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Stimuli-Responsive Drug Delivery Systems: A Review

D Jayanth*, K Ramesh Kumar[1], R Arun Kumar[2], S Mohamed Yaser[2], R Shalini[2]

*M. Pharm, Department of Pharmaceutics, College of Pharmacy, Madras Medical College, Chennai - 600003 India.
1 Associate Professor, Department of Pharmaceutics, College of Pharmacy, Madras Medical College, Chennai - 600003 India.
2 M. Pharm, Department of Pharmaceutics, College of Pharmacy, Madras Medical College, Chennai - 600003 India.

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ABSTRACT

Stimuli-Responsive Drug Delivery Systems (SRDDS) also known as Smart delivery systems are novel carriers which undergoes physiochemical changes in contact with certain endogeneous and exogeneous stimuli which results in the spatial and temporal regulation of the medicament. This review focuses on current achievements in stimuli-responsive drug delivery systems (SRDDS), concentrating on design principles, material classes, release mechanisms, therapeutic uses, and translational obstacles. It categorizes SRDDS by trigger type—external (light, magnetic field, ultrasound, electric field) and internal (pH, enzymes, redox, temperature) and covers common responsive polymers and nanocarrier designs used to achieve spatial and temporal release of medicament. Key release mechanisms including polymer swelling/shrinkage, phase transitions, stimulus-cleavable bond hydrolysis, and instability of self-assembled nanoparticles and liposomes are also described briefly in this review. Highlighted are examples of clinical and preclinical applications, such as glucose-responsive insulin delivery, infection-site enzyme-activated antibiotics, blood-brain-targeted formulations, ocular and wound-healing systems, and representative multistimuli platforms (dual and triple responsive). Concerns about safety and toxicity, immunological clearance, biological barriers, and material degradation that hinder clinical translation are also covered in the review. In order to increase therapeutic precision and lessen off-target effects, it ends by describing prospects for incorporating digital control, enhancing biocompatibility, and creating sturdy multiresponsive carriers.

Keywords: Stimuli-responsive drug delivery systems, External triggers, Internal triggers, Responsive polymers, multiresponsive systems

1.0 INTRODUCTION

This drug delivery system, which enables the release of medications in response to particular biological events and environmental triggers, such as endogenous and external stimuli, marks a significant therapeutic milestone (1). These "smart" delivery systems provide precise drug release management by undergoing a variety of physiochemical changes when exposed to different stimuli, such as pH shifts, temperature variations, enzyme actions, light radiation, and magnetic fields (2)(3). Due to its tailored drug delivery, this kind of delivery system is currently garnering attention in the domains of cancer, diabetes, and neurodegenerative illnesses. Conventional formulations, such tablets, injections, or transdermal patches, mostly use passive release techniques and frequently encounter significant difficulties like non-specific dispersion throughout the body, inadequate concentrations at the intended target site, and elevated systemic side effects systemic side effects and reduced compliance from patients (4). To tackle these challenges, stimuli-responsive drug delivery systems (SRDDS) have been developed as nanocarriers that modulate drug release in reaction to internal (endogenous) or external (exogenous) stimuli. Acidic pH levels in tumors or inflammatory regions, increased thrombin activity throughout the coagulation cascade, hypoxia, redox imbalances, and fluctuating temperatures are just a few of the distinctive microenvironmental alterations that diseased tissues frequently display. SRDDS can deliver their payload precisely at the target site by using these signals, improving therapeutic precision and reducing off-target adverse effects (5). The invention of implantable silicone rubber capsules for prolonged drug release in 1964 marked the beginning of the development of stimulus-responsive drug delivery devices (6). Responsive delivery was first created using its principles during the 1970s through temperature-sensitive liposomes, but the significant advances emerged in the late 1990s with pH-responsive polymers that leverage tumors' acidic microenvironments (7). Inadequate pharmacokinetics, drug resistance, and poor bioavailability are problems that this drug delivery system helps to solve by releasing its content only under physiological conditions and minimizing unintended or undesirable side effects (8)(9). During the 1970s, researchers achieved controlled macromolecule release from polymeric materials (10). In the 1980s, polymer-drug conjugate research introduced acid-sensitive links to the pharmaceutical industry (11). Scientists made progress in redox-responsive and enzyme-responsive systems in the early 2000s (12). Following the start of research on photodegradable polymers, the topic of light-responsive materials gained importance (13). As ThermoDox® (temperature-sensitive liposomal

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doxorubicin) began clinical trials in the 2010s, the commercialization of stimuli-responsive drug delivery grew quickly (14). Phase III trials for ThermoDox® began in 2011, and between 2020 and 2024, new technical advancements integrated digital systems into sophisticated biological platforms to create intricate nanocarrier systems. Recently, smart insulin delivery systems that provide insulin based on blood glucose levels have also hit the market (15). The types, different polymeric materials, and uses of stimuli-responsive drug delivery devices are briefly covered in this article.

