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# Stimuli-Responsive Drug Delivery Systems: Design Strategies, Mechanisms, and Clinical Translation

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## Abstract:

Conventional drug delivery systems often lack spatial and temporal control, leading to nonspecific distribution, subtherapeutic drug concentrations at target sites, and dose-limiting toxicities in healthy tissues. These limitations are particularly pronounced for modern therapeutics such as peptides, proteins, nucleic acids, and poorly soluble small molecules. Stimuli-responsive drug delivery systems (SDDS), also known as smart drug delivery systems, have emerged as a promising strategy to address these challenges by enabling site-specific and controlled drug release in response to internal or external triggers.This review provides a comprehensive overview of the design principles, materials, mechanisms, and translational landscape of SDDS. Stimuli are broadly classified into endogenous triggers, including pH gradients, redox potential, enzymes, reactive oxygen species, hypoxia, and metabolites, and exogenous triggers such as temperature, light, ultrasound, magnetic fields, and mechanical forces. The article discusses key carrier platforms, including polymeric micelles and nanoparticles, liposomes, inorganic nanoplatforms, hydrogels, electrospun nanofibers, biomacromolecular systems, and cell-mediated carriers. Mechanistic pathways of stimulus-induced release, such as covalent bond cleavage, conformational transitions, pore gatekeeping, and multi-stage disassembly, are examined in relation to pharmacokinetics, biodistribution, and therapeutic index.Preclinical and early clinical evidence across oncology, inflammatory disorders, metabolic diseases, neurological conditions, and infectious diseases is critically evaluated. Despite strong experimental support, clinical translation remains limited due to biological heterogeneity, manufacturing complexity, regulatory challenges, and the need to demonstrate clear clinical benefit. Future progress will depend on simplified and scalable design, robust characterization, patient stratification, and integration with precision medicine and artificial intelligence.

**Keywords**

Stimuli-responsive drug delivery; Smart drug delivery systems; Nanomedicine; Controlled release; pH-responsive systems; Redox-responsive systems; Thermosensitive liposomes; Drug targeting;

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## 1. Introduction

### 1.1 Background of conventional drug delivery

Conventional dosage forms such as immediate-release tablets, solutions, and simple injections generally distribute drug molecules systemically without fine control over spatial or temporal exposure. This non-specific distribution often leads to subtherapeutic concentrations at the disease site and excessive exposure in healthy tissues, causing dose-limiting toxicities and narrow therapeutic windows. Moreover, many modern therapeutics, including peptides, proteins, nucleic acids, and highly lipophilic small molecules, suffer from instability, poor solubility, or limited membrane permeability, further constraining their clinical utility [1-2].

### 1.2 Rationale for stimuli-responsive and smart systems

Stimuli-responsive drug delivery systems (SDDS), also termed smart drug delivery systems (SDDSs or SRDDSs), seek to overcome these limitations by coupling drug carriers to internal or external triggers that induce controlled release preferentially at the target site. These systems are engineered so that changes in pH, redox state, enzymatic activity, temperature, light, ultrasound, magnetic or electric fields, or mechanical forces alter the structure or properties of the carrier, releasing the payload in a programmed manner. The overarching rationale is to increase the fraction of dose reaching the diseased tissue at the right time and rate, thereby enhancing efficacy, minimizing systemic toxicity, and enabling complex combination therapies [3-4].

### 1.3 Evolution of the field

Early generations of "smart" systems focused on single-stimulus-responsive hydrogels and polymers, such as pH-sensitive enteric coatings and thermo-responsive polymers with lower critical solution temperature (LCST) behavior. With the advent of nanotechnology, research expanded to polymeric micelles, liposomes, dendrimers, and inorganic nanocarriers decorated with stimuli-responsive linkers, charge-switching groups, or cleavable coronas. Over the last decade, there has been a strong shift toward multi-stimuli-responsive platforms, supramolecular self-assembly systems, biomacromolecular carriers, and cell-mediated smart vehicles, alongside application in cancer, inflammatory, infectious, metabolic, neurological, and even viral diseases such as COVID-19 [5-6].

### 1.4 Scope and organization of this review

This numbered review focuses on design strategies, materials, and mechanisms underlying SDDS; their impact on pharmacokinetics (PK), biodistribution, and therapeutic index; preclinical and emerging clinical evidence across major therapeutic areas; and key translational hurdles from concept to market. Particular emphasis is placed on literature from approximately 2018–2025, including recent insights on biomacromolecular systems, cell-mediated platforms, and supramolecular nanomaterials, while also discussing future directions and the integration of SDDS with precision medicine and artificial intelligence (AI) .

## 2. Classification of Stimuli and Conceptual Framework

### 2.1 Endogenous versus exogenous stimuli

Endogenous stimuli originate from physiological or pathological differences within the body, such as pH gradients, redox potential, enzymatic activities, hypoxia, ROS levels, ionic strength,

and metabolite concentration. These internal cues are particularly prominent in tumors, inflamed tissues, infected sites, ischemic regions, and specific organ compartments (e.g., GI tract segments, endosomes, lysosomes), allowing SDDS to exploit microenvironmental signatures of disease. Exogenous stimuli, in contrast, are externally 3139-2741 signals including temperature (hyperthermia), light (UV/visible/NIR), ultrasound, magnetic fields, electric fields, and mechanical forces, offering physician-controlled on-demand activation at a desired anatomical site [7-8] Table 1. The overall conceptual framework of stimuli-responsive drug delivery systems, linking disease microenvironment to controlled release and clinical outcome, is illustrated in Figure 1

