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Advances in Stimuli-Responsive Smart Drug Delivery Systems: A Systematic Review

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Abstract

Imagine a world where medicines work smarter, not harder. Stimuli-responsive drug delivery systems (SRDDS) are transforming healthcare by releasing therapeutic agents in response to specific triggers. These triggers can be internal, like changes in pH or temperature, or external, like light or magnetic fields. By leveraging these triggers, SRDDS can optimize treatment and minimize side effects. The potential applications of SRDDS are vast, from cancer treatment to gene delivery and tissue engineering. Researchers are exploring ways to develop advanced materials and technologies to improve these systems. By integrating SRDDS with cutting-edge technologies, like artificial intelligence and machine learning, we can enhance their precision and effectiveness. Personalized SRDDS could revolutionize patient care by enabling tailored treatment strategies that cater to individual needs. As research advances, SRDDS will likely play a crucial role in shaping the future of medicine. These systems have the potential to improve treatment outcomes, reduce healthcare costs, and enhance quality of life. By harnessing the power of SRDDS, we can unlock new opportunities for improving human health and transforming the pharmaceutical landscape. With ongoing research, SRDDS will continue to evolve and become a vital component of modern medicine, enabling precise and efficient treatment of various diseases. The future of SRDDS is promising, and its impact on patient care will be significant, very soon now too.

Keywords: Stimuli-responsive drug delivery, targeted therapy, personalized medicine, advanced drug delivery systems, smart medicine, precision medicine, controlled release technology

INTRODUCTION

Stimuli-responsive drug delivery systems have emerged as a promising approach to overcome the limitations of traditional drug delivery methods. These innovative systems are designed to release therapeutic agents in response to specific physiological or external stimuli such as changes in pH, temperature, or light. By harnessing the power of stimuli-responsive materials, researchers can create targeted delivery platforms that enhance treatment efficacy while minimizing adverse reactions.

The development of stimuli-responsive drug delivery systems requires a deep understanding of the underlying biology and physiology of the disease being targeted. For instance, pH-sensitive nanoparticles can be designed to release anticancer drugs in the acidic microenvironment of tumors, thereby reducing systemic toxicity and enhancing therapeutic efficacy. Similarly, temperature-responsive hydrogels can be used to deliver insulin in response to changes in glucose levels, providing a more precise and efficient approach to diabetes management (Liu Y. &., 2018).

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Stimuli-responsive drug delivery systems are revolutionizing the way we approach disease treatment. By leveraging specific physiological or external cues, these systems can target specific cells or tissues, releasing therapeutic agents in a controlled and precise manner (Gao, 2020). This approach not only enhances treatment efficacy but also minimizes adverse reactions, leading to improved patient outcomes and reduced healthcare costs (Zhang Y. &., 2019).

The adaptability of stimuli-responsive systems is a significant advantage, enabling their application in various medical fields, including oncology, diabetes management, and cardiovascular disease therapy (Chen X. &., 2019). For instance, nanoparticles can be engineered to respond to the acidic environment of tumors, delivering cancer-fighting medicine directly to the site of the disease (Wang Y. &., 2020). Similarly, hydrogels can be designed to release insulin in response to changes in blood sugar levels, providing a more accurate and efficient way to manage diabetes (Chen X. &., 2019).

One of the most significant benefits of stimuli-responsive systems is their ability to target specific areas of the body, reducing off-target effects and improving treatment outcomes. These systems can also be designed to respond to multiple stimuli, allowing for a more nuanced and adaptive approach to medicine delivery (Zhang Y. &., 2020). The development of stimuli-responsive drug delivery systems requires a deep understanding of the underlying biology and physiology of the disease being targeted (Wang Y. &., 2018). By combining advances in materials science, nanotechnology, and biomedical engineering, researchers can create complex and sophisticated delivery platforms that provide precise and efficient medicine delivery (lie, 2020). As research in this field continues to advance, we can expect to see innovative systems that will transform the way we treat diseases (Zhang Y. &., 2020). With their potential to improve patient care and outcomes, stimuli-responsive drug delivery systems hold great promise for the future of pharmacotherapy (Figure 1) (Zhang Y. &., 2020).

