REVIEW PAPER

Stimuli-Responsive Drug Delivery Systems for Neurological, Cardiovascular, and Metabolic Disorders: Pharmacological Triggers and Therapeutic Applications

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ABSTRACT

Stimuli-responsive drug delivery systems (SRDDs) represent a paradigm shift in drug formulation strategies, moving from static formulation design to dynamic formulation architecture based on pathophysiology. SRDDs exploit disease-specific microenvironmental stimuli to enhance therapeutic and pharmacokinetic outcomes compared to conventional delivery system. BBB obstructs more than 98% of substances in CNS, atherosclerotic plaque creates enzyme-rich, oxidatively stressed microenvironments largely inaccessible in CVS, and the oscillating insulin kinetics in diabetes requires novel drug delivery systems like SRDD to overcome these limitations. SRDD carriers are designed to trigger drug release by a physicochemical change in the presence of biomarkers, such as oxidative biomarkers, matrix metalloproteinases (MMPs), pH gradients, glucose concentration, hemodynamic shear stress, hypoxia, and temperature deviation, at the pathological sites and in a particular time. Oxidative stress responsiveness is universal among SRDDs, their structural designs, carrier platforms, and cargoes are disease-modified. SRDDs improve therapeutic indices and plasma half-life, and their pharmacokinetics can be tailored to biological demand. Emerging multi-stimuli-responsive platforms and AI- driven formulation optimisation further advance SRDD translational potential. Therefore, SRDDs signify a comprehensive and promising pharmacological approach for clinical and personalised medicine.

Keywords: SRDD, BBB, atherosclerosis, Oxidative stress, nanomedicine, translational therapeutics.

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1. Introduction

Neurological, cardiovascular, and metabolic disorders are among the major challenges representing the primary drivers of global morbidity and mortality in modern clinical practice. Neurological disorders, such as Alzheimer's disease (AD), Parkinson's disease (PD), and stroke, affect more than 1billion people globally and are responsible for a disproportionately high number of disability-adjusted life years and socioeconomic cost (GBD Neurological Disorders Collaborator Group,). According to the World Health Organization (WHO) and the Global Burden of Disease (GBD) analysis, neurological disorders now affect more than 3 billion people worldwide and represent the leading cause of disorders globally, with conditions such as stroke, Alzheimer's disease, and Parkinson's disease contributing substantially to neurological mortality and disability burden (WHO,) [1]. Cardiovascular disorders (CVDs) continue to be the leading cause of death worldwide, accounting for approximately 19.8 million deaths annually in , representing nearly 32% of all global deaths; notably, around 85% of these deaths are due to heart attack and stroke (WHO,) [2]. Metabolic disorders, particularly diabetes mellitus, have also reached alarming prevalence levels. The International Diabetes Federation (IDF) Diabetes Atlas 11th Edition reported that approximately 589 million adults aged 20–79 years were living with diabetes globally in –, with projections rising to 853 million cases by 2050. Diabetes was additionally associated with nearly 3.4 million deaths worldwide in (IDF) [3]. These 3 share a critical pharmacological deficiency: conventional therapeutic approaches provide significant benefits at the population level but lack the spatiotemporal precision required to address the complexity of these disorders. Traditional drug delivery systems are based on pharmacokinetic principles established before knowledge of the disease microenvironment existed.

Protein therapeutics, such as insulin, GLP-1 receptor agonists, and neuroprotective growth factors, are characterized by rapid proteolytic degradation, suboptimal plasma half-life, and lack of ability to cross important physiological barriers, such as the BBB. The inadequacy has led to the development of stimuli-responsive drug delivery systems (SRDDs), which are uniformly designed drug carriers that harness endogenous pathological signals to control drug release with pharmacological precision [4]. SRDDs represent a new paradigm in the drug–carrier relationship. Instead of being passive vehicles, SRDDs act as biochemical sensors that respond to the most relevant physicochemical changes occurring during pathological processes, such as the acidic pH observed in ischemic or plaque microenvironments, ROS overproduction observed in neurodegenerative or post-infarct states, matrix metalloproteinase activity that triggers the destabilization of atherosclerotic plaques, glucose concentration variability that defines diabetes, and hemodynamic shear stress that characterizes the different flow patterns that are atherogenic. All of these stimuli are not just epiphenomena of disease but rather a key, specific to each disease, for which the SRDD is the engineered lock [5]. SRDDs have therapeutic uses beyond delivery efficiency and fundamentally shift the pharmacokinetic– pharmacodynamic (PK–PD) relationship by increasing effective tissue concentrations and reasing systemic exposure, thereby enhancing the therapeutic index and allowing the use of therapeutic agents with exceptionally narrow therapeutic windows. Furthermore, the self-regulatory properties of some SRDDs, especially glucose-responsive insulin systems, enable homeostatic functionality that resembles physiological control loops and represents a fundamentally new type of pharmacological intervention [6]. SRDDs have been applied in the fields of neurology and cardiovascular and metabolic diseases, representing different pathological microenvironments that serve as endogenous triggers for therapy. Evaluating various SRDD platforms reveals their distinct clinical applications and significant effects on the pharmacokinetic–pharmacodynamics (PK–PD) profile. Moreover, recent preclinical data clearly define the path for translating these systems into clinical use.

Methodology

Systematic electronic databases including PubMed, Scopus, Web of Science, Google Scholar, were explored with a strategy to gather experimental, mechanistic effects of gut microbiota on different endocrine-axis accompanying conceptually relevant peer-reviewed articles published primarily from 2000 -2026. Keywords used were - SRDD, BBB, atherosclerosis, Oxidative stress, nanomedicine, pharmacokinetics, translational therapeutics. The - eligible studies included original research studies, high impact reviews published in the English language that had evidence of gut-microbiota biological effects or mechanistic relevance to gut- endocrine axis.

2. Types of SRDDs and Platforms

Stimuli-responsive drug delivery systems (SRDDs) can be categorized as endogenous (from the microenvironment of the disease) or exogenous (from the outside by the clinician) [7]. Endogenous stimuli include pH, ROS, enzymes, glucose, hypoxia, and biomolecular gradients (antigens and RNA sequences) [8]. Temperature, light (NIR, UV), magnetic fields, and ultrasound are examples of exogenous stimuli [9]. This classification is clinically relevant because endogenous-stimuli systems are inherently self-regulatory and do not need to be operated by the patient or the clinician, and are thus suitable for chronic disease management [10], while exogenous-stimuli systems provide precision in spatial and temporal control but require infrastructure (magnets, light sources, thermal devices) and skilled oversight [11].

2.1 pH-Responsive Systems

The most clinically translatable type of SRDDs are pH-responsive SRDDs, which take advantage of the acidification of microenvironments in ischemic, inflammatory, and metabolic diseases [12]. Poly(acrylic acid) (PAA), poly(methacrylic acid) (PMAA), and poly(β-amino ester) (PBAE) are some of the most commonly used pH-sensitive polymers, which protonate or change their charge below a certain pKa value, disrupting the electrostatic interactions in the carrier structure and thus releasing the drug [13]. The ischemic penumbra, with a pH of 6.2-6.5, is a reliable spatial trigger for the pH-responsive release of neuroprotectants, especially for neurological diseases such as ischemic stroke [14]. In the case of cardiovascular diseases, the pH of the plaque (6.0 – 6.5) can be used to selectively deliver drugs to vulnerable lesions [15]. In metabolic diseases, the GI pH gradient can be used for organ-segment-targeted drug delivery [16]. Diseases such as ischemic stroke and atherosclerosis exhibit local pH drops that allow for targeted drug delivery with reduced off-target activation [15].

