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Review

Stimuli Responsive Drug Delivery Systems: Types, Mechanisms, and Pharmaceutical Applications

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ABSTRACT

Modern exogenous and endogenous-based stimuli-responsive drug delivery systems (DDSs) for temporal and spatial drug release were examined aiming to focus on the shortcomings of traditional treatment approaches. This review addresses the mechanism of action and smart chemistry of numerous stimuli-responsive polymeric carriers, which are important in both the exogenous and endogenous domains of sick cells or tissues. Research is being conducted globally to build new stimuli-responsive DDSs, both internal and external, for biomedical, and/or pharmaceutical applications. A crucial component of designing so-called "smart" DDSs, which sophisticatedly regulates drug loading, adjusts the mechanism of drug release, controls individual

variability, and offers targeted drug delivery, is the polymeric carriers' dual/multi-responsive, internal, and even external behavior. Numerous DDSs have been invented, proposed, and used thus far. These systems include electrical, photo/light, pH, magnetic, temperature, ultrasonic, redox responsive DDSs, and multi-responsive DDSs (linking two or more from any of the aforementioned). To close the research gap, several difficult issues still need to be resolved despite the tremendous advancements made in the DDSs field. The drug release mechanisms and the uses of exogenous and endogenous stimuli-responsive DDSs in therapeutic settings were therefore highlighted.

Keywords: Drug delivery systems, drug release kinetics, stimuli-responsive targeting, exogenous stimuli, and endogenous stimuli.

1. Introduction

DDSs are devices or formulations fabricated to introduce an active pharmaceutical substance to the body, thereby improving its safety and effectiveness through controlling the site, and time of drug release [1]. This encompasses the delivery of the pharmaceutical formula, the regulated liberation of its active constituents, and the consequent conveyance of these active constituents to the intended site of activity [2].

Traditional DDSs are restricted by their incapability to precisely control dosing, and attain site targeting [3]. Conventional approaches of drug delivery encounter difficulties in sustaining optimal drug levels while minimizing side effects and preventing drug toxicity [4,5].

To cope with the restrictions of traditional DDSs, and to improve the patients' care quality, the pharmaceutical research field addresses the necessity for the development and design of novel DDSs (NDDSs) [6]. The necessity for elevated performance, and modified drug release is triggered by the paramount importance of enhancing patient compliance, achieving superior clinical efficacy, and extending product lifespan via controlled drug release systems [7]. Additionally, these systems offer the distinct economic advantage of reduced frequency and expenses of administration. Furthermore, the evolution from conventional to NDDSs can lead to significant improvements in therapeutic efficacy, safety profile, and patient compliance. Consequently, NDDSs might be one of the most rapidly expanding sectors in the pharmaceutical industry [8].

NDDSs are meticulously fabricated to optimize the delivery and efficiency of existing medications in comparison with traditional systems. These innovative systems employ advanced

techniques and novel dosage forms to precisely achieve targeted, regulated, and modulated drug delivery [4,9–11]. Ideally, NDDSs strive to fulfill two key prerequisites: site-specific drug delivery at rate and extent dictated via the body's requirements, and monitoring of the drug level throughout the treatment period [12]. The core impetus behind the progression of NDDSs lies in enabling sustained and controlled drug release, thereby maintaining optimal therapeutic drug levels along with concurrent reduction of adverse effects [13,14].

Recently, advancements in nanoparticle-based DDSs, have gained the attention of pharmaceutical and biomedical researchers. This is primarily attributed to their potential to significantly enhance the effectiveness of various drugs, particularly those targeting cancer, viruses, and microbial infections [15–19].

In addition to their usage in drug delivery, nanoparticles have found extensive application in biomedical imaging due to their capacity for targeted augmentation. This feature permits the integration of contrast ants and allows for the tuning of pharmacokinetic profiles [20]. Furthermore, theranostic nano-carriers provide synchronized diagnosis, therapy, and medication response monitoring [21].