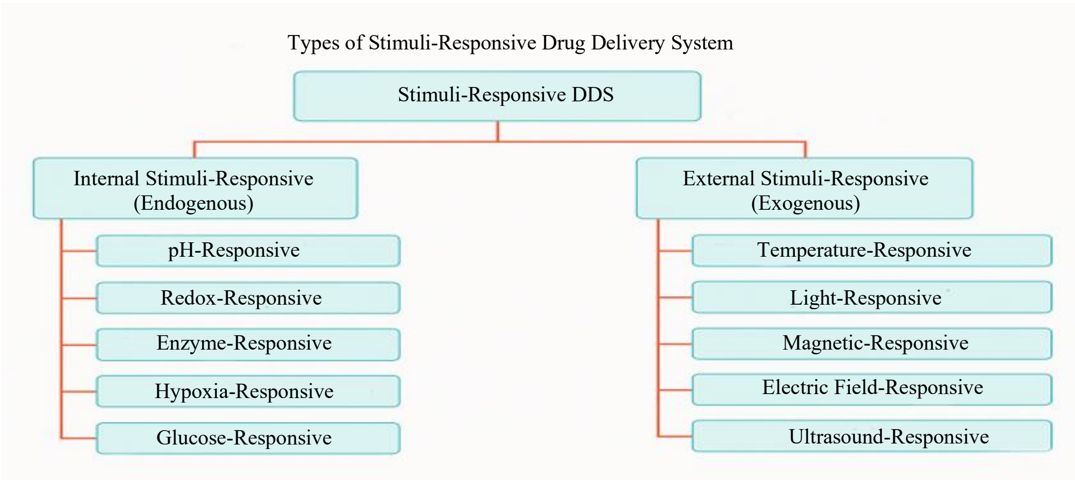

Figure 1. Types of stimuli responsive drug delivery system.

ADVANTAGES OF SRDDS

- *Precise Targeting:* SRDDS can be engineered to target specific sites in the body, thereby enhancing therapeutic efficacy and minimizing adverse effects. For instance, pH-sensitive nanoparticles can be designed to release therapeutic agents in acidic environments such as those found in tumors. This precise targeting capability can lead to improved treatment outcomes and reduced side effects (Wang Y. &., 2018).
- *Controlled Release Profiles:* SRDDS can be tailored to release therapeutic agents in response to specific stimuli, allowing for precise control overdosing and minimizing toxicity. Temperature-sensitive hydrogels, for example, can release drugs in response to changes in body temperature, providing a controlled release profile. This controlled release approach can enhance therapeutic efficacy while reducing adverse effects (Gao, 2020).

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- *Enhanced Bioavailability:* SRDDS can improve the bioavailability of therapeutic agents by releasing them in response to specific stimuli, thereby enhancing their therapeutic efficacy. Redox-sensitive nanoparticles, for instance, can release drugs in response to high levels of glutathione in cancer cells, improving the bioavailability of the therapeutic agent. This enhanced bioavailability can lead to improved treatment outcomes and reduced side effects (Zhang Y. &., 2020).
- *Minimized Adverse Effects:* SRDDS can minimize adverse effects by releasing therapeutic agents only in response to specific stimuli, thereby reducing exposure to healthy tissues. Light-sensitive nanoparticles, for example, can release drugs in response to specific wavelengths of light, allowing for precise control over drug release and minimizing adverse effects. This minimized adverse effect profile can improve patient outcomes and quality of life (Wang Y. &., 2020).
- *Personalized Treatment Strategies:* SRDDS can enable personalized treatment strategies by allowing for tailored approaches that cater to individual needs. Stimuli-sensitive nanoparticles can be designed to respond to specific biomarkers or physiological conditions, enabling personalized treatment approaches. This personalized medicine approach can improve treatment outcomes and patient care (Chen X. &., 2019).

