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Review Article

Engineering Smart Stimuli-Responsive Carriers for Precision Drug Delivery: Current Trends and Future Outlook

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ABSTRACT

Stimuli-Responsive Drug Delivery Systems (SRDDS), also regarded as smart" drug delivery systems, have emerged as a vital element of precision pharmaceutics, with the ability of a spatiotemporally controlled therapeutic release for patients individualized physiology or outside-served stimuli. These systems utilize endogenous stimuli (pH, redox gradients, enzyme activity) or external stimuli (temperature, light, magnetic fields, and ultrasound) to activate a drug at the disease site, enhance the therapeutic effect, and decrease body toxicity. In this sense, we provide an updated summary with critical perspectives on the recent advancements regarding SRDDS, emphasizing the essential new ones in terms of materials, nanocarrier proxies, and design strategies that lead to the new generations of SRDDS remaining studied in depth and well characterized in preclinical animal models. We classify SRDDS based on the type of stimulus and highlight their individual and combination for advanced disease treatment, including cancers, neurodegenerative diseases, infectious diseases, and chronic inflammation. We also outline the regulatory, manufacturing, and translational challenges that are current barriers to clinical implementation and approaches to overcome them. Lastly, we present the current directions in this area, including multi-stimuli responsive systems, hybridization with biosensing technologies, and prospective applications for mRNA and gene delivery. In this review, we summarize and delineate various opportunities offered by SRDDS for next-generation precision therapeutics.

Keywords: Stimuli-responsive drug delivery, Smart therapeutics, Nanocarriers, Controlled release, Precision pharmaceutics, Biosensors, Multi-responsive systems.

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INTRODUCTION

Recently, the historic paradigm of drug delivery has progressed from basic delivery techniques to advanced systems to achieve individualized, on-demand therapeutic release. One particular prominent development in precision pharmaceutics over the past few decades is the emergence of Stimuli-Responsive Drug Delivery Systems (SRDDS). MODEL SYNERGY: Immediate release, when the systems are made to sense a stimulus (internal, bioactive species, e.g., pH, redox potential, enzymes) or external (temperature, magnetic field, light, ultrasound, etc.), allows drugs to release only in certain defined physiological or physicochemical environments. As illustrated in Figure 1, these smart carriers respond to specific internal or external stimuli to trigger a controlled release at the target site (Mura *et al*., 2013).

Such developments are motivated by an increasing requirement for precision treatment, particularly in the treatment of complex and heterogeneous diseases, including cancer, autoimmune conditions, and neurological disorders. The conventional drug administration scheme often shows poor bioavailability, increased systemic toxicity, frequent dosing requirements, and bad patient compliance. Alternatively, SRDDS provides controlled, site-specific release, which increases therapeutic index and diminishes unwanted side effects (Zhang *et al*., 2008).

Underpinning these technologies is a fusion of materials science, nanotechnology, and biomedical engineering. Responsive vehicles-made of polymers, lipids, dendrimers, inorganic nanomaterials, or hybrid systems-are designed to experience conformational or structural changes triggered by appropriate stimuli. For example, pH-sensitive polymers swell or degrade in response to low pH in acidic tumor microenvironments, or redox-sensitive nanocarriers release their payload in cancer cells when reactive uptake species exist in abundance. SRDDS is an emerging field, rapidly growing in research output and patent filings but with little clinical translation. These include complex formulation methods, challenges in scalability, regulatory uncertainty, and a lack of long-term biocompatibility data. In addition, the absence of consolidated regulatory guidelines across

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various regions remains a challenge for product development and approval (Torchilin, 2014).

We hope to provide a comprehensive and forward-looking synopsis on SRDDS in this review. We start our overview of SRDDS with a classification derived from the nature of the stimuli, and then we describe materials platforms and nanocarriers in detail. We then recount therapeutic applications in different disease contexts, regulatory and translational issues, and, lastly, burgeoning developments that may reshape the field. We hope that by summarizing existing knowledge while predicting trends, we will highlight the critical influence of SRDDS on the evolution of precision medicine.

CLASSIFICATION OF STIMULI-RESPONSIVE DRUG DELIVERY SYSTEMS (SRDDS)

Based on the nature of stimuli responsible for drug release, Stimuli-Responsive Drug Delivery Systems (SRDDS) can be categorized into two groups. The major classes of stimuli, their mechanisms, responsive materials, and application areas are systematically presented in Table 1 (Shi *et al.*, 2017). They can be divided into endogenous (intrinsic) and exogenous (extrinsic), each type carrying specific benefits for constructing systems ideally suited for given disease pathologies and treatment situations. These classifications provide a detailed understanding to develop smart delivery systems with substantial control over release kinetics and site-specific delivery (Mura *et al.*, 2013).

Stimuli-Responsive Systems that are Endogenous

Endogenous stimuli take advantage of the innate biochemical or physiological divergences from health to diseases, thus allowing exceptionally selective targeting without exogenous equipment. Endogenous triggers of the most studied type include pH gradients, redox potential, and expression of enzymes.

pH-Responsive Systems

Tissues and cellular compartments typically have disparate pH values. For instance, tumor microenvironments (pH 6.5), endosomes (pH 5.0-6.0), and inflamed sites exhibit lower pH levels than normal physiological pH (~7.4) (Peer *et al.*, 2007; Wang *et al.*, 2010); mechanistic knowledge of how decreased pH supplies a potent driving force for the biomolecular machinery remains elusive. Ionizable polymers like poly (L-histidine), poly (acrylic acid), and chitosan are used in pH-sensitive carriers and they exhibit protonation, swelling, or dissolving at lower pH. Such a pH-controlled mechanism is useful for intracellular delivery, particularly in cancer and infection treatment (Raza *et al.*, 2019).

For example, Lee *et al.*, (2021) showed, as well, that pH-sensitive polymeric micelles using doxorubicin delivered site-specific release in breast cancer cells, resulting in enhanced therapeutic efficacy with reduced cardiotoxicity.

Redox-Responsive Systems

Redox-sensitive systems take advantage of the significantly elevated levels of Glutathione (GSH) inside the cells (up to 100-1000 times higher than the extracellular matrix in cancer cells). which can be 100-1000 times higher than in the extracellular matrix. Nanocarriers are designed using disulfide bonds or redox-cleavable linkers that undergo cleavage in high-GSH environments, releasing the therapeutic payload selectively for example, disulfide-bridged mesoporous silica nanoparticles loaded with paclitaxel showed significantly enhanced cytoplasmic drug release and antitumor activity *in vitro* (Zhang *et al.*, 2020).