Notably, the remarkable advancements in materials science and pharmaceutics have facilitated the development of a diverse array of nano-carriers with varying surface properties, sizes, and structures [22].

Moreover, the tremendous progress in drug delivery has addressed the formulation of on-demand (switch on/off) mechanisms. These innovative systems offer tailored drug release mechanisms with exceptional temporal and spatial drug delivery [23]. The paradigm of on/off drug delivery is made possible by the formulation of stimuli-responsive systems which possess the ability to detect their microenvironment and dynamically respond, imitating the inherent responsiveness observed in living organisms [24]. Nevertheless, the implementation of this approach exhibits a considerable challenge for its complexity [25].

The pioneering inception of stimuli-responsive DDSs was initially proposed in the 1970s, sparking a surge of research activity focused on the development of such materials for targeted therapeutic delivery [26]. Stimuli-responsive systems may demonstrate sensitivity to particular endogenous stimuli, including reduced interstitial pH, elevated concentrations of glutathione, or heightened activity of specific enzymes [27,28]. Additionally, the application of exogenous

physical stimuli, such as electric fields, magnetic changes, temperature variations, ultrasound, and light, can also be employed [29,30].

In this Review, we elucidate the substantial advancements achieved in the realm of stimuli-responsive nanocarriers for drug delivery.

2. Exogenous stimuli-responsive drug delivery systems

Exogenous stimuli-responsive DDSs have been reported to be advantageous over endogenous stimuli-responsive DDSs for their potential to circumvent inter-individual variability in drug release. This advantage stems from the ability to precisely control these external stimuli compared to the inherent variability of internal physiological factors (e.g., pH, enzyme levels). Various external stimuli have been demonstrated to be effective in regulating drug release. Since the majority of these stimuli result in the liberation of heat, thermo-responsive polymers may perform a crucial role in developing these DDSs. Through temperature-sensitive materials, this temperature rise can promote the release of drugs [31].

2.1. Thermoresponsive systems

Thermoresponsive DDSs stand as one of the extensively researched approaches, particularly in the field of oncology. The responsiveness to temperature is typically dictated by a nonlinear and abrupt alteration in the characteristics of at least one constituent of the system components along with changes in temperature. These abrupt changes instigate the drug release in response to fluctuations in the surrounding temperature [32].

Two approaches for the formulation of thermoresponsive drug release have been described: one uses external stimuli to generate hyperthermia to facilitate thermal-based therapy; the other responds to higher temperatures of the diseased tissues for burst release. Approaches based on external stimuli seem more promising for controlling drug delivery when compared to techniques based on internal stimuli because of their exact control and production feasibility [33].

Thermoresponsive polymers exert a pivotal part in these systems due to their ability to react to temperature variations. Two distinct behaviours have been observed for thermoresponsive materials, namely the upper critical solution temperature (UCST) and the lower critical solution temperature (LCST) [34]. For polymers exhibiting UCST characteristics, increasing temperature above the UCST results in enhanced hydrophilicity, that governs the swelling performance of the carriers, thereby modulating the drug release. Conversely, for polymers exhibiting LCST

characteristics, decreasing temperature below the LCST results in increased swelling, while increased temperature results in decreased swelling [35].

Liposomes, polymer micelles, or nanoparticles with a LCST are examples of thermoresponsive systems [36]. Thermoresponsiveness in liposomes is often caused by the shift of the lipid components phase and the corresponding changes in the bilayer structure. Heat is often employed *in-vivo* via radiofrequency oscillators, tiny annular-phased array microwaves, or temperature-controlled water sacks [37]. Thermosensitive liposomes arguably represent the most well-developed class of thermoresponsive nano-systems, a fact evidenced by their successful implementation in various clinical trials [38].