Types of Stimuli-Responsive Systems

Exogeneous (or) External Stimuli Responsive Systems	Endogeneous (or) Internal Stimuli Responsive Systems	Multiple Stimuli Responsive Systems
•Light Responsive Systems •Magnetic Responsive Systems •Ultrasound Responsive Systems •Electric Field/Electro Responsive Systems	•pH Responsive System •Enzyme Responsive System •Redox Responsive System •Temperature Responsive System	•pH/Temperature Responsive System •pH/Redox Responsive Systems •Dual pH Responsive Systems

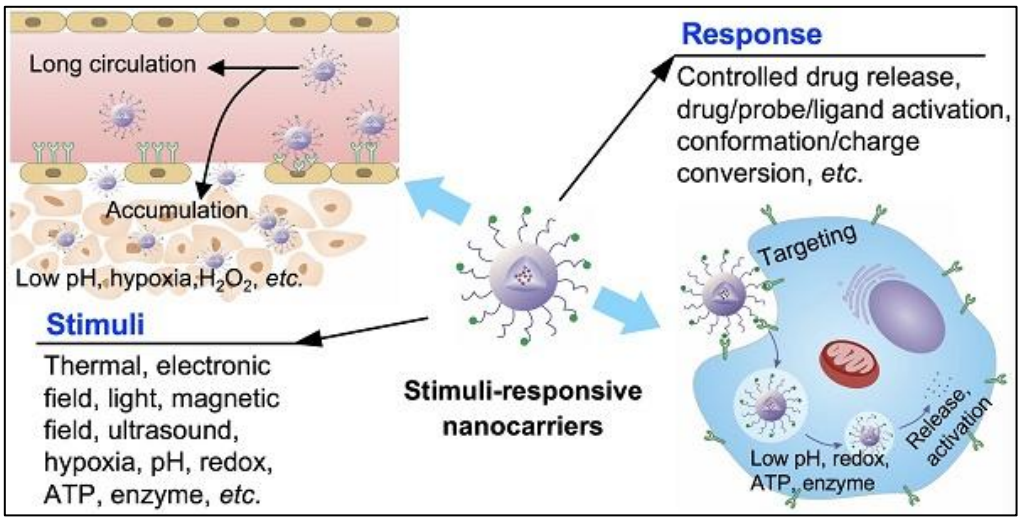

Figure 1: Schematic representation of Drug release from Stimuli Responsive Nanocarriers (16)

2.1 Exogeneous (or) External Stimuli-Responsive Systems

2.1.1 Light Responsive Systems

Light activation enables precise regulation of drug release both spatially and temporally. Near-infrared (NIR) light is commonly utilized in NIR responsive nanocarriers, because it may penetrate tissues more effectively than UV or visible light, Breaking photochemical bonds, photoisomerization (as in the case of azobenzene and spiropyran), and photothermal effects are among the mechanisms at play. A recent review centered on metal–organic framework (MOF) based carriers highlights the significance of light driven release, with sensitivity to interior stimuli. Critical design issues comprise wavelength penetration, phototoxicity, thermal management, and safe utilization in living creatures (12).

2.1.2 Magnetic Responsive Systems

Externally applied magnetic field is used to stimulate the drug release on demand. These systems consist of a drug carrier such as nanoparticles, and materials like magnetite (Fe_3O_4), maghemite (α-Fe_2O_3), iron, nickel, cobalt, and samarium-cobalt, which react to an applied magnetic field and induces the drug release at the targeted site. The magnetic characteristics of these materials are determined by their magnetic susceptibility, i.e. ratio of the induced magnetisation to the applied magnetic field (13).

2.1.3 Ultrasound Responsive Systems

Ultrasound creates acoustic cavitation, droplet vaporisation and localized heat generation which improves the tissue permeability of the drug. It has been used in the delivery of anticancer antibiotic doxorubicin by forming microbubbles and disrupting the microbubbles by externally applying ultrasound. According to a recent pre-print, ultrasound-sensitive carriers are improving mechanistic precision by using microbubbles to create cyclic jetting in the presence of ultrasound, which can penetrate cell membranes and improve cellular uptake (17).

2.1.4 Electric Field/Electron Responsive Systems

Electrical stimulation can trigger redox reactions, ion movement, changes in polymer shape, or variations in swelling in electro-responsive materials. These technologies are frequently used in wearable or implantable devices, where drug release is controlled by an applied voltage. These technologies are becoming popular for transdermal patches and implantable delivery methods, even though they are not yet widely used in clinical settings (18).