Enzyme-Responsive Systems

Enzyme-triggered drug release takes advantage of disease-specific overexpression of Matrix Metalloproteinases (MMPs), cathepsins, or phospholipases. These substances will use peptide linkers, polysaccharides, or polymer backbones degraded starting with a targeted enzyme that will release the medication preferentially.

An example is hyaluronic acid-based nanoparticles engineered to degrade during hyaluronidase overexpression in tumor tissues, resulting in increased cellular uptake and tumor regression (Liu *et al.*, 2019).

Responsive Systems to Exogenous Stimuli

Exogenous stimuli provide committed external control and temporal regulation of drug release as opposed to internal stimuli. These comprise temperature, magnetic fields, light, and ultrasound.

Thermo-Responsive Systems

Thermo-sensitive carriers use thermodynamic differences between healthy and disease tissues, or localized hyperthermia, as a trigger for cytotoxic drug release. Further, polymers with Low-Critical Solution Temperature (LCST) near 32°C, for example, poly(N-isopropylacrylamide) (PNIPAM), continue to have special clinical applications, such as driving release when heated.

E.g., Thermo-responsive liposomes encapsulating chemotherapeutics in combination with focused ultrasound-induced hyperthermia have been explored to improve tumor targeting and accumulation.

Systems Based on the Magnetic-Responsive Attribute

Magnetic-responsive systems utilize Superparamagnetic Iron Oxide Nanoparticles (SPIONs) to aid in site-specific delivery through guidance via external magnetic fields. Besides targeted navigation, alternating magnetic fields generate localized heat (magnetothermal therapy), which can induce drug release from thermosensitive matrices.

For instance, plenty of drug and therapeutic molecules have already been encapsulated in PLGA nanoplatforms, including some in the form of hybrid nanosphere composites.

Light-Responsive Systems

This simple configuration enables light-activated systems, which is a versatile approach to stimulate photothermoelectric reactions via UV, visible, or Near-IR (NIR) light in carrier materials that induces alterations in macromolecular conformation or chemical changes. NIR-responsive systems, due to deeper tissue penetration with lower phototoxicity, are of special interest.

Light-triggered release is accomplished by,

- Photoisomerization (azobenzene systems, for e.g.).
- Photocleavage (nitrobenzyl linkers, etc.,).
- Photothermal conversion (e.g., gold nanoshells or carbon nanotubes).

For instance, one example is NIR-responsive liposomes conjugated with indocyanine green, which have been shown to provide rapid release of doxorubicin with NIR exposure, leading to spatially resolved photochemotherapy.

Ultrasound-Responsive Systems

Low-Intensity Focused Ultrasound (LIFU) has shown great promise, as it induces acoustic cavitation and enhances membrane permeability, leading to the release of encapsulated drugs. Microbubbles, nanobubbles, and echogenic liposomes are frequently used carriers.

For instance, echogenic PLGA nanoparticles showed EPR in solid tumors upon activation with diagnostic ultrasound, resulting in increased drug accumulation with no systemic toxicity.

Multi-Stimuli-Responsive Systems

Developments in next-generation SRDDS are increasingly engineered to respond to multidimensional stimuli. Combining internal and external triggers greatly improves the precision, safety, and robustness of these synergistic systems (Sharma *et al.*, 2022). For instance, a pH- and redox-sensitive dendrimer system incorporating an NIR-activated photosensitizer proved able to release chemotherapeutical and photodynamic agents on demand in a triple-negative breast cancer (Sharma *et al.*, 2022).

MATERIALS AND NANOCARRIERS IN STIMULI-RESPONSIVE DRUG DELIVERY SYSTEMS

Selection of materials and nanosystems is crucial to the design and performance of nanoparticle-based Stimuli-Responsive Drug Delivery Systems (SRDDS). These parts not only encapsulate the therapeutic agent but also dictate the system's responsiveness, release kinetics, stability, and biocompatibility. The architectural diversity of nanocarriers used in SRDDS, including micelles, liposomes, dendrimers, and hybrid nanoparticles, is shown in Figure 2 (Kamaly *et al.*, 2012). SRDDS should ideally comprise stimuli-sensitive, stable, non-toxic, and biodegradable materials, in addition to those that can be surface-functionalized for targeted delivery (Li *et al.*, 2021).

A comparative summary of material types, stimuli-responsiveness, carrier forms, and typical applications is compiled in Table 2 (Duncan, 2006). Nanocarriers employed for SRDDS are generally divided into polymeric (13), lipidic (14), dendrimeric (15), inorganic (16), and hybrid (17) systems, each possessing unique structural characteristics and tailor-made responsiveness to stimuli (Peer *et al.*, 2007).

Polymeric Nanocarriers

Polymers constitute one of the most abundant series of materials exploited in SRDDS owing to their versatile chemical architecture, high throughput of fabrication regarding their complexity, and tunable responsiveness. They can be obtained from natural or synthetic sources and are designed to respond to a range of stimuli, including swelling, degradation, or solubility changes (Wang *et al.*, 2010).

Biodegradable and biocompatible natural polymers [e.g., chitosan, alginate, gelatin]. They are frequently responsive to changes in pH and enzymatic activation.

Synthetic polymers, including poly (lactic-co-glycolic acid) (PLGA), poly (N-isopropylacrylamide) (PNIPAM), and Polyethylene Glycol (PEG)-based copolymers, allow precise control over physicochemical properties and multi-stimuli responsiveness.

Depending on the selected application and the route of administration, polymeric nanocarriers may include micelles, nanogels, nanoparticles, or hydrogels.

Lipid-Based Carriers

Due to their structural similarity to biological membranes, lipid-based nanocarriers are extensively utilized in clinical and preclinical SRDDS, as they improve compatibility and drug loading efficiency. These carriers can be fine-tuned to release drugs in response to pH changes, temperature changes, or external stimuli like light and ultrasound. (Qiu and Park, 2012)

Extensively used liposomes and Solid Lipid Nanoparticles (SLNs) have been used for both hydrophilic and lipophilic drugs.

- Nanostructured Lipid Carriers (NLC) have better drug entrapment and sustained release characteristics because of a mixture of solid and liquid lipids in their formulation.
- Such carriers can also be surface-functionalized with the targeting ligands or stabilizing agents that allow

for improved circulation time and site-specific drug accumulation.

