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SMART STIMULI-RESPONSIVE DRUG DELIVERY SYSTEMS: EMERGING PLATFORMS, THERAPEUTIC APPLICATIONS AND TRANSLATIONAL PERSPECTIVES

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Abstract:

Smart stimuli-responsive drug delivery systems have become advanced pharmaceutical tools that can control drug release through stimulation by specific physiological, pathological, or external stimuli. They overcome a number of problems associated with traditional drug delivery, such as unspecific drug delivery, premature drug release, low bioavailability, toxic effects, and insufficient localization of drugs for therapy. In this review, we provide a brief summary of the design features, stimuli, nanocarrier platforms, applications, and translational aspects of smart drug delivery systems. Stimuli of both endogenous (such as pH, enzymes, redox conditions, reactive oxygen species, temperature, and glucose) and exogenous types (light, magnetic fields, ultrasound, and electrical signals), along with their action mechanisms in terms of the triggered controlled release of drugs are discussed. Carrier platforms, which include polymeric nanoparticles, liposomes, micelles, nanogels, dendrimers, lipid nanoparticles, hybrid nanocarriers, and biomimetic systems, are emphasized. The applications of the above smart nanocarrier platforms in cancer therapy, diabetes, infectious diseases, nucleic acid delivery, vaccination, and theragnostics are also provided. Recent advances in multifunctional responsiveness, biomimetic drug delivery systems, artificial intelligence-based formulation design, and precision medicine are reviewed. However, despite significant achievements, the issues of biological heterogeneity, safety, stability, scalability, reproducibility, manufacture, and regulation approval still limit clinical translation of these systems. Future development in the field should focus on clinically relevant formulations, thorough validation of efficacy in vivo, scalable manufacture, and personalized medicine approaches.

Keywords: Smart drug delivery; Stimuli-responsive systems; Nanocarriers; Targeted drug delivery; Controlled drug release; Precision medicine; Nanomedicine

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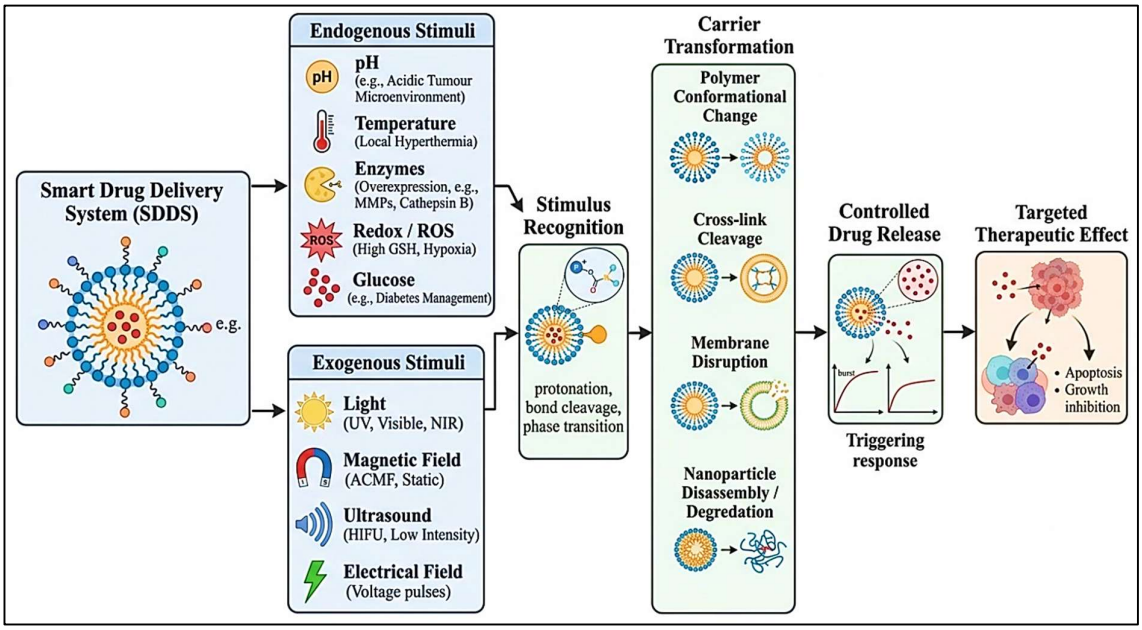
Graphical Abstract



1. INTRODUCTION

Drug delivery systems (DDS) play a significant role in the process of administering medication, since they ensure safe and effective drug delivery. The main purpose of DDS is to keep drugs at therapeutic levels during an appropriate time period to increase their efficiency and minimize their toxicity [1,2]. Traditional dosage forms such as tablets, capsules, injections, suspensions, creams, and ointments are still extensively used because of well-known manufacturing techniques, simple administration methods and acceptability among patients. However, traditional systems are characterized by various drawbacks, including non-specific drug distribution, poor aqueous solubility, poor bioavailability, rapid elimination, drug degradation and multiple administrations [3,4]. These issues may cause fluctuations in drug concentration, decreased efficacy, toxicity and poor patient compliance. Various disadvantages associated with the use of traditional drug delivery technologies have stimulated the emergence of more modern drug delivery techniques that allow controlling the spatial and temporal distribution of therapeutic compounds. The trend in the field of drug delivery has changed from traditional techniques to controlled-release, targeted and nanotechnology-based approaches. Controlled-release techniques allow increasing the exposure time and reducing dosing frequency while targeted delivery attempts to improve the accumulation of drugs in certain target organs or cells [5,6]. Moreover, nanotechnology has significantly widened these opportunities by creating new systems such as polymeric nanoparticles, liposomes, micelles, nanogels, dendrimers, lipid nanoparticles and others [7]. However, the biological environment is still very dynamic and diverse, which requires systems that would be able to adjust to certain physiological or pathological situations. Smart drug delivery systems (SDDS) are modern delivery systems that are capable of responding to changes in their environment and regulating drug release according to it. Such systems include therapeutic cargo, carrier, targeting moiety, and stimulus-responsive unit that make it possible to deliver the drug selectively and control its release [8,9]. Unlike traditional drug delivery systems, where drug release is mainly determined by the properties of the delivery system itself, SDDS can be tailored to respond to certain stimuli. Stimuli-responsive drug delivery system is one of the main concepts of smart drug delivery systems. The nanocarrier can alter some of its physicochemical or structural properties depending on some external signals that trigger controlled release of the drug into the required place [8]. The stimuli can be internal (pH, temperature, enzyme activity, reduction potential), or external (light, magnetic field) [8,10]. The stimulus can cause degradation of the polymer, its swelling or deswelling, change in configuration, breakage of