DISADVANTAGES OF SRDDS

- *Complexity in Design and Development:* The design and development of SRDDS can be intricate and demanding, necessitating sophisticated materials and technologies. This complexity arises from the need to integrate multiple components, such as stimuli-responsive materials, drugs, and targeting moieties, into a single system. Furthermore, the development of SRDDS requires a deep understanding of the underlying biology, materials science, and pharmaceutical principles. As a result, the development process can be time-consuming, labor-intensive, and costly (Zhang Y. &., 2020).
- *Limited Scalability:* SRDDS can be challenging to scale up for mass production, which can limit their widespread adoption. The complexity of SRDDS, combined with the need for precise control over material properties and drug loading, can make it difficult to reproduce these systems on a large scale. Additionally, the scalability of SRDDS can be affected by factors such as batch-to-batch variability, material sourcing, and equipment limitations. As a result, the development of scalable manufacturing processes for SRDDS can be a significant challenge (Gao, 2020).
- *Potential Toxicity:* Some stimuli-responsive materials used in SRDDS can be toxic, which can limit their use in certain applications. The toxicity of these materials can arise from various factors, including their chemical composition, degradation products, and interactions with biological systems. Furthermore, the potential toxicity of SRDDS can be influenced by factors such as the dose, duration of exposure, and route of administration. As a result, it is essential to thoroughly evaluate the safety and toxicity of SRDDS before their use in humans (lie, 2020).
- *Limited Stability:* SRDDS can be sensitive to environmental conditions, which can affect their stability and performance. These systems can be influenced by factors, such as temperature, pH, light, and humidity, which can cause degradation or changes in their properties. Furthermore, the stability of SRDDS can be affected by the storage conditions, handling, and transportation of these systems. As a result, it is crucial to develop strategies to enhance the stability of SRDDS and ensure their performance over time (Zhang Y. &., 2019).
- *High Cost:* SRDDS can be expensive to develop and produce, which can limit their accessibility. The high cost of SRDDS can arise from factors, such as the complexity of their design, the use of advanced materials and technologies, and the need for specialized manufacturing processes. Furthermore, the cost of SRDDS can be influenced by factors such as the scale of production, material sourcing, and regulatory compliance. As a result, it is essential to develop cost-effective strategies for the development and production of SRDDS to make them more accessible to patients (Chen X. &., 2019).

Internal Stimuli-Responsive System

- *pH-Responsive Systems:* The development of pH-responsive systems has revolutionized the field of drug delivery and biomedical applications. These innovative materials undergo a change in properties or behavior in response to changes in pH levels, enabling controlled release of therapeutic agents. Notably, the slightly acidic environment of tumor tissues, with a pH of approximately 6.5, and the more acidic environment of intracellular endosomes and lysosomes, with a pH range of 5.0–6.0, provide a unique opportunity for targeted delivery. Recent advancements in polymer science have led to the creation of pH-sensitive polymers and nanogels that exhibit improved pH-sensitivity and biodegradability. For instance, pHsensitive polymers – like poly(β-amino esters) – have been designed to release doxorubicin, a potent chemotherapeutic agent, specifically in the tumor microenvironment, thereby enhancing the efficacy of cancer treatment while minimizing side effects. By harnessing the power of pH-responsive systems, researchers can develop more effective and targeted therapies for various diseases (Tao Wang, 2023).