Dendrimers

Dendrimers are hyperbranched, monodisperse macromolecules with a well-defined core-shell architecture. They have multiple terminal groups that can provide opportunities for surface modification, stimuli-sensitive linker attachment, and high drug loading capability (Bae *et al*., 2003).

Regular dendrimer generations are prepared through controlled polymerization methodology.

Such engineered stimuli-responsiveness can be achieved through cleavable bonds that are responsive to pH, redox, or enzymes, or through conformational changes

By virtue of their uniform size and modifiable surface at the molecular level, dendrimers have great potential for precision-targeted delivery (Koo *et al*., 2011).

Inorganic Nanoparticles

Due to their strong physiochemical properties and responsiveness to external stimuli, inorganic materials are gaining some interest as SRDDS. These nanocarriers may be prepared in different forms and sizes and are generally adopted for controlled release, imaging, and therapeutic functioning.

Due to their light, magnetic, and redox environment responsiveness, gold nanoparticles, iron oxide nanoparticles, and Mesoporous Silica Nanoparticles (MSNs) are often used.

Molecular gates, targeting ligands, and/or biocompatible coatings might be utilized to functionalize their surfaces.

These carriers can also be used as theragnostic, where diagnosis and therapy are performed simultaneously by a single carrier (Soppimath *et al*., 2005).

Nanocarriers Hybridization and Smart Assemblies

Hybrid systems involve merging different kinds of materials together in order to exploit the advantages of each and mitigate the weaknesses. Examples include lipid-polymer hybrids, polymer-inorganic composites, and multi-layered smart assemblies.

Day 20-above: an excellent effort at multi-stimuli responsiveness designed into the drug carriers, which give a refined release of the drug in the complex biological milieu.

Hybrid systems are especially promising for advanced therapeutic strategies, including co-delivery of several drugs, combination therapy, or integrated diagnostic ability (Saito *et al*., 2003),

Design Considerations

Design of SRDDS materials and carriers is governed by the following critical parameters: (Binauld and Stenzel, 2013)

- Threshold of sensitivity to stimulus (e.g., pH trigger point, redox potential range).
- Biodegradability and toxicity profile.
- Drug loading efficiency and stability of encapsulation.
- Surface charge, hydrophobicity and targeting ability.
- Indices of release under normal and abnormal conditions.

APPLICATIONS OF STIMULI-RESPONSIVE DRUG DELIVERY SYSTEMS IN DISEASE TREATMENT

The employment of SRDDS encompasses a wide variety of therapeutic areas, in which the desired effect is that of targeted and site-specific as well as temporally precise drug release. The distribution of different types of SRDDS according to disease areas is depicted Figure 3**,** highlighting oncology as the most explored therapeutic application (Chytil *et al*., 2012). Smart therapeutic systems hold promise for revolutionizing the state-of-the-art therapeutic schemes, reducing systemic off-target effects, increasing therapeutic efficiency, and increasing patient compliance. In particular, SRDDSs have been studied for oncology, neurological, inflammatory, infectious, and autoimmune disease therapies, to name a few (Gao *et al*., 2010).

Oncology

Cancer is among the most active areas for SRDDS due to the intrinsic limitations of traditional chemotherapies, such as off-target toxicity, poor pharmacokinetics, and multidrug resistance. The tumor tissue possesses multiple exploitable characteristics for smart delivery: (Liu *et al*., 2014).

- Acidic extracellular pH.
- Low availability of oxygen and very high oxidative stress.
- Upregulation of prominent enzymes (MMPs).
- Poorly functioning vasculature supported by the enhanced permeability and retention (EPR) effect.

Oncology-application-specific SRDDS may use:

- Intracellular cytoplasmic release with pH- and redox-responsive nanocarriers.
- Tumor-selective systems through cleavage by enzymes.
- Non-invasive activation using external stimulation (e.g., NIR light, magnetic field).

These systems have the advantages of on-demand drug release with minimal side effects and enhanced drug deposition in tumor

tissues. Furthermore, multiple stimuli-responsive systems are widely applied to address tumor heterogeneity and resistance to treatment (Iyer *et al.*, 2006).

Neurological Disorders

As mentioned, one of the greatest difficulties of treating Central Nervous System (CNS) diseases like Alzheimer's disease, Parkinson's disease, epilepsy, and brain tumors is to deliver drugs across the Blood-Brain Barrier (BBB). Types of SRDDS are currently being developed that either bypass or modulate the BBB:(Kamaly *et al.*, 2012)

- External field-guided magnetic-responsive nanoparticles.
- Neuroinflammatory marker-triggered, enzyme-sensitive carriers.
- Thermo- or ultrasonically-responsive liposomes for localized BBB disruption.

While focusing on regions affected by neurodegeneration, these approaches aim to increase the therapeutic index as well as limit systemic neurotoxicity. In addition, smart delivery platforms could render real-time imaging or biomarker-responsive dosing possible, potentially increasing the feasibility of personalized neuromodulation efforts.

Inflammatory and Autoimmune Diseases

Inflammatory conditions, including rheumatoid arthritis, Inflammatory Bowel Disease (IBD), and psoriasis, are associated with localized alterations in pH, enzyme activity, and oxidative stress. As these diseases are organ-specific, the release of anti-inflammatory agents at the inflamed site using SRDDS would alleviate systemic immunosuppressive side effects and help in obtaining local tissue concentrations of the desired drug (Wang *et al.*, 2015).

Key features include

- pH-responsive polymer-based systems for IBD colonic delivery.
- Enzyme responsive systems triggered by cathepsins or myeloperoxidase.
- High Reactive Oxygen Species (ROS)-responsive redox-sensitive hydrogels or nanoparticles.

These systems provide greater control for therapeutic release in a dynamic inflammatory milieu and increase drug residence time at sites of disease (Lee *et al.*, 2020).

Infectious Diseases

Introduction: Antibiotic resistance and off-target toxicity in the treatment of bacterial, viral, and fungal infections represent a

Table 1: Classification of Stimuli-Responsive Drug Delivery Systems (SRDDS) (Shi *et al.*, 2017).