bonds, destabilization of the membrane, and some other processes in the nanocarrier, leading to drug release. The attention in regard to internal stimuli is paid to the difference in pH between physiological tissues, pathological microenvironment and compartments of cells [10,11]. The pH-responsive polymers can protonate, deprotonate, swell, dissolve or degrade due to changes in the pH of the surrounding environment. Such systems have been developed, especially as an approach to the treatment of cancer when one may take advantage of the disparity between tumor-associated and normal physiological environment in terms of drug localization. Similarly, redox-responsive systems utilize the difference in redox potential of the extracellular and intracellular compartments. Chemical bonds sensitive to the reduction process will be fairly stable in circulation but easily decomposed in reducing intracellular medium and thus enable intracellular release of drugs [12]. Temperature-responsive systems provide yet another approach wherein the release of a drug is determined by changes in temperature. Thermosensitive polymers are capable of reversibly phase transition at a certain temperature allowing the release of drugs to be controlled by physiological or artificially-induced temperature change [10]. Exogenous stimuli like light or magnetic field can be used for externally-controlled drug delivery because they can be applied to a certain anatomical location. Therefore, a combination of endogenous and exogenous stimuli creates considerable interest in multi-functional and multi-stimuli-responsive delivery systems. There are a number of applications of smart delivery systems for the treatment of difficult diseases. For example, the area of oncology has widely been studied for the improvement of delivery of anti-cancer drugs minimizing the risk of affecting normal tissues. The target of action can be achieved by passive targeting related to tumor physiology or actively targeting using ligand–receptor interactions [5,6]. Besides cancer, smart drug delivery systems can be used for controlled delivery of insulin, antimicrobial drugs, nucleic acids, genes and other types of therapy including vaccination. Recent progress in this field has resulted in expanding the concept of smart drug delivery by using nanocarriers that possess multiple functions, biomimetic approaches, theranostic approaches, and computer techniques. The goal of these systems is not only to control drug release but also to combine targeting, imaging, diagnostics, and therapy into one delivery system. These strategies could facilitate advancement of precision medicine and enable drug delivery systems to become responsive to disease-specific physiological conditions. However, the development of smart drug delivery systems from experimental research stage to clinical application is rather difficult due to problems of their long-term safety, biocompatibility, formulation stability, reproducibility, large-scale production, cost issues, regulatory issues, and predictability of in vivo behavior. Besides, biological heterogeneity may affect the consistency of stimulus-induced response when stimulus differs significantly among patients or various stages of disease. Hence, careful optimization and extensive preclinical and clinical testing are crucial for validation of the therapeutic potential of these advanced drug delivery systems. The current review provides an overview of the basic principles, classification, types of stimuli and their response, nanocarriers utilized for their activation in smart drug delivery systems. Furthermore, the review provides information on the most significant applications of these systems, technological innovations, the challenges of the translation of these advanced systems to clinic and future directions.

2. DESIGN PRINCIPLES AND COMPONENTS OF SMART STIMULI-RESPONSIVE DRUG DELIVERY SYSTEMS

Effective stimuli-responsive drug delivery systems are developed to change the physicochemical properties due to certain biological or external stimuli in order to ensure the temporally and spatially controlled delivery of therapeutic agents. Stimuli-responsive systems are capable of integrating drug loading, detection of stimulus, stability of the carrier, ability to target the desired biological site and a particular mode of drug delivery [13,14].

2.1 Therapeutic Payload

Therapeutic payload represents the active pharmaceutical ingredient delivered using the developed system. The smart delivery systems are capable of accommodating various drugs such as small molecule drugs, peptides, proteins, nucleic acids, vaccines or a mixture of drugs depending on the therapeutic goal. Encapsulation, adsorption, conjugation and chemical incorporation of the payload into the carrier help to protect the sensitive

molecules from degradation and improve pharmacokinetics [15]. The choice of the method used to incorporate the drug into the carrier depends on its solubility, molecular weight, stability, the nature of the carrier and the mode of release.

2.2 Carrier Matrix

Carrier is a matrix used to transport and protect the therapeutic payload. Various carriers used for delivery of drugs include polymeric nanoparticles, liposomes, micelles, nanogels, dendrimers, lipid nanoparticles and hybrid nanoparticles [13,16]. The physicochemical properties of the carrier (particle size, morphology, charge, hydrophobicity, degradation and drug-loading capacity) significantly affect biodistribution, cellular uptake, stability and therapeutic effect. The ideal carrier is the one which is able to remain stable in vivo and then to change its structure upon the exposure to the selected stimulus.

2.3 Stimulus-Responsive Element

Stimulus-responsive element is the fundamental component of smart delivery systems which acts as a means for detecting any specific change in the biological environment or any stimulus signal. Responsive material may contain ionizable groups, cleavable chemical groups, thermo-responsive components, enzyme-cleavable bonds, redox-responsive groups, photosensitive groups, or magnetically-responsive groups [14,17]. Stimulation will lead to a process of hydrolysis, bond cleavage, protonation/de-protonation, conformational change, swelling, contraction, degradation, destabilization of the membrane, or change in solubility of the responsive group. These responses bring about a change in the interaction between the carrier and the cargo, thereby leading to release.

2.4 Targeting and Recognition Elements

Targeting elements facilitate the localization of drug-laden carriers to specific tissue, cell or sub-cellular compartments. Targeting may be passive, active or stimulus-dependent. Passive targeting takes advantage of the difference in permeability, architecture or physiology of healthy and diseased tissues. Active targeting makes use of targeting agents including antibodies, peptides, aptamers, carbohydrates or receptor-specific molecules that bind to the over-expressed cellular receptors [18]. Targeting increases the uptake of the drug carrier but its efficacy may be affected by biological variability, protein corona, receptor expression and tissue penetration barriers.