Currently, doxorubicin-loaded thermoresponsive liposomes, are undergoing phase II clinical investigation for their efficacy in treating breast cancer, and advanced to phase III investigations for treatment of hepatocellular carcinoma [39,40]. Furthermore, smith et al., developed specifically targeted thermosensitive liposomes, for the treatment of breast cancer [41].

Thermoresponsiveness can also be triggered by transient decrease in temperature, a phenomenon known as cold shock or cryotherapy. This rapid temperature shift triggers reversible swelling or deswelling of the nanocarrier, resulting in enhanced drug release through increased porosity. For instance, nano-capsules composed of Pluronic F127 and polyethyleneimine were employed for the efficient delivery of small interfering RNA (siRNA) into the cytosol, subsequently leading to the suppression of a specific messenger RNA [42].

2.2. Magnetic responsive systems

The inherent ability of magnetic fields to penetrate biological tissues resulted in its utilization in magnetic resonance imaging (MRI) [43]. Beyond imaging purposes, controlled drug release can be achieved via the utilization of magnetic field-responsive carriers. These carriers have the ability to modify drug release through the application of an exogenous magnetic stimulus. Moreover, there is a potential for integrating diagnostics and therapy within a unified system, commonly referred to as the theranostic approach [44–46].

The potentials of magnetically responsive nanomaterials are their chemical stability, large surface area, high loading capacity rate, and minimal intraparticle diffusion, which make them appealing for use in a variety of industries [47,48]. There are four categories of magnetic-responsive nanomaterials: metallic, coated metal, oxides, and coated oxides [49]. The most studied

group consists of iron oxides, also known as ferrite nanoparticles, arranged in a crystalline form as magnetite or maghemite [50].

Following the administration of magnetically responsive DDSs, drug targeting is commonly achieved through directing an exogenous magnetic field toward the target tissue. This approach has shown significant promise in pre-clinical cancer treatment. Mesoporous silica shell nanocapsules [51], magnetic nanoparticle-based delivery systems [52], superparamagnetic Liposomes [53], and porous metallic nano-capsules [54] have been emerged as potential delivery systems.

Thirunavukkarasu et al., formulated superparamagnetic iron oxide nanoparticles (SPIONs), where doxorubicin (DOX) and SPIONs have been loaded in a temperature-sensitive matrix for a theranostic purpose [45].

2.3. Ultrasound-responsive systems

Ultrasound, traditionally known for diagnostic imaging, has emerged as a multifaceted tool in therapeutic medicine, particularly in drug delivery systems. Beyond its role in inducing hyperthermia, ultrasound energy offers nonthermal effects, enhancing drug release mechanisms through various physical actions. From triggering cavitation phenomena to facilitating vessel permeability, ultrasound's versatility enables precise spatiotemporal control over drug delivery, mitigating side effects on healthy tissues [55–59].

2-Tetrahydropyranyl methacrylate (THPMA), is a mechano-labile functional group that can hydrolyze in response to Ultrasonic exposure. It is an ultrasound-responsive hydrophobic monomer that is present in the polymeric gate. The acetal group of this initially hydrophobic unit; was broken after exposure to ultrasound, producing the hydrophilic product of methacrylic acid (MAA). Gates could be opened and closed by hydrophobic-hydrophilic transformation. The hydrophobic THPMA units changed into a hydrophilic MAA when ultrasound was applied, increasing the polymeric nano-gate's total solubility. Ultrasound-induced drug release behavior was caused by the dissolved polymer gate losing its blocking ability [60].

2.4. Light/Photo responsive systems

To create intricate scaffolding for regulating cellular behaviour inducing the release of entrapped chemicals, the construction of light-responsive smart biomaterials is an appealing approach [61,62]. Compared to other stimuli, the light stimulus has the advantage of being quickly

imposed and precisely given in precise amounts, allowing for less intrusive methods to control both space and time [63,64].