Stimulus Type	Trigger Mechanism	Representative Materials	Example Applications
pH (Endogenous)	Ionization, polymer swelling or dissolution in acidic/basic pH.	Chitosan, Poly(L-histidine), Poly (acrylic acid), Eudragit®	Tumor-targeted chemotherapy, colon-specific drug delivery.
Redox (Endogenous)	Disulfide bond cleavage in high glutathione (GSH) environments.	Disulfide-bridged dendrimers, PEG-SS-PLA, thiolated polymers.	Intracellular cancer drug release, redox-activated gene delivery.
Enzyme (Endogenous)	Enzymatic degradation of polymer/ linker by disease-associated enzymes.	Hyaluronic acid (hyaluronidase-sensitive), MMP-cleavable peptides, gelatin.	Targeted delivery in cancer, inflammation, bacterial infections.
Temperature (Exogenous)	Phase transition above/below critical temperature (e.g., LCST).	PNIPAM, Pluronic® F127, thermosensitive liposomes.	Hyperthermia-enhanced chemotherapy, localized inflammation therapy.
Magnetic Field (Exogenous)	Magnetic guidance and/or magnetothermal heating.	SPIONs, Fe_3O_4-embedded PLGA, magnetic nanogels.	Brain-targeted delivery, magnetic hyperthermia in cancer.
Light (Exogenous)	Photochemical bond cleavage, photoisomerization, photothermal effects.	Azobenzene, nitrobenzyl linkers, gold nanorods, indocyanine green.	NIR-triggered phototherapy, spatially controlled drug release.
Ultrasound (Exogenous)	Acoustic cavitation enhancing membrane permeability.	Echogenic liposomes, microbubbles, PLGA nanobubbles.	Tumor penetration, sonoporation-mediated drug/ gene delivery.
Multi-Stimuli (Hybrid)	Combination of above mechanisms for enhanced specificity and control.	pH/Redox-sensitive dendrimers, light/magnetic-responsive composites.	Smart theranostics, dual therapy (e.g., chemo + photodynamic).

major hurdle in modern therapy. SRDDS enhance the efficacy of antimicrobial therapy by

- Antibiotics released in response to β-lactamases secreted by pathogens.
- Triggering delivery in acidic or hypoxic infection foci.
- Mediating biofilm penetration via ultrasound or light-induced means.

Such systems can reduce unnecessary exposure to antimicrobials while fighting resistance through targeted delivery of optimized doses to just the infection locus (Das *et al.*, 2009).

Cardiovascular Disorders

SRDDS is also being investigated in cardiovascular medicine, especially for myocardial infarction, atherosclerosis, and thrombosis. Here, the goal is to achieve

- Intralesional delivery of anti-inflammatory drugs or growth factors.
- Thrombolytic release at the clot periphery induced by enzyme or pH at the site of clot.
- Oxidative stress-responsive nanocarriers for plaque stabilization.

To further promote the translation of SRDDS in vascular remodelling and regeneration, such SRDDS could be integrated with stents or injectable hydrogels (Maeda, 2010).

Emerging Frontiers: Gene, mRNA, and Protein Delivery

With the success of mRNA vaccines and advances in gene editing, SRDDS are increasingly being designed to deliver:

- mRNA constructs (e.g., cancer immunotherapy, protein replacement).
- siRNA or CRISPR-Cas9 complexes for gene silencing/editing.
- Proteins or peptides that need to be protected from degradation.

The multi-layered nanocarriers that react to intracellular triggers (pH, redox) benefit these fragile payloads by ensuring release in the cytoplasm or nucleus. Responsiveness upon delivery also allows for reduced immune recognition and improved intracellular bioavailability (Karimi *et al.*, 2016).