**Figure 1.** Conceptual Overview of Stimuli-Responsive Drug Delivery Systems

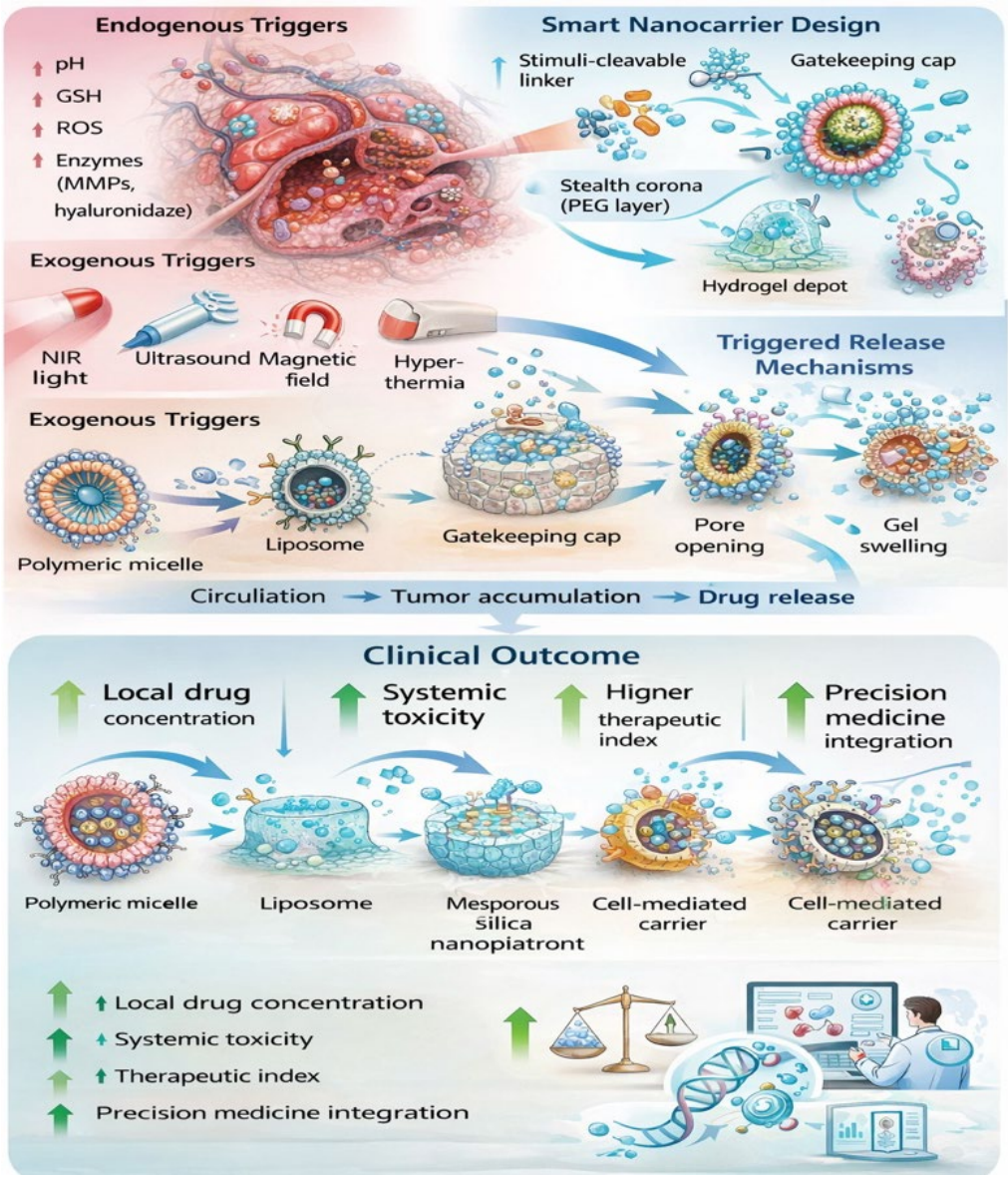

**Table 1**. Classification of Stimuli Used in Smart Drug Delivery Systems

| Stimulus category | Specific trigger (examples) | Typical site / context | Representative materials & designs | Advantages | Main limitations |
|---|---|---|---|---|---|
| Endogenous – pH | Tumor ECM (pH ~6.5–6.9), endosome/lysosome (pH 4.5–6), inflamed tissue, GI segments. | Solid tumors, inflamed joints, IBD lesions, periodontal pockets, endosomes/lysosomes. | Hydrazone/imine/ketal linkers; poly(β-amino esters); pH-sensitive liposomes; enteric coatings. | Simple, well-understood stimulus; widely present in disease; easy in vitro testing. | pH gradients sometimes small; off-target activation in other acidic sites; interpatient variability [9]. |
| Endogenous – redox | High intracellular GSH (1–10 mM), altered redox in tumors/inflamed tissues. | Cytosol of cancer cells, inflamed tissues. | Disulfide / diselenide crosslinked micelles and nanogels; redox-cleavable polymer–drug conjugates. | Strong intra vs extracellular gradient; efficient intracellular release. | Redox status heterogeneous; animal–human differences; risk of premature cleavage in high-GSH normal tissues [10]. |
| Endogenous – enzymes | MMPs, hyaluronidase, proteases, phospholipases, glycosidases. | Tumor stroma, inflamed tissues, infected sites. | Enzyme-cleavable peptides as gatekeepers; HA shells; enzyme-degradable hydrogels. | High biochemical specificity; can be tailored to disease-specific enzymes. | Enzyme expression/activity varies by patient, tumor type, and over time; requires good biomarker data [11]. |
| Endogenous – ROS / | High ROS; hypoxic TME; local ATP or glucose changes. | Tumors, ischemic tissue, inflamed organs. | Thioketal, boronic ester linkers; hypoxia-cleavable azobenzenes; | Directly linked to pathology; enables | Hard to quantify non-invasively; large |

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| hypoxia / metabolites | | | ATP-responsive aptamer systems. | theranostic combinations. | intra-tumor heterogeneity [12]. |
| Exogenous – temperature | Local hyperthermia 40–45 °C (RF, microwave, FUS), mild fever. | Solid tumors, superficial lesions, joints, subcutaneous depots. | LCST hydrogels (PNIPAM, PEG-based); lyso-thermosensitive liposomes; thermo-gels. | Non-invasive, on-demand; compatible with imaging-guided FUS. | Needs equipment and temperature control; risk of burns or tissue damage [13]. |
| Exogenous – light (UV/Vis/NIR) | External illumination, often NIR window (650–900 nm). | Superficial tumors, skin, eye, endoscopically accessible tumors. | Photocleavable linkers; azobenzene; gold/graphene/black-phosphorus photothermal agents. | High spatial and temporal precision; easy on/off control. | Limited deep-tissue penetration; phototoxicity; specialized hardware [14]. |
| Exogenous – ultrasound | Low/high intensity ultrasound; focused ultrasound pulses. | Deep tumors, brain (BBB opening), thrombi. | Micro/nanobubbles; phase-change droplets; US-responsive polymer vesicles. | Deep penetration; can transiently open BBB; can be image-guided. | Cavitation damage risk; parameter optimization needed; device-dependence [15]. |
| Exogenous – magnetic / electric / mechanical | Static/alternating magnetic fields; electric stimulation; shear/compression. | Tumors, joints, thrombi; implantable devices. | Magnetic iron oxide carriers; electro-responsive hydrogels; shear-responsive capsules. | Remote control; potential synergy with imaging and hyperthermia. | Complex hardware; regulatory and safety challenges; difficult standardization [16]. |

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### 2.2 Chemical versus physical stimuli

From a mechanistic standpoint, stimuli can be broadly categorized as chemical (e.g., pH, redox, enzymatic, metabolite, ROS) or physical (e.g., temperature, light, ultrasound, magnetic and electric fields, mechanical stress). Chemical stimuli generally modulate covalent bond cleavage, protonation states, or biochemical transformations, resulting in degradation of carriers, cleavage of linkers, or de-crosslinking of networks. Physical stimuli tend to affect non-covalent interactions, phase transitions, or structural dynamics, as seen in thermo-responsive hydrogels, light-triggered photolysis or isomerization, ultrasound-induced cavitation, and magnetically induced heating or movement [17-18].