2.1.5 Polymers used in External Stimuli Responsive System(19)

S.No	Type	Description	Example
1.	Light Responsive System	Light responsive polymers contains specific that respond to a specific wavelength of light i.e. chromophore.The response of chromophore groups may be based on one of three presented mechanisms: photolysis, photoisomerization, and photorearrangement.	azobenzenes, stilbene, cyanostilbene, stiff-stilbene, diarylethene, spiropyrans, hydrazones and coumarins
2.	Magnetic Responsive System	A class of materials known as magnetic field-responsive polymers can alter their density, optical characteristics, and structure in reaction to a magnetic field [24]. By introducing magnetic particles—which are activated by a magnetic field—these particular characteristics can be obtained.	magnetite—Fe_3O_4, maghemite—γ-Fe_2O_3
3.	Ultrasound Responsive System	Waves can be classified as low (<1MHz), medium (1-5MHz), or high (5-10MHz) based on their frequency. The material can be affected by ultrasounds in two ways: (a) thermally, when an increase in temperature is noticed; and (b) nonthermally, also referred to as cavitation, when gas bubbles develop as a result of ultrasonic vibrations.	dodecyl isocyanate-modified PEG-grafted poly(2-hydroxyethyl methacrylate), polyglycolides, or polylactides
4.	Electric Field/Electron Responsive Systems	The physical characteristics of electric field-sensitive polymers change in response to slight variations in electric current. The transformation of electrical energy into mechanical energy has caused changes in the electric field. There are two groups of materials: Ionic EAPs (electro-active polymers)—the electric field induces a change in local ion concentrations and the onset of electroreactivity. poor reactivity, poor reaction speed, and the requirement for low voltages are their defining characteristics. Electrostatic forces between two electrodes applied to the system cause the response in dielectric EAPs. fast reactivity, fast reaction speed, and the requirement for high voltages are their defining characteristics.	Pyrrole, polyaniline, Poly(3,4-ethylene dioxythiophene) (PEDOT)

2.2 Endogeneous (or) Internal Stimuli Responsive Systems

2.2.1. pH Responsive System

The medication is released when the biomaterials that react to pH levels sense changes in pH and undergo physical and chemical changes in their polymer chains. Compared to other stimuli, these materials are primarily used for medication release that is driven by pH changes. The pH levels in different organs, including the stomach and intestines, determine how successful the traditional pH-responsive carriers are (9). Polyacids, which detect and release at alkaline pH, and polybases, which react to acidic pH and release the medication, are two categories of pH-sensitive polymers. Eudragit S100 is a citrus-coated pectin nanoparticle designed to deliver 5-fluorouracil, an anticancer medication, to the colon. Changes in pH levels at specific disease regions, such as ischemic tumor areas and inflammatory tissues, can be detected by carriers made specifically for this purpose (20).

2.2.2 Enzyme Responsive Systems

In medication delivery systems, enzymes act as catalysts. They have unique qualities like strong selectivity in mild environments and specificity to their substrates. Enzymes can aid in the targeted release of medications at inflammatory areas because of their intimate connection to biological and metabolic processes. The requirement for exact control over the initial release phase is a major obstacle when using enzyme-responsive drug delivery systems. The way these systems interact with effector molecules determines how they are categorized. Because they are involved in almost every biological and metabolic process, enzymes such as lipase, phospholipases, proteases, and glycosidases are helpful for promoting medication release through enzyme-mediated pathways in inflammatory or malignant tissues (21).

2.2.3 Redox Responsive Systems

Drug release from redox-sensitive biomaterials is triggered by changes in redox potential. These substances are frequently used in intracellular drug delivery systems to treat diseases. The development of redox-sensitive drug delivery devices benefits from the fact that different tissues in microenvironments have different redox potentials. One well-known redox mechanism present in cancer cells is the reduction of glutathione (GSH). While GSH concentrations in blood and normal extracellular matrices are found to be between 2 and 20 μM, levels within cancer cells vary from 2 to 10 mM, reflecting an increase of 100 to 500-fold compared to normal levels. Redox-responsive delivery systems are an attractive method for creating drug delivery systems intended to target certain intracellular locations within tumors because of the significant difference in GSH levels between malignant and normal cells.

2.2.4 Temperature Responsive System

The release of medicines is triggered by temperature. The critical solution temperature (LCST) of thermoresponsive polymers is lower. These polymers are soluble, hydrated, and prone to swelling at temperatures below LCST, which is the situation during drug loading. On the other hand, these polymers contract and dehydrate when the temperature rises above LCST, which causes drug release.

2.2.5 Polymers used in Internal Stimuli Responsive System (19)

S.No	Type	Description	Example
1.	pH Responsive System	The presence of one of the groups—acidic or basic—whose job it is to accept or donate protons in response to a change in pH is a distinctive and defining trait of pH-responsive polymers. The polymer chain's structure is altered by the overall shift in charge, which shows up as changes in surface activity, configuration, or solubility. Protons adhere to acidic polymers at low pH and are released at high pH. In the pH range of 7–11, basic polymers react by ionization or deionization.	Natural: Chitosan, Hyaluronic acid, alginates Synthetic: Polyacids- poly(acrylic acid), Polybases- poly[(2-dimethylamino) ethylmethacrylate]
2.	Enzyme Responsive System	Utilizing characteristics of enzymes, such as their capacity to catalyze physicochemical changes and biorecognition, they are highly helpful in creating systems that are especially helpful in areas where an enzyme is overexpressed. Enzyme-responsive polymers provide several benefits, such as higher permeability, enhanced resistance to degradation, a vast	Utilization of Thrombin cleavable peptide in the site specific delivery of anti-coagulants