- *Redox-Responsive Systems:* Redox-responsive systems represent a promising approach in the field of drug delivery and biomedical applications. These systems are designed to undergo a change in properties or behavior in response to changes in redox potential, enabling controlled release of therapeutic agents. Notably, tumor cells exhibit higher levels of glutathione (GSH) compared to extracellular fluids, creating a distinct redox environment that can be leveraged for targeted delivery. Redox-sensitive linkers, such as disulfide bonds, are specifically designed to break in high GSH environments, allowing for the release of therapeutic agents. By incorporating these linkers into drug delivery systems, researchers can achieve precise control over drug release. For instance, disulfide-crosslinked micelles have been developed to degrade into high-GSH environments, releasing paclitaxel and providing a targeted and efficient approach to cancer treatment. This innovative strategy holds great promise for improving the efficacy of various therapies while minimizing side effects (Li Zhou, 2025).
- *Enzyme-Responsive Systems:* Enzyme-responsive systems represent a cutting-edge approach in smart drug delivery, designed to undergo specific chemical or physical changes in response to enzymatic stimuli. This enables precise control over the release of therapeutic agents, ensuring targeted delivery to specific sites within the body. The overexpression of certain enzymes, such as matrix metalloproteinases (MMPs), in tumors or inflamed tissues provides a unique opportunity for enzyme-responsive systems to selectively target these areas. By incorporating enzyme-cleavable peptides or polymers, these systems can degrade in the presence of specific enzymes, releasing therapeutic agents in a controlled and site-specific manner. For example, hyaluronic acid-based carriers have been engineered to degrade in response to hyaluronidase, an enzyme overexpressed in certain cancer cells, allowing for targeted delivery of therapeutic agents and enhancing the efficacy of cancer treatment. This innovative strategy holds great potential for improving the precision and effectiveness of various therapies (Aszad Alam, 2023).
- *Hypoxia Responsive System:* Hypoxia-responsive systems represent a cutting-edge approach in drug delivery, leveraging the distinct characteristics of low-oxygen environments found in various diseases such as solid tumors and ischemic tissues. These innovative platforms are engineered to detect hypoxia and trigger targeted therapeutic responses, including drug release or prodrug activation. By incorporating hypoxia-sensitive components, these systems remain dormant under normal oxygen conditions but become activated in hypoxic environments. This targeted approach enhances treatment efficacy while minimizing side effects. Given that hypoxia is a hallmark of aggressive tumors, exploiting this feature offers a promising strategy for precise and controlled drug delivery (Song, Niu, Lin, Wang, & Gong, 2022).
- *Glucose Responsive System:* Glucose-responsive systems are innovative platforms that detect fluctuations in glucose levels and respond accordingly, typically by releasing insulin or other therapeutic agents. These systems utilize various materials and mechanisms, such as enzyme-based systems, phenylboronic acid-based systems, and glucose-binding protein-based systems, to achieve precise glucose monitoring and controlled insulin release. A notable example is glucose-sensitive insulin delivery systems, which release insulin in response to elevated glucose levels, offering a more precise and automated approach to insulin therapy. By providing a more tailored and responsive treatment strategy, these systems hold great potential for improving glucose management and enhancing the quality of life for individuals with diabetes (Liu, Yu, Wang, Shen, & Teng, 2020).

External Stimuli-Responsive Systems

- *Temperature-Responsive Systems:* Temperature-responsive systems are advanced materials or devices that undergo a phase transition or property change in response to temperature fluctuations. This unique ability enables controlled release of therapeutic agents or alterations in material properties, making them ideal for various biomedical applications. Thermosensitive polymers, such as poly(N-isopropylacrylamide) (PNIPAAm), exhibit a phase transition at body temperature, allowing for precise control over material properties. For instance, injectable gels have been developed to release insulin in response to slight temperature increases, demonstrating the potential of temperature-responsive systems for managing diabetes and other conditions. By harnessing the power of temperature responsiveness, researchers can design innovative solutions for targeted and efficient therapy (Khan, et al., 2023).
- *Light-Responsive Systems:* Light-responsive systems are cutting-edge materials or devices that change their properties or behavior in response to light. This ability enables precise control over various processes, including the release of therapeutic agents, modulation of biological processes, or alterations in material properties. By harnessing the power of light, these systems can undergo changes in solubility, swelling, degradation rates, or optical properties. For instance, photo-sensitive linkers can be cleaved by UV or near-infrared (NIR) light, triggering a response. Additionally, photolabile bonds can cleave or undergo photoisomerization, changing the structure of polymers under light. A notable example is the use of NIR-triggered gold nanorods, which can release anticancer agents on demand, providing a targeted and efficient approach to cancer treatment. By leveraging light responsiveness, researchers can design innovative solutions for precise and controlled therapy (Chen, Wang, & Yang, 2020).
- *Magnetic and Ultrasound-Responsive Systems:* Magnetic nanoparticles can be precisely guided to target sites and triggered by alternating magnetic fields, enabling controlled drug release. Additionally, ultrasound can induce mechanical disruption of vesicles, further enhancing the delivery of therapeutic agents. When exposed to an external magnetic field, these nanoparticles can generate hyperthermia or undergo mechanical disruption, triggering the release of drugs. For instance, magnetic liposomes have been developed to release doxorubicin in response to ultrasound stimulation, showing promise for the treatment of glioblastoma. By combining magnetic guidance and external stimulation, researchers can design targeted and efficient drug delivery systems for various diseases (Liu, Jang, Issadore, & Tsourkas, 2019), (Cai, et al., 2020).
- *Electric Field Responsive System:* Electric field-responsive systems are innovative materials or devices that alter their properties or behavior in response to electric fields. This responsiveness enables precise control over various processes, including the release of therapeutic agents, modulation of biological processes, or changes in material properties. By leveraging electric fields, these systems can undergo changes in solubility, swelling, degradation rates, or electrical conductivity. A notable example is electroresponsive hydrogels, which swell or shrink in response to electric fields, allowing for controlled release of therapeutic agents. This property makes them ideal for applications, such as drug delivery, tissue engineering, and biosensors, where precise control over material properties is crucial. By harnessing the power of electric field responsiveness, researchers can design advanced systems for various biomedical application (Gao, 2020).