### 2.3 Single-stimulus versus multi-stimulus systems

Single-stimulus systems are activated by one dominant trigger (e.g., acidic pH in tumors, elevated GSH in the cytosol, or NIR light for deep-tissue photothermal therapy). Multi-stimuli-responsive systems (MSR-DDS) integrate two or more stimuli, often arranged hierarchically for example, pH-triggered charge reversal and shell shedding followed by redox-triggered core disassembly and drug release inside cells. Such MSR-DDS can be designed according to logic gates (AND, OR) so that drug release occurs only when multiple conditions are met (e.g., low pH AND high GSH), thereby improving selectivity but increasing design and regulatory complexity [19-20].

### 2.4 Conceptual framework: From stimulus to clinical outcome

Linking stimuli to clinical benefit involves a multi-step framework: (1) identification of a reliable stimulus associated with disease; (2) design of a responsive material that converts the stimulus into a measurable physicochemical change; (3) translation of that change into drug release, activation, or exposure modulation; and (4) demonstration that this programmed exposure yields better clinical outcomes and acceptable safety. Failures often occur at steps 1 and 4, where pathophysiological heterogeneity undermines stimulus reliability and clinical trials fail to translate mechanistic advantages into survival or quality-of-life benefits [21-22].

## 3. Types of Stimuli and Representative Designs

### 3.1 pH-responsive systems

#### 3.1.1 Biological basis of pH gradients

Physiological pH is tightly regulated near 7.4 in blood, but substantial deviations occur in pathological conditions and subcellular compartments. Solid tumors and inflamed tissues often exhibit extracellular pH values around 6.5–6.9 due to glycolytic metabolism, poor perfusion, and lactic acid accumulation, while endosomes and lysosomes are even more acidic (pH 4.5–6.0). The GI tract further offers segmental pH variation from acidic gastric fluid to near-neutral intestinal fluid, which can be exploited for oral colon-targeted or enteric delivery [23-24].

#### 3.1.2 pH-sensitive linkers and materials

pH-responsive SDDS commonly employ acid-labile linkers such as hydrazones, acetals, ketals, cis-aconityl groups, or imine bonds that are relatively stable at neutral pH but rapidly hydrolyze in acidic environments, thereby releasing conjugated drugs or destabilizing the carrier.

Alternatively, ionizable polymers (e.g., poly(β-amino esters), carboxylated or aminated polysaccharides, certain PEG–polyacid or polybase block copolymers) undergo protonation/deprotonation, inducing swelling, collapse, charge switching, or micelle disassembly. Several studies demonstrate that such systems provide minimal leakage at pH 7.4 while enabling rapid release under tumor or endosomal pH, resulting in amplified intracellular drug accumulation in cancer cells [25].Table 2

**Table 2.** Overview of Major Nanocarrier Classes in Stimuli-Responsive Drug Delivery

| Carrier class | Typical size range | Example materials | Dominant stimuli used | Applications | Advantages | Limitations |
|---|---|---|---|---|---|---|
| Polymeric micelles / nanoparticles | 10–200 nm | PEG-PLA, PEG-PCL, PEG-PBAE, dendrimers, poly(organophosphates). | pH, redox, enzymes, temperature. | Cancer chemo, gene delivery, imaging. | High loading of hydrophobic drugs; tuneable size/surface; easy functionalization. | Potential polymer toxicity; complex synthesis; EPR heterogeneity [26-27]. |
| Liposomes / lipid nanoparticles | 50–300 nm | Phospholipids, cholesterol, thermo-sensitive lipids; SLN, NLC. | pH, temperature, enzymes, ultrasound. | Oncology, vaccines, nucleic acid delivery. | Clinically validated class; high biocompatibility; scalable manufacture. | Physical instability, leakage; RES uptake; limited active targeting success in clinic [28-29]. |
| Inorganic nanoplatforms | 10–150 nm typically | Mesoporous silica, gold, iron oxide, black phosphorus, quantum dots. | pH, redox, light, magnetic, enzymes. | Theragnostic, PTT/PDT, MRI/CT contrast, cancer therapy. | High surface area; multimodal imaging; strong photothermal/ magnetic response. | Long-term fate, potential inorganic toxicity, regulatory caution [30]. |
| Hydrogels / nanogels | Macro- (mm–cm) to nano-scale. | PNIPAM, PEG-based, alginate, chitosan, HA, PEG-PEGDA, PEG-PLGA hybrid. | pH, temperature, redox, enzymes, light. | Local depots, intra-articular, ocular, skin, CNS depots. | Prolonged local release; injectable in situ gelation; high water content. | Diffusion-limited penetration; sometimes poor mechanical strength; |

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| | | | | | | sterilization issues [31]. |
| Electro spun nanofibers | 50–1000 nm diameter. | PCL, PLA, PLGA, chitosan, gelatine, blended systems. | pH, enzymes, temperature, light. | Wound dressings, implants, periodontal and dermal delivery. | High surface area; tuneable porosity; can incorporate multiple drugs. | Mainly local use; scaling uniform fibbers can be challenging [32]. |
| Bio macromolecular nanoparticles | 20–300 nm. | Proteins, polysaccharides (alginate, chitosan, HA, dextran), DNA/RNA. | pH, enzymes, redox, glucose. | Cancer, autoimmune diseases, vaccines. | Biocompatible, biodegradable, often low toxicity; potential regulatory familiarity. | Batch variability; stability and storage challenges; immunogenicity risk [33]. |
| Biomimetic / cell-mediated | Cell-size (5–20 µm) or vesicles 50–200 nm. | Erythrocytes, leukocytes, platelets, MSCs, exosomes; coated nanoparticles. | pH, redox, enzymes; plus light, ultrasound, magnetic (external). | Oncology, regenerative medicine, dermatology, CNS targeting. | Natural homing, immune evasion, long circulation. | Complex manufacturing; cell safety; regulatory category similar to ATMPs [34]. |

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### 3.1.3 Applications and challenges

pH-responsive carriers have been widely studied for chemotherapy, gene delivery, vaccination, and localized therapy in inflammatory bowel disease and infection. Challenges include modest pH differences between diseased and normal tissue in some indications, off-target activation in other acidic environments (e.g., stomach, sites of acute infection), and interpatient variability in tumour acidosis. Strategies to mitigate these issues include combining pH-responsiveness with additional triggers or active targeting ligands to refine tissue specificity [35].

## 3.2 Redox- and ROS-responsive systems

### 3.2.1 Redox gradients in cells and tissues

Intracellular compartments, particularly the cytosol and cell nucleus, contain high concentrations of reducing agents such as glutathione (GSH), often in the millimolar range, whereas extracellular fluids have substantially lower GSH levels. Many tumors and inflamed tissues exhibit altered redox homeostasis and elevated ROS, including superoxide, hydrogen peroxide, and hydroxyl radicals, providing a rationale for redox- and ROS-responsive SDDS [36].