		number of enzymes that can be utilized in a range of applications, specificity of action within the cell, and the potential for spatiotemporal control of secretion.	
3.	Redox Responsive System	They respond with specific reactions to changes in the redox state. The presence of oxidants or reducers in the surroundings causes the reaction. Numerous elements, including temperature, pH, and light, can trigger these changes. Although there are many uses for these materials, hydrogels and medication release due to redox responsiveness are frequently discussed.	An example of a polymer reacting to redox reaction is PNIPAAm hydrogel containing tris(2,2-bipyridyl) ruthenium (II) (Ru2+ → Ru3+)
4.	Temperature Responsive System	Temperature-responsive polymers are able to change their properties (often solubility) in response to changes in temperature (heating or cooling) in the external environment. Temperature is a parameter that can be measured and monitored very easily, and the systems for doing so are well understood. For this reason, it is often as the name suggests, temperature-responsive polymers are able to change their properties (often solubility) in response to changes in temperature (heating or cooling) in the external environment. Temperature is a parameter that can be measured and monitored very easily, and the systems for doing so are well understood. For this reason, it is often used in the production of smart polymers. A given material can acquire or change its temperature-responsive properties by adding additional substances to the system, such as plasticizers, salts, and surfactants. The reaction is based on the transition from the sol-gel state. Heating causes phase separation in LCST (Lower Critical Solution Temperature) polymers and single-phase formation in UCST (Upper Critical Solution Temperature) polymers.	PNIPAAm (poly(N-isopropylacrylamide))- Its has a similar LCST temperature of 32–33ºC close to the human body temperature.

2.3 Multiple Stimuli Responsive Systems

A variety of stimuli, such as light, mechanical force, temperature, pressure, electric or magnetic field, pH, concentration gradients, humidity, biological environment, and many more, can cause multiresponsive polymer materials to become sensitive. Importantly, polymeric characteristics can alter permanently or reversibly due to physical, chemical, and biological influences. For instance, the literature has identified materials that react to many factors, including light/temperature, enzyme/pH, pH/temperature, temperature/pH/redox, and many more (22).

2.3.1 pH/Temperature Responsive System

Dual-responsive polymers will be formulated by conjugating a pH-sensitive polymer to a thermo-sensitive polymer. How ever, some have used a mixture of the two different classes of sensitive polymers. The most common building block for thermo-responsiveness is poly(N-isopropylacrylamide) (PNIPAAm). This particular polymer can go from a water-soluble state to a water insoluble state through an LCST transition. The building blocks for pH-responsiveness are often polymers such as weak acids, acrylic acids, poly[2-(diisopropylamine)ethylmethacrylate] (PDPA), and chitosan. Once mixed, they follow the same process of a normal block copolymer to create micelles or nanoparticles. pH and temperature-responsive polymers are frequently proposed for potential cancer therapies since the tumor environment has an increased temperature and a decreased pH (22).

In the research of Zhang et al., the effectiveness of nanoparticles made from a block copolymer of thermo-responsive hydrophilic poly(N-isopropylacrylamide-co-acrylic acid) [P(NIPAM-co-AAc)] and a hydrophobic polycaprolactone (PCL), was explored. [P(NIPAM-co-AAc)] is a common polymer used for thermo-sensitive applications and PCL was chosen for its good drug encapsulation properties. This study showed that the nanoparticles released the encapsulated drug much faster at higher temperature and lower pH conditions, as are commonly seen in the tumor environment (23).

2.3.2 pH/Redox Responsive Systems

These two triggers are highly desirable for drug delivery applications since redox reactions and pH variations occur naturally in the body. These kinds of polymers have been developed for a wide range of uses, including improving drug delivery and tumor cell uptake. Since the body naturally experiences redox reactions and pH variations, these two stimuli are highly desirable for drug delivery applications. These polymers have been developed for a wide range of purposes, including improving drug delivery and tumor cell uptake, accelerating drug release in the cytoplasm and nucleus, and further strengthening the stability of nanoparticles in vivo (24).

Bahadur et al. created an RPDSG polymer by conjugating polyethylene glycol and cyclo(Arg-Gly-Asp-d-Phe-Cys) (cRGD) peptide to poly(2-(pyridin-2-yldisulfanyl)ethyl acrylate) (PDS). This copolymer was used to generate nanoparticles, which contained DOX. The experiment employed different concentrations of GSH to cause a redox reaction. The concentration of GSH was reported to be 1–11 mM intracellularly and less than 0.01 mM in the extracellular fluid. Following testing at various pH levels and GSH concentrations, it was discovered that the DOX release rate was significantly slower at higher pH levels. A faster release rate was obtained at pH 5.5 than at pH 7.4 because the ester linkages of PDSG can be hydrolyzed in acidic environments to create a faster release rate than at neutral pH. Additionally, it was shown that a higher GSH content increased the amount of DOX released.

2.3.3 Dual pH Responsive Systems

Du et al. created DOX-encapsulated nanoparticles using PPC-Hyd-DOX-DA, a polymer that could react to two distinct pH levels. When this nanoparticle is exposed to the pH of a tumor environment (~6.8), its surface charge shifts from negative to positive. The tumor cells' cellular internalization is encouraged by this shift in surface charge. The pH (~5.0) inside the endosome causes the cell to release DOX. Before being released, this method aids guarantee that medications intended for tumors are precisely within the site (25).