2.5 Recognition of Stimulus and Signal Transduction

An important design principle is the transduction of external or biological stimulus to a physical and chemical response by the carrier. A reduction in the environmental pH will lead to protonation of ionizable groups in the polymer chain and this will lead to swelling or destabilization of the carrier. Also, intracellular reduced condition causes the cleavage of disulfide bonds while disease associated enzymes can lead to cleavage of peptide or polymeric linkages [14,19]. The strength and rate of the response will depend on the sensitivity of the responsive element, the stimulus concentration, duration of exposure, the composition of the carrier and biological environment.

2.6 Controlled Drug Release

Drug release in the case of intelligent systems may take place through diffusion, degradation of polymers, swelling, erosion, desorption, breaking of bonds, membrane disruption, and any combination of these factors. In an optimal system, the drug release should be minimal during circulation and fast or sustained once the right stimulation environment is reached. The process of releasing can be controlled by changing polymer composition, degree of cross-linking, size of the particles, interaction between the drug and the carrier, responsive bond chemistry, and the stimulation environment sensitivity [13,20]. A very important aspect is the relation between the level of stimulus intensity and the rate of drug release, since too much sensitivity leads to early release, while too little – reduces therapeutic effect.

2.7 Biocompatibility and Biodegradability

Biocompatibility is one of the key features in the design of intelligent drug delivery systems. Materials that cause the minimum possible negative immune response and inflammation, and, if necessary, degrade and be excreted after releasing the drug are sought for. Biodegradable polymers and physiologically relevant lipids have received significant attention [16]. However, the biocompatibility of the nanocarriers is not just related to its chemical composition, but to the particle size, surface characteristics, method of administration, degradation products and multiple doses. A complete study of acute and chronic

toxicity should be carried out before clinical applications.

2.8 Important Features in the Design of Intelligent Systems

The behavior of a smart, responsive system depends on the interaction of several features, and not just the sensitivity to stimuli. Particles' size and surface properties affect biodistribution and cellular uptake; loading and stability of the carrier define the dose. Sensitivity to stimulus defines the location and the rate of drug release, while biodegradability and toxicity influence the safety. Rational design needs optimization of all features at the same time [15,16].

3. CLASSIFICATION OF SMART STIMULI-RESPONSIVE DRUG DELIVERY SYSTEMS

Stimuli-responsive drug delivery systems may be classified according to the type and source of the stimulus that triggers the drug release process. According to such classification, they are broadly divided into endogenous stimuli-responsive systems and exogenous stimuli-responsive systems. Endogenous systems make use of naturally existing biochemical or physiological differences within the organism, while exogenous systems make use of externally applied physical stimuli to provide spatial and temporal control of the drug release process. Major endogenous stimuli include pH, enzymes, redox, reactive oxygen species (ROS), hypoxia, and glucose, while major exogenous stimuli include temperature, light, magnetic field, ultrasound, and electricity [21,22]. The selection of the right type of stimulus is determined by the microenvironment of the disease, its localization, the type of the drug and nanocarrier used (Table 1).

3.1 Endogenous Stimuli-Responsive Systems

The endogenous stimuli-responsive systems make use of naturally occurring physiological or pathological stimuli to trigger the drug release. They are especially advantageous in the fact that they do not need to involve any external devices or processes in their operation. Diseased tissues may differ in the level of pH, enzymatic activity, redox potential, ROS concentration or metabolism from healthy tissues. This difference may be utilized in the design of nanocarriers to provide targeted or diseased tissue-dependent drug activation or release [21,23]. Unfortunately, endogenous stimuli are not always sufficient to distinguish diseased from healthy tissues and also vary depending on the stage of the disease, localization and even individual patient. Thus, their sensitivity should be properly optimized.

3.1.1 pH-Responsive Systems

pH-sensitive delivery vehicles take advantage of variations in hydrogen ion concentration in different biological compartments. There are notable pH differences between blood circulation and intracellular organelles, such as endosomes and lysosomes, and many pathological tissues, especially solid tumors, have an acidic extracellular microenvironment [21,24]. The pH-sensitive carriers usually contain ionizable groups or acid-labile chemical bonds. pH variation may cause protonation or deprotonation, which results in changes in the polymer solubility, swelling, electrostatic interaction, membrane stability, or carrier structure. Acid-labile bonds can be hydrolyzed to induce carrier degradation or drug-carrier linkage cleavage and, thus, drug release [24]. There have been developed various pH-sensitive systems: polymeric nanoparticles, micelles, liposomes, nanogels, and hydrogels for anticancer, intracellular, and nucleic acid delivery. The main advantage of these systems is the use of physiologically relevant pH differences; however, the relatively small difference in the pH of normal and pathological extracellular tissues may limit the selectivity. Therefore, the transition point and reaction kinetics need to be properly engineered.

3.1.2 Temperature-Responsive Systems

Temperature-responsive systems use temperature differences to change the physical properties or permeability of drug carriers. Thermosensitive polymers can demonstrate reversible changes in hydration, polymer chain conformation, solubility, or phase transition at certain temperature [21,25]. Polymers that demonstrate the lower or upper critical solution temperature lower critical solution temperature (LCST) or upper critical solution temperature (UCST) can be incorporated into nanocarriers and hydrogels. If the temperature reaches the required transition point, the polymer can contract, swell, phase-separate, or change the permeability. One should also note that temperature-sensitive systems are especially promising for localized therapy in view of external generation of the stimulus. Thus, local hyperthermia could be combined with thermosensitive nanocarriers for better targeted drug delivery. Thermosensitive liposomes and polymeric systems for chemotherapy and combined therapy were investigated [25].

However, one should not forget about the importance of proper temperature control since improper heating might not lead to sufficient drug release while overheating might cause harm to healthy tissue.

3.1.3 Enzyme-Responsive Systems

Enzyme-responsive systems make use of different expression or activity levels of particular enzymes linked to certain tissues and diseases. The use of enzymes as biotriggers is reasonable because enzymes can show increased activity level in tumors, inflamed tissue, infections, and certain intracellular compartments [21,26]. In this way, systems usually contain peptides or polymeric linkers that could be cleaved by the enzyme; in addition, they contain enzymes-sensitive moieties that become degraded in response to the presence of the enzyme [26]. The major advantage of enzyme responsiveness is its possibility for disease-related activation. At the same time, it is important to note that enzyme concentration varies from patient to patient and from tissue to tissue. In addition, it is possible that the same enzymes or enzymes with similar activity are present in healthy tissue and thus could activate the carrier.