2.2 ROS-Responsive Systems

In the three classes of diseases, ROS-responsive systems take advantage of the increased levels of H_2O_2, superoxide, and hydroxyl radicals, which are typical of oxidative stress [17]. The most important ROS-sensing structural motifs are thioketal linkers (cleavable by H_2O_2), selenium-containing polymers (oxidised and degraded by ROS), poly(propylene sulfide) (PPS, converted from hydrophobic to

hydrophilic upon oxidation), and oxalate ester crosslinks (H_2O_2-responsive dissolution) [18]. Importantly, ROS-responsive carriers can also confer pharmacological benefits through structural degradation and ROS scavenging, leading to enhanced therapeutic efficiency and reduced side effects [19]. Diseases best suited for this approach are myocardial infarction (I/R injury) and Alzheimer's disease (Aβ-associated ROS), where pathological ROS levels are highest, and the therapeutic need to deliver antioxidants is most pressing [20].

2.3 Enzyme-Responsive Systems

In the enzyme-responsive SRDDs, the specificity for the disease can be maximum of all endogenous triggers (MMP-2/9 activity in atherosclerotic plaques, lipases in the small intestine, and HAase in inflamed sy ium) [21]. MMP-cleavable peptide conjugates (PLGLAG, GPQGIASQ), hyaluronidase (HAase)-degradable hyaluronic acid carriers, and protease-responsive protein conjugates exploit enzyme gradients in certain disease microenvironments [22,23]. Polymer-drug conjugates with protease-cleavable linkers (e.g., cathepsin B-responsive GFLG tetrapeptide) target drug release to the lysosomal compartment of macrophages and tumour cells, taking advantage of the enzyme environment of the cell [24]. Best disease: atherosclerosis: MMP-2/9 activity is a direct ker of plaque vulnerability and could be a perfect pharmacological trigger for drug delivery to the highest-risk plaques [21].

2.4 Glucose-Responsive Systems

Glucose-responsive systems are the most clinically relevant in the metabolic disease domain [25]. All three main sensing mechanisms (GOx-catalytic, PBA-competitive, and glucose-binding molecules including Con A-displacement) have their own clinical advantages and disadvantages [25]. Highly sensitive GOx-based systems that detect glucose in the 1–20 mM range exhibit fast response kinetics and provide binary pH/ROS triggers [26]. However, biocompatibility issues arise due to the production of H_2O_2 at high glucose levels and high GOx loading [25]. PBA-based systems are hydrogen-peroxide- free, biocompatible, and reversibly responsive, but exhibit pH-dependent selectivity, which requires careful formulation optimisation to operate under physiological conditions at pH 7.4 [27]. Recently developed closed-loop glucose-responsive insulin delivery patches include GOx or PBA in microneedle array platforms for transdermal subcutaneous delivery [28]. The disease with the greatest need for fully autonomous closed-loop delivery and the greatest therapeutic impact from closed-loop delivery is type 1 diabetes, in which no endogenous insulin is secreted; thus, the need for fully autonomous closed-loop delivery is most important, and closed-loop delivery is most therapeutically impactful.

2.5 Multi-Stimuli Responsive Systems:

As advanced SRDDs are developed, they increasingly include combinations of two or three stimuli, as a single one could be triggered by an off- target pathological state; for example, the pH and ROS characteristics of a wound site or tumor are similar to those of ischemia and neurodegeneration. The dual-responsive systems of pH/ROS offer logical AND-gating, meaning that drug release will occur only when both pH is lowered, and ROS is increased, which is more disease-specific than either alone [29]. Glucose/pH dual-responsive insulin carriers take advantage of the dual stimulation (low pH and high glucose levels) of the post-meal intestinal environment to improve the oral absorption of insulin. Temperature/ROS dual- responsive systems for post-myocardial infarction (MI) adjunct thermal therapy have been designed, involving mild hyperthermia and ROS-triggered drug release. Multi-stimuli systems can significantly rease the risk of false activation and allow for more sophisticated pharmacological responses to the heterogeneous disease microenvironment because of their combinatorial specificity, which is possible with these systems. This is the latest state-of-the-art in multi-stimuli SRDD design [30].

3. Stimuli Drug Delivery Platforms:

Disease-Specific Engineering However, the rational design of SRDD platforms must consider the physicochemical properties of the carrier, which must match the type of stimulus, as well as the biological geometry of the delivery challenge, such as BBB penetration requirement for CNS delivery, vascular wall adhesion requirement for cardiovascular targeting, and mucosal absorption enhancement requirement for oral metabolic drug delivery, each of which imposes fundamentally different platform constraints. Table 3 shows an exhaustive cross-disease comparison of the way in which major SRDD platforms are built to be useful for disease-specific purposes [31].

3.1 Liposomes

The most clinically advanced and translationally successful SRDD platform to date is the liposome, and multiple FDA-approved formulations have paved the way for the safety and scalability of the lipid nanoparticle technology. Receptor-targeting ligands (transferrin, lactoferrin, and Angiopep-2). PEGylated liposomes can deliver 1–5% of the injected dose per gram of brain tissue, which is modest in absolute terms but 10–50-fold higher than that achieved with unconjugated formulations for CNS delivery [32]. Thermosensitive liposomes (TSLs) containing DPPC/DSPC/DPEG-DSPE lipid compositions that

undergo gel-to-liquid crystal transition at 40-42°C have been demonstrated to be suitable for cardiac applications and release cytarabine or doxorubicin specifically in hyperthermic regions around radiofrequency ablation (RFA) zones [33]. For the delivery of GLP- 1 (glucagon-like peptide-1) peptides in the cytosol of intestinal epithelial cells, pH-sensitive fusogenic liposomes containing dioleoylphosphatidyl-ethanolamine (DOPE) take advantage of endosome acidification, which protects the peptide from degradation in lysosomes.

3.2 Polymeric Nanoparticles

Poly([lactic-co-glycolic acid]) and polylactic acid (PLA) polymeric nanoparticles are FDA-approved, biodegradable with tunable degradation time (days to months depending on the co-polymer ratio), and can be easily functionalized for disease-specific targeting. Intranasal instillation of PLGA nanoparticles enables nose-to-brain delivery via the olfactory nerve pathway for BBB-penetrating CNS applications, thereby avoiding systemic clearance and the BBB, and delivering dopaminergic agents directly to the olfactory bulb and striatum in PD models [34]. Shear-activated PLGA assemblies, designed to dissociate from micron-sized clusters into drug-releasing nanoparticles under arterial shear stress, offer hemodynamic specificity without chemical conjugation for cardiovascular applications. The ability to scale up PLGA nanoparticles with well-defined GMP manufacturing protocols makes this platform the most promising near-term clinical translation candidate for SRDD-based CVD and metabolic therapies [35].

3.3 Hydrogels

Injectable hydrogels have a special place in SRDD pharmacology as carriers and structures. In the heart, hydrogels can be injected into the myocardium or the space surrounding the heart (pericardial space) to mechanically strengthen the infarcted wall and prevent it from paradoxical bulging during systole, while simultaneously releasing cardioprotective cargo in response to local stimuli [36]. Embedded growth factors (VEGF, IGF-1) are released specifically from hyaluronic acid–gelatin composite hydrogels crosslinked with MMP-degradable peptides in response to MMP activity after MI to provide spatiotemporally appropriate angiogenic stimulation [37]. The GOx, catalase (for converting H_2O_2 to water to reduce toxicity), and HRP are included in subcutaneously injectable glucose- responsive hydrogels that convert glucose sensing into an H_2O_2-independent pH shift, used to regulate the hydrogel's porosity and insulin release kinetics, with reduced oxidative by-products [38].

