation time, reducing protein adsorption, and minimizing immune clearance (27,44).

5. Applications

SRDDS have been widely explored across multiple therapeutic areas due to their precision, reduced side effects, and enhanced drug accumulation at pathological sites (10,28).

5.1 Cancer Therapy

Tumor regions exhibit acidic pH, high GSH, hypoxia, and overexpressed enzymes. These abnormalities allow precise targeting using pH-, redox-, enzyme-, light-, or magnetothermal-responsive systems. Triggered release improves tumor accumulation, reduces systemic toxicity, and allows combination therapy (chemo + photo) (1,4,7,33).

5.2 Inflammation and Autoimmune Disorders

Enzyme-responsive and ROS-responsive carriers release anti-inflammatory drugs in response to MMPs and other inflammation-related enzymes, improving localized therapy (19,43).

5.3 Neurological Disorders

Responsive nanocarriers may enhance BBB penetration and release drugs in response to oxidative stress or local temperature shifts, supporting treatments for neurodegenerative diseases (16,26,8,43).

5.4 Wound Healing and Regenerative Medicine

ROS-responsive hydrogels and enzyme-sensitive dressings facilitate controlled delivery of antimicrobials and growth factors, promoting tissue repair and accelerated wound closure (20,43).

6. Advantages and Limitations

Stimuli-responsive drug delivery systems offer several transformative advantages in modern therapeutics. Their ability to respond selectively to internal or external triggers allows for spatially and temporally controlled drug release, resulting in enhanced therapeutic efficacy and reduced systemic toxicity. SRDDS can improve drug solubility, prolong circulation time, and achieve targeted delivery to pathological sites such as tumours, inflamed tissues, or hypoxic microenvironments. Additionally, these systems support co-delivery strategies for combination therapies (e.g., chemo-photothermal or chemo-immunotherapy), enable reduction of dose frequency, and may enhance patient compliance.

However, significant challenges remain. The synthesis of smart materials is often complex and may involve multi-step chemistries that hinder scale-up. Batch-to-batch variability, difficulties in reproducible manufacturing, and issues related to long-term storage stability complicate translation. Biological heterogeneity—such as variable pH gradients, inconsistent enzyme expression, or uneven nanoparticle penetration—can reduce the predictability of stimulus-triggered responses in vivo. Moreover, potential immunogenicity and the long-term fate and clearance of inorganic or hybrid nanomaterials require thorough toxicological evaluation and regulatory scrutiny. Addressing these limitations requires interdisciplinary collaboration among chemists, engineers, pharmacologists, and clinicians.

Stimuli-responsive drug delivery systems offer unique benefits such as targeted activation, reduced systemic toxicity, improved therapeutic index, and compatibility with multiple drug classes (1,3,28). However, challenges include material complexity, scalability issues, potential immunogenicity, risk of premature activation, regulatory hurdles, and variability in in vivo performance (32,37,40).

7. Future Perspectives

Future research in SRDDS will focus on several converging directions to accelerate clinical translation. First, the development of fully biodegradable, immunologically inert materials will reduce long-term safety concerns and facilitate regulatory approval. Second, multi-stimuli and logic-gated systems that require combinatorial cues (for example, pH AND enzyme, or redox AND light) will increase targeting specificity and reduce off-target activation.

Third, integration with diagnostic imaging (theranostics) and real-time biosensing will allow clinicians to monitor drug release and therapeutic responses, enabling adaptive and personalised dosing. Fourth, advances in AI-driven material discovery and computational modelling can optimize carrier design, predict in vivo behaviour, and shorten development timelines. Fifth, scalable manufacturing approaches—such as microfluidic synthesis, continuous processing, and standardized GMP workflows—will be critical for reproducible production. Finally, closer engagement with regulatory agencies to define clear safety and efficacy endpoints for nanomaterials will streamline translation into clinical practice.

8. Conclusion

Stimuli-responsive drug delivery systems hold substantial promise for precision medicine by enabling controlled, site-specific drug release in response to defined biological or external cues. Their versatility across material platforms and stimuli types supports tailored therapeutic strategies for oncology, inflammation, neurological disorders, and regenerative medicine. Nonetheless, a concerted effort to address manufacturing scalability, long-term safety, and regulatory clarity is essential. Continued interdisciplinary research and translational partnerships will be key to realizing the clinical potential of SRDDS.

9. References

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