3.1.4 Redox-Responsive Systems

Redox-responsive systems take advantage of the differences in redox states in extracellular and intracellular environments. The intracellular environment, especially the cytoplasm, normally demonstrates more reducing character compared to the extracellular environment due to a relatively high concentration of glutathione and other reducing compounds [21,27]. Disulfide bonds are one of the most used redox-sensitive linkages. Disulfide bonds may demonstrate sufficient stability in systemic environment, while being cleaved under reducing intracellular conditions. It can lead to the disruption of the polymer cross-links, destabilization of nanoparticles or dissociation of the cargo from the carrier, providing an opportunity for drug release into the intracellular compartment [27]. The redox-responsive systems are especially relevant for the intracellular delivery of anticancer drugs, proteins, peptides and nucleic acids. The recent research is focused on the redox-sensitive nanocarriers able to modulate oxidative stress and deliver simultaneously therapeutic substances [28]. However, the variations in intracellular glutathione level and redox state of the cells may affect the efficiency of the approach.

3.1.5 Reactive Oxygen Species-Responsive Systems

The ROS-responsive systems use abnormal oxidative stress in the case of such pathologies as cancer, inflammation, cardiovascular diseases and some infectious diseases. The redox-sensitive carriers contain oxidizable moieties which may experience the chemical or structural changes due to increased ROS level [21,29]. The oxidation of the moieties can result in increasing the hydrophilicity, degradation of the polymer, weakening of the carrier, or unmasking the cargo. It allows the drugs' release in the oxidative environment, as well as prevention of premature release in physiological conditions. The difficulty is that the ROS levels are quite variable and can differ in various diseases, tissues, and at various stages of the pathological process. Therefore, the sensitivity and activation threshold of the ROS-responsive material should be precisely optimized.

3.1.6 Glucose-Responsive Systems

Glucose-responsive drug delivery systems are of specific importance for the management of diabetes and insulin administration. In such systems, glucose levels affect release of insulin. Glucose sensing can be achieved via using glucose oxidase, phenylboronic acid derivatives, or other glucose receptors [22,30]. For example, glucose oxidation results in pH change or other alteration in chemical properties that affects carrier properties and triggers insulin release. Phenylboronic acid can interact with glucose reversibly causing changes in the properties of the polymer and drug release. Despite all the advantages, glucose-responsive drug delivery still has some disadvantages like sensitivity, selectivity, stability issues, and inability to reliably adjust insulin release to physiological demands for glucose.

3.2 Exogenous Stimuli-Responsive Systems

Exogenous stimuli-responsive drug delivery systems use physical stimuli to control drug release. The main benefit of such systems is the fact that exogenous stimulus can be applied whenever and wherever it is necessary providing better control compared to many endogenous systems [21,22]. Commonly used exogenous stimuli include light, magnetic field, ultrasound, and controlled temperature.

3.2.1 Light-Responsive Drug Delivery Systems

In light-responsive drug delivery systems, light application allows remote control of the process of drug release. Various photosensitive components, photocleavable linkers, photothermal materials, and photochemical components can be included into the system to induce structural and chemical changes in the system under irradiation [21,31]. Application of light may result in photochemical bond cleavage, isomerization, decomposition, or photothermal effects. Photothermal nanoparticles can convert light energy into heat that, in turn, will destroy thermosensitive carriers or increase permeability of the membrane. The near-infrared (NIR) region is also more attractive due to its ability to provide greater tissue penetration compared to ultraviolet light. For that reason, NIR-responsive systems have been studied for local cancer treatment, photothermal therapy, controlled drug release, and therapeutic diagnosis [31]. However, although the aforementioned benefits, light penetration limitations represent one of the major restrictions, especially for deep tissues. Other issues to be considered during the process of translating systems for their practical use include phototoxicity, tissue heating, the necessity for irradiation, and special instrumentation.

3.2.2 Magnetic-Responsive Systems

Magnetic responsive systems normally involve the use of magnetic nanoparticles, mostly iron oxide-based ones, in drug carriers. An external magnetic field may affect the localization, motion, or heating of carriers thus allowing targeted delivery and stimulation of drug release [21,32]. In addition, magnetic nanoparticles are capable of producing heat when affected by an alternating magnetic field; this process is called magnetic hyperthermia. When applied with thermosensitive carriers, magnetic hyperthermia becomes able to cause drug release from the carrier. Hence, magnetic systems have a potential to combine targeting, imaging, magnetic hyperthermia, and drug delivery. The effectiveness of magnetic targeting depends on several factors including strength of the magnetic field, characteristics of the nanoparticles, blood flow, tissue depth, and ability to produce sufficient magnetic forces in the target area.

3.2.3 Ultrasound-Responsive Systems

Ultrasound is a favorable form of external stimuli because of its non-invasive application and common use in medical imaging and therapy. Sound waves could lead to mechanical, cavitation, membrane rupture, and local heating effect, thus assisting in drug release and increased tissue penetration [21,33]. Ultrasound-responsive delivery has been attempted using liposomes, nanoparticles, microbubbles, and hybrid carriers. Acoustic stimulation may cause disruption of delivery vehicle and increase membrane permeability, leading to localized drug delivery. Also, ultrasound can be used in combination with microbubbles to enhance vascular permeability and deliver drugs. Response to ultrasound is very dependent on ultrasound frequency, intensity, duration of exposure, delivery vehicle, and biological tissue properties. Too much acoustic energy may have unwanted effects on biological tissue; therefore, optimization of treatment is essential.

3.2.4 Electrical-Field-Responsive Systems

Electrical stimulation can induce changes in the swelling, permeability, conformation, and degradation of electrically responsive polymers and hydrogels. Application of electric field changes ion distribution and interactions within the polymer and leads to drug release [21,34]. Electrical responsive systems are potentially good for localized and programmable drug delivery especially when there is an implantable or externally controlled electrical source available. However, their application in pharmaceutics is limited by the requirement of appropriate electrical interfaces and difficulties associated with in vivo stimulation.