Wide range of UV to NIR wavelengths have been used as light stimuli. However, UV light is frequently used as a stimulus, yet it may not be safe and can't enter tissues deeply. NIR, on the other hand, is more suited for biomedical purposes, particularly for being less energetic, causing less damage to biological tissues, and capable of entering tissues more deeply [62].

For instance, when photo-responsive micelles of polyglycerol-containing spiropyran were exposed to UV light, the breakdown of the hydrophobic spiropyran resulted in the formation of hydrophilic merocyanine [65]. Additionally, Petriashvili et al., fabricated spiropyran doped liquid crystal microspheres [66]. Advanced photopolymerizable linear or crosslinked polymers [67] and hydrogels [68] have been fabricated for tissue engineering, cell encapsulation, and drug delivery.

Moreover, Photo-switchable polyacrylamide hydrogels containing an azobenzene molecule have been thoroughly investigated for their application in regenerative medicine [69]. Gold nanoparticles-based photoresponsive liposomes are widely used for controlled drug delivery [70]. Because of its customizable optical and photothermal properties, inertness, and lack of toxicity, gold nanoparticles are widely used based on their surface chemistry, size, and form [71].

2.5.Electrical responsive systems

After administering electro-responsive drug carriers, a mild electric field can be administered over the targeted tissue to achieve regulated on-site drug release. Different methods, such as the oxidation-reduction process, carrier structural disruption, and activation of thermo-responsive carriers, have been shown to control drug release through electrical stimulation [72]. Neumann et al., have disclosed a novel approach for drug delivery that is electro-responsive. They controlled the release of the medication through a pH-sensitive substance by using the local pH change brought on by an electrochemical reaction [73]. They used a pH-sensitive copolymer, poly(methyl methacrylate-co-methacrylic acid), to create drug-loaded nanofilms. Additionally, they discovered that buffer action stopped the drug release in the off-state by causing the pH drop caused by the electrical signal to rebound fast when the stimulus was removed [74].

Electrical signals can be effective in potentially delivering drugs in a controlled manner [75,76], regenerating damaged tissues [77,78], and modulating cell proliferation and differentiation [79,80]. Polyvinylidene fluoride (PVDF) is one of the polymers that has been utilized extensively in tissue engineering, for example, to treat neurological illnesses. In place of

traditional neurotrophin treatments, Hoop and colleagues [81] have created a PVDF membrane to encourage neuronal differentiation, resulting in neurite outgrowth uniform in all directions. This is likely because the cells' calcium channels were activated by the piezoelectric stimulation, which raised the Ca^{2+} content of the cells and started the adenylyl cyclase (AC) pathway.

One of the examples of electrical responsive drug delivery is hydrogels; including polyelectrolytes, which are polymers with comparatively large concentrations of ionizable groups along the backbone chain, representing the basis for electrically-responsive hydrogels, which are also pH-responsive [82]. Although polycations and an amphoteric polyelectrolyte [83] have also been employed, polyanions have accounted for the majority of the polymers examined. Both artificial and naturally occurring polymers have been utilized, either singly or in combination. Examples of polymers that occur naturally Hydrogels' reaction to an electric field. Numerous researchers have examined how polyelectrolyte hydrogels react to an applied electric field using various experimental setups. The gel may or may not be submerged in a buffer, saline solution, or other electroconductive media.

3. Endogenous stimuli-responsive drug delivery systems

These DDSs initiate drug delivery through tissue regulation in the microenvironment, interaction between antibodies and antigens, and over-expression of enzymes.

3.1. pH-responsive systems

The extracellular organelles and bloodstream typically maintain a pH of 7.4, while the stomach exhibits a pH range of 1–3 and the duodenum and ileum of the gastrointestinal tract maintain pH levels between 6.6–7.5. Intracellular sub-endosomal and lysosomal organelles maintain pH ranges of 5.5–6.8 and 4.5–5.5, respectively. This wide range of pH values is crucial to consider during the fabrication of pH-responsive systems [77].