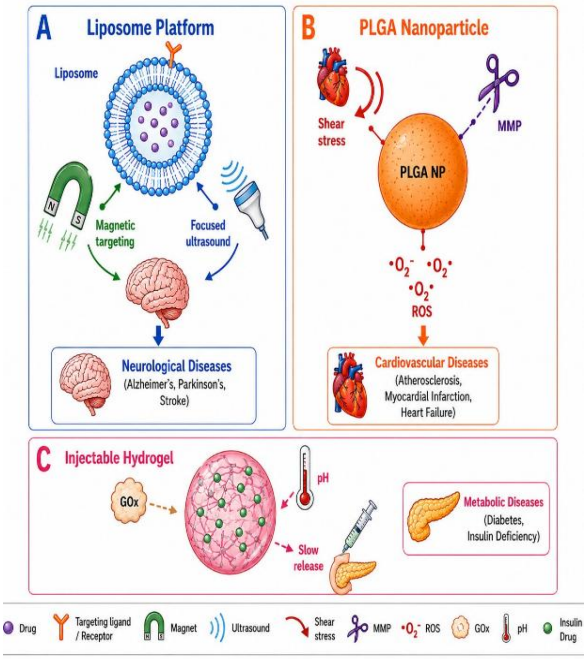


Figure 1. Comparison of stimuli-responsive drug delivery system (SRDD) platforms across neurological, cardiovascular, and metabolic diseases.
(A) Liposome-based systems utilize receptor targeting, magnetic guidance, and focused ultrasound to enhance site-specific delivery across neurological barriers. (B) PLGA nanoparticles respond to cardiovascular disease-associated stimuli, including shear stress, matrix metalloproteinases (MMPs), and reactive oxygen species (ROS), enabling localized therapeutic release in vascular lesions. (C) Injectable hydrogels incorporating GOx and pH-responsive mechanisms provide sustained, glucose-regulated drug release for metabolic disorders such as diabetes. The figure highlights disease-specific trigger mechanisms and platform adaptability across major therapeutic domains.

3.4 Exosome-Mimetic Mimetic Na vesicles

A horizon of bioinspired SRDD design is exosome-based and biomimetic membrane-coated nanoparticles. Exosomes are endogenously secreted vesicles of 40–150 nm that exhibit organ-specific tropism owing to their surface protein composition, such as targeting to the CNS (microglia-derived exosomes), cardiac tissue (cardiomyocyte-derived exosomes), and liver (hepatocyte-derived exosomes) [39]. Synthetic responsiveness is combined with biological targeting by engineering exosomes with stimulus-responsive components, including ROS-sensitive lipid tails and pH- responsive membrane-fusogenic peptides [40]. Polymeric nanoparticles coated with platelets leverage platelets' inherent properties of binding to damaged vascular endothelium and to platelet- activating factor receptors at sites of atherosclerosis to deliver the nanoparticles to sites of CVD without the use of synthetic targeting ligands [45].

Table 1. Stimuli Drug Delivery Platforms and Disease- Specific Engineering Design Principles

Platform	Design Features for Neurological Diseases	Design Features for CVD	Design Features for Metabolic Diseases	References
Liposomes	PEGylated, transferrin/lactoferrin ligands for BBB transcytosis; ROS-sensitive lipid tails (e.g., DPPC-DSPE-PEG)	Thermosensitive DPPC formulations; MMP-responsive PE-peptide conjugates for plaque delivery	pH-sensitive PEG-lipid shells for GI stability; Glucose-DPPC assemblies for pancreatic targeting	[46–49]
Polymeric Nanoparticles (PLGA, PLA)	Nose-to-brain delivery; enzyme-responsive PLGA-peptide; thioketal-PLGA for ROS-triggered CNS release	Shear-activated PLGA aggregates; PLGLAG-peptide NPs for MMP-triggered plaque unloading	Boronic acid-PLGA nanoparticles for glucose sensing; enteric-coated PLGA for colon drug delivery	[49,50]
Hydrogels (Injectable)	Thermoresponsive PNIPAM hydrogels for intracranial sustained release; hyaluronic acid-ROS gels	Pericardial injectable hydrogels with ROS/hypoxia dual triggers for MI therapy; cardiac patch scaffolds	Subcutaneous glucose-responsive hydrogels with GOx-embedded core for closed-loop insulin delivery	[51,52]
Dendrimers (PAMAM, PPI)	Surface-functionalized with angiopep-2/transferrin for LRP1-mediated BBB crossing; ROS-labile cores	Targeted PAMAM with MMP-peptide for plaque macrophage delivery; heparin-functionalized for thrombosis	PAMAM-PBA conjugates for glucose-triggered insulin complexation and release	[47]
Micelles (Block Copolymers)	PEG-PCL, PEG-PLGA micelles with pH-sensitive cores; BBB-penetrating RVG-modified micelles	PEG-PLA shear-responsive micelles; oxidation-sensitive PEG-poly(propylene sulfide) for ROS release	PEG-poly(aspartate) pH-sensitive micelles for GLP-1 oral delivery; enzyme-responsive triglyceride micelles	[53]
Exosome-Mimetic Na esicles	Brain-targeting exosomes with RVG peptide; natural CNS tropism; minimal immunogenicity	Cardiac progenitor cell-derived exosomes for post-MI angiogenesis; platelet-membrane coated NPs	Adipocyte/hepatocyte-derived exosome mimetics for metabolic reprogramming; gut microbiome exosomes	[47,48]
Inorganic Nanocarriers (MSN, SPION)	Mesoporous silica NPs (MSN) with pH/redox dual-gated pores; SPION for MRI-guided CNS delivery	SPIONs with external magnetic guidance for coronary artery targeting; MSN-stent coating for restenosis	Calcium phosphate NPs with pH-triggered insulin release; SPION-hydrogel composites for glucose sensing	[54]

4. SRDD and Microenvironment of Disease:

4.1 Neurological Disorders

The central nervous system (CNS) is unique among all other organ systems because of the re kable selectivity of the blood-brain barrier (BBB), which is composed of brain microvascular endothelial cells (BMECs) linked by tight junctions, pericytes, astrocyte endfeet, and an underlying basement membrane [55]. This architecture limits paracellular molecular diffusion, necessitates the active transport of most nutrients, and contains efflux transporters (P-glycoprotein, BCRP, and MRP family), which actively exclude a large number of pharmacological agents [55]. Quantitative analyses have shown that more than 98% of small-molecule drugs and essentially 100% of protein therapeutics do not reach therapeutically relevant CNS concentrations after systemic administration. This pharmacological failure is not a drug potency issue but a drug- delivery issue: a fundamental mismatch between systemic pharmacokinetics and CNS pharmacodynamics [56]. The disease microenvironment contributes to BBB pathophysiology in neurodegenerative diseases [57]. Alzheimer's disease (AD) is characterised by an increase in hydrogen peroxide (H_2O_2) and superoxide anion concentrations (ROS), neuroinflammatory cytokine release (IL-1β, TNF-α, IL-6), glutamate excitotoxicity, and mitochondrial dysfunction, all of which are caused by the progressive accumulation of amyloid-β (Aβ) plaques and neurofibrillary tau tangles. In contrast, beta-amyloid oligomers directly impair TJ integrity, paradoxically increasing BBB permeability in affected areas while globally compromising barrier function, resulting in pathological leakage rather than a therapeutic window [58]. Dopaminergic neurons of the substantia nigra pars compacta selectively degenerate in Parkinson's disease, leading to a nigrostriatal microenvironment with elevated oxidative stress due to dopamine auto-oxidation, mitochondrial complex I dysfunction, and microglial activation [59]. Lewy body pathology (α-synuclein aggregates) spreads neuroinflammation by activating the NLRP3 inflammasome and toll-like receptor 2 [60]. The BBB is partially intact in early PD but becomes increasingly compromised, and the blood– cerebrospinal fluid barrier at the choroid plexus is another pharmacological barrier for targeting drugs to the CNS. Ischemic stroke creates the most dramatic and time-dependent pathological microenvironment in the CNS. After cerebral arterial occlusion, within minutes, the ischemic core (oxygen/glucose deprivation < 20% of normal) becomes anaerobic, ATP is rapidly depleted, cytotoxic oedema develops, and catastrophic ionic gradient failure ensues. Potentially salvageable peri-ischemic tissue (penumbra) is characterised by a pH of 6.2-6.5 (lactic acidosis), ROS burst, calpain/caspase activation, MMP-2/9 upregulation, and neuroinflammation [61]. This penumbra is the critical therapeutic target, salvageable for ~6 hours in favourable anatomy; it is the window for SRDD intervention. Conventional pharmacotherapy fails in neurological diseases due to multiple factors, which are systematically described. Drugs used to treat AD, such as cholinesterase inhibitors (donepezil and rivastigmine), have only modest symptomatic effects and do not alter the course of the disease, as they cannot reach the Aβ-deposited areas at therapeutic doses and cannot affect the inflammatory microenvironment in these regions [62]. Anti-amyloid monoclonal antibodies (lecanemab, donanemab) show some benefit but have significant side effects, including amyloid- related imaging abnormalities (ARIA), due to non- specific antibody binding at the BBB. L-DOPA for PD is converted to dopamine in the periphery before reaching the CNS, and its efficacy is restored by monoamine oxidaseand catechol-O- burden of polypharmacy and increase the risk of drug interactions and dyskinesia. Tissue plasminogen activator (tPA) for ischemic stroke has thrombolytic activity but no neuroprotective ability and causes hemorrhagic transformation risk if administered outside of the narrow therapeutic window [63].