3.3 Multi-Stimuli-Responsive Systems

Sometimes single stimuli systems will not be sufficient if the biological environment in which a drug carrier operates presents multiple or changing stimuli. Therefore, multi-stimuli-responsive systems use two or more stimuli for drug delivery [22,35]. A sequential multi-stimuli design can be adopted in such a way that the first stimulus leads to increased tissue permeation or cell entry, whereas a later stimulus results in intracellular release of the cargo. The sequential responses may help to prevent the early release of drugs and improve the targeting accuracy. There is an ongoing trend towards designing the systems capable of responding to multiple stimuli, including both endogenous and exogenous. For example, the pH-responsive carriers may be combined with the ultrasound or photothermal components to use both the disease markers and externally controlled stimuli [35]. However, increasing complexity of the system may

create additional issues related to fabrication, reproducibility, characterization, toxicity, and evaluation of safety. In general, there is a shift in designing the stimuli-responsive delivery systems from relatively simple one-trigger systems towards multistage, multifunctional and multi-stimuli systems. Recently, it has been observed that the integration of the pH-, redox-, enzymatic-, thermal-, magnetic-, light- and ultrasound-sensitive responsiveness of advanced nanocarriers is getting considerable attention; however, clinical translation is still much harder task.

Table 1. Major stimuli-responsive drug delivery systems

Stimulus	Type	Mechanism	Applications	Limitation	Refs.
pH	Endogenous	Protonation, swelling, bond cleavage	Cancer, intracellular delivery	Limited pH difference	[21,24]
Temperature	Endo/Exogenous	Phase transition	Cancer, controlled release	Temperature control	[21,25]
Enzyme	Endogenous	Enzymatic cleavage	Cancer, infection	Variable enzyme levels	[21,26]
Redox/ROS	Endogenous	Bond cleavage/oxidation	Cancer, gene delivery	Biological variability	[27-29]
Glucose	Endogenous	Glucose-induced swelling/release	Insulin delivery	Response control	[30]
Light	Exogenous	Photocleavage/photothermal effect	Cancer, phototherapy	Limited penetration	[31]
Magnetic field	Exogenous	Magnetic targeting/heating	Cancer, imaging	Limited penetration	[32]
Ultrasound	Exogenous	Cavitation/mechanical disruption	Cancer, localized release	Tissue safety	[33,35]
Multi-stimuli	Both	Combined stimulus response	Precision therapy, theranostics	High complexity	[23,35]

4. SMART NANOCARRIER PLATFORMS

The effectiveness of stimuli-responsive delivery systems highly depends not only on the nature of the triggering stimulus, but also on the physicochemical properties of the carrier used for transportation and delivery of the drug. Nanocarriers possess several unique features, which include high surface area, adjustable physicochemical properties, protection of the drug from degradation, enhanced solubility, and the possibility of surface modification. Therefore, polymeric and lipid-based nanoparticles, liposomes, micelles, nanogels, dendrimers, and hybrid nanocarriers became important platforms for developing smart delivery systems [36,37]. Recent studies have paid attention to the integration of these carrier structures with various stimuli.

4.1 Polymeric Nanoparticles

Polymeric nanoparticles are another extensively studied class of stimuli-responsive drug delivery systems due to the possibility of rational modification of their composition, degradation kinetics, surface properties, and release mechanisms. Biodegradable polymers like PLGA, poly(lactic acid), or synthetic stimuli-responsive polymers can be modified to contain pH-, temperature-, enzymatic-, or redox-sensitive components [36,38]. Stimulus-responsive polymeric nanoparticles can hydrolyze, swell, degrade, change their charge, and reorganize their structure upon encountering a certain trigger. The drug release can be additionally regulated via inclusion of functional groups or cleavable linkers within the polymer structure or surface coating with polyethylene glycol (PEG), targeting ligands, peptides, or antibodies. The main advantages of polymeric nanoparticles are their high structural diversity, protection of drugs, and the possibility to combine targeting with controlled drug release. However, synthesis of the nanoparticles, their batch-to-batch variability, presence of residual solvent, scalability, and stability over time are the critical factors for translation.

4.2 Liposomes

Liposomes are vesicle-based drug carriers made predominantly from the phospholipid bilayers enclosing the aqueous core. Due to their amphiphilic nature, hydrophilic drugs can be included in the aqueous core while hydrophobic drugs can associate with the phospholipid bilayer [37,39]. Stimuli-responsive liposomes can be designed to destabilize the membrane or alter its permeability depending on pH, temperature, enzymatic activity, light, ultrasound, or some other stimulus. Thermosensitive liposomes, for example, are released after heating of the certain area and pH-sensitive liposomes will be subjected to destabilization of the membrane upon acidic conditions. Translational advantage of liposomes is provided by clinical experience with liposomal drugs. However, traditional liposomes may suffer from the lack of stability, drug leakage, fast mononuclear phagocyte system uptake, and somewhat complicated fabrication process.

4.3 Polymeric Micelles

Polymeric micelles are nanostructures that form through self-assembly of amphiphilic polymers consisting of a hydrophobic core and a hydrophilic shell. Such nanoparticles can be especially useful for improving the solubility and delivery of water-insoluble drugs [38,40]. In addition, they may be designed to change their core stability, hydrophobic/hydrophilic ratio, or polymer structure depending on pH, redox state, temperature, enzymatic or photostimuli. Therefore, a change in their structure due to an applied stimulus may facilitate the drug release at the site of action. Small size and high solubilizing properties make micelles suitable for systemic delivery. However, stability following dilution in physiological medium, early drug release, and interaction with proteins in the bloodstream may influence their performance in vivo.

4.4 Nanogels

Nanogels are three-dimensional cross-linked polymeric networks having nanometer size and high swelling properties. The nanoparticle-like nature of nanogels combined with gel-like properties make them especially interesting for the design of stimuli-responsive systems [36,41]. Depending on pH, temperature, ionic strength, enzymes, redox environment, or other factors, they may change by swelling, deswelling, degradation, or network permeability. Such properties enable controlled release of small molecules or macromolecules. Natural or synthetic polymers can be used to prepare nanogels, making it possible to vary their physical and chemical properties to achieve a certain purpose. Nowadays, much attention is paid to the development of smart nanogels for targeted drug delivery, mainly in oncology and other disease areas.