### 3.2.2 Disulfide, diselenide, and ROS-cleavable linkers

Redox-responsive systems frequently incorporate disulfide or diselenide bonds within polymer backbones, crosslinkers, or drug–polymer conjugates that are cleaved under high GSH conditions inside cells, leading to rapid de-crosslinking or drug release. ROS-responsive linkers such as thioketals, boronic esters, or peroxalate esters degrade in oxidative environments, enabling selective activation in ROS-rich tumors or inflamed sites. Combinations of pH and redox sensitivity, for example in block copolymer micelles with both ionizable blocks and disulfide crosslinks, provide dual-level control over stability and release [37].

### 3.2.3 Opportunities and limitations

Redox- and ROS-triggered SDDS have shown impressive performance in preclinical cancer models, enhancing intracellular delivery of chemotherapeutics, photosensitizers, proteins, and nucleic acids. However, redox and ROS levels are heterogeneous across tumor subtypes, disease stages, and patient populations, and murine models may exaggerate these gradients compared with human tissues, complicating direct translation. Careful quantitative characterization of redox conditions in human disease and robust in vitro models must thus accompany development of such systems [38].

## 3.3 Enzyme-responsive systems

### 3.3.1 Disease-associated enzymes

Numerous enzymes are overexpressed or dysregulated in disease microenvironments, including matrix metalloproteinases (MMPs), hyaluronidase, phospholipases, proteases, glycosidases, and esterases. Their substrate specificity and local activity can be exploited for site-selective degradation of polymers, cleavage of peptide or polysaccharide gatekeepers, or activation of prodrugs [39].

### 3.3.2 Peptide and polysaccharide gatekeepers

Enzyme-responsive designs often place peptide sequences or polysaccharide chains on the surface of nanocarriers or across pores that are cleaved by target enzymes such as MMP-sensitive

peptides capping mesoporous silica or hyaluronic acid shells degraded by hyaluronidase. These gatekeepers mask targeting ligands, block drug diffusion, or maintain stealth properties until degradation in the enzyme-rich microenvironment triggers shell shedding, exposure of ligands, or release of drug [40].

### 3.3.3 Specificity and variability

Enzyme-responsive SDDS offer high biochemical specificity but are sensitive to interpatient variability in enzyme expression, regulation, and localization. In addition, enzyme activity can change during therapy due to tumor evolution or inflammatory resolution, which may alter responsiveness over time. Validating enzyme profiles in patient biopsies and integrating companion diagnostics could help select patients most likely to benefit from such systems [41].

## 3.4 Temperature-responsive systems

### 3.4.1 Thermo-sensitive hydrogels and polymers

Temperature-responsive polymers such as poly(N-isopropylacrylamide) (PNIPAM) and various PEG–polyester or polysaccharide-based materials exhibit LCST or upper critical solution temperature (UCST) behavior, leading to sol–gel transitions or volume phase changes in response to small temperature variations. These properties enable injectable in situ gelling depots, transdermal patches, and implantable systems that remain liquid at room temperature but gel at body or locally elevated temperatures, controlling drug diffusion and release [42].

### 3.4.2 Thermosensitive liposomes and hyperthermia

Thermosensitive liposomes with phase transition temperatures slightly above physiological temperature (e.g., 40–42 °C) release their encapsulated drug rapidly upon local hyperthermia induced by radiofrequency, microwave, or focused ultrasound. Such formulations aim to deliver high local drug levels to tumors exposed to hyperthermia while minimizing systemic exposure, and several have entered clinical testing in oncology indications [43].

### 3.4.3 Prospects and safety considerations

Thermal triggers offer non-invasive, reversible control and deep-tissue reach when combined with advanced hyperthermia technologies, but require accurate temperature monitoring and control to avoid tissue damage. Integration with imaging modalities (e.g., MRI-guided focused ultrasound) and real-time thermometry can enhance safety and precision. Patient discomfort, potential burns, and the need for specialized equipment are practical barriers that must be weighed against the therapeutic gains [44].

## 3.5 Light-responsive systems

### 3.5.1 Photocleavable and photoisomerizable moieties

Light-responsive SDDS rely on chromophores that undergo bond cleavage (e.g., o-nitrobenzyl, coumarin derivatives), isomerization (e.g., azobenzene), or photothermal conversion under specific wavelengths. Incorporation of these groups into drug–polymer linkers, crosslinkers, or capping agents allows precise spatiotemporal control of release upon illumination [45].

### 3.5.2 NIR-triggered photothermal and photodynamic systems

Near-infrared (NIR) light is preferred for in vivo applications because it offers deeper tissue penetration and reduced photodamage compared with UV or visible light. NIR-absorbing

materials such as gold nanorods, graphene, and black phosphorus can convert light into heat or ROS, enabling photothermal or photodynamic therapy combined with drug release in smart theranostic platforms. For example, black phosphorus-based nanocarriers loaded with chemotherapeutics have demonstrated synergistic tumor ablation upon NIR irradiation in preclinical cancer models [46].

### 3.5.3 Clinical utility and limitations

Light-responsive systems are attractive for superficial tumors, dermatologic conditions, and endoscopically accessible lesions, but their use in deep organs is limited by light attenuation and scattering. Safety concerns include unintended phototoxicity, thermal damage, and the need to avoid systemic photosensitization, particularly with prolonged or repeated treatments [47].

## 3.6 Ultrasound-, magnetic-, electric-, and mechano-responsive systems

### 3.6.1 Ultrasound-triggered delivery and BBB modulation

Ultrasound-responsive SDDS use microbubbles, nanobubbles, phase-change droplets, or ultrasound-sensitive polymers to achieve cavitation-induced release or enhanced tissue penetration. When combined with focused ultrasound, such carriers can transiently open the blood–brain barrier (BBB) to deliver chemotherapeutics, antibodies, or nucleic acids to the CNS, as shown in multiple preclinical studies. Careful control of acoustic parameters is essential to maximize delivery and minimize hemorrhage or neurotoxicity [48].

### 3.6.2 Magnetic- and electric-responsive platforms

Magnetic nanoparticles, particularly iron oxide-based systems, can be guided or concentrated at target sites using external magnetic fields and can also generate localized heating for magnetothermal therapy, which in turn triggers drug release from surrounding matrices. Electric fields can modulate electro-responsive hydrogels or membranes, changing their porosity, swelling, or charge distribution, and have been investigated in implantable devices for on-demand drug administration [49].

### 3.6.3 Mechano-responsive and shear-sensitive carriers

Mechanical forces, including shear stress in blood flow or compression in joints, can be harnessed to design mechano-responsive carriers that release drugs under pathological mechanical conditions such as thrombosis or osteoarthritis. Although still emerging, such designs may allow highly localized therapy in mechanically distinctive microenvironments, provided that mechanical thresholds are carefully calibrated to avoid off-target activation [50].