SRDDs can cross the BBB via receptor-mediated transcytosis, which takes advantage of the enhanced expression of transferrin receptor, low-density lipoprotein receptor-related protein 1 (LRP1), and lactoferrin receptor in the brain microvascular endothelium during disease. SRDDs can achieve brain drug concentrations 10-30 times higher than those obtained with unconjugated formulations by functionalizing the surface of nanocarriers with transferrin, lactoferrin, Angiopep-2 (an LRP1- targeting peptide), or the rabies virus glycoprotein- derived peptide RVG-29 (which binds nicotinic acetylcholine receptors on BMECs and neurons). Importantly, the SRDD architecture can be combined with this targeting to control drug release methyltransferase inhibitors, which add to the ensuring it occurs only when the carrier reaches the pathological microenvironment. For example, a ROS-responsive thioketal-linked nanoparticle loaded with curcumin and functionalized with Angiopep-2 can cross the BBB by transcytosis via LRP1, but remains intact in normal parenchyma and only releases curcumin when it encounters elevated ROS levels (50-500μM) in brain regions laden with nanoparticles are protonated and switch from neutral to cationic at pH < 6.5, which causes endosomal escape and drug delivery

into the cytoplasm of ischemic neurons. The passive physicochemical properties of this pH sensor were converted into a spatially controlled drug-delivery system, effectively utilising the disease itself as the signal for drug delivery. For example, Curcumin Nanoparticles for Alzheimer's Disease Problem: Curcumin, a polyphenolic compound found in turmeric, has been shown to have strong Aβ disaggregation and anti-inflammatory effects in vitro; however, it has low oral bioavailability (< 0.1%) and does not cross the BBB. Even when mice are fed high levels of curcumin, it cannot be detected in their brains using HPLC in APP/PS1 transgenic Alzheimer's mice. SRDD Solution: Angiopep-2- conjugated ROS-responsive thioketal-linked polymeric nanoparticles encapsulating curcumin. LRP1 is expressed on the brain microvascular endothelium, where it binds Angiopep-2 with a Kd of ~50 nM and facilitates receptor-mediated transcytosis [65,66]. Thioketal linkages (derived from 1H-pyrrole-2,5-dione) are not cleaved at normal levels of H_2O_2 (< 10 nM in healthy parenchyma) but are cleaved at H_2O_2 levels associated with Aβ plaques (50–500 μM). Outcome: Curcumin NPs showed an 8× higher brain AUC than free curcumin in APP/PS1 mice. Brain region- specific distribution revealed that curcumin was present at three-fold higher concentrations in the hippocampus and cortex (Aβ-laden) than in the cerebellum (Aβ-free), indicating disease-selective drug release. The Aβ plaque burden was reduced by 60% at 4 weeks compared with vehicle control and by 35% compared with non-responsive curcumin nanoparticles, demonstrating the ROS-responsive release advantage. The Morris water maze test showed a 42% reduction in escape latency, indicating improved memory function. This case study demonstrates that the therapeutic effect of curcumin in AD is pri ily delivery-dependent and that dual targeting (receptor-mediated BBB crossing and stimulus-gated release) provides a synergistic pharmacological advantage [67].

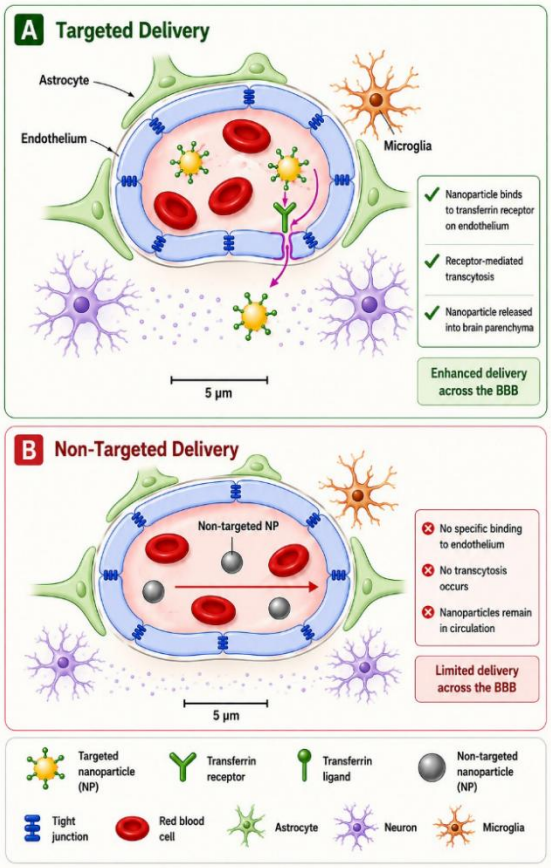


Figure 2. Targeted versus non-targeted nanoparticle delivery across the blood–brain barrier (BBB): [A] Targeted nanoparticles functionalized with transferrin ligands undergo receptor-mediated transcytosis via transferrin receptors on brain endothelial cells, enabling selective BBB penetration and delivery into the neural microenvironment. (B) Non-targeted nanoparticles exhibit limited BBB interaction and reduced transport across endothelial tight junctions, resulting in poor CNS accumulation. Astrocytes, microglia, endothelial tight junctions, and circulating red blood cells are illustrated to highlight the neurovascular interface involved in targeted CNS drug delivery.

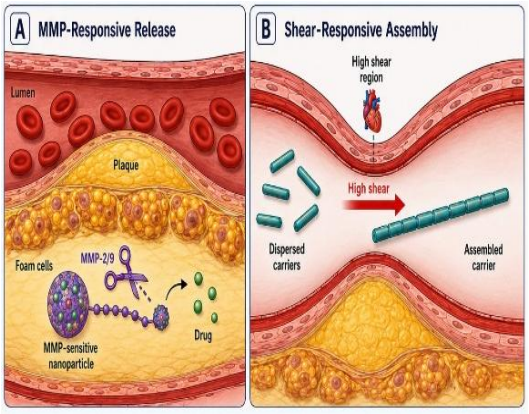
4.2 Cardiovascular Disorders

Atherosclerosis is a chronic inflammatory disease of large and medium-sized arteries, initiated by subendothelial retention of apolipoprotein B-containing lipoproteins, propagated by the infiltration of monocyte-macrophages, and perpetuated by foam cell formation, smooth muscle cell proliferation, and fibrous cap development. Mature atherosclerotic plaques are pathological microenvironments with various coexisting stimuli that can be exploited by SRDD [21]. The pH of the extracellular fluid in plaque areas drops to approximately 6.0–6.8 as a result of anaerobic glycolysis in hypoxic cores that are rich in macrophages, the production of lactic acid by activated macrophages, and the retention of CO_2 in poorly perfused tissue [21,68]. NADPH oxidase, xanthine oxidase, and uncoupled endothelial nitric oxide synthase (eNOS) are the major sources of ROS, which are generated in large quantities and oxidise LDL into highly pro-inflammatory oxLDL, promoting foam cell formation and endothelial activation [69]. The main mechanism of vulnerable plaque rupture, the trigger for acute coronary syndromes, is the degradation of the fibrous cap and extracellular matrix, which is mediated by the matrix metalloproteinases MMP-2 and MMP-9, synthesised and secreted by activated macrophages and smooth muscle cells [70]. The concentration of MMP-2/9 is 10–100-fold higher in unstable plaques than in normal arterial tissue, offering an enzyme gradient with re kable pharmacological specificity. Hemodynamic shear stress, especially oscillatory low shear stress at arterial bifurcations and inner curvatures, induces the activation of endothelial mechanoreceptors (Piezo1, TRPV4, junctional complex proteins) that lead to activation of NF-kB, VCAM-1, and ICAM-1, thereby sustaining the inflammatory response and recruitment of monocytes [71]. In stenotic lesions, disturbed flow creates turbulent, high-shear pockets (>70 dynes/cm²) that can mechanically trigger shear- sensitive drug carriers.