4.5 Dendrimers

Dendrimers are branched, nanometer-sized macromolecules characterized by a highly ordered structure and many functional groups on the periphery. The controlled structure and surface functional groups allow using dendrimers for drug encapsulation, functionalization, targeting, and stimulus-responsive modifications [37,42]. Dendrimers designed as stimuli-responsive nanocarriers could contain acid labile, redox-sensitive, enzymatically cleavable, or other responsive linkages. Environmental changes could cause the cleavage of specific bonds or change in dendrimer properties, leading to the release of the payload. Despite their architectural advantages, there are some potential drawbacks, such as possible toxicity (mainly because of highly cationic surface groups) and difficulties in synthesis, purification, and large-scale production.

4.6 Lipid Nanoparticles

Lipid nanoparticles (LNPs) have attracted particular attention in the field of nucleic-acid delivery. The lipid nature of LNPs allows improving drug encapsulation, protection, cell entry, and intracellular drug release [39,43]. It is important to note that ionizable lipids play a special role because of the changing properties regarding charge depending on the environmental pH. This feature allows encapsulating nucleic acids and endosomal escape after internalization. Successful applications of nucleic-acid-based LNPs showed that there is great clinical potential in this area. The use of other stimuli-responsive components would allow achieving selective intracellular delivery of drugs. However, there are still several problems, such as lipid oxidation, stability, immune response, etc.

4.7 Hybrid Nanocarriers

Hybrid nanocarriers contain two or more material types to combine their advantages. The examples include polymer–lipid nanoparticles, lipid-polymer hybrids, inorganic–polymeric hybrids, and biomimetic nanocarriers [37,44]. Hybridization may provide enhanced structure stability, high drug loading capacity, controllable degradation, targeting

properties, and response to various stimuli. For example, polymeric core may provide controlled drug entrapment, whereas lipid shell increases biocompatibility and cell interaction. In addition, inorganic particles may provide magnetic, photothermal, and imaging functionalities. Main benefit of hybrid systems is their multifunctionality. However, increased structural complexity poses difficulties in characterization, reproducibility, scale-up, quality control, and regulatory evaluation.

4.8 Biomimetic and Cell-Derived Nanocarriers

Biomimetic systems involve utilization of biological structures and membranes that can enhance circulation, immune evasion, targeting, and cell interactions. Recently, nanoparticles with cell membrane coating, extracellular vesicles, exosomes, and cell-mediated delivery systems gained increased interest as drug delivery vehicles [44,45]. These systems may also be modified to include stimuli-responsive elements, thus combining biological targeting with controlled drug release. For example, exosome-based systems are able to combine intrinsic biological interactions, and stimuli-responsive elements can control payload release. Recent publications stressed the potential of cell-mediated, stimuli-responsive systems as delivery vehicles to combine biological targeting with pH-, redox-, enzyme-, light-, ultrasound-, and magnetically responsive systems. Biomimetic systems, however, face a number of difficulties related to variability of sources, biological heterogeneity, isolation/purification, characterization, storage, scaling up, and regulatory issues.

4.9 Comparative Considerations for Smart Nanocarriers

There is no universal drug delivery system for all applications. Drug physicochemical properties, desired way of administration, target tissue, stimulus parameters, release kinetics, toxicity, and manufacturing processes should be taken into account when choosing carrier. Polymeric nanoparticles and nanogels have numerous possibilities for structure modification; liposomes and lipid nanoparticles have lipid-based delivery possibilities; micelles are especially beneficial for poor solubility drugs; dendrimers and hybrids offer wide variety of multifunctionalities [36,37]. This area continues to progress into the realm of multifunctional nanocarriers that combine localization, stimulus-responsiveness, imaging, and drug delivery in one system. However, increase in functionality must be balanced with regard to reproducibility, manufacturing, safety, and regulatory feasibility. Current translational approaches show that problems like protein corona formation, scale-up, characterization, and regulations continue to hinder the clinical translation of stimuli-responsive nanocarriers.

5. THERAPEUTIC APPLICATIONS OF SMART STIMULI-RESPONSIVE DRUG DELIVERY SYSTEMS

Due to high potential in enhancing localization of drugs, disease-specific release, and reducing adverse effects on healthy tissues, smart stimuli-responsive drug delivery systems were investigated in many therapeutic fields. The relevance of their therapeutic properties is especially notable for diseases characterized by presence of distinct pathological microenvironment compared to physiological one. Main applications include treatment of cancer, diabetes, infectious diseases, gene and nucleic-acid therapy, and theranostics [46,47].

5.1 Cancer Therapy

Cancer represents one of the most studied applications of stimuli-responsive drug delivery systems. Traditional chemotherapy may cause non-specific distribution of drugs, adverse systemic side effects, poor tumor penetration, and development of drug resistance. Stimuli-responsive nanocarriers can overcome these shortcomings through tumor targeting and drug release induced by stimuli [46,48]. The features of tumor cells' environment such as low pH value, high ROS content, altered redox environment, hypoxia, and overexpression of certain enzymes can be used as triggers. pH-responsive systems enable drug release at acidic tumor sites or inside of cells due to low pH, while redox-responsive systems allow release at intracellular level through destruction of reduction-sensitive bonds. Enzyme-responsive systems utilize higher protease activity in tumor microenvironment. Potential smart nanocarriers might bear ligands responsible for the specific binding to the receptors overexpressed in the cancer cells. Therefore, a two-step strategy, including active targeting of the carrier with following its stimulation by an external agent, is formed [49]. Exogenous stimuli provide further possibilities for localized delivery of therapeutics to the cancer cells. Light-activable nanocarriers enable photothermal or photochemical stimulation,

magnetic nanoparticles can be used to achieve magnetic targeting or hyperthermia, ultrasound might lead to the breakdown of carriers and increased tissue penetration [50]. These stimuli can be used in combination with imaging, immunotherapy, phototherapy, and gene therapy. However, due to tumor heterogeneity, despite numerous preclinical success stories, the clinical implementation of stimulus-responsive nanocarriers encounters difficulties since differences in vascularization, extracellular pH, enzymatic activity, receptor presence, extracellular matrix composition, and immune cells in tumors can significantly affect their accumulation and stimulation.