2.3.4 Triple Stimuli Responsive Systems

Poddar et al. synthesized a triple-stimuli-responsive polymer to achieve the release of a drug under the conditions of pH 5, 40ºC, and GSH ≥ 10 mM [106]. In this study, they synthesized two different polymers, 2-(2-((4-(hexyloxy)benzyloxy)carbonyl)ethylthio)ethyl acrylate (HBCEEA), which is sensitive to pH, and the copolymer of N-isopropyl acrylamide (NIPA) and poly(ethylene glycol methyl ether acrylate) (PEGMA), which is sensitive to temperature and redox potential. The combination of these polymers creates the triple-responsive polymer poly[HBCEEM-b-(NIPA-r-PEGMA)] (PHNP) [105]. The drug release from the polymer is much faster in the presence of all three stimuli (26).

3.0 Mechanism of Drug Release

Through a sequence of physicochemical and molecular interactions, stimuli-responsive drug delivery systems (SRDDS) transform ambient conditions or externally applied triggers into measurable material reactions that aid in drug release. This process can be visualized as a series of changes that start with the expansion or contraction of polymers, progress to changes in phase or bond cleavage reactions, and often end with the disruption of membranes or breakdown of nanocarriers, which leads to the drug's diffusion or release into the biological environment.

3.1. Expansion and Contraction of Polymers

Swelling or contraction is the main and often reversible reaction of polymer networks to an external stimulus. In contrast to hydrophobic transformations or ionic crosslinking, which might cause contraction and eject the drug through convective flow, hydrophilic polymers absorb water, increasing their mesh size and enabling the outward diffusion of drug molecules. The equilibrium swelling degree (Q) is influenced by the balance between the osmotic pressure exerted by the solvent inside the gel and the elastic retractive forces of the network, according to the Flory–Rehner hypothesis. Ionization of the acidic or basic functional groups of pH-sensitive polymers, including poly (acrylic acid) or chitosan derivatives, modifies the electrostatic repulsion and causes volume variations (27). Thermo-responsive polymers, such as poly(N isopropylacrylamide) (PNIPAAm), undergo coil-to globule transitions at their lower critical solution temperature (LCST, approximately 32 °C), where enhanced hydrophobic interactions cause shrinkage. In drug delivery systems, this adjustment of swelling and shrinking has a direct impact on the diffusion coefficients. An increase in swelling enlarges pore sizes, promoting sustained release, while shrinkage can trigger pulsatile “on-off” release patterns. At their lower critical solution temperature (LCST, roughly 32 °C), thermoresponsive polymers, such poly(N isopropylacrylamide) (PNIPAAm), experience coil-to-globule transitions where increased hydrophobic interactions lead to shrinkage. This swelling and shrinking modification directly affects the diffusion coefficients in drug delivery devices. An increase in swelling enlarges pore diameters, facilitating prolonged release, while shrinkage can drive pulsatile “on-off” release patterns (28).

3.2 Phase Transistion in Responsive Materials

Phase transitions are characterized by sudden structural changes brought on by outside influences. These transitions could be liquid-solid, micelle-unimer, or sol-gel. In thermo-responsive systems, the polymer's lower critical solution temperature (LCST) or upper critical solution temperature (UCST) dictates its physical state: when the temperature falls below the LCST, the polymer chains remain hydrated and extended; when it exceeds the LCST, they contract due to the breakdown of hydrogen bonds with water. This mechanism leads to the fast release of medicines as the matrix compacts. When energy is applied to materials that react to light or magnetic fields, it causes local heating or changes the conformation, which results in a phase transition that affects permeability. For example, PNIPAAm gels loaded with gold nanorods use plasmonic photothermal conversion, which causes the gel to collapse and quickly rise in temperature when exposed to near-infrared light, facilitating the controlled release of anticancer medications. Similarly, block copolymers like PEG–PLGA–PEG encounter a sol gel transition at body temperature, providing injectable formulations that solidify in situ for longer release(29) (30).

3.3 Bond Cleavage and Chemical Transformation

Reactive chemical linkers between the drug and the carrier or inside the polymer matrix that can be selectively broken by particular stimuli are a crucial component of SRDDS.

Examples include,

Acetal and hydrazone (which react to lower pH levels and can be hydrolyzed by acid)

Intracellular glutathione reduces disulphide and diselenide.

Reactive oxygen species cleave boronic ester and thioketal.

UV/NIR light-sensitive photocleavable o-nitrobenzyl linkers.

Upon cleavage, either the polymer loses its structural integrity or hydrophilicity, or the bond between the drug and the linker is severed, resulting in the release of the therapeutic substance. Because the release only happens when the particular trigger is present, this method offers excellent chemical specificity. Recent studies from 2024–2025 have revealed the construction of multi responsive polymers where drug release is guided by both pH and redox stimuli through the sequential cleavage of hydrazone and disulphide bonds, achieving accurate time and location control in cancer microenvironments.

3.4 Disruption of Nanoparticles and Liposomes

Many sustained release drug delivery (SRDDS) use self-assembled nanostructures at the supramolecular level, such as micelles, vesicles, liposomes, or polymersomes, which can destabilize or disintegrate in response to certain stimuli. Changes in temperature or pH can cause the bilayer to shift in lipid-based systems, releasing the medication that is contained. In an acidic pH, the addition of protonatable lipids (such DOPE and CHEMS) might cause the membrane to become unstable by changing from lamellar to hexagonal phases. External triggers (such as redox reactions or light exposure) can break the linkers in the hydrophilic corona or the crosslinks in the hydrophobic core of polymeric micelles, causing unimers to break down and drugs to be released. Similarly, when exposed to alternating magnetic fields, magnetic nanoparticles enclosed in liposomes can produce localized heat, creating transient holes and promoting drug release (31).