The microenvironment of the plaque offers an unprecedented collection of SRDD triggers, facilitating discrimination of pathological from normal vessels. One such example is Matrix Metalloproteinases (MMP)-cleavable peptide sequences—especially the PLGLAG hexapeptide, a preferred substrate for gelatinases MMP-2 and MMP-9—which have been used as surface gatekeepers for drug release from nanoparticles [72]. When systemically administered PLGLAG- linked nanoparticles loaded with atorvastatin or pioglitazone encounter the MMP-rich plaque microenvironment, cargo is released directly at sites of vulnerability.

Khatri et al. demonstrated PLGA nanoparticles functionalized with PLGLAG delivered 3–5× higher drug concentration in atherosclerotic tissue compared to healthy aortic tissue in ApoE$^{-/-}$ mice. This resulted in 38% greater plaque regression than the same dose of free statin, with a 60% lower total dose, significantly reducing the risk of hepatotoxicity (Khatri et al.,). This exemplifies two pharmacokinetic benefits of SRDDs: improved target activity and reduced systemic toxicity. In addition, shear-responsive carriers represent an elegant hemodynamic exploitation strategy. For example, Korin et al. created drug delivery assemblies by aggregating PLGA-PLA nanoparticles, which are too small to adhere to the vascular wall, into drug-releasing assemblies within a high-shear environment at stenotic sites, harnessing the mechanical pathology of the lesion to induce local drug release [73]. Furthermore, the shear-sensing mechanism was adapted for thrombolytic delivery: Von Willebrand factor-mimetic thrombus-targeting carriers selectively release tissue plasminogen activator at sites of highest shear-induced platelet activation, which enables reduced systemic drug doses and effective thrombolysis [74]. For example, ROS-Scavenging Hydrogel for Post-MI Cardioprotection Problem: I/R injury-associated ROS caused by Acute MI are causally related to cardiomyocyte apoptosis, microvascular obstruction, and adverse remodelling [75]. Conventional antioxidant therapy (N-acetylcysteine, vitamin C) is ineffective because of rapid clearance, systemic distribution, and failure to concentrate in the ischemic myocardium [76]. SRDD Solution: PVAX injectable hydrogel, a poly(vinyl alcohol) (PVA) derivative containing reactive oxygen species (ROS)-labile oxalate ester crosslinks, was injected into the ischemic myocardium immediately following reperfusion via a percutaneous intramyocardial catheter [77]. PVAX crosslinks are broken by H_2O_2 from both sides: on the one hand, gel degradation consumes ROS (antioxidant function), on the other hand, degradation products (carbon dioxide, a diol) are not toxic [78]. VEGF and basic FGF are co-encapsulated and gradually released as the hydrogel breaks down over 1-3 weeks [77]. Outcome: In a rat LAD ligation-reperfusion MI model, PVAX hydrogel injection resulted in a 50% reduction in myocardial ROS (measured by DHE fluorescence), 30% reduction in cardiomyocyte apoptosis (TUNEL), 2-fold increase in capillary density at 4 weeks (CD31 immunohistochemistry), and improvement in ejection fraction from 28% ± 4% (untreated MI) to 51% ± 6% (PVAX-treated), approaching sham-surgery

values of 65%. LVEDD, an important index of pathological remodelling, raised by 22%. This study (Joo et al., Biomaterials) is one of the most compelling preclinical demonstrations of multifunctional SRDD cardioprotection, showing that the dual-function ROS-scavenging/drug-releasing carrier architecture yields results superior to those of either ROS- scavenging or drug-releasing carriers alone [79]. Pathological stimuli in the injured myocardium are a series of spatiotemporally distinct stimuli that occur during acute myocardial infarction. In ischemia, the pH drops (intracellular pH 6.8-7.0) due to anaerobic metabolism. The sudden reoxygenation results in a large "burst" of ROS, ischemia-reperfusion (I/R) injury, and the production of superoxide anions by NADPH oxidase, xanthine oxidase, and mitochondrial complexes I/III, which exceed the body's ability to neutralise them. This oxidative storm activates the NLRP3 inflammasome and caspase-1, triggering pyroptosis of cardiomyocytes and elevating myocardial IL-1β and IL-18 levels. Post-infarct cardiac remodelling is a process that occurs over weeks to months and involves the activation of fibroblasts, collagen deposition, progressive ventricular dilatation, and the evolution to heart failure, all of which offer distinct therapeutic targets [80]. SRDDs using I/R-related ROS have shown unprecedented cardioprotective efficacy in preclinical models. Injectable hydrogels containing ROS-scavenging groups, such as oxalate ester crosslinks in PVAX hydrogels, can protect against ROS (by scavenging them) [78]. PVAX hydrogel injection immediately after an infarction reduced myocardial ROS by 50%, doubled capillary density, and improved EF from 28% to 51% after 4 weeks, an amount of functional recovery not often achieved by a single pharmacological agent. The two-in-one role of the hydrogel as a ROS scavenger and drug depot is a good example of how the carrier can also serve as a pharmacological agent, not just a cargo carrier, in the design of sophisticated SRDDs [17,81].



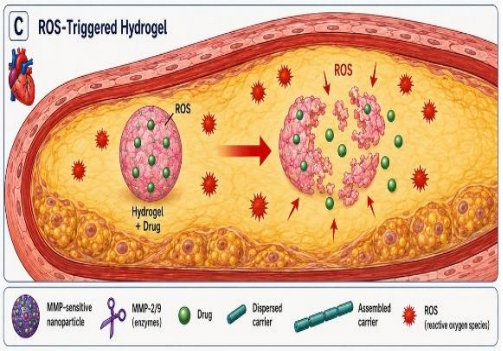


Figure 3. Stimuli-responsive drug delivery strategies for atherosclerosis and myocardial injury: (A) MMP-responsive nanoparticles undergo enzymatic cleavage by plaque-associated MMP-2/9, enabling site-specific drug release within atherosclerotic lesions. (B) Shear-responsive carriers assemble under disturbed high-shear flow at stenotic regions, promoting localized therapeutic accumulation. (C) ROS-triggered hydrogels degrade in oxidative microenvironments, releasing encapsulated drugs in response to elevated reactive oxygen species (ROS) during vascular inflammation and myocardial injury. Foam cells, plaque architecture, and vascular lumen are illustrated to highlight disease-specific pathological triggers.