5.2 Diabetes and Glucose-Responsive Drug Delivery

Diabetes mellitus requires chronic pharmacological treatment, and in addition to insulin therapy, patients with diabetes can experience fluctuations in the level of blood glucose and hypoglycemia. Glucose-responsive systems have been developed for insulin delivery in order to manage insulin release under the changes in glucose concentration [51]. Glucose-responsive systems might include glucose oxidase, phenylboronic acid or other compounds recognizing glucose. In the case of glucose oxidase–based systems, the oxidation of glucose leads to gluconic acid formation and alteration of local environment, namely pH changes. It may result in changes in swelling, degradation, or permeability of the carrier. Phenylboronic acid–based systems provide the reversible interaction with glucose, which could lead to conformational or charged polymer changes [51,52]. It is possible to develop a feedback-controlled delivery system, where elevated glucose will trigger greater insulin release. Theoretically, this method is likely to be more physiological compared to conventional administration. However, fast, predictable, and sufficiently responsive delivery in a physiologically relevant glucose range is challenging to achieve. Other factors include enzyme stability, immune reaction, oxygen requirement for glucose-oxidase-based systems, material stability, and reproduction of the kinetic profile of physiological insulin release. Thus, despite the promising idea of a glucose-responsive delivery system, much improvement and validation are needed.

5.3 Infectious Diseases

In recent years, stimuli-responsive delivery systems have been used for treating bacterial, fungal, viral, and parasitic infections. Conventional antimicrobial therapy is limited by poor penetration into infected sites, intracellular pathogen localization, toxicity, and antimicrobial resistance [53]. Specific conditions of infected areas could be regarded as endogenous stimuli. Bacterial infection often correlates with pH change, elevated activity of enzymes, increased reactive oxygen species formation, etc. The nanocarrier could be designed to remain stable in circulation and deliver the antimicrobial agent in response to these stimuli [53,54]. Moreover, the nanocarrier might increase the efficiency of the antimicrobial action due to higher drug accumulation in the infected site or intracellular delivery into the phagocytes harbouring the pathogens. Functionalization with target ligands could also be applied to increase interaction with the infectious agent or infected cells. Stimuli-responsive antimicrobial delivery systems could be combined with photothermal or photodynamic therapy. Light stimulation of the photosensitizer or photothermal agent generates reactive species or local heating, contributing to the death of the microorganism [54]. Variations in infection sites, microbes, biofilm, pH, and host immune responses can affect the process of stimulus-responsive drug delivery. Thus, an assessment based on clinically relevant pathogens and infection models is necessary.

5.4 Gene and Nucleic-Acid Delivery

The delivery of nucleic acids, including siRNA, mRNA, microRNA, plasmid DNA, and genetic material in general, is another significant example of applications for smart nanocarriers. As is known, nucleic acids are highly sensitive to enzymes and have relatively low permeability for cell membranes, which requires the use of delivery systems [55]. Polymer and lipid nanoparticles can protect nucleic acids during systemic administration and their cellular uptake. The stimulus-responsive systems can be used to induce endosomal escape and intracellular release of the payloads. In particular, acid-sensitive systems should be noted since the acidification of endosomes allows for the protonation of the payload or modification of carrier structure. After that, redox-sensitive systems can utilize the reduced intracellular environment for

payload release [55,56]. The development of mRNA-based therapeutic agents delivered by lipid nanoparticles has proven the effectiveness of the nucleic acid delivery at nanoscale. Further development of responsive carriers can improve tissue specificity, intracellular delivery, endosomal escape, and controlled release. However, nucleic-acid delivery is hindered by such problems as low stability, activation of innate immunity, limited tissue delivery, endosomal entrapment, and potential off-target effects. Thus, the advanced responsive delivery systems will require fine-tuning of both carrier design and nucleic-acid chemistry.

5.5 Vaccination and Immunotherapy

Nanocarriers with stimuli-responsive behavior have been designed for vaccine and immunotherapy applications as well. Nanocarriers protect vaccines or modulating agents from degradation and enable delivery to antigen-presenting cells [57]. Response to intracellular conditions (like endosomal pH or certain enzymes) might increase the efficacy of antigen processing via targeted antigen delivery and its interaction with the immune system pathways. Nanocarriers could also carry both antigens and adjuvants simultaneously, thus potentially improving immune response to vaccination. In the case of cancer immunotherapy, smart nanocarriers could deliver immune checkpoint inhibitors, cytokines, nucleic acids, or even tumor-associated antigens. Targeted delivery and stimulus-dependent release might improve local immune response while reducing systemic effects. However, interactions with the immune system are complicated and show significant interindividual differences, which should be considered carefully.

5.6 Theranostic Applications

Theranostics combines treatment and diagnostics in one system. Stimuli-responsive nanocarriers can be loaded not only with therapeutic components but also with imaging components, thus allowing to locate the diseased area, treat it, and monitor the treatment efficiency [58]. Imaging components could include fluorescent probes, magnetic nanoparticles, radiolabeled parts, and other contrast enhancement material. Stimulus-responsive systems can be designed in such a way that nanocarrier activation will simultaneously release the cargo and emit a signal used in imaging, allowing the localization of the nanocarrier or the moment of treatment activation. For example, multifunctional nanocarrier can be loaded with anticancer drugs, magnetic imaging components, and pH- or enzyme-responsive release mechanism. At the point of tumor accumulation, stimulus-dependent release will be triggered by the local stimulus, and imaging will allow the visualization of nanocarrier distribution. These systems are promising in the field of precision medicine since they would allow integrating the process of diagnosis, therapy, and follow-up of treatment. Yet, the increased multifunctionality of these systems brings the increased formulation complexity and increased manufacturing and regulation challenges [58,59].

5.7 Personalized and Precision Drug Delivery

The final goal of smart drug delivery systems is to provide patients with an intervention that corresponds to their biological features. Disease-related stimuli can differ considerably between patients, and this fact could influence the operation of responsive systems. Biomarker information, molecular profiling, imaging, pharmacokinetics, and mathematical modeling might help in selecting or designing of delivery systems, which are appropriate for certain diseases. The use of artificial intelligence and machine learning techniques could be useful in the prediction of the formulation features, release kinetics of drugs, biodistribution, and the outcome of treatment [60]. This emerging concept is going to improve smart delivery systems from the stimulus-responsive formulations to more flexible therapies. Yet, personalized delivery systems require the availability of reliable biomarkers, proper characterization of delivery systems, clinical validation of models and adequate data about patients. In general, smart stimuli-responsive systems show the wide potential for application in cancer, metabolic, infectious diseases, nucleic acid delivery, vaccination, and theranostics. Yet, most of these concepts still belong to the preclinical and translational level. Further development would require proving of therapeutic benefits, safety, feasibility, and clinical relevance in humans.