# 4. Materials and Architectures for Stimuli-Responsive Delivery

## 4.1 Polymeric nanoparticles and micelles

### 4.1.1 Block copolymer micelles and nanospheres

Amphiphilic block copolymers self-assemble into micelles or nanospheres with hydrophobic cores and hydrophilic coronas, serving as versatile platforms for loading hydrophobic drugs and decorating surfaces with targeting ligands and responsive groups. Incorporation of pH-, redox-, enzyme-, or temperature-sensitive blocks or crosslinkers allows modulation of micelle stability and trigger-dependent disassembly. For example, polymeric micelles with disulfide crosslinks

in the core remain stable in circulation but rapidly release drugs upon intracellular reduction, enhancing cytotoxicity in cancer cells [51].

#### 4.1.2 Dendrimers and hyperbranched polymers

Dendrimers are hyperbranched, monodisperse macromolecules with a high density of surface functional groups that can be conjugated with drugs, imaging agents, and targeting ligands. Stimuli-responsive dendrimers often feature cleavable linkers between core and shell or within the branches, enabling controlled drug release in response to pH, redox, or enzymatic stimuli. Their well-defined architecture makes them attractive for structure–activity correlation studies, but potential toxicity and manufacturing costs are key concerns [52].

### 4.2 Lipid-based nanocarriers

#### 4.2.1 Liposomes and solid lipid nanoparticles

Liposomes encapsulate hydrophilic drugs in their aqueous core and hydrophobic drugs in the bilayer, and can be modified with pH-sensitive lipids, cholesterol derivatives, or polymer coatings to achieve stimulus-responsive release. Solid lipid nanoparticles and nanostructured lipid carriers offer solid or semi-solid cores that can be engineered for pH-, enzyme-, or thermo-responsiveness and are often composed of biodegradable, pharmaceutically acceptable lipids [53].

#### 4.2.2 Hybrid lipid–polymer systems

Lipid–polymer hybrid nanoparticles combine the structural stability of polymeric cores with the biocompatibility and stealth properties of lipid shells, allowing incorporation of multiple responsive components. Such hybrids have been used to synchronize pH-responsive core release with enzyme- or ligand-mediated surface interactions, particularly in cancer and inflammatory disease models [54].

### 4.3 Inorganic and supramolecular systems

#### 4.3.1 Mesoporous silica and metal-based carriers

Mesoporous silica nanoparticles (MSNs) provide high surface area, tunable pore sizes, and facile surface functionalization, making them prime candidates for gatekeeper-based SDDS. Peptide, polymer, or saccharide caps are attached to the pore openings via cleavable linkers that respond to pH, enzymes, redox, or light, thereby converting environmental cues into pore opening and drug release. Metal and metal-oxide nanoparticles (e.g., gold, iron oxide) similarly offer platforms for combining photothermal, magnetic, or imaging functions with responsive release [55].

#### 4.3.2 Supramolecular and self-assembly nanomaterials

Supramolecular self-assembly systems built from small molecules, peptides, cyclodextrins, host–guest complexes, or other building blocks can spontaneously form nanostructures that are responsive to stimuli. Stimuli-sensitive supramolecular assemblies exploit non-covalent interactions (e.g., hydrogen bonding, π–π stacking, host–guest inclusion) that are disrupted or rearranged by pH, redox, ions, or light, leading to structural changes and drug release. Recent reviews underscore their promise for highly modular, tunable, and reversible SDDS in oncology [56].

### 4.4 Hydrogels, nanogels, and electrospun fibers

#### 4.4.1 pH/thermo/enzyme-responsive hydrogels and nanogels

Hydrogels crosslinked, water-swollen networks can be designed to undergo volume phase transitions or biodegradation in response to pH, temperature, redox, or enzymatic cues, making them suitable for local sustained release. Nanogels, which are hydrogel particles at nanoscale, offer high loading, soft deformability, and responsiveness to internal (pH, enzymes) or external (light, temperature) stimuli, with alginate-based nanogels being prominent for cancer therapy. These systems have been explored for intratumoral injection, intra-articular delivery, and mucosal administration [57].

#### 4.4.2 Electrospun nanofibers

Electrospun nanofiber mats made from polymers and biopolymers provide high surface area, tunable porosity, and the ability to incorporate drugs and stimuli-responsive components for controlled release. Stimuli-responsive electrospun systems respond to pH, temperature, enzymes, or light to modulate release profiles and are especially promising for topical, wound, and implantable applications. They can be further combined with nanoparticles or hydrogels to create multi-layered, hierarchical SDDS [58].

### 4.5 Biomacromolecular and cell-mediated systems

#### 4.5.1 Biomacromolecular carriers from concept to market

Biomacromolecular systems based on proteins, polysaccharides, nucleic acids, and hybrid biopolymers are increasingly investigated for stimuli-responsive delivery because of their inherent biocompatibility, biodegradability, and functional diversity. A recent review on "concept to market" biomacromolecular systems highlights pH-, redox-, and enzyme-responsive nanoparticles, dendrimers, lipid-based carriers, and polymer–drug conjugates, with some progressing toward clinical trials. Challenges include batch-to-batch reproducibility, immunogenicity, and stability, but clinical precedent with certain biopolymers supports their translational potential [59].

#### 4.5.2 Cell-mediated and biomimetic SDDS

Cell-mediated SDDS use erythrocytes, platelets, leukocytes, stem cells, or exosomes as carriers, often combining intrinsic homing capabilities with engineered stimuli-responsive release modules. For example, immune cells loaded with nanoparticles can migrate into tumors or inflamed sites where internal stimuli (pH, enzymes) or external triggers (light, ultrasound, magnetic fields) prompt local drug release. Such systems promise improved targeting and prolonged circulation but raise complex safety, regulatory, and manufacturing questions typical of advanced cell therapies [60].

## 5. Mechanisms of Stimulus-Responsive Drug Release

### 5.1 Covalent bond cleavage and prodrug activation

Many SDDS employ prodrugs or conjugates in which the active drug is covalently linked to polymers, lipids, or small molecules through labile bonds that cleave in response to stimuli.

Acid-labile hydrazone linkers, disulfide bridges, ROS-sensitive thioketals, or light-cleavable o-nitrobenzyl groups are examples that have been systematically studied to determine how linker chemistry affects release rates, stability, and pharmacokinetics. In principle, these systems can convert an otherwise systemically active drug into a locally activated agent, thereby improving selectivity and reducing off-target toxicity [61].

### 5.2 Conformational changes and phase transitions

Responsive polymers can undergo conformational changes such as coil–globule transitions, micelle–unimer transitions, or sol–gel transitions upon exposure to stimuli. For example, thermo-responsive PEG–PNIPAM copolymers collapse above their LCST, expelling water and potentially squeezing out drugs, while pH-responsive polybases become protonated in acidic environments, causing swelling or disassembly. These changes alter diffusional pathways and surface properties, driving modulated release kinetics [62].