4.3 Metabolic Disorders

The pathophysiology of diabetes mellitus is the central theme: an absolute defect in insulin secretion (type 1 diabetes, T1DM), with autoimmune destruction of pancreatic β-cells, or a relative insulin deficiency and insulin resistance (type 2 diabetes, T2DM). The therapeutic problem in diabetes is not only insulin deficiency but also temporal misalignment of insulin secretion. Physiological insulin release from B-cells is exquisitely regulated by moment-to-moment fluctuations in glucose, with insulin levels increasing steeply within seconds of sensing glucose and returning to normal levels when glucose levels normalise. Conventional insulin therapies (basal-bolus, premixed) are not similarly regulated. The mismatch between pharmacodynamics (fixed dose) and dynamic glucose (postprandial) levels results in postprandial hyperglycemia (glycation, oxidative stress, and end- organ damage) and potentially life-threatening hypoglycemia (the single biggest impediment to tight glycemic control) [82,83]. Pharmacological glucose-responsive hydrogel (GRH) systems and glucose-responsive nanoparticles (GRNPs), which increase insulin release with increasing glucose concentration and release it when glucose is normalised. Three main glucose-sensing approaches to closed-loop glycemic control include

mechanisms have been realized in SRDDs: (1) enzymatic oxidation using glucose oxidase (GOx), where glucose is enzymatically oxidized to gluconic acid, producing H_2O_2 and reasing the local pH, causing pH-sensitive or H_2O_2-responsive carrier disassembly; (2) competitive binding using phenylboronic acid (PBA), which forms reversible covalent bonds with diols in glucose and glycated polymers, leading to conformational swelling in pH-responsive hydrogel networks proportional to the glucose concentration; and (3) competitive binding using concanavalin A (Con A), where glucose competes with glycosylated insulin for Con A binding sites, releasing insulin upon glucose elevation [84]. The oral delivery of peptide therapeutics is the therapeutic frontier most limited by delivery challenges for T2DM and the broader metabolic syndrome, including GLP-1 receptor agonists (liraglutide, semaglutide, and dulaglutide), insulin, and glucose-dependent insulinotropic polypeptide (GIP) analogues. Although GLP-1 agonists are very potent insulin secretagogues and have weight loss, cardiovascular, and renal protective properties, their oral bioavailability without delivery protection is ~0.4–1.0% because they are rapidly denatured by the acidic environment of the stomach (pH 1.5–3.5) and are subject to proteolytic degradation by pepsin, trypsin, and chymotrypsin. The GI pH gradient from the gastric pH of 1.5-3.5 to the duodenal neutral pH of 5.0-7.0 and the jejunal/ileal alkaline pH of 7.0-8.0 represents an axially predictable stimulus for enteric SRDD systems.[85,86] The polymers Eudragit L100 and S100 are methacrylic acid-co-methyl methacrylate polymers that have a classical enteric dissolution transition at pH 6.0–7.0 and 7.0–7.5, respectively. More advanced chitosan/sodium alginate multilayer nanoparticles take advantage of the pH gradient for stage-specific release: mucoadhesive at jejunal pH for more absorption and susceptible to enzymes (chitosanase) for intestinal mucosal cell-specific delivery. These systems have shown improvements in the oral bioavailability of GLP-1 analogues in preclinical models, and proof- of-principle in humans was demonstrated with data from the FDA-approved oral semaglutide [87].

In addition to glucose and pH, metabolic diseases produce a variety of enzymatic stimuli that are useful for SRDDs. Pancreatic lipases and esterases, which are abundantly found in the duodenum and upper jejunum, hydrolyse the ester bonds in triglycerides and are therefore a trigger for LBDDS, where lipophilic ADA (pioglitazone and fenofibrate) are released only in the absorptive part of the small intestine. Hepatic stellate cell (HSC) activation in non-alcoholic steatohepatitis (NASH) and non-alcoholic fatty liver disease (NAFLD) leads to increased levels of matrix metalloproteinases, lysyl oxidase, and prolyl hydroxylase, which are enzymes that can be targeted by nanocarrier systems through receptor-mediated hepatic uptake (mannose receptor, asialoglycoprotein receptor [88,89]). Retinol-conjugated nanoparticles selectively target activated HSCs via the vitamin A receptor (RBPA), which is overexpressed on these cells, for delivering TGF-β siRNA or anti-fibrotic small molecules specifically to the cells that drive hepatic fibrosis. For example, GOx-Hydrogel Closed-Loop Insulin Delivery for T1DM Problem: The ability to mimic the minute-to-minute insulin secretory function of healthy β-cells with conventional subcutaneous insulin injections is limited. Even with continuous subcutaneous insulin infusion (CSII, insulin pumps), external glucose monitoring, and manual or algorithm-based insulin dosing, the system remains open-loop, dependent on sensor accuracy and patient engagement. The ultimate goal of a diabetes management system is to be fully automatic and release insulin in a glucose-proportional manner without external inputs [90]. SRDD Solution: injectable nanonetwork composed of insulin-loaded chitosan nanoparticles and glucose oxidase-loaded dextran nanoparticles co-assembled with H_2O_2-degradable poly(ethylene glycol) diacrylate crosslinks. GOx oxidises glucose to gluconic acid with the production of H_2O_2 at high glucose levels (> 200 mg/dL). H_2O_2 cleaves the peroxide-labile PEG crosslinks, causing the nanonetwork to fall apart and releasing preloaded insulin. GOx activity reases as the glucose level returns to normal, crosslink cleavage slows, and the nanonetwork partially re-anneals (full reversibility is a second-generation engineering issue) [91,92]. Outcome: The nano-network maintained blood glucose levels below 200 mg/dL for 10 days after a single subcutaneous injection in streptozotocin-induced T1DM mice, whereas the same amount of free insulin was effective for < 24 hours. In contrast, conventional insulin-treated mice experienced multiple hypoglycemic episodes (glucose levels never dropped below 70 mg/dl), whereas none were observed in the present study. This was an autonomous insulin release proportional to glucose, representing a clinically meaningful closed-loop glycemic control window of 10 days, achievable with a single injection, and highlighting the transformative potential of PK–PD-driven diabetes management using SRDD [93].

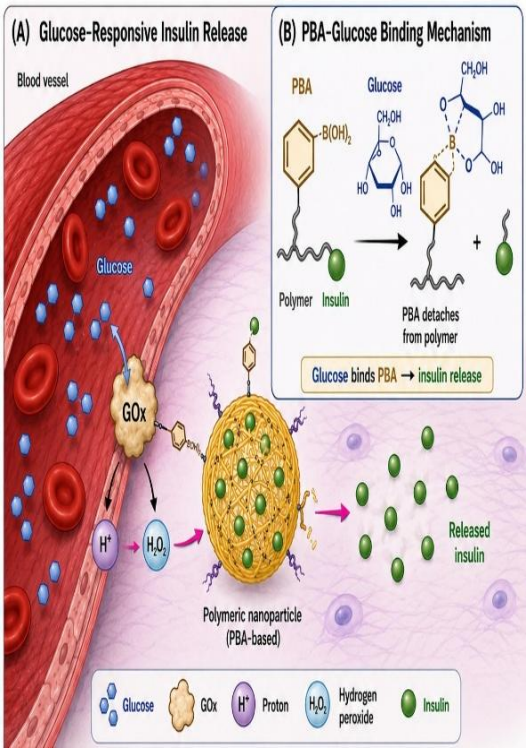


Figure 4. Glucose-responsive insulin delivery mechanisms mediated by GOx and phenylboronic acid (PBA).

(A) Elevated glucose levels are sensed by glucose oxidase (GOx), generating H^+ and H_2O_2 that trigger pH-sensitive polymeric nanoparticle destabilization and controlled insulin release.

(B) In the PBA- based mechanism, glucose competitively binds phenylboronic acid moieties, disrupting polymer– insulin interactions and promoting glucose- dependent insulin release. Together, these systems enable autonomous, closed-loop glycemic regulation for diabetes management.