6. FUTURE PERSPECTIVES

It is predicted that future stimuli-responsive smart drug delivery systems will evolve from single-stimulus-based systems into more complex multi-functionable, adaptive, biomimetic, and personalized systems. These new systems will incorporate all possible functionalities, such as targeting, stimuli sensing, controlled release, diagnosis, and therapeutic monitoring. The

utilization of multi-stimuli-responsive structures based on a combination of endogenous stimuli such as pH, redox environment, enzymes, hypoxia, or reactive oxygen species (ROS) with exogenous stimuli such as light, magnetic field, ultrasonic waves, or temperature can provide increased spatiotemporal control over drug release. Structures can be designed to react to several biological stimuli consecutively, thus limiting premature release and ensuring efficient intracellular delivery. However, the increasing complexity should not overlook the considerations about reproducibility, fabrication processability, safety, and regulatory aspects. Moreover, artificial intelligence (AI) and machine learning (ML) are predicted to play a significant role in the design of stimuli-responsive smart drug delivery systems. The computational tools are valuable for predicting the properties of the formulations, tuning the particle size and composition, designing drug release kinetics, identifying the appropriate stimuli-responsive materials, and investigating the structure-activity relationships. AI can be integrated with pharmacokinetics, imaging, molecular, and clinical data for stratifying patients and selecting delivery systems compatible with individual features of the disease. However, the reliability of AI methods depends on the quality, diversity, and external validation of the datasets used. Another promising strategy includes utilizing biomimetic nanocarriers with the use of cell membrane–coated nanoparticles or extracellular vesicle-based systems. Combining the advantages of these biological carriers with stimuli-responsive systems can produce more advanced carriers capable of recognizing pathological tissues and releasing therapeutic compounds selectively. Additionally, theranostics, combining drug delivery and molecular imaging, can become another approach to delivering drugs to target sites. It is imperative to develop a long-term goal in which closed-loop delivery devices will be designed that can sense a biomarker level and release drugs based on therapeutic needs. An illustrative example of such devices is glucose-sensitive insulin delivery in which the concentration of glucose controls the delivery of insulin. Other types of biomarkers associated with different diseases can also be targeted in the same manner using similar feedback control strategies in the future. These systems could revolutionize the concept of stimuli-responsive delivery and make it an adaptable therapy system. However, clinical application of these systems will involve more attention towards scaling, quality assurance, long-term safety, predictable pharmacokinetics, and standardized regulation. Key quality attributes that include particle size, polydispersity, surface properties, drug encapsulation efficacy, sensitivity to stimuli, release kinetics, stability, and biodegradability need to be controllably reproducible through manufacturing. Furthermore, methods for testing sensitivity to stimuli and performance in vivo are required. Most importantly, future clinical trials need to ascertain whether responsiveness to stimuli improves treatment over current therapies, not just in laboratory experiments. Therefore, the future of smart drug delivery will rely on achieving the right balance between technological innovation and practicality for clinical application. The most prospective candidates for future use are those that exhibit biomarker-targeting ability, stimulus-responsiveness control, AI-assisted optimization, scalable manufacturing, and proven therapeutic effect in clinical settings. Such successful integration of these attributes could make stimuli-responsive delivery a key component of precision pharmacotherapy for cancer, metabolic, infectious, inflammatory diseases, and nucleic acid-based therapies.

7. CONCLUSION

The development of novel stimuli-responsive intelligent delivery systems represents a remarkable achievement in drug delivery, allowing for the regulation of the drug release depending on certain physiological, pathological, or external signals. Contrary to the conventional dosage forms, these systems can be designed in order to provide improved spatiotemporal regulation of the drug release that might enhance the drug efficacy as well as minimize side effects by reducing its general circulation. Endogenous stimuli (pH, enzymes, redox state, reactive oxygen species, temperature, glucose), along with exogenous stimuli (light, magnetic field, ultrasound, electric field) represent the tools for achieving controlled and targeted release of drugs. There is a wide range of smart drug delivery systems based on polymeric nanoparticles, liposomes, micelles, nanogels, dendrimers, lipid nanoparticles, hybrid nanocarriers, and biomimetic systems which allow combining several functions into one system, namely drug loading, targeting, responsiveness to certain stimuli, diagnostic imaging, and therapeutic monitoring. Various fields

such as cancer treatment, diabetes treatment, infectious diseases treatment, nucleic acid delivery, vaccination, and theranostics reveal great potential of these novel tools in overcoming the shortcomings of traditional pharmacological treatment. Despite all the progress that was made, the majority of stimuli-responsive delivery systems stay in the preclinical and preliminary translational stage. The problems related to biological variability, low specificity to stimuli, premature drug release, toxicity, interaction with the immune system, poor tissue penetration, formulation instabilities, complex manufacturing process, and lack of regulatory guidance still represent the challenges in this area. At the same time, it should be mentioned that being proved to respond to stimuli in vitro does not mean that the nanosystem will exhibit the same characteristics in vivo. The combination of responsiveness to multiple stimuli, biomimetic nanotechnology, theranostics, artificial intelligence and precision medicine holds great promise to take the field even further. The optimization of formulations through artificial intelligence techniques and biomarker-driven patient selection could help in the creation of more predictable and personalized delivery systems, while closed-loop systems may eventually be able to provide therapy that is timed based on physiologic requirements. However, the growing complexity of such systems needs to be balanced out with the need for practicality, economy, quality control and regulatory compliance. To conclude, the potential value of smart drug delivery needs to be assessed not only in terms of the degree of complexity of the vehicle and the number of stimuli used, but in terms of the capability of providing reproducible and clinically relevant therapy in a safe manner. Close cooperation between pharmaceutical scientists, material scientists, clinicians, computational scientists, manufacturing facilities and regulatory bodies is required to turn experimental developments into clinically valuable products. With proper optimization and validation, smart drug delivery systems responsive to stimuli can become an important part of future precision pharmacotherapy.

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