Variations in pH can impact crosslinking processes, especially significant for injectable hydrogels and self-healing materials. Additionally, protonation or deprotonation of acidic or basic groups can influence release profiles, and potentially target specific tissues or cells. Furthermore, engineered hydrogels can modulate physicochemical properties, directly affecting the fate of encapsulated cells [84].

The pH responsiveness observed in such systems primarily arises from the acid hydrolysis of chemical bonds, the ionizable groups' protonation, and through conformational or chemical alterations within the used polymeric materials. Notably, in comparison to small molecule sensors,

responsive nano-systems exhibit remarkably high sensitivity in their response, owing to a positive synergy characteristic of supramolecular self-assembly systems. At a molecular level, the pH sensitivity of these nanosystems may be attributed to various factors such as ionic bonds, hydrogen bonds, π-π stacking, or hydrophobic interactions within the nanocarrier structure [85].

pH variations have been ingeniously harnessed to regulate the targeted distribution of medications within distinct bodily regions, including vagina, GIT, and intracellular locales as lysosomes or endosomes. Additionally, these variations in pH serve as pivotal cues to initiate the release of drugs precisely when subtle alterations in the environment are indicative of pathological conditions [86,87].

The buffering capacity of polyethyleneimine arises from its diverse amine groups with varying pKa values. These groups undergo protonation to various extents depending on the pH conditions [88]. This phenomenon primarily stems from the abnormal angiogenesis observed in rapidly growing tumors, resulting in a swift depletion of nutrients and oxygen. Consequently, there is a metabolic shift towards glycolysis, resulting in the accumulation of acidic metabolites in the tumor. Thus, effective pH-responsive systems have to swiftly respond to even subtle changes in pH within the tumor extracellular microenvironment. For instance, chitosan exhibits swelling upon protonation of its amino groups, facilitating the release of entrapped tumor necrosis factor-alpha in tumor tissues. Additionally, the abrupt dismantlement of PEG–poly(β-amino ester) micelles triggers the leak of encapsulated camptothecin. This pH-mediated triggered delivery approach has also demonstrated successful protein delivery into the ischemic area [89].

In infected tissues, the acidic environment poses a challenge, although it's noteworthy that cutaneous wound pH dynamically correlates with wound healing stages [29]. For instance, the inflammation stage tends to be acidic, while granulation shifts pH to alkaline range, and the remodeling phase restores the skins' initial pH. pH-responsive wound dressings can be developed by crosslinking materials using various polymerization methods. These hydrogels exhibit tunable properties, making them promising for stage-responsive wound dressings [90].

Cell recruitment, infiltration, and vascularization are critical challenges in wound healing. pH-responsive scaffolds, such as HEMA/DMAEMA scaffolds photopolymerized at different molar ratios, demonstrate pH-dependent swelling behavior, with increased oxygen penetration and cell infiltration under acidic conditions. These scaffolds promote a pro-healing environment,

fostering significant levels of tissue formation and vascularization, thus holding the potential for enhancing wound healing processes [91].

3.2. Redox responsive systems

Redox-responsive materials may exert a key function in the intracellular and extracellular regions of diseased cells or tissues [92]. Notably, a considerable redox potential difference exists between the extracellular and the reducing intracellular environments. The cellular nuclei and cytosol show a much higher concentration of a reducing agent, such as glutathione (GSH), than the extracellular and intercellular fluids [93,94]. The greater concentration of GSH inside cells determines the reduced microenvironment in the cytoplasm [95]. Therefore, redox-sensitive nanocarriers have gained more attention [96]. Moreover, glutathione-responsive DDSs were fabricated for on-demand and responsive intracellular drug release [97].