### 5.3 Gatekeeping and pore capping

In mesoporous and core–shell systems, gatekeeping moieties such as polymers, peptides, or molecular caps obstruct pores or stabilize shells until removal by stimuli. This “on–off” behavior can provide near-zero release in circulation and rapid burst release at the target, particularly when caps are degraded by specific enzymes or reduced by intracellular GSH. Careful tuning is required to avoid overly tight gating that prevents release even at the target site or too loose gating that leads to premature leakage [63].

### 5.4 Carrier disassembly and multi-stage activation

Multi-stage SDDS incorporate nested structures that disassemble in a sequential manner as they encounter different biological barriers and stimuli, such as blood, tumor interstitium, cellular uptake, and intracellular compartments. For instance, an outer stealth layer may shed at mildly acidic tumor pH, exposing cationic or ligand-functionalized cores that enhance cell uptake, followed by redox-triggered disintegration of the core and release of drugs in the cytosol. This approach aims to balance circulation stability with efficient tumor penetration and intracellular delivery [64].

## 6. Impact on Pharmacokinetics, Biodistribution, and Therapeutic Index

### 6.1 Pharmacokinetic modulation

SDDS typically alter classic PK parametersCmax, Tmax, area under the curve (AUC), clearance, and volume of distribution by affecting absorption, distribution, metabolism, and excretion. Nanocarriers and depots can prolong circulation, reduce clearance, and sustain release, while stimuli-responsiveness adds a layer of spatial and temporal control that decouples systemic exposure from local delivery. For example, cyclodextrin-based nanomedicine CRLX101 produces prolonged and controlled release of camptothecin, improving tumor exposure and PK relative to free drug in clinical studies [65].

### 6.2 Biodistribution and tumor accumulation

Size, surface charge, shape, and surface chemistry of SDDS influence their biodistribution, including accumulation in tumors via the enhanced permeability and retention (EPR) effect and uptake by the reticuloendothelial system. Stimuli-responsive features can enhance tumor

deposition by facilitating charge switching or size shrinking at tumor sites, as demonstrated in mathematical and in vivo models of programmable size-changing nanoparticles for improved penetration. Nevertheless, EPR is highly heterogeneous among tumor types and between animal models and patients, raising questions about the generalizability of preclinical data [66].

### 6.3 Therapeutic index and safety profile

By concentrating active drug levels in diseased tissues and limiting systemic exposure, SDDS can increase the therapeutic index defined as the ratio between doses (or exposures) causing toxicity and those providing efficacy. In multiple preclinical models, stimuli-responsive carriers have produced superior antitumor effects with reduced cardiotoxicity, myelosuppression, or off-target organ damage compared with conventional formulations. However, immunogenicity of carriers, long-term accumulation, and off-target activation of stimuli (e.g., systemic ROS, fever, incidental light exposure) can counteract these benefits and require careful risk management [63].

## 7. Preclinical Applications in Major Disease Areas

### 7.1 Oncology

#### 7.1.1 Solid tumors and metastases

Cancer remains the most intensively studied field for SDDS, with numerous pH-, redox-, enzyme-, temperature-, light-, ultrasound-, and multi-stimuli-responsive systems targeting solid tumors and metastases. Stimuli-responsive polymeric micelles, liposomes, nanogels, and MSNs loaded with doxorubicin, paclitaxel, platinum agents, or targeted therapies have shown improved tumor suppression and survival benefits in rodent models. Platinum-based drugs, in particular, have been the focus of stimuli-responsive nanocarriers aiming to mitigate nephrotoxicity and neurotoxicity while overcoming drug resistance [64].

#### 7.1.2 Lung, breast, and head and neck cancers

Dedicated reviews describe SDDS for lung cancer, breast carcinoma, and head and neck cancers, emphasizing combination therapies and theranostics. For lung cancer, SDDS have been integrated with inhalation routes, systemic administration, and imaging agents to provide targeted diagnosis and therapy. In breast cancer, innovative thermo-, pH-, and enzyme-responsive nanocarriers have been explored to target diverse subtypes, including triple-negative disease, often in combination with photothermal or immunotherapies [65].

### 7.2 Inflammatory and autoimmune diseases

Responsive systems targeting enzyme-rich and acidic inflamed tissues have been studied in rheumatoid arthritis, inflammatory bowel disease, psoriasis, and other autoimmune or inflammatory conditions. Smart polymer-based topical systems for the skin demonstrate temperature- and pH-responsive release of anti-inflammatory drugs, corticosteroids, and immunomodulators, improving local efficacy and minimizing systemic absorption in preclinical and early clinical evaluations [66].

### 7.3 Metabolic and endocrine disorders

Thermo- and glucose-responsive hydrogels and depots have been investigated for insulin delivery, aiming to automatically adjust insulin release in response to physiological or induced changes. Stimuli-responsive depots for other hormonal and metabolic therapies (e.g., GLP-1

analogues, PTH) are also under exploration, though translation is still constrained by safety, device integration, and long-term stability concerns [67].

### 7.4 Neurological and CNS diseases

Ultrasound-responsive carriers combined with focused ultrasound have achieved transient BBB opening and enhanced brain delivery of chemotherapeutics, antibodies, and nucleic acids in models of brain tumors and neurodegenerative disorders. Emerging reviews describe microenvironment-responsive nano-drug delivery for neurological diseases, highlighting the potential for SRDDS to address heterogeneity in BBB integrity, inflammation, and oxidative stress. However, the narrow safety margin of the CNS and the complexity of neurological pathology demand rigorous translational research and monitoring [68].

### 7.5 Infectious diseases and COVID-19

Stimuli-responsive systems have also been proposed for antimicrobial delivery and vaccine adjuvants, including SDDS targeting intracellular pathogens and biofilms. During the COVID-19 pandemic, SDDS were discussed as potential tools to improve antiviral drug delivery, modulate immune responses, and manage individual variability, though practical clinical implementations are still in early stages. Endogenous and exogenous triggers such as pH, ROS, and physical stimuli have been examined for site-specific delivery to infected tissues [69].