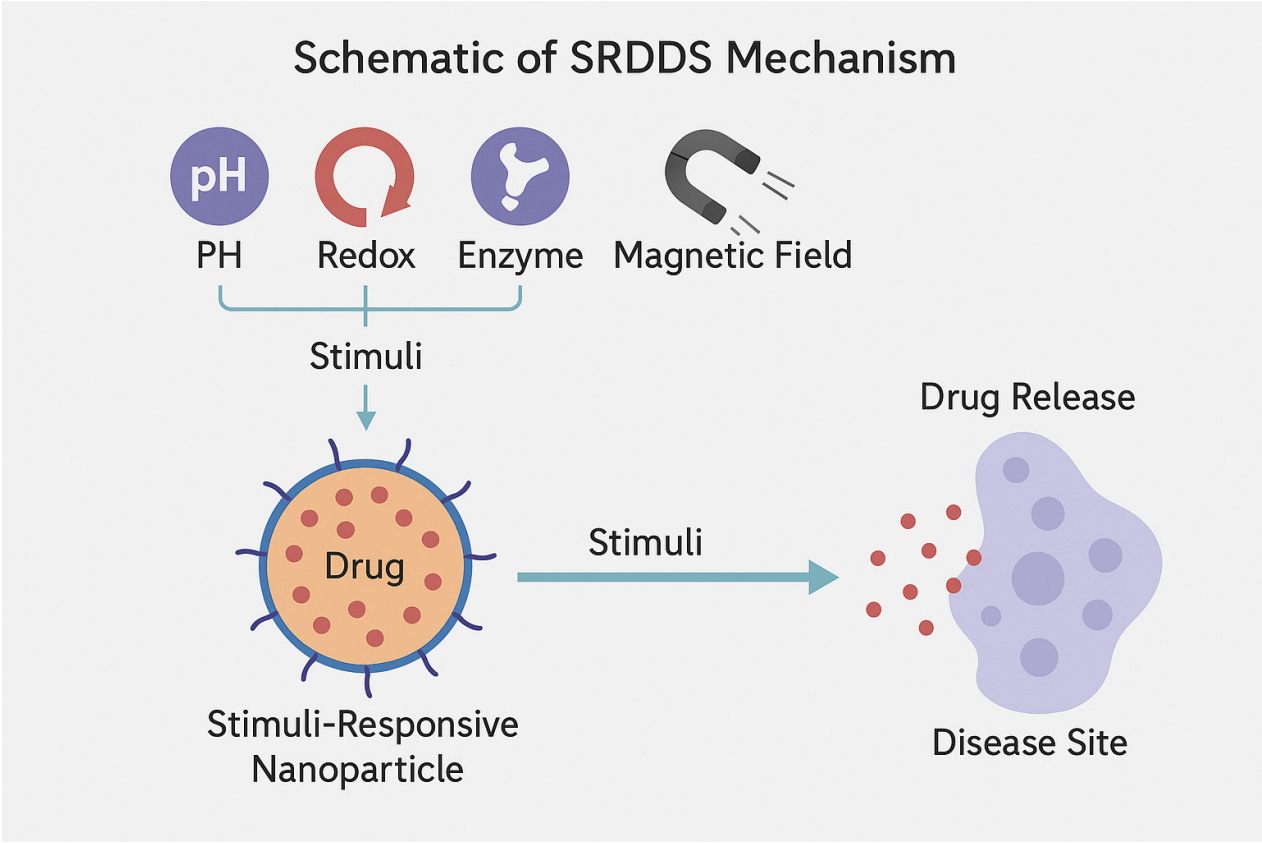

Figure 1: Schematic of SRDDS Mechanism. [The diagram titled "Schematic of SRDDS Mechanism" illustrates how different stimuli-such as pH, redox, enzyme activity, and magnetic fields-activate smart drug delivery systems. At the top, various stimuli are depicted triggering a stimuli-responsive nanoparticle, which encapsulates the therapeutic drug. Once exposed to the appropriate internal or external stimulus, the nanoparticle undergoes a structural or chemical change, leading to controlled drug release at the targeted disease site. The flow is clear, colourful, and well-labelled, offering a concise visual explanation of how SRDDS work for precise and site-specific therapy] (Mura *et al.*, 2013).

Table 2: Summary of Materials and Nanocarriers Used in SRDDS (Duncan, 2006).

Material Type	Stimuli Responsive To	Common Carrier Forms	Key Features	Typical Applications
Natural Polymers	pH, Enzymes	Nanoparticles, Hydrogels	Biocompatible, biodegradable, limited mechanical strength.	Oral, mucosal, inflammation-targeted delivery.
Synthetic Polymers	pH, Redox, Temperature	Micelles, Nanogels, Copolymers	Tunable chemistry, scalable, controllable architecture.	Tumor-targeted, parenteral delivery.
Lipid-Based Carriers	pH, Temperature, Light, Ultrasound	Liposomes, SLNs, NLCs	Biomimetic, high drug loading, modifiable surface.	Cancer, infection, topical and systemic use.
Dendrimers	pH, Redox, Enzymes	Branched macromolecules (e.g., PAMAM)	High drug loading, modifiable surface, controlled size.	Gene delivery, intracellular targeting.
Inorganic Nanoparticles	Magnetic Field, Light, Redox	AuNPs, SPIONs, MSNs	Stimulus conversion ability, rigid structure, imaging potential.	Theranostics, phototherapy, MRI-based delivery.
Hybrid Systems	Multi-stimuli	Lipid-polymer hybrids, core-shell structures	Synergistic functionality, responsive to complex environments.	Smart drug release, combination therapy.

REGULATORY AND TRANSLATIONAL CONSIDERATIONS

Stimuli-Responsive Drug Delivery Systems (SRDDS) are landmark novel agents in precision therapeutics; however, their clinical translation success remains a challenge. While preclinical outcomes are promising, few SRDDS enter clinical trials or commercial development. This disparity is largely due to regulatory grey areas, manufacturing restrictions, safety concerns, and inadequate agreement on evaluation protocols (Alvarez-Lorenzo and Concheiro, 2014).

They classify firms based on decades of sector definitions.

Because of the dynamic, responsive nature of their mechanisms of action, SRDDS often operate outside of the traditional drug or device categories. Pharmaceuticals undergo assessment by regulatory bodies like the U.S. Food and Drug Administration (FDA) and European Medicines Agency (EMA) using longstanding parameters that are well suited for static, passive drug formulations. In contrast, SRDDS are complex, hybrid systems including polymers, lipids, nanoparticles, and other external hardware for stimulus application. Consequently, these platforms can be categorized as drugs, medical devices, combination products, or biologics depending on both their design and primary mode of action (Napoli *et al.*, 2004).

Moreover, the necessity for external stimuli, such as magnetic fields, light, or ultrasound, introduces other issues relating to the control, safety, and reproducibility of stimulus activation within a human clinical setting. This ambiguity complicates regulatory submissions, extends review timelines, and deters investment in commercial-scale development, subject only to early regulatory clarity (Jang *et al.*, 2012).

Safety Assessment and Preclinical Data Evaluation

Demonstration of safety and efficacy in preclinical studies is a major hurdle in SRDDS development. These systems have distinct physicochemical properties (size, shape, surface charge, degradability, and multi-component architecture) that determine their pharmacokinetics, biodistribution, and clearance. In addition, their responsiveness to physiological or pathological conditions results in an active behavior that is challenging to monitor with classical *in vitro* and *in vivo* assays (Park, 2014).

There are no standardized evaluation protocols for stimuli-specific performance. It can be technically difficult, for example, to show consistent drug release profiles in response to pH or redox gradients in different biological systems. Additionally, several of the SRDDS utilize innovative materials, which may elicit immunogenic reactions or accumulate in specific tissues and therefore require extensive long-term toxicity evaluations. These requirements can also lead to further delays in progressing to clinical trials and a higher cost and complexity of gaining regulatory approval (Mitragotri *et al.*, 2014).

Challenges in Manufacturing and Scalability

Upscaling of SRDDS production from laboratory to commercial scale is non-trivial. A large number of systems require multistep synthesis approaches, from polymer functionalization to nanoparticle assembly through surface modification with targeting ligands. These processes are condition-dependent and demand-controlled precision to ensure batch-wise uniformity. Hybrid systems those that respond to multiple stimuli or combine

organic and inorganic components are especially challenging to mimic at scale (Zhu *et al.*, 2021). In addition, additional external equipment is necessary for some SRDDS, including near-infrared lasers or electromagnetic applicators, which increases the complexity of product and regulatory classification. Good Manufacturing Practice (GMP) as per current standards needs to be revised in accordance with the complexities of SRDDS. While the application of Quality-by-Design (QbD) principles, microfluidic synthesis platforms, and continuous manufacturing technologies holds real potential going forward, they are underutilized in this sector (Ganta *et al.*, 2008).

Translation to Clinical and Commercial Utility

The paucity of SRDDS under clinical development mirrors the challenges stated above. Animal models provide an important avenue for testing the feasibility of targeted therapies, the utility of imaging agents, and the safety and efficacy of new drug classes, but translation to human systems is so riddled with uncertainty that even positive outcomes are met with widespread skepticism due to interspecies differences in metabolism, immune response, and disease progression. In addition, the infrastructure required to enable clinical applications of stimulus-activated systems (e.g., imaging-guided drug release, wearable actuators) may not yet be widely deployed in hospital environments (Ulbrich *et al.*, 2016).

