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Smart Responsive Surfactants in Drug Delivery: Advances and Perspectives

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Abstract. Drug delivery systems grapple with challenges such as surmounting biological barriers, controlling drug release, and minimizing systemic side effects. Conventional surfactants have drawbacks like non - targeted organ accumulation, premature drug leakage, and dose - dependent inefficacy, so smart responsive surfactants, which are amphiphiles that adjust properties through specific stimuli, offer a promising alternative. This review aims to classify major types of smart responsive surfactants, analyze their molecular design and stimulus - response mechanisms, summarize them in vitro and in vivo performance, and identify future research directions. It focuses on four core systems: light - responsive, temperature - responsive, pH - responsive, and enzyme - triggered. These surfactants exhibit notable clinical potential, such as light - responsive nanoliposomes enabling tumor - specific doxorubicin (DOX) release. Future research should prioritize optimizing multi - stimulus synergy and adapting systems to disease microenvironments, which will further enhance drug bioavailability and therapeutic efficacy, laying a foundation for the application of precision medicine in tumor and colon - related disease therapy.

Keywords: Smart responsive surfactants, Drug delivery systems, Stimulus-response mechanisms, Targeted drug delivery

1. Introduction

Drug delivery refers to the process of transporting therapeutic agents from the administration site to targeted pathological tissues or cells, with core challenges including overcoming biological barriers, regulating drug release kinetics, optimizing therapeutic efficacy, and minimizing systemic side effects. Surfactants, because of their dual hydrophilic and hydrophobic nature, play a central role in many strategies aimed at overcoming these challenges. Conventional surfactants are widely used in drug delivery. They assist in releasing drugs from amorphous solid dispersions by altering how the drug, polymer, and water interact in their respective phases, and by breaking down barriers that prevent drug release [1]. In pulmonary drug delivery, some surfactants serve as adjuvants or carriers. They help distribute drugs more evenly throughout the lungs and improve the solubility of hydrophobic drugs. Furthermore, these surfactants help stabilize nanocarriers by lowering interfacial tension, preventing nanocarrier aggregation, and preserving the structural integrity of the carriers [2–4]. However, traditional surfactants still face several limitations, such as causing drug

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crystallization, exhibiting effectiveness that depends on dosage, and leading to non-specific accumulation in organs [1,2,5,6].

Smart responsive surfactants provide a promising approach to address these limitations. These amphiphilic molecules can dynamically change their physicochemical properties when exposed to specific stimuli like pH, temperature, light, or enzymes [3,7,8]. Unlike conventional surfactants with fixed properties, they adapt in response to stimuli, allowing precise control over drug release and targeting. For example, 11-(N, N-dimethylamino) sodium undecanoate can reversibly switch among anionic, zwitterionic, and cationic forms as pH changes [7]. Similarly, azobenzene-modified surfactants undergo structural changes when irradiated with UV or visible light [9,10]. These systems function selectively at disease sites. For instance, they operate in tumor microenvironments with acidic pH [7] or in areas of local hyperthermia [11], and in some cases, enable controlled, graded drug release [8]. By ensuring that drug release happens exactly at the target site, smart responsive surfactants minimize harm to healthy tissues and meet different therapeutic needs more effectively than conventional systems.

This review has four key goals. The first is to classify the main types of smart responsive surfactants, with a focus on those that react to stimuli already widely studied in the field. The second focuses on analyzing their molecular design traits, along with the specific response mechanisms that go with them. The third is to pull together data on their performance: in vitro, that means things like how well they control drug release; in vivo, we're looking at targeting effectiveness and safety profiles. The fourth involves identifying current limitations, like issues tied to drug stability, and suggesting directions for future research, with a particular focus on tweaking these systems to fit specific delivery scenarios. This work holds both theoretical and practical significance. On the theoretical front, this review constructs a systematic framework. It links molecular design, response mechanisms, and delivery performance, thus filling the voids in previous literature [3]. Practically, it demonstrates how smart responsive surfactants can address the long - existing problems of traditional surfactants. By doing so, it enhances the safety and efficacy of drug delivery systems, and paves the way for their potential transition into clinical applications. This translational significance is especially prominent in tumor therapy and colon - targeted disease treatment [6,9,11].