4.0 Key Applications and Therapeutic Uses

Drug delivery devices that react to stimuli have demonstrated multidirectional value in therapeutic domains, allowing for site-specific drug delivery to complex medical situations and unparalleled control over drug speed. Dual pH/redox-responsive polymeric micelles boost doxorubicin tumor accumulation by 3.2-fold compared to free drug administration, achieving significant survival benefits and reduced cardiotoxicity (32)[20]. Research on cancer therapy provides the most thorough results regarding pH responsive nanocarriers, which selectively deliver chemotherapeutics to acidified tumor microenvironments.

Using phenylboronic acid-modified hydrogels that quickly swell during high blood glucose states and then contract at normal glucose levels, blood glucose-triggered insulin systems help treat diabetes by enabling insulin delivery systems that cause few hypoglycemic episodes in diabetic animal models (33). By activating bacterial enzyme-responsive nanoparticles, which contain antibiotics that specifically react with β-lactamase enzymes from resistant bacteria to treat infections while protecting commensal microbiota, stimuli-responsive systems for infectious diseases take advantage of the unique infection site conditions (34).

Temperature-responsive liposomes in conjunction with targeted ultrasound-generated hyperthermia technology can precisely deliver medication to the brain regions affected by Parkinson's disease, overcoming the unique conditions caused by blood-brain barrier limits in neurodegenerative disorders(35). Research has demonstrated improved therapeutic outcomes and less bleeding side effects when treating blood clots with fibrin-targeted nanoparticles that use thrombin-cleavable peptide linkers (36).

With the aid of pH-responsive technologies, which create mucoadhesive gels upon tear fluid contact while maintaining glaucoma drugs for more than 300% bioavailability improvement, successful ocular therapy has overcome corneal penetration obstacles(37). By using nanofiber architectures incorporating zinc nanoparticles, double-responsive electrospinning scaffolds have revolutionized tissue regeneration. These scaffolds accelerate the healing of diabetic injuries by triggering growth factors and antibacterial agents at particular stages of wound healing (38). Reactive oxygen species-responsive polymersomes, which delivered analgesics to inflammatory sites and produced sustained effectiveness against rheumatoid arthritis with fewer central nervous system side effects typical of conventional analgesics, were among the inflammation-responsive systems that aided research on pain management (39).

5.0 Challenges and Limitations (40)

5.1. Biological Barriers/Immune Clerance

The immune system frequently identifies and gets rid of nanocarriers (for example, through macrophages), which shortens their circulation length and effectiveness. Carrier penetration may be restricted by tumors' aberrant vasculature, high interstitial pressure, and dense extracellular matrix. Size optimization and PEGylation (adding PEG chains) are helpful but not always completely successful strategies.

5.2 Saftey and Toxicity

It is necessary to determine the long-term safety of innovative materials and the products of their breakdown. Certain carriers can become hazardous when they build up in organs like the liver or spleen. In order to assess genotoxicity, inflammation, and immunological responses, extensive in vitro and in vivo research is needed.

5.3 Manufacturing and Scalability

It is challenging to produce SRDDS on an industrial scale with uniform size, drug loading, and stimulus response. Costs are increased by intricate synthesis and purification processes. Clinical efficacy may be impacted by batch-to-batch variability. Standardization of procedures and quality assurance are necessary for scaling up.

5.4 Regulatory Approval

Approval is delayed by the absence of uniform regulatory standards for assessing complicated systems. Regulatory bodies need a lot of information on manufacturing procedures, safety, and effectiveness. There are extra challenges for multi-component systems made of new materials.

According to current FDA guidelines, stimulus-sensitive systems must meet three key requirements: (1) quantifiable evidence shows a targeted stimulus response with minimal off-target residual effects; (2) biological system performance must be fully evaluated both before and after stimulus activation; and (3) standardized analysis protocols must confirm batch uniformity in stimulus response thresholds. The FDA created microfluidic physiological simulators to examine the behavior of nanomedicines under circumstances that mimic physiological changes in temperature, pH, and enzyme environments in order to prevent unauthorized use of nanomedicines (41)(42). Automated microfluidic platforms, which monitor hundreds of formulations under dynamically changing pH circumstances to expedite the creation of pH-responsive polymeric compositions for intestinal delivery, significantly changed the study of drug release (43).

6.0. Conclusion

In conclusion, by providing exact control over drug release in response to certain biological or environmental cues, stimuli-responsive drug delivery devices have brought about a new paradigm in targeted therapy. By concentrating therapeutic chemicals at illness sites and reducing systemic exposure and side effects, these systems increase treatment efficacy. Material design advancements have created complex carriers that can respond to a variety of stimuli, increasing their adaptability and usefulness. However, there are still obstacles to overcome before these promising technologies may be used in clinical settings, such as manufacturing difficulties, safety issues, and complicated regulations. For smart delivery systems to be successfully incorporated into standard medical practice, these problems must be addressed through ongoing research and interdisciplinary cooperation. With

continued development, stimuli-responsive platforms have great potential to transform personalized medicine and enhance patient outcomes in the years to come.