From a commercialization perspective, SFFS built with materials that are already sequestered for their safety (e.g., PEG, PLGA, lipids) and those developed for high-need or orphan indications have a comparatively increased likelihood of market success. However, strong intellectual property protection continues to be critical, given that the innovation of SRDDS often resides in the stimulus-responsive mechanism, nanostructure design, or combination with therapeutic modalities (e.g., gene editing, immunotherapy). Because of the interdisciplinary nature of these systems, which span materials science, bioengineering, and pharmacology, the patent landscape is complex (Khemtong *et al.*, 2009).

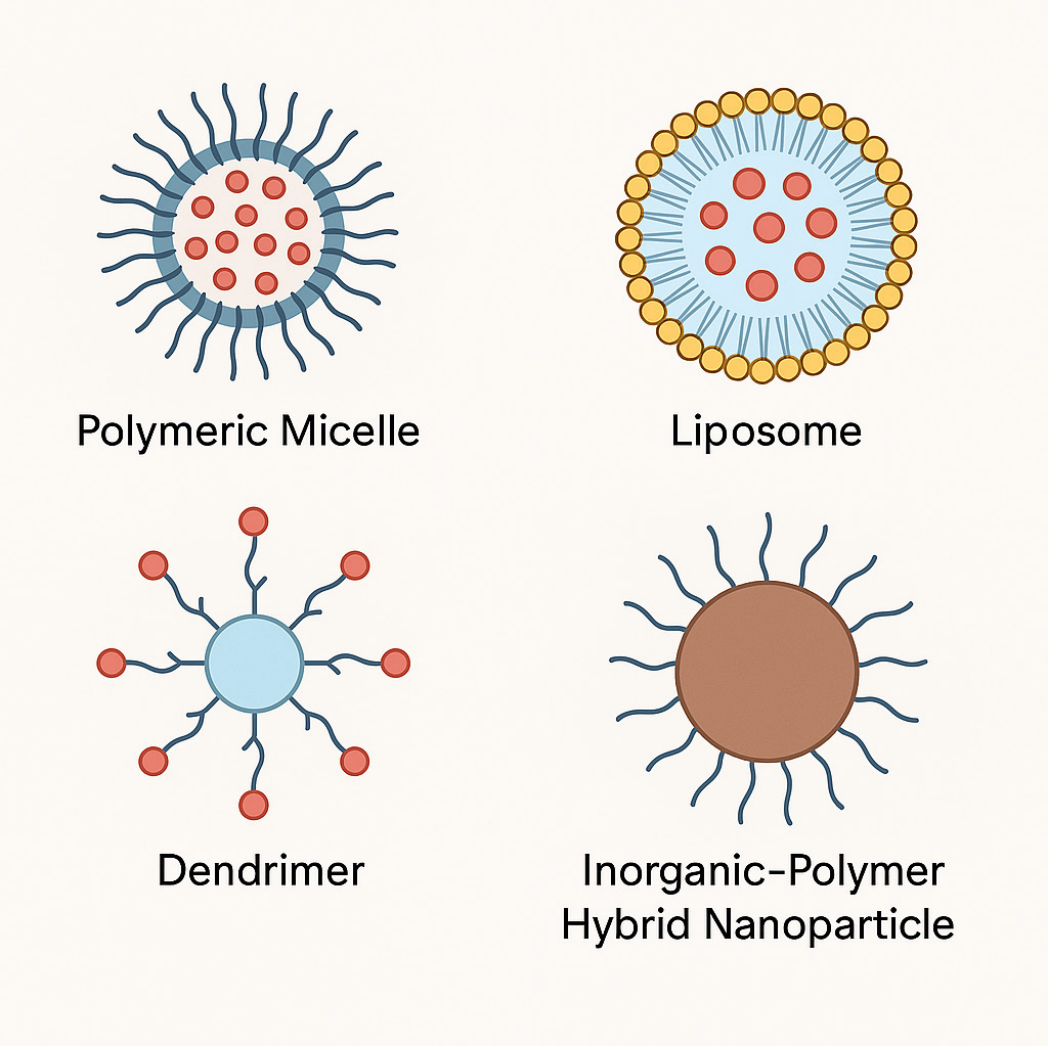

Figure 2: Design Architecture of Nanocarriers. [The diagram shows four key nanocarriers-polymeric micelle, liposome, dendrimer, and hybrid nanoparticle-highlighting their structural features and drug-loading capabilities. It illustrates how each type supports smart, stimuli-responsive drug delivery through unique architectures and functional components] (Kamaly *et al.*, 2012).