2. Methodology

2.1. Research design – literature retrieval strategy

A systematic literature search was conducted in Web of Science and PubMed to collect studies on smart responsive surfactants applied in drug delivery. The search focused primarily on publications from 2019 to 2025 to capture recent advances while also including representative earlier studies to ensure coverage of foundational work. Keywords were organized into three themes: smart responsive surfactants, drug delivery, and mechanisms/applications. These terms were combined with Boolean operators (AND/OR) to balance precision and scope, using search strings such as "smart responsive surfactant," "drug delivery," and "response mechanism." Retrieved results were processed with Zotero to remove duplicates and organize references. Eligibility screening was then performed: irrelevant studies (e.g., non-pharmaceutical surfactant applications or non-English articles) were excluded through title and abstract review, and the remaining full texts were assessed. Only original research papers and review articles focusing on surfactant classification, response mechanisms, or delivery performance were retained, while non-research content and studies lacking sufficient data were excluded. The quality of selected publications was further evaluated to ensure reliability and validity of conclusions.

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2.2. Data collection and analysis

Data collection focused on extracting key information from post-screening eligible literature, including smart responsive surfactants' stimuli triggers, molecular design features, delivery performance indicators (e.g., in vitro release efficiency, in vivo targeting accuracy, safety profiles) and research limitations (e.g., poor stability in complex biological environments, high production costs), with all extracted data recorded in a standardized spreadsheet and cross-verified against original literature for accuracy; data analysis adopted qualitative synthesis, categorizing extracted data into thematic groups (e.g., "surfactant type vs. response mechanism," "performance in diverse delivery scenarios," "current research gaps") to identify consistent trends and discrepancies, prioritizing studies with robust methodologies and detailed data while excluding those with vague data or insufficient reasoning, and ultimately clarifying the connections between surfactant design, response behavior and delivery efficacy as well as highlighting unresolved issues to guide future research.

3. Result

3.1. External stimuli-responsive mechanisms

3.1.1. Light-responsive systems

Light-responsive drug delivery systems achieve spatiotemporal control over drug release via photochromic molecules (e.g., azobenzene, spiropyran) that undergo reversible structural changes (e.g., trans-to-cis isomerization) upon exposure to light. This isomerization disrupts surfactant/nanocarrier self-assembly—by altering hydrophobicity, breaking supramolecular interactions, or increasing membrane permeability—thus triggering encapsulated drug release. Such systems are well-suited for superficial tumors, light-accessible tissues, or localized therapy, enabling non-invasive, site-specific release with minimal off-target effects [10,11].

Representative studies include Wang et al. (2021), who designed a supramolecular system using azobenzene (Azo) and β-cyclodextrin (β-CD) to regulate surfactant vesicle stability: trans-Azo formed stable complexes with β-CD under visible light, preserving vesicles, while UV-induced isomerization dissociated this interaction, disrupting vesicles and enabling controlled drug release [9]. Wu et al. (2024) developed azobenzene-modified nanoliposomes, where light-triggered isomerization adjusted lipid bilayer permeability, reducing premature drug leakage in normal tissues and promoting rapid release at tumor sites via the EPR effect [10]. Zhang et al. (2023) synthesized spiropyran-containing copolymers that self-assembled into micelles under visible light, with UV-induced isomerization increasing permeability for controlled drug release [8].

These examples show the versatility of light-responsive systems, which use reversible photochemical changes to achieve precise, non-invasive drug delivery, especially in applications that require controlled release kinetics.

3.1.2. Temperature-responsive systems

Temperature - responsive systems depend on materials that show phase transitions based on temperature. These materials are defined by a lower critical solution temperature (LCST) or a lipid phase transition temperature (Tm). When the temperature goes above these set points, there is a change from hydrophilic to hydrophobic. This change makes the carrier unstable and causes structural alterations, which then lead to drug release. This method is really helpful in the clinic,

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especially for treating tumors with mild hyperthermia. The reason is that when the local area is heated, it can trigger the release of drugs without harming healthy tissues [11,12].

Martinez Espinoza et al. (2024) synthesized a thermoresponsive copolymer with an LCST matching physiological hyperthermia. When incorporated into thermosensitive liposomes, it reduced the lipid bilayer Tm under heating, accelerating drug release [11]. Zhang et al. (2023) integrated N - isopropylacrylamide (NIPAAm) into a copolymer. By leveraging its temperature - dependent hydrophilicity, they achieved graded control over micellar drug release rates [8]. Li et al. (2023) developed injectable thermosensitive hydrogels that gel at body temperature and release drugs during hyperthermia, minimizing systemic exposure [12].

In summary, temperature-responsive systems synergize effectively with hyperthermia therapy. They offer tunable drug release and localized action, which are crucial advantages for enhancing therapeutic efficacy while reducing systemic toxicity.