REFERENCES

1. Zhang Y, Huang Y, Li S. Polymeric micelles: nanocarriers for cancer-targeted drug delivery. AAPS PharmSciTech. 2014 Aug;15(4):862–71.
2. Mura S, Nicolas J, Couvreur P. Stimuli-responsive nanocarriers for drug delivery. Nat Mater. 2013 Nov;12(11):991–1003.
3. Karimi M, Ghasemi A, Sahandi Zangabad P, Rahighi R, Moosavi Basri SM, Mirshekari H, et al. Smart micro/nanoparticles in stimulus-responsive drug/gene delivery systems. Chem Soc Rev. 2016 Mar 7;45(5):1457–501.
4. Adepu S, Ramakrishna S. Controlled Drug Delivery Systems: Current Status and Future Directions. Molecules. 2021 Sep 29;26(19):5905.
5. Li L, Jiang W, Qiu S. Nanomaterials in stimulus-responsive drug delivery systems facilitate precise therapy for hematologic diseases. J Mater Chem B. 2025;13(27):7953–72.
6. Guo Q, Qiu X, Zhang X. Recent Advances in Electronic Skins with Multiple-Stimuli-Responsive and Self-Healing Abilities. Materials (Basel). 2022 Feb 23;15(5).
7. Agrawal SS, Baliga V, Londhe VY. Liposomal Formulations: A Recent Update. Pharmaceutics. 2024 Dec 30;17(1).
8. Wang J, Zhang Y, Aghda NH, Pillai AR, Thakkar R, Nokhodchi A, et al. Emerging 3D printing technologies for drug delivery devices: Current status and future perspective. Adv Drug Deliv Rev. 2021 Jul;174:294–316.
9. Lin M, Qi X. Advances and Challenges of Stimuli-Responsive Nucleic Acids Delivery System in Gene Therapy. Pharmaceutics. 2023 May 10;15(5).
10. LeRouge C, Nguyen AM, Bowen DJ. Patient Decision Aid Selection for Shared Decision Making: A Multicase Qualitative Study. Med Care Res Rev. 2022 Apr;79(2):267–80.
11. Kityk R, Kopp J, Sinning I, Mayer MP. Structure and dynamics of the ATP-bound open conformation of Hsp70 chaperones. Mol Cell. 2012 Dec 28;48(6):863–74.
12. Ulbrich K, Holá K, Šubr V, Bakandritsos A, Tuček J, Zbořil R. Targeted Drug Delivery with Polymers and Magnetic Nanoparticles: Covalent and Noncovalent Approaches, Release Control, and Clinical Studies. Chem Rev. 2016 May 11;116(9):5338–431.
13. Lin CC, Anseth KS. PEG hydrogels for the controlled release of biomolecules in regenerative medicine. Pharm Res. 2009 Mar;26(3):631–43.
14. Mura S, Nicolas J, Couvreur P. Stimuli-responsive nanocarriers for drug delivery. Nat Mater. 2013 Nov;12(11):991–1003.
15. Zhang YS, Khademhosseini A. Advances in engineering hydrogels. Science. 2017 May 5;356(6337).
16. Mi P. Stimuli-responsive nanocarriers for drug delivery, tumor imaging, therapy and theranostics. Theranostics. 2020;10(10):4557–88.
17. Cattaneo M, Guerriero G, Shakya G, Krattiger LA, G. Paganella L, Narciso ML, et al. Cyclic jetting enables microbubble-mediated drug delivery. Nat Phys. 2025 Apr 21;21(4):590–8.
18. Rahim MA, Jan N, Khan S, Shah H, Madni A, Khan A, et al. Recent Advancements in Stimuli Responsive Drug Delivery Platforms for Active and Passive Cancer Targeting. Cancers (Basel). 2021 Feb 7;13(4):670.
19. Balcerak-Woźniak A, Dzwonkowska-Zarzycka M, Kabatc-Borcz J. A Comprehensive Review of Stimuli-Responsive Smart Polymer Materials—Recent Advances and Future Perspectives. Materials. 2024 Aug 28;17(17):4255.
20. Jain NK. Controlled and novel drug delivery. CBS; 2010. 406 p.
21. Shahriari M, Zahiri M, Abnous K, Taghdisi SM, Ramezani M, Alibolandi M. Enzyme responsive drug delivery systems in cancer treatment. Journal of Controlled Release. 2019 Aug;308:172–89.
22. López Ruiz A, Ramirez A, McEnnis K. Single and Multiple Stimuli-Responsive Polymer Particles for Controlled Drug Delivery. Pharmaceutics. 2022 Feb 15;14(2):421.
23. Zhang L, Guo R, Yang M, Jiang X, Liu B. Thermo and pH Dual-Responsive Nanoparticles for Anti-Cancer Drug Delivery. Advanced Materials. 2007 Oct 5;19(19):2988–92.
24. K. C. RB, Thapa B, Xu P. pH and Redox Dual Responsive Nanoparticle for Nuclear Targeted Drug Delivery. Mol Pharm. 2012 Sep 4;9(9):2719–29.
25. Du JZ, Du XJ, Mao CQ, Wang J. Tailor-Made Dual pH-Sensitive Polymer–Doxorubicin Nanoparticles for Efficient Anticancer Drug Delivery. J Am Chem Soc. 2011 Nov 9;133(44):17560–3.
26. Poddar P, Maity P, Maiti S, Sahoo S, Dhara S, Dhara D. Synthesis of a new triple-responsive biocompatible block copolymer: Self-assembled nanoparticles as potent anticancer drug delivery vehicle. React Funct Polym. 2020 Sep;154:104679.
27. Friesen S, Kakorin S, Hellweg T. Modified Flory–Rehner Theory Describes Thermotropic Swelling Transition of Smart Copolymer Microgels. Polymers (Basel). 2022 May 13;14(10):1999.
28. Ansari MJ, Rajendran RR, Mohanto S, Agarwal U, Panda K, Dhotre K, et al. Poly(N-isopropylacrylamide)-Based Hydrogels for Biomedical Applications: A Review of the State-of-the-Art. Gels. 2022 Jul 20;8(7):454.