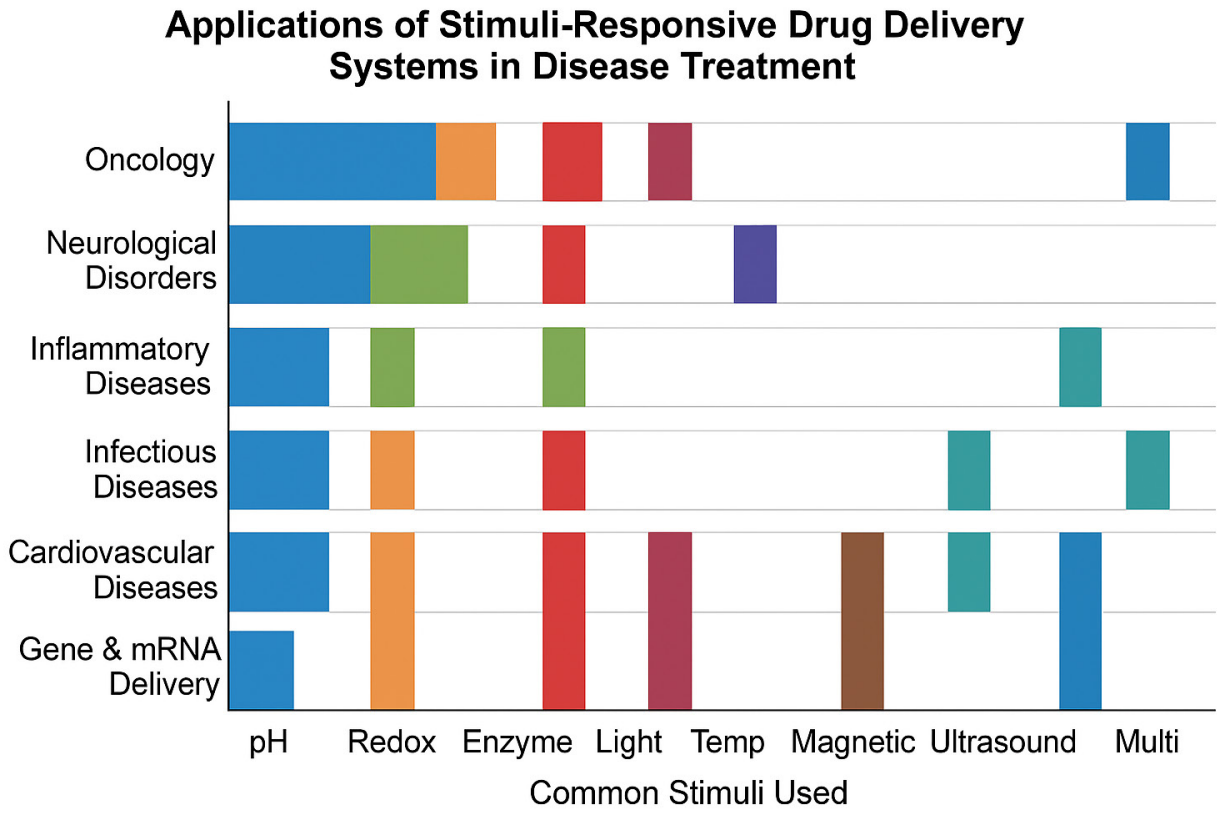

Figure 3: Application of Stimuli-Responsive Drug Delivery Systems in Disease. [The bar graph highlights the prevalence of different stimuli-responsive drug delivery systems by different disease types. Oncology has an extensive scope of use, using all varieties of stimuli of pH, redox, enzyme, light, temperature, magnetic field, ultrasound, and multi-stimuli systems, indicating that smart delivery has been studied extensively. Magnetic systems are more frequently utilized for neurological disorders, and the enzyme, ultrasound, and temperature-sensitive systems target neurological disorders; on the other hand, pH, enzyme, and redox are mostly targeted towards inflammatory diseases. Infectious diseases use pH, enzyme, light, and ultrasound-responsive carriers; cardiovascular conditions depend mainly on pH, enzyme, and redox sensitivity. Arranging cellular and encapsulating agents into gene and mRNA delivery systems, responsive to pH, redox and multi-stimuli, underscore the intracellular targeting challenge faced by non-viral delivery approaches] (Chytil *et al.*, 2012).

Working Towards Harmonization and Global Frameworks

Harmonized regulatory approaches are being developed for both nanomedicine and smart drug delivery systems, which may provide guidance for any new nanomaterial-based therapeutics. Innovation via quality-by-design strategies is broadly underpinned by the ICH (International Council for Harmonization) guidelines, in particular the ICH Q8 (pharmaceutical development), Q9 (quality risk management), and Q10 (pharmaceutical quality system) guidelines. A regulatory mechanism like the FDA's Emerging Technology Program and another one by the EMA-Innovation Task Force (ITF)-has already been established, which serves as a platform for early discussion and feedback to developers from regulators. [37] specialized organizations (e.g., the Nanotechnology Characterization Laboratory, or NCL, and the Pharmaceutical Inspection Co-operation Scheme, or PIC/S) are currently working to develop standardized methods of analysis, including those related to nanomaterial characterization, biodistribution, and toxicological studies (Ma *et al.*, 2021).

To facilitate the path of SRDDS technologies from the lab bench to the clinic bedside, relevant stimuli-specific evaluation criteria, safety testing frameworks, and regulatory pathways will need to be established globally as these technologies mature.

CHALLENGES AND FUTURE PERSPECTIVES

Stimuli-Responsive Drug Delivery Systems (SRDDS) represent an innovative concept of precision medicine that delivers therapeutics at the right place, at the right time, and in the right dose. Although there have been significant advances in material science, nanotechnology, and bioengineering, the domain of SRDDS is still hampered due to multiple scientific, technical, and translational challenges. Moreover, it also represents an exciting innovation shift towards smarter, multifunctional systems that could expand the horizons of personalized therapy (Wu *et al.*, 2020).

Runner(s) Needed: The Scientific and Technical Challenges

Limited knowledge on *in vivo* stimuli environments among existing studies has been one of the most significant scientific challenges. The physiological conditions such as pH, redox gradients, enzymatic activity, and inflammatory markers are not only different from one individual to another but also differ in various locations in the same tissue. This heterogeneity makes it difficult to design SRDDS that can be relied on to produce drug release in all pathological conditions. Maintaining accurate stimulus thresholds without inciting preterm release or inadequate activation is still a key hurdle to overcome (Li and Szoka, 2007).

Moreover, the stability of SRDDS under physiological conditions, manufacturing, and storage still needs to be further optimized. Many systems that respond appropriately to controlled laboratory incubation conditions may undergo degradation, aggregation, or otherwise become unresponsive in a complex (Tang *et al.*, 2013) and dynamic *in vivo* environment. Nanocarriers are made of foreign materials that may be recognized, opsonized, or cleared by the Mononuclear Phagocyte System (MPS), limiting the bioavailability and circulation time of nanocarriers.

Another challenge that has persisted is the ability to reproduce and scale the efforts. Synthesis processes and functionalization steps of multi-component, multi-responsive systems can be complex yet sensitive steps that are challenging to standardize across production batches. While integrating quality-by-design principles into SRDDS development is crucially important, systematic exploitation of this concept in academic research environments is still underexamined (Kim *et al.*, 2014).

The integration with theragnostic and biosensors

Beyond controlled delivery, the future of SRDDS also includes responsive integration with diagnostics in the concept of theragnostic. Because it combines drug delivery with real-time monitoring of disease biomarkers, SRDDS can theoretically adjust the timing or dosage of the drug without human intervention, based on the patient's condition. pH-Responsive Sequences of Imaging Agents and Carriers for Cancer Therapy and Imaging Diagnostic feedback and therapeutic action can be integrated in pH-responsive systems that use pH-sensitive imaging agents combined with pH-triggered carriers that result, simultaneously, in therapeutic action and diagnostic feedback in the tumor or inflamed tissue (Duan and Li, 2013).

Furthermore, the compatibility of SRDDS with biosensors and wearable devices allows for external modulation and real-time monitoring of drug delivery. Closed-loop feedback systems that couple physiological data to either stimulate or inhibit the release of drugs are increasingly feasible with the recent development of minimally invasive electronics/invasive sensors. Such "smart" drug delivery systems will be crucial in managing chronic diseases, which require long-term, tailored treatment (Banskota *et al.*, 2019).