3.2. Internal stimuli-responsive mechanisms

3.2.1. pH-responsive systems

pH-responsive drug delivery systems leverage physiological pH gradients (neutral in blood/normal tissues, slightly acidic in tumor microenvironments, highly acidic in endosomes/lysosomes) to trigger drug release. Protonation or deprotonation of functional groups in these systems alters carrier charge, solubility, or assembly state, enabling autonomous release at target sites—an advantage over conventional carriers that lack site specificity [1,7,13].

Representative designs include charge-reversible surfactants: Jiang et al. (2021) synthesized 11 - (N, N-dimethylamino) sodium undecanoate (DMUa), which switches from anionic (blood-compatible) to cationic in acidic tumors. This charge transition destabilizes emulsions, triggering rapid drug release (85% within 2 h at tumor pH) [7].Another approach targets poorly soluble drugs: Yang et al. (2023) used SDS in ritonavir-based amorphous solid dispersions (ASDs); in acidic endosomes, SDS protonates to reduce phase separation, doubling drug release efficiency compared to surfactant-free ASDs [1]. Metal-polymer coordination systems also show promise: Zhao et al. (2023) developed Zn^{2+}-polymer carriers that stay stable at neutral pH but dissociate in acidic tumors, achieving 2.5-fold higher tumor accumulation than non-responsive carriers [13].

Compared with conventional carriers, pH-responsive surfactants excel at matching physiological pH differences to minimize off-target release while boosting delivery efficiency, which makes them widely applicable for tumor and intracellular drug delivery.

3.2.2. Enzyme-triggered systems

Enzyme-triggered drug delivery systems exploit the overexpression of enzymes in diseased tissues to cleave specific bonds. This cleavage disrupts surfactant/nanocarrier structure, enabling tissue-specific release that avoids healthy tissues, which is a key improvement over non - targeted systems [3,6,14].

For tumor therapy, Li et al. (2022) designed MMP-2-responsive peptide-surfactant micelles (MMP-2 is overexpressed in most breast cancers). MMP-2 cleavage drives micelle-to-fiber transformation, releasing drugs and enhancing tumor penetration [14]. Mi et al. (2020) targeted ovarian cancer with uPA-responsive liposomes: a uPA-cleavable peptide masks cationic groups in the bloodstream, while cleavage at tumor sites exposes these groups to boost cell uptake, leading to 60% higher DOX release than non-targeted liposomes [3]. For colon delivery, Chen et al. (2022)

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developed azo bond-functionalized nanocarriers; azoreductases in colonic bacteria cleave these bonds, releasing 90% of 5-ASA locally and reducing systemic concentrations by 10-fold vs. oral tablets [6].

Enzyme-triggered systems stand out for their high tissue specificity. By leveraging disease-associated enzyme overexpression, they achieve precise release in tumors or the colon, addressing the long - standing challenge of non - specific drug distribution in traditional delivery.

4. Conclusion

This review synthesized the design principles, response mechanisms, and applications of four major smart responsive surfactant systems, including light-, temperature-, pH-, and enzyme-responsive types. Unlike earlier studies that focused on single stimuli, this work integrates both external and internal triggers within a unified framework and emphasizes potential synergies. For example, combinations of light and temperature responsiveness enable non-invasive control aligned with clinically relevant hyperthermia, while enzyme-triggered assemblies illustrate how overexpressed biological markers can enhance tissue penetration. This broader perspective provides a systematic overview of current strategies and highlights their translational relevance for clinical application.

The analyzed systems show clear potential for therapeutic use. Light-responsive nanocarriers demonstrate the ability to achieve tumor-specific drug release, while temperature-responsive formulations are optimized for mild hyperthermia in the clinical range. Despite these advantages, several challenges remain, including limited evaluation of long-term in vivo safety, insufficient scalability of synthetic routes, and underrepresentation of newer classes of responsive surfactants. These limitations indicate that although progress has been made, the knowledge base is still incomplete and requires further consolidation before these systems can advance toward reliable clinical translation.

Future research should focus on three key directions. First, optimizing multi-stimulus synergy is necessary to increase adaptability across complex disease environments. Second, developing cost-effective and scalable synthetic methods will be crucial to facilitate broader application. Third, standardized performance and toxicity assessment protocols must be established to ensure safety and comparability across studies. Progress in these areas will require close collaboration between materials science, chemistry, and pharmacology to link advances in molecular design with therapeutic validation. By addressing these challenges, smart responsive surfactants can evolve from experimental concepts into clinically viable drug delivery systems that support precision medicine for solid tumors, inflammatory conditions, and other complex diseases.

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