5. Pharmacokinetic – Pharmacodynamic (PK-PD) Effect of SRDDs

Stimulus-responsive delivery is a paradigm-changer in the field of pharmacokinetics– pharmacodynamics. In traditional pharmacology, the PK–PD relationship is expressed by a plasma concentration-effect model in which the plasma concentration of the drug is the cause of effect in the tissue, which is mediated by the interaction of the drug with the receptor at the target organ. The implicit assumption is that the amount of drug at the target is the same as the amount of drug in the plasma; however, for most disease targets, this is not the case: BBB impermeability will separate the CNS from plasma; plaque avascular zones will separate the arterial wall from the lumen; subcutaneous insulin pharmacokinetics is determined by injection site physiology, not glycemic need. SRDDs redefine the relevant pharmacological concentration from plasma drug concentration to carrier-drug conjugate concentration at the pathological microenvironment to allow direct PD-relevant exposure control [94,95]. The most important change in the PK–PD relationship that is made by SRDDs is the shift from a static to a dynamic stimulus-proportional dose– response relationship. The insulin release rate in glucose responsive insulin delivery systems is a continuous function of the ambient glucose concentration, which is exactly the same as the physiological insulin secretion kinetic of the β-cells. This makes the conventional linear dose–response (fixed dose, fixed plasma concentration, fixed hypoglycemic effect) relationship into a closed-loop feedback system similar to a physiological control system. The PD consequence is dramatic compression of glycemic variability, with the standard deviation (SD) of blood glucose reasing from 2–4 mM (conventional insulin) to < 1 mM (closed-loop SRDD), and both hyperglycemic area under the curve (AUC) and hypoglycemic events are reduced simultaneously, a PK–PD feat not possible with conventional delivery [96,97].

The PK advantage of cardiovascular SRDDs is mostly distributional. MMP-responsive systems are capable of delivering 20–40% of the injected dose of nanoparticles to atherosclerotic plaques compared to < 5% for non-targeted nanoparticles and < 1% for free drug, greatly improving the plaque-to-plasma drug concentration ratio, which is the denominator of the therapeutic index in cardiovascular therapy [98,99]. Improved localization enables therapeutic plaque drug levels to be achieved at lower systemic doses than those used in conventional therapy, thereby minimizing the hepatotoxic, myopathic and rhabdomyolytic risks that are associated with high dose statin therapy [100,101]. The clinical implication is that patient groups currently not treated optimally with statins because of dose- limiting side effects may be able to benefit from statin regimens formulated with SRDD that have similar anti-atherosclerotic efficacy at greatly reduced systemic exposure. The PK–PD transformation for neurological SRDDs includes two aspects—one is barrier penetration (how to get a near zero brain AUC to a therapeutic exposure)
[102] and the second is stimulus-gated release (how to ensure that BBB-penetrant nanocarriers release drug only in the pathological tissue and not in normal parenchyma) [103]. This spatial PD selectivity is of particular importance for drugs with narrow therapeutic indexes such as NMDA receptor antagonists and calcium channel blockers that can protect neurons from excitotoxic death at low concentrations, but disrupt normal synaptic transmission at slightly higher concentrations [104], as the sub-parenchymal precision of stimulus-gated release will prevent

supraphysiological drug concentrations in healthy brain regions adjacent to the pathological focus.

Table 2. PK–PD Parameter Comparison: Conventional vs. SRDD-Based Drug Delivery

PK/PD Parameter	Conventional Delivery	SRDD-Based Delivery	Disease-Specific Advantage	References
Bioavailability (CNS)	< 2% BBB penetration for most drugs; rapid plasma clearance	10–30× improved CNS exposure via receptor-mediated transcytosi; prolonged t½	Higher AUC in brain tissue; reduced peripheral side effects in neurological diseases	[105, 106]
Volume of Distribution (Vd)	Wide, non-specific tissue distribution; off-target accumulation	Reduced systemic Vd; preferential accumulation at pathological locus (plaque, ischemia)	Minimizes cardiac/hepatic toxicity in CVD treatment; reduces diabetic complications	[107, 108]
Drug Release Rate	Rapid bolus kinetics; peaks/troughs; subtherapeutic troughs	Pulsatile or sustained release governed by pathological stimulus intensity	Self-regulating insulin dosing in T1DM; burst neuroprotection at stroke onset	[109, 110]
Half-life (t½)	Short for peptides (minutes); rapid renal clearance	Extended t½ via PEGylation and nanoencapsulation (hours to days	Reduced dosing frequency; improved patient adherence in chronic CVD/metabolic disease	[111, 112]
Therapeutic Index (TI)	Narrow TI for neurotoxic/	Broadened TI via site-specific delivery;	Safer use of otherwise systemic-toxic agents (e.g.,	[113]
	cardiotoxic drugs	reduced peak plasma concentrations	amphotericin B for CNS infection)	
Drug–Drug Interactions	High; shared metabolic pathways (CYP450)	Reduced systemic concentrations minimize DDI potential	Important for polypharmacy in diabetic/cardiovascular comorbidity patients	[114]
Pharmacodynamic Response	Fixed dose–response; poor individualization	Stimulus-proportional response; PD effect tracks disease severity dynamically	Glucose-proportional insulin release mirrors physiological β-cell function	[115]

6. Challenges and Limitations

One of the challenge in the clinical translation of SRDDs is the biological heterogeneity of the disease microenvironment. Depending on the maturity of the atherosclerotic plaque, the number of macrophages, and the plaque's inflammatory activity, MMP-2/9 activity, pH, and oxidative state can vary significantly from one patient to another and even between plaques in the same patient. The ischemic microenvironment in stroke depends on collateral circulation, time from symptom onset, and therapeutic intervention. This heterogeneity implies that SRDDs with average stimulus intensities might not be sufficiently responsive in patients with lower stimulus intensities or responsive enough in patients with higher pathological signals. Thus, the generation of patient-stratification bio kers, such as imaging, serum, or genetic bio kers, that predict the intensity of the stimulus in the disease microenvironment is an important prerequisite for SRDD personalisation. Although significant progress has been made in developing BBB- targeting strategies, the most efficient receptor- targeted nanoparticles have delivered only ~1% of the injected dose to the brain [116]. This efficiency limitation makes it imperative to either increase the number of injections or the dose of the drug in the CNS, which may increase the immunogenic concern for ligand-orated carriers for chronic neurological diseases where constant drug exposure is required. At high nanoparticle doses, excess transferrin- functionalized nanoparticles may compete with endogenous transferrin for binding to the transferrin receptor, paradoxically reasing targeting efficiency to the CNS

[117]. Furthermore, the expression of receptors that can be used to target the BBB (transferrin receptor, LRP1) is non-uniform in different brain areas and changes during disease.

The design of advanced SRDDs is complex, with several functional elements (targeting ligands, stimuli-responsive linkers, PEG corona, hydrophobic core, and multiple cargo molecules), which pose significant challenges for GMP- compliant manufacturing [118,119]. The multi-step chemistry required for ligand attachment, stimulus- sensitive linker incorporation, and surface PEGylation is difficult to reproduce in a batch-to- batch-consistent manner, which is essential for drug approval [120,121]. Although manufacturing paradigms exist for liposomes and PLGA nanoparticles (microfluidic nanoprecipitation and thin-film hydration, respectively), multi-stimuli systems with three or more functional components are mainly laboratory constructs. The characterisation of multi-component nanosystems (particle size distribution, surface charge, ligand density, drug loading, in vitro trigger-release kinetics, and in vivo biodistribution) is much more complex and burdensome than that of conventional formulations, thereby increasing development time and cost [122]. Currently, there are no specific regulatory pathways for stimulus-responsive nanomedicines at the FDA and EMA, and only traditional drug approval pathways apply; therefore, there is a regulatory gap in which fundamentally different pharmacological entities are subjected to these pathways [123]. The dynamic, disease-state- dependent pharmacokinetics of SRDDs, in which the rate of drug release varies with the level of the stimulus, are challenging to assess with traditional single-point PK studies and require new regulatory science paradigms that involve physiologically based pharmacokinetic (PBPK) modelling with stimulus-response parameters [124]. Extensive safety characterisation of stimulus-responsive polymer degradation products and inorganic nanocarrier components (iron oxide and silica) following repeated dosing, as well as the immunogenicity of protein-based targeting ligands, is required for clinical approval [125]. The regulatory translation gap in the nanomedicine field is highlighted by the fact that the first FDA approval of a stimulus-responsive nanomedicine has yet to be achieved [126].