Comparative Overview

Stimuli-responsive drug delivery systems can be categorized into internal and external systems, each with its own advantages. Internal systems utilize the body's natural conditions to trigger drug release, allowing for autonomous targeting, which is particularly useful for treating diseases in deep tissue or hard-to-reach areas. External systems, on the other hand, provide spatial and temporal control over drug release, offering precise dosing, although they often require complex devices. Hybrid systems that respond to both internal and external stimuli are a promising area of research, offering greater flexibility and control, potentially leading to improved therapeutic outcomes. Recent advances in these systems have shown significant promise, and further research is needed to address key challenges, such as biocompatibility, safety, and scalability, to facilitate clinical translation.

STIMULI RESPONSIVE HYDROGELS

PH Responsive Hydrogels

The pH of biological fluids plays a significant role in drug delivery, enabling the development of innovative therapeutic strategies. Advanced drug delivery systems, such as hydrogels and nanogels, have been designed to adapt to pH fluctuations, allowing for precise control over drug release. These systems can be engineered to respond to specific pH environments, such as those found in diseased tissues, enabling targeted delivery (Kanamala, Wilson, Yang, Palmer, & Wu, 2016).

There are two primary strategies employed in pH-responsive drug delivery systems. The first involves utilizing polymers with ionizable groups that undergo protonation or deprotonation in response to pH changes. This property enables the polymers to swell or shrink, controlling drug release. The second strategy involves designing polymers with acid-sensitive bonds that degrade in acidic environments, triggering drug release. Researchers have explored various chemical groups to create acid-sensitive bonds, allowing for customized polymer design (Kocak, Tuncer, & Bütün, 2017).

A study by Zou et al. (2014) demonstrated the potential of pH-responsive drug delivery systems. The researchers developed a drug conjugate, poly(ethylene oxide)-block-polyphosphoester-graft-PTX (PEO-b-PPE-g-PTX G2), that showed controlled release patterns in response to pH changes. The conjugate released 20% of PTX over 8 days under neutral conditions and approximately 50% under acidic conditions (Zou, et al., 2014). This study highlights the promise of pH-responsive systems for targeted drug delivery.

Redox Responsive Hydrogels

Redox-responsive hydrogels are a type of stimuli-responsive polymer network that can change structure or function in response to redox conditions. These hydrogels have potential applications in biomedicine, particularly in targeted drug delivery and tissue engineering, due to the distinct redox gradients between healthy and diseased tissues. Intracellular compartments, especially in cancer cells, have high concentrations of glutathione (GSH), while extracellular fluids have much lower levels, enabling selective responsiveness (Song, Niu, Lin, Wang, & Gong, 2022).

Disulfide bonds are a common example of reversible chemical linkages used in redox-responsive hydrogels. These bonds are stable under oxidative conditions but cleaved in reducing environments, allowing for targeted drug release. For instance, disulfide-crosslinked hydrogels have been used to deliver doxorubicin, releasing the drug selectively in the high-GSH tumor microenvironment. Other moieties, such as selenide groups, can also respond to reactive oxygen species (ROS), enabling targeted reactions (Duan, et al., 2013).