The mechanism of endocytosis allows nanocarriers to enter the cell. As it gets closer to the cytosol, GSH breaks down the disulfide bonds, explodes, and releases the medication [96]. The vast majority of glutathione-responsive block copolymers have the ability to form "Shell-Sheddable" micelles because of the disulfide connection that unites hydrophilic and hydrophobic blocks. These micelles provide the therapeutic substance when they destabilize upon encountering glutathione. In-vitro and in-vivo studies shown that disulfide linkers in GSH-responsive micelles were quickly destabilized after cell penetration, releasing the ingredients of thiols, which bind to the micelle's core or shell or adhere to the Drug molecules by disulfide bonding. Increased concentrations of reducing agents inside intracellular regions support the disulfide-containing polymers [94].

Ren et al., fabricated self-assembled nanostructures by exploiting solubility changes caused by oxidation in selenium block copolymers [98]. The spherical micelles with hydrophobic selenium centers were made using copolymers. The micelles were disintegrated, and the hydrophilicity was increased when selenium was converted from hydrogen peroxide to selenoxide. Upon the addition of reductants, spherical micelles could be replicated. It was shown that these selenium-containing nano ampules may easily form spherical micelles in both oxidizing and reducing environments. Thus, redox-responsive characteristics fully recovered [98].

A vesicle composed of layer-by-layer construction has been utilized to deliver drug medications. This process involves alternatingly depositing polyelectrolytes onto a template to form nanocarriers. The Caruso group used a disulfide crosslinker in combination with poly(N-

vinyl pyrrolidone) and poly(methyl methacrylate) to develop redox-responsive capsules that were capable of enclosing DOX and plasmid DNA [99,100] The DOX-loaded capsules demonstrated a 5000-times increase in cytotoxicity compared to DOX alone [99]. Up until now, the disulfide bond has been frequently used to create reduction-susceptible nanocarriers. The primary problem was in-vivo stability because the extracellular compartment contains cysteine and GSH, which might lead to an early outburst [100]. This could be solved by using multiple disulfide connections, which would change the number of disulfide cross-links [101,102].

3.3. Enzyme responsive systems

Enzyme-dependent drug delivery system is a system whose physicochemical characteristics change macroscopically as a result of the enzyme's biocatalytic activity [16]. The fabrication of a uniquely promising responsive element for DDS is largely dependent on the regulation and/or dysregulation of enzymes in the intracellular microenvironment. Enzyme-responsive DDSs show tremendous qualities that are highly beneficial in bio-nanomedicine, including process efficacy, biorecognition, catalytic activity, selectivity, and sensitivity [16,103].

Diseases' different pathological states can be identified and monitored utilizing novel ultra-sensitive in-vivo DDSs, prompted by enzyme-mediated dysregulation in diseased organelles. Regarding enzyme-responsive DDS, the enzyme-mediated degradation of a polymeric moiety resulted in controlled drug release out of the carriers [16].

Antibody-directed enzyme prodrug therapy and polymer-directed enzyme prodrug therapy are two widely utilized strategies for the enzyme-specific release of conjugated medicines at the tumor site [104]. The majority of invasive diseases, such as cancer, are typified by the overexpression and upregulation of several secreted or membrane-bound enzymes, such as proteases, cathepsins, and matrix metalloproteinases [105]. Various novel DDSs are fabricated based on the altered expression of certain enzymes in infectious diseases, wherein active drugs are accumulated at the intended biological target [106].

The vast majority of enzyme-mediated DDSs rely on the enzyme's expression in the extracellular environment. According to modern research, modified liposomes [107], bioresponsive mesoporous silica nanoparticles [108], or dextran-coated iron oxide nanoparticles [109] can be linked with surface PEG chains by short peptide chains that are then broken down by matrix metalloproteinases.

Enzymes can also be employed to transport medications into intracellular compartments. For example, the selective delivery of DOX utilizing mesoporous silica scaffolds joined with polysaccharide derivatives, following lysosomal enzyme-mediated breakage of the glycoside linkages and reduction of the polysaccharide chain lengths [110]. Similarly, drug release was achieved by the rapid enzymatic degradation of polymersomes by the lysosomal enzyme cathepsin B, which was overexpressed in numerous malignant tumors [111].