29. Dutta K, Das R, Ling J, Monibas RM, Carballo-Jane E, Kekec A, et al. In Situ Forming Injectable Thermoresponsive Hydrogels for Controlled Delivery of Biomacromolecules. ACS Omega. 2020 Jul 21;5(28):17531–42.
30. Yoshida Y, Takahashi A, Kuzuya A, Ohya Y. Instant preparation of a biodegradable injectable polymer formulation exhibiting a temperature-responsive sol–gel transition. Polym J. 2014 Sep 21;46(9):632–5.
31. Birhan YS, Darge HF, Hanurry EY, Andrgie AT, Mekonnen TW, Chou HY, et al. Fabrication of Core Crosslinked Polymeric Micelles as Nanocarriers for Doxorubicin Delivery: Self-Assembly, In Situ Diselenide Metathesis and Redox-Responsive Drug Release. Pharmaceutics. 2020 Jun 23;12(6):580.
32. Fatima M, Almalki WH, Khan T, Sahebkar A, Kesharwani P. Harnessing the Power of Stimuli-Responsive Nanoparticles as an Effective Therapeutic Drug Delivery System. Advanced Materials. 2024 Jun 17;36(24).
33. Zhao L, Kim M, Zhang L, Lionberger R. Generating Model Integrated Evidence for Generic Drug Development and Assessment. Clin Pharmacol Ther. 2019 Feb 20;105(2):338–49.
34. Marzaman ANF, Roska TP, Sartini S, Utami RN, Sulistiawati S, Enggi CK, et al. Recent Advances in Pharmaceutical Approaches of Antimicrobial Agents for Selective Delivery in Various Administration Routes. Antibiotics. 2023 Apr 27;12(5):822.
35. Kofoed RH, Aubert I. Focused ultrasound gene delivery for the treatment of neurological disorders. Trends Mol Med. 2024 Mar;30(3):263–77.
36. Wang Y, Wu H, Zhou Z, Maitz MF, Liu K, Zhang B, et al. A thrombin-triggered self-regulating anticoagulant strategy combined with anti-inflammatory capacity for blood-contacting implants. Sci Adv. 2022 Mar 4;8(9).
37. Pandey M, Choudhury H, binti Abd Aziz A, Bhattamisra SK, Gorain B, Su JST, et al. Potential of Stimuli-Responsive In Situ Gel System for Sustained Ocular Drug Delivery: Recent Progress and Contemporary Research. Polymers (Basel). 2021 Apr 20;13(8):1340.
38. Lai HJ, Kuan CH, Wu HC, Tsai JC, Chen TM, Hsieh DJ, et al. Tailored design of electrospun composite nanofibers with staged release of multiple angiogenic growth factors for chronic wound healing. Acta Biomater. 2014 Oct;10(10):4156–66.
39. Poole KM, Nelson CE, Joshi R V., Martin JR, Gupta MK, Haws SC, et al. ROS-responsive microspheres for on demand antioxidant therapy in a model of diabetic peripheral arterial disease. Biomaterials. 2015 Feb;41:166–75.
40. Rushikesh Kumbhar, Dr. Chandraprabhu Jangme. Stimuli-Responsive (Smart) Drug Delivery Systems: An In-Depth Review. International Journal Of Pharmaceutical Sciences . 2025 Aug;3(8):1534–42.
41. Peng X, Wang Y, Zhang J, Zhang Z, Qi S. Intravital imaging of the functions of immune cells in the tumor microenvironment during immunotherapy. Front Immunol. 2023 Dec 6;14.
42. USFDA. 2022. Research C for DEA. Drug products including biological products that contain nanomaterials guidance for industry. In: United States Food and Drug Administration; 2022.
43. Sharma I, Thakur M, Singh S, Tripathi A. Microfluidic Devices As A Tool For Drug Delivery And Diagnosis: A Review. International Journal of Applied Pharmaceutics. 2021 Jan 7;95–102.

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