## 8. Clinical Translation: Current Status and Examples

### 8.1 Early clinical nanomedicines and lessons learned

Several nanomedicines with passive targeting and controlled-release properties, including liposomal doxorubicin and albumin-bound paclitaxel, are clinically approved and offer proof that nanoparticle-based modulation of PK and biodistribution can confer real patient benefit. However, many advanced nanoplatforms with sophisticated targeting and responsive features have failed to demonstrate clear superiority in late-phase trials due to modest incremental benefits, unanticipated toxicities, or trial design issues [70]. Table 3

**Table 3**. Clinical Translation Status of Selected Smart and Nano-Enabled Drug Delivery Systems

| Category | Representative example(s) | Stimulus used | Clinical stage / status | Indication(s) | translational points |
|---|---|---|---|---|---|
| Conventional nanomedicine with partial "smartness" | PEGylated liposomal doxorubicin, nab-paclitaxel. | Mainly passive (size/EPR); some pH-dependent leakage. | Approved products. | Various solid tumours. | Demonstrated that nano-PK modification can improve safety/efficacy, but without complex logic gating [71-72]. |
| Thermosensitive liposomes | Lyso-thermosensitive liposomes combined with hyperthermia (e.g., formulations analogous to Thermador). | Temperature (40–42 °C) + local hyperthermia. | Phase I–III trials in liver and other tumours; mixed outcomes. | HCC, liver-dominant metastases, others. | Proof of temperature-triggered release in humans; emphasizes need for tight control of heating and patient selection [73]. |
| Cyclodextrin-based nanomedicine | CRLX101 (calprotectin–cyclodextrin polymer). | Controlled release from polymer conjugate (not strongly multi-stimuli). | Multiple phase I/II oncology trials; not approved. | Solid tumours, including renal cell carcinoma, rectal cancer. | Shows feasibility of polymer–drug conjugate nanomedicine in clinic; highlights challenges in showing superiority vs SOC [74]. |
| Stimuli-responsive micellar / hydrogel systems | PEG-based hydrogels, micelles with pH/enzyme-sensitive crosslinks in cancer trials. | pH, enzymes, redox (depending on design). | Early-phase or exploratory clinical/clinical-like studies. | Cancer local therapy, depot systems. | Biodegradable PEG-based platforms seen as relatively "regulator-friendly"; may |

| | | | | | |
|---|---|---|---|---|---|
| | | | | | be among first truly SRDDS to reach market [75]. |
| Smart SDDS – broad clinical perspective | Smart nanoplatforms integrating active targeting and stimuli-responsiveness. | Internal (pH, redox, enzymes) and external (light, magnetic, US) triggers. | Predominantly preclinical; few early human studies. | Mainly oncology; exploratory in autoimmune, neuro, infection. | Major obstacles: scale-up, batch control, regulatory path, and proving clinical benefit beyond simpler nano formulations [76]. |

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### 8.2 Stimuli-responsive systems in clinical trials

Thermosensitive liposomes combined with local hyperthermia and ultrasound-triggered carriers are among the most clinically advanced SDDS. Cyclodextrin-based nanomedicines such as CRLX101, although not strictly multi-stimuli-responsive, embody controlled release and nano-encapsulation principles and have been evaluated in multiple phase I–II trials in solid tumours, showing manageable toxicity and signs of efficacy. Clinical studies of micellar systems and PEG-based hydrogels increasingly incorporate stimuli-responsive elements, such as pH- or enzyme-sensitive crosslinks, reflecting gradual translation of SRDDS concepts [77].

### 8.3 Barriers to clinical impact

Key translational barriers include difficulties in scaling up complex architectures under GMP, limited standardization of characterization methods for responsiveness and in vivo behaviour, and gaps between preclinical models and human pathophysiology. Moreover, regulators and clinicians require clear evidence that added complexity (e.g., multi-stimulus gating, theragnostic integration) translates into robust, clinically meaningful improvements over existing therapies, including cost-effectiveness and patient acceptability [78].

## 9. Manufacturing, Regulatory, and Translational Challenges

### 9.1 Scale-up, reproducibility, and quality-by-design

Multi-component SDDS with responsive polymers, inorganic cores, targeting ligands, and labile linkers often necessitate multi-step synthesis and assembly, each introducing potential variability. Quality-by-design (QbD) approaches emphasize identification of critical quality attributes (e.g., size, polydispersity, zeta potential, loading, release profile, responsiveness metrics) and process parameters to ensure batch consistency. Advanced manufacturing methods such as microfluidics, continuous processing, and in-line monitoring are increasingly 3139-2741 to improve control and scalability [79].

### 9.2 Analytical characterization of responsiveness

Robust characterization of SDDS requires in vitro and ex vivo assays that simulate physiological and pathological conditions and quantify stimulus-dependent changes in structure and release. Techniques include dynamic light scattering, electron microscopy, NMR, spectroscopy, rheology, calorimetry, and advanced imaging modalities to monitor morphological transitions and drug diffusion. However, standardized protocols for evaluating responsiveness (e.g., defined pH ranges, redox conditions, enzymatic activities, temperature profiles) are still evolving and must be harmonized to support regulatory submissions [80].

### 9.3 Regulatory frameworks and risk–benefit assessment

Regulatory agencies treat SDDS as complex drug–device or combination products, requiring integrated assessments of carrier materials, stimuli sources, and drug payloads. Risk–benefit evaluation considers not only traditional pharmacology and toxicology but also potential off-target

activation, device-related hazards (e.g., hyperthermia, ultrasound, electromagnetic exposure), and long-term fate of nanocarriers. Regulatory experience with earlier nanomedicines and polymer therapeutics provides some precedent, but stimulus-responsiveness introduces additional layers of complexity [81].

## 10. Emerging Trends and Future Directions

### 10.1 Bio macromolecular systems from concept to market

Recent reviews emphasize that bio macromolecular systems (proteins, polysaccharides, nucleic acids) are moving from conceptual laboratory constructs toward market-ready products, driven by their tuneable stimuli-responsiveness and established clinical acceptability of many biopolymers. Dual- and multi-stimuli natural polymeric nanocarriers, such as chitosan, alginate, and hyaluronic acid-based systems, are under investigation for clinical translation, with several in or approaching clinical trials [82].

### 10.2 Cell-mediated and tissue-specific SDDS

Stimuli-responsive, cell-mediated SDDS represent a convergence of nanomedicine, cell therapy, and synthetic biology. Erythrocyte- or leukocyte-based carriers equipped with pH- or redox-sensitive release modules could act as “Trojan horses” delivering drugs directly to tumours or inflamed tissues, while stem cell–based carriers might support regenerative therapies with on-demand factor release. Dermatologic applications are also emerging, where immune or stem cells are used as vehicles for targeted, sustained delivery to skin lesions [83].

### 10.3 Programmable and AI-guided design

Mathematical modelling, systems pharmacology, and AI-driven optimization are increasingly employed to rationally design SDDS, predict in vivo performance, and optimize parameters such as size, charge, and trigger thresholds. Integrating patient-specific data (e.g., imaging, omics, microenvironmental profiling) with SDDS design could enable personalized smart therapies where formulations and stimuli are customized to an individual’s disease characteristics [84].

### 10.4 Integration with diagnostics and digital health

Theragnostic SDDS that combine imaging agents with responsive drug release can provide real-time feedback on carrier distribution, activation, and treatment response. Coupled with digital health tools and remote monitoring, such systems could support adaptive dosing, early detection of non-response, and more efficient clinical trials. However, data privacy, interoperability, and regulatory oversight of digital components will become increasingly important [85].