Polymer-based delivery systems bearing a cationic peptide as the substrate of intracellular proteases (or kinases) that are exclusively produced in human immunodeficiency virus-infected cells [112] or inflammatory cells [113] have been used to enable transgene expression with great cell specificity. Gene release and transcription were promoted by the disintegration of polymer–DNA electrostatic interactions by enzymes [114]. Developed lipase-sensitive polymeric triple-layered nanogel for the on-demand release of vancomycin antibiotics. This system dramatically inhibited Staphylococcus aureus growth and effectively terminated intracellular bacteria [115].

4. Dual / multi stimuli-responsive drug delivery systems

Multi-stimuli responsive DDSs represent a significant advancement in the field of targeted therapeutics. Unlike conventional stimuli-responsive systems that respond to a single stimulus, multi-stimuli-responsive DDS is designed to respond to two or more stimuli [116]. These smart carriers are emerging as game-changers, responding to specific triggers in the body, and releasing their cargo only when certain conditions are met [117]. This enhances targeting and reduces side effects [118].

Multi-stimuli responsive DDSs are engineered to react to various endogenous and exogenous stimuli [118]. Zhang et al., fabricated a pH/reduction dual-responsive and folate-decorated polymeric micelles for targeted chemo-photothermal combination therapy [119]. DOX and indocyanine green were co-encapsulated into those carriers for enhanced imaging and chemo-photothermal combination therapy.

You et al., employed redox/NIR light dual stimulus-responsive polymeric nanoparticles for targeted delivery of cisplatin [120]. These nanoparticles revealed in-vitro drug release of 99.35% after 72 hours at pH 7.4, compared to 73.46% in systems responsive to NIR alone, 58.45% for glutathione-responsive systems, and 12.35% without any stimulus. Cui et al., employed pH and temperature dual responsive ionically self-assembled nanoparticles utilizing doxorubicin as a model drug [121]. While enhanced DOX delivery through thermosensitive liposomes utilizing

temperature-responsive N-isopropylacrylamide and pH-responsive propylacrylic acid was fabricated by Ta et al. [122].

Light and pH dual responsive mesoporous silica was fabricated by exploiting the resonance surface properties of palladium and silver for enhanced targeting of the anticancer drug, doxorubicin [103]. Other hybrid mesoporous silica nanoparticles showed a response to temperature and magnetic field for remotely controlled release of methotrexate to skeletal muscles [123]. Hegazy et al., constructed magnetic, reductive, and thermos-sensitive triple stimuli responsive mesoporous silica nanoparticles loaded with indocyanine green and DOX [124]. These systems represent a promising candidate in the formulation of targeted delivery of therapeutic agents to temperature and more reductive environment tissues, such as tumors and inflammatory sites.

5. Novel Approaches in stimuli-responsive drug delivery systems

4D Printing stimuli-responsive drug delivery systems

Four-dimensional printing is an interesting field of study that integrates intelligent materials into three-dimensional printing. Using this method, objects that can gradually change form in response to environmental stimuli, such as moisture, electric or magnetic fields, UV light, temperature swings, pH variations, or alterations in the composition of ions, can be created [125,126]. Intelligent materials, such as shape memory polymers, alloys, hydrogels, ceramics, and composites, which can react to external stimuli, are essential for 4D printing. Unlike traditional 3D printing, the ability of 4D printed materials to undergo structural and/or property alterations expands their applications across industries such as aerospace, biomedical, soft robotics, engineering, and fashion, potentially revolutionizing manufacturing [127–129]. In biomedical applications, however, 3D printed constructs fell short of expectations mainly due to their inability to adequately mimic dynamic human tissues. To date, most of the 3D printed biomedical structures are largely static and inanimate as they lack the time-dependent dimension. To adequately address the dynamic healing and regeneration process of human tissues, 4D printing emerges as an important development where “time” is incorporated into the conventional concept of 3D printing as the fourth dimension [130].