Concerns about Off-Target Activation and False-Trigger Disease microenvironment stimuli are not necessarily disease-specific: ROS elevation is observed in wounds, inflammation, and normal ageing [127]; MMP activity is observed in wound healing and normal tissue remodelling [128]; and pH gradients are observed in the normal GI tract and physiological body compartments [129]. Single- trigger SRDD systems are thus prone to off-target activation whenever the trigger is present outside the pathological site. This is a particular problem with systemically injected ROS-responsive nanoparticles in patients with generalised inflammatory diseases because nanoparticles can be activated at non- pathological inflammatory sites and lose their drug cargo before reaching their target [130] Multi- stimuli AND-gated systems partially overcome this drawback by combining two or more stimuli (which are more disease-specific), but with the drawback of increased design complexity and possibly reduced overall release efficiency [31]

7. Future Perspectives

7.1 Multi-stimuli-responsive and cascading systems

The next generation of SRDDs will take advantage of cascading stimulus-response architectures, in which a single pathological trigger initiates a molecular amplification cascade that leads to drug release at stimulus concentrations too low to directly trigger conventional responsive release. The 'signal amplification' paradigm is based on the idea that trace amounts of disease MMP can trigger the release of an active fragment from a nanoparticle surface that initiates endosomal disruption, intracellular cargo delivery, and transcriptional reprogramming in a single initiating enzymatic event. Cascading systems have been suggested for Alzheimer's disease (Aβ-initiated caspase cascade triggering gene therapy release) [131], atherosclerosis (oxLDL-triggered lipid peroxidation cascade inducing the release of anti-inflammatory microRNAs) [132], and diabetes (glucose-triggered GOx cascade inducing the release of insulin and GLP-1 analogue for synergistic glycemic control)
[133] Cascading architectures are an example of SRDD engineering and system pharmacology.

7.2 The application of Artificial Intelligence to SRDD Design

The formulation development for SRDD is now being revolutionised by artificial intelligence and machine learning methodologies [134]. Libraries of stimulus-responsive polymer–drug interactions have been used to train generative adversarial networks (GANs) and variational autoencoders (VAEs), which can predict optimal linker chemistry, crosslink density, and drug loading for targeted trigger thresholds [135,136]. By leveraging molecular dynamics simulation data of polymer behaviour under simulated pathological conditions (H_2O_2 exposure, pH shift, enzymatic cleavage), graph neural networks (GNNs) can assist with the in silico screening of SRDD formulation candidates before synthesis [137]. The formulation-to-preclinical testing process is now being shortened from years to months by the use of high-throughput microfluidic combinatorial platforms and AI-guided design of experiments (DoE) [138]. Importantly, AI

systems that combine patient-specific bio ker information and SRDD formulation parameters to make personalised formulation recommendations for individual disease microenvironment profiles represent the translational interface between precision medicine and precision drug delivery [139,140].

7.3 Precision Medicine Integration and Companion Diagnostics

The clinical potential of SRDDs will be fully realised within companion diagnostic frameworks that describe the disease microenvironment stimulus landscape in individual patients before SRDD selection. Monitoring MMP activity using PET- MRI imaging (with DTPA-PLGLAG radiopharmaceutical probes) in patients with cardiovascular disease could identify MMP-hot atherosclerotic lesions most susceptible to MMP- triggered SRDD therapy [141]. ROS-sensitive fluorescence imaging agents (boronic acid-protected fluorophores) can be used to generate ROS maps in pre-stroke patients to stratify responsiveness to SRDD formulations. Continuous glucose monitoring (CGM) with closed-loop coupling to subcutaneous SRDD insulin depots already is the clinical realisation of precision metabolic drug delivery. The wider integration of microenvironment characterisation at the patient level with personalised SRDD selection is the vision of precision medicine in SRDD pharmacology [142].

7.4 Biological and biohybrid SRDDs

A visionary combination of synthetic biology and stimulus-responsive pharmacology is exemplified by engineered living materials, such as engineered bacteria that produce therapeutic agents in response to stimuli [143], platelet membrane-coated responsive nanoparticles that combine biological targeting with synthetic responsiveness [144], and CAR-T-cell-inspired living drug factories that secrete therapeutic proteins in response to disease- specific molecular triggers [145]. Pancreatic β-cell mimetics, which are micro-organ constructs containing GLP-1 receptor-responsive gene circuits that encode and express insulin on glucose stimulation [146] and are implantable in the peritoneum of mouse models of T1DM [147], have shown sustained normoglycemic maintenance in T1DM mouse models [147] and are progressing toward human islet transplant scale [148]. Such biohybrid systems transcend the concept of drug delivery to that of regenerative medicine and can enable SRDDs to function not only as delivery vehicles but also as pharmacological organ replacements.

8. Conclusion

Stimuli-Responsive Drug Delivery Systems are not only technological improvements over traditional drug formulation approaches but also a new paradigm in pharmacology. SRDDs are now considered as pharmacological architectures tailored to specific diseases, which leverage the enzymatic and physicochemical properties of the pathological microenvironment to deliver drugs that is difficult to be achieved with traditional drug formulations. In neurological, cardiovascular, and metabolic disorders, SRDDs play different but essential roles: barrier penetration and neuroprotection in the central nervous system (CNS) in neurological diseases; microenvironment discrimination and anti-inflammatory delivery targeting plaques in cardiovascular diseases; and autonomous homeostatic regulation in metabolic diseases. A cross-disease analysis, indicates that the concentration, spatial distribution, and temporal dynamics of common triggers such as ROS, pH, and enzymes are disease-specific, requiring individually tailored SRDD architectures. The engineering insight that a single trigger can be used at different sensitivity levels by varying the chemical design of the linker, the pKa of the polymers, or the specificity of the enzyme substrates paves the way for disease- specific SRDD libraries rather than universal platforms. Pharmacokinetic–pharmacodynamic analysis has demonstrated that SRDDs fundamentally change drug distribution, increase half-life, and enhance therapeutic indices. In their most advanced form, glucose responsiveness and dynamic pharmacological homeostasis can be achieved, resembling endogenous physiological control. The journey towards translating SRDDs is already underway. Thermosensitive liposomes for cardiovascular applications are in late-stage clinical trials, and clinically approved pH-responsive enteric delivery of oral semaglutide and glucose-responsive insulin patch technologies are in early-stage clinical evaluation (Phase I/II). Although the other challenges are daunting, they are not insurmountable. Biological heterogeneity, manufacturing scalability, regulatory frameworks, and long-term safety characterisation are formidable but tractable and can be addressed by transformative near-term solutions enabled by the rapid evolution of AI-guided formulation design, companion diagnostics, and biohybrid living materials. Diseases, nanotechnology, responsive materials science, and precision medicine are all coming together in SRDD research, which is the most fruitful intersection in today's pharmaceutical science. The more is learnt about the microenvironment of a disease through single-cell transcriptomics, in vivo metabolomics, and advanced functional imaging, the more precisely SRDDs can target its biochemical signatures. SRDDs are no longer in the realm of a therapeutic future in which drugs are administered not on a fixed schedule but directly proportional to pathological need, in which pharmacology and physiology speak the same dynamic language;

however, researchers are actively working towards the future to make it a clinical reality. One of the most important advances in the therapeutic arena of the twenty-first century is the rapid translation of SRDDs from bench to patients' bedside.

Statements and declarations

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Ethics statement:

This article, "*Stimuli-Responsive Drug Delivery Systems for Neurological, Cardiovascular, and Metabolic Disorders: Pharmacological Triggers and Therapeutic Applications*," involves no experimental research, human subjects, or animal studies that need ethical approval. For academic openness and integrity, all acknowledged sources were appropriately referenced. Authors have tried their best to provide an objective, accurate, and thorough literature review free from any conflicts of interest that could affect how the data are interpreted. The development of this paper did not involve any instances of scientific misconduct, data manipulation, or plagiarism.

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