Towards multi-stimuli Responsiveness

The dominant SRDDS types seen today are one-stimulus-responsive, which may be insufficient to tackle the complex microenvironments associated with multifactorial diseases such as cancer, diabetes, or neurodegeneration. Recently, the next generation of stimuli-responsive systems has been developed to address these limitations by integrating the dual (or triple) trigger mechanisms (e.g., pH/redox-enzyme, temperature/light, magnetism/light). Such dual (or triple)-triggered systems thus represent the sense of specificity, control, and therapeutic precision (Shi *et al.*, 2020).

This provides the advantage of logical gating, and drug release only takes place when multiple pathological cues are detected within the same time frame. This minimizes off-target effects, making treatment more selective. However, the design of such systems calls for precise tuning of material response kinetics and cooperative functionality.

Clever Uses of Non-Viral Gene Delivery-Expanding into Gene, mRNA and Macromolecule Delivery

SRDDS are well-positioned to facilitate the delivery of such fragile and sensitive biomacromolecules, with the increased development of genetic and molecular therapies (i.e., mRNA vaccines, RNA Interference (RNAi), and CRISPR-based gene editing) posing great challenges for drug delivery due to their inherent instability. Such payloads are extremely susceptible to degradation and may also require protection and site-specific cytoplasmic or nuclear delivery (Luo *et al.*, 2022).

Nanocarriers responsive to stimuli under intracellular redox gradients or sensitive to endosomal pH may facilitate escape from endosomal compartments and promote effective release into the relevant cellular compartments. The design of nucleic acid-compatible, biodegradable, and immune-evasive carriers will play a pivotal role in the successful implementation of SRDDS in the next generation of biotherapeutics (Tang *et al.*, 2023).

AI+CDI-Artificial Intelligence and Computational Design

Another revolutionary trend is the use of Artificial Intelligence (AI) and Machine Learning (ML) for the optimization and design of SRDDS. Computational techniques are able to predict the behavior of materials, simulate the kinetics of drug release, and optimize formulations with respect to patient-specific data. AI-powered platforms could shorten the development cycle, minimize trial-and-error testing, and allow the delivery to be adjusted in real time based on biosensor feedback (Li *et al.*, 2022).

Moreover, digital twin models-i.e., virtual replicas of patients-can enable simulations of the expected behavior of SRDDS given a specific physiological environment, optimizing personalized therapy planning before implementation in a clinical setting (Gao *et al*., 2014).

Toward Clinical Impact

The successful clinical translation of SRDDS as they mature will rely on multidisciplinary teamwork involving material scientists, pharmacologists, clinicians, regulatory experts, and engineers. Future potentials include not just more precise delivery systems but also pathways to incorporate these systems within the larger healthcare ecosystem. From the management of chronic disease to interventions for acute complications, SRDDS can provide the first step toward a paradigm shift in medicine from reactive to proactive. To speed up this transition, there is a need for concerted efforts to Engagement of specific regulatory frameworks for stimuli Put into place new technologies for real-time monitoring Adopt modular, confidence in scalable manufacturing platforms Encourage commercialization through public-private partnerships (Sharma *et al*., 2014).

CONCLUSION

Drug Delivery Systems (SRDDS), which can be used as an effective platform toward targeted, controlled, and patient-specific therapy. These systems respond to internal stimuli (pH, redox potential, and enzymes) or external stimuli (light, temperature, and magnetic fields), improving therapeutic efficacy while reducing systemic toxicity. Their versatility and potential in the clinic are underscored by their successful application across a range of diseases, including cancer, neurological disorders, and conditions characterized by chronic inflammation. Yet there are still obstacles that must be overcome in converting these technologies from bench to bedside. Regulatory uncertainty, manufacturing challenges, and variation of *in vivo* stimulus environments still limit the widespread adoption. Future directions should focus on the development of multi-stimuli systems, integration with biosensors and AI, and the establishment of scalable, reproducible manufacturing processes. By continued interdisciplinary collaboration and regulatory evolution, SRDDS are positioned to lead the next generation of precision pharmaceutics.

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ABBREVIATIONS

SRDDS: Stimuli-Responsive Drug Delivery Systems; **GSH:** Glutathione; **MMPs:** Matrix Metalloproteinases; **LCST:** Low-Critical Solution Temperature; **PNIPAM:** Poly(N-isopropylacrylamide); **SPIONs:** Superparamagnetic Iron Oxide Nanoparticles; **PLGA:** Poly (lactic-co-glycolic acid); **NIR:** Near-IR; **LIFU:** Low-Intensity Focused Ultrasound; **EPR:** Enhanced Permeability and Retention; **PEG:** Polyethylene Glycol; **SLNs:** Solid Lipid Nanoparticles; **NLC:** Nanostructured Lipid Carriers; **MSNs:** Mesoporous Silica Nanoparticles; **CNS:** Central Nervous System; **BBB:** Blood-Brain Barrier; **IBD:** Inflammatory Bowel Disease; **ROS:** Reactive Oxygen Species; **mRNA:** messenger RNA; **siRNA:** small interfering RNA; **CRISPR:** Clustered Regularly Interspaced Short Palindromic Repeats; **FDA:** U.S. Food and Drug Administration; **EMA:** European Medicines Agency; **GMP:** Good Manufacturing Practice; **QbD:** Quality-by-Design; **ICH:** International Council for Harmonization; **NCL:** Nanotechnology Characterization Laboratory; **PIC/S:** Pharmaceutical Inspection Co-operation Scheme; **MPS:** Mononuclear Phagocyte System; **RNAi:** RNA Interference; **AI:** Artificial Intelligence; **ML:** Machine Learning; **PEG-SS-PLA:** Polyethylene Glycol-Disulfide-Polylactic Acid; **PAMAM:** Polyamidoamine; **AuNPs:** Gold Nanoparticles; **MRI:** Magnetic Resonance Imaging.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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AUTHORS CONTRIBUTIONS

Yash M. Salve conceptualised and finalised the review, supervised the literature analysis and acted as the corresponding author. Mayur R. Dandekar and Isha A. Mirzapure conducted literature searches, analyzed the data, and drafted key sections of the manuscript. Umesh B. Telrandhe contributed to the methodology, validated the data, and drafted the technical sections, ensuring scientific accuracy.

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