Redox-responsive hydrogels have been explored for various applications, including targeted chemotherapy delivery and gene delivery. For example, gelatin/silica-aptamer nanogels have been designed to release siRNA in response to GSH, selectively targeting nucleolin-positive cells (Zhao, et al., 2019). These advanced drug delivery systems can release drugs quickly at targeted sites in response to specific biological stimuli, offering promising opportunities for biomedical applications.

Photo Responsive Hydrogels

Photo-responsive hydrogels are smart materials that change their physical or chemical properties when exposed to light. Due to their ability to respond to external light stimuli, they are widely explored in biomedical applications such as drug delivery, tissue engineering, and biosensing. One of their key advantages is the precise control they offer over time and location, making them highly useful for targeted therapies. These hydrogels work by incorporating light-sensitive components – like photochromic molecules or functional groups – into their structure. When exposed to specific wavelengths, these components undergo reversible structural changes, leading to variations in properties like swelling, degradation, or mechanical strength. For example, molecules – like spiropyran and azobenzene – can alter hydrophobicity, while groups – such as nitrobenzyl and coumarin – enable light-triggered cleavage or crosslinking. By adjusting the type of light-sensitive material and light conditions, their behavior can be finely tuned. Recent developments also include near-infrared (NIR) light-controlled systems, which allow targeted drug release and show promising results in cancer treatment (Chen X. &., 2019).

Glucose Responsive Hydrogels

Glucose-responsive hydrogels (GRHs) are smart biomaterials that can control drug release in response to changes in glucose levels. These systems are especially useful for diabetes management, where maintaining proper blood glucose levels is important to avoid complications. GRHs are designed in such a way that they can swell, shrink, or undergo sol–gel transitions when exposed to glucose, which helps in the controlled release of drugs like insulin.

The glucose sensitivity in these hydrogels is achieved by incorporating glucose-responsive components – such as glucose oxidase (GOx), phenylboronic acid (PBA), or concanavalin A (Con A) – into the polymer network. For example, GOx converts glucose into gluconic acid, which lowers the pH and causes changes in pH-sensitive hydrogels, leading to swelling or degradation. In another system, PBA-based hydrogels form reversible bonds with glucose through diol interactions, which helps in regulating the structure of the hydrogel and controlling drug release.

Due to their ability to respond to natural glucose variations in the body, these hydrogels are widely studied for improving diabetes treatment. They offer benefits – such as better patient compliance, reduced dosing frequency, and more stable blood glucose control – compared to traditional insulin delivery methods. Some advanced systems also combine multiple components – like enzymes and insulin – within a single hydrogel matrix for self-regulated insulin release. In such systems, insulin is released more when glucose levels are high and less when glucose levels are low, allowing for smart and controlled therapy.

CONCLUSION

Stimuli-responsive drug delivery systems (SRDDS) have emerged as a promising approach for improving the efficacy and safety of therapeutic interventions. By harnessing the power of specific stimuli, such as pH, temperature, or light, SRDDS can target specific sites in the body, control the release of therapeutic agents, and enhance treatment outcomes. The development of SRDDS has the potential to revolutionize the field of medicine by enabling precise, efficient, and effective treatment of various diseases.

The advantages of SRDDS, including improved targeting, controlled release, and enhanced bioavailability, make them an attractive option for treating a wide range of diseases. However, SRDDS also present several challenges, including complexity in design and development, limited scalability, potential toxicity, limited stability, and high cost. Addressing these challenges will be crucial to fully realizing the potential of SRDDS.

Further research is needed to overcome the challenges associated with SRDDS and to explore their full potential. This research should focus on developing new materials and technologies, improving the scalability and stability of SRDDS, and reducing their cost. Additionally, more studies are needed to evaluate the safety and efficacy of SRDDS in humans and to explore their potential applications in various diseases.

In conclusion, SRDDS represents a promising approach for improving the treatment of various diseases. While challenges remain, the potential benefits of SRDDS make them an exciting area of research and development. With continued innovation and investment, SRDDS have the potential to transform the field of medicine and improve human health.

This detailed conclusion summarizes the key points of SRDDS, highlights their potential benefits and challenges, and emphasizes the need for further research to fully realize their potential.

Competing interests

The authors have no competing interests to declare.

Declarations of interest

None.

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