## 11. Discussion

Stimuli-responsive drug delivery systems have evolved from relatively simple pH-sensitive coatings and thermo-responsive polymers into highly engineered, multi-layered nanoplatforms capable of integrating biological sensing, controlled release, and even imaging functions. The central promise of these systems is conceptually clear: convert a disease-associated signal into a localized pharmacological response. Across oncology, inflammatory diseases, metabolic disorders, CNS conditions, and infections, preclinical data consistently demonstrate improved

local drug concentration, reduced systemic exposure, and enhanced therapeutic indices compared with conventional formulations. Translation into routine clinical practice remains limited [86].

One of the most important themes emerging from recent literature is the gap between mechanistic elegance and clinical reality. Many endogenous triggers such as pH, redox gradients, ROS, and enzyme overexpression are indeed detectable in diseased tissues, but their magnitude and spatial distribution are highly heterogeneous in patients. Tumour acidosis, for example, may vary not only between tumour types but also within different regions of the same tumour. Similarly, glutathione and ROS levels that appear robust in murine models are often less pronounced in human tissues. As a result, systems optimized under controlled laboratory conditions may not activate as predictably in clinical settings. This heterogeneity directly challenges the first step of the conceptual framework: reliable identification of a disease-specific stimulus [87].

Exogenous triggers, including hyperthermia, light, ultrasound, and magnetic fields, address some of these limitations by offering external control. Among these, thermosensitive liposomes and ultrasound-mediated systems have progressed furthest clinically. They demonstrate that externally 3139-2741 triggers can induce measurable, site-specific drug release in humans. However, this approach introduces its own complexity. It requires precise control of energy delivery, imaging guidance, trained operators, and specialized infrastructure. Variability in device performance and patient anatomy can influence outcomes as much as carrier design. Therefore, SDDS based on exogenous stimuli must be evaluated as integrated drug–device systems rather than standalone formulations [88].

Another recurring issue is the balance between complexity and benefit. Multi-stimuli systems with hierarchical logic gating are scientifically appealing and may enhance specificity. However, each additional responsive module increases manufacturing difficulty, batch variability, analytical burden, and regulatory scrutiny. From a translational standpoint, the question is not whether a system can respond to three or four stimuli, but whether that added sophistication produces a clinically meaningful improvement in survival, symptom control, or quality of life. Historical experience with nanomedicine suggests that incremental but robust improvements in safety and pharmacokinetics may be more successful than highly complex constructs with marginal benefit [89-90].

Material choice also strongly influences translational feasibility. Lipid-based systems and PEG-containing polymers have benefited from decades of regulatory familiarity, which partially explains their dominance in clinical nanomedicine. In contrast, inorganic nanoplatforms and hybrid supramolecular systems offer powerful imaging and photothermal capabilities but raise questions about long-term biodistribution, biodegradation, and chronic toxicity. Bio macromolecular carriers and natural polymers appear attractive due to their biocompatibility and biodegradability, yet they face challenges related to batch-to-batch reproducibility and immunogenicity. Cell-mediated and biomimetic systems, while promising for targeting and

immune evasion, enter the regulatory territory of advanced therapy medicinal products, where manufacturing, scalability, and safety monitoring become even more demanding.

Pharmacokinetic and biodistribution advantages of SDDS are well documented in preclinical models. Controlled release, prolonged circulation, tumour accumulation, and intracellular activation have been repeatedly demonstrated. However, the enhanced permeability and retention effect, which underpins much of tumour-targeted nanomedicine, is highly variable in humans. Consequently, future development should rely less on assumed passive accumulation and more on quantitative patient stratification, imaging-based assessment of accumulation, and biomarker-driven selection. Companion diagnostics may become essential for identifying patients whose tumours or inflamed tissues exhibit sufficient stimulus intensity to activate the system [91-92].

Manufacturing and regulatory science will play a decisive role in the next phase of development. Quality-by-design principles, advanced microfluidic assembly, and real-time analytical monitoring can improve reproducibility and scalability. At the same time, standardized assays for stimulus responsiveness under physiologically relevant conditions are urgently needed. Regulatory agencies increasingly require comprehensive characterization of carrier composition, degradation pathways, and interaction with biological systems. Demonstrating not only safety but also clear clinical superiority over existing therapies will be essential to justify cost and complexity.

Emerging trends provide cautious optimism. Integration of mathematical modelling and artificial intelligence allows rational optimization of size, charge, and trigger thresholds before extensive in vivo testing. Patient-specific data from imaging and molecular profiling may guide personalized smart formulations. Theragnostic systems that combine imaging and responsive release offer the possibility of monitoring activation in real time, thereby linking mechanism to outcome more directly. If these tools are used to reduce uncertainty and tailor therapy, SDDS may move from proof-of-concept to precision medicine platforms.

Overall, the field stands at a transitional stage. The scientific foundation is strong, preclinical validation is extensive, and early clinical examples demonstrate feasibility. The major challenge is no longer whether stimuli-responsive delivery works in principle, but how to align material science, pathophysiology, clinical need, and regulatory strategy into coherent, scalable, and economically viable therapies [93-94].

## 12. Conclusion

Stimuli-responsive drug delivery systems represent a rational and increasingly sophisticated approach to overcoming the limitations of conventional dosage forms. By exploiting endogenous cues such as pH, redox gradients, enzymes, ROS, and metabolites, or by applying controlled external triggers including temperature, light, ultrasound, and magnetic fields, these systems aim to achieve spatially and temporally precise drug release. Advances in polymer chemistry, lipid engineering, inorganic nanotechnology, supramolecular assembly, bio macromolecular design, and cell-mediated platforms have greatly expanded the range of materials and architectures available.

Preclinical studies consistently show improved pharmacokinetics, enhanced local drug accumulation, and superior therapeutic indices across oncology, inflammatory disorders, metabolic diseases, neurological conditions, and infectious diseases. Early clinical experiences with nanomedicines and thermosensitive or controlled-release systems confirm that modulation of drug distribution can translate into patient benefit. Nevertheless, only a limited number of truly stimuli-responsive systems have reached advanced clinical stages, underscoring the persistent challenges of heterogeneity, manufacturing complexity, regulatory pathways, and demonstration of meaningful clinical advantage.

Future progress will depend on rigorous characterization of disease-specific stimuli in humans, simplified and scalable design strategies, standardized analytical methods, and careful integration with imaging, diagnostics, and digital tools. Personalized approaches that match trigger intensity and carrier design to individual patient profiles may enhance responsiveness and therapeutic gain. Ultimately, the success of smart drug delivery will be measured not by the number of responsive mechanisms incorporated into a carrier, but by its ability to deliver safer, more effective, and clinically transformative therapies.

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