6. Applications

Over the last decades, DDSs have been developed and improved to increase the efficacy and safety of drugs aiming to improve health and decrease side effects. Applications of stimuli responsive DDS are applied in many fields of medicine like diagnosis, treatment, and imaging.

5.1. Exogenous stimuli-responsive drug delivery systems

Exogenous responsive DDSs are at the forefront of pharmaceutical innovation, employing external stimuli to precisely control drug release. Table 1 shows examples of thermos-responsive, electrical-responsive, ultrasound-responsive, light/Photo-responsive, and magnetic-responsive DDSs.

5.2. Endogenous stimuli-responsive drug delivery systems

Endogenous responsive DDSs represent a groundbreaking approach in pharmaceuticals, leveraging the body's physiological cues for precise drug targeting and release. Table 2 shows examples of pH-responsive, enzyme-responsive, and redox-responsive DDSs.

Table 1: Applications of Exogenous stimuli-responsive drug delivery systems

Drug	Type of stimuli	Outcome	Ref.
Doxorubicin	Thermo-responsive	Drug-loaded liposomes were prepared with enhanced localization of the drug in tumor cells	[131]
Curcumin	Thermo-responsive	Chitosan nanogels were developed with enhanced intracellular drug delivery	[132]
Doxorubicin	Thermo-responsive	Thermos-sensitive vesicles were created and were effective against multidrug resistant cancer cells	[133]
Geldanamycin	Magnetic-responsive	Magnetic nanoparticles were prepared to release drug in response to an alternating magnetic field, inducing effective apoptosis of cancer cells	[134]
Doxorubicin	Magnetic-responsive	Polymeric micelles of doxorubicin were developed which could generate magnetic hyperthermia leading to controlled drug release against breast cancer cells	[135]
Topotecan	Ultrasound-responsive	Enhanced uptake of topotecan-loaded liposomes into cancer cells because of a targeted focused ultrasound waves	[136]

Paclitaxel	Ultrasound-responsive	Combining paclitaxel-liposomes with ultrasound waves for treatment of glioblastoma	[137]
Doxorubicin	Light/Photo-responsive	Combining photothermal processes under near-infrared light with chemotherapy resulted in tumor ablation	[138]
Zoledronic acid	Light/Photo-responsive	Photochemical cellular internalization was achieved with simultaneous intracellular drug release	[139]
Dexamethasone	Electro-responsive	Drug is released in linear profile in response to voltage stimulation	[140]
Diclofenac sodium	Electro-responsive	Faster release of the anionic drug was achieved by external electric voltage application	[141]

Table 2: Applications of Endogenous stimuli-responsive drug delivery systems

Drug	Type of stimuli	Outcome	Ref.
Insulin	pH-responsive	pH-sensitive hydrogels were used and the variations in their swelling ratios in the stomach and intestine led to the control in the drug release rate	[142]
Ketoprofen	pH-responsive	Drug-loaded calcium alginate beads were prepared and the cross-linking degree changes with variations in pH leading to controlled drug release	[143]
Naproxen	pH-responsive	Chitosan/poly vinyl alcohol pH-sensitive hydrogels were developed with maximum swelling occurring at neutral pH overcoming the negative impact of naproxen on GI epithelium	[144]
Methotrexate	pH-responsive	Modified trimethyl chitosan nanoparticles were prepared with prolonged drug release over 72 hours at pH 7.4	[145]
Doxorubicin	Redox-responsive	Faster drug release of the drug from redox-sensitive liposomes	[146]
Paclitaxel	Redox-responsive	PEG-functionalized liposomes were prepared with enhanced cellular uptake into tumor cells due to tumor-reductive environment	[147]
5-Fluorouracil	Redox-responsive	Chitosan-cystamine-methoxy poly(ethylene glycol) redox sensitive polymeric nanoparticles were developed and the reduction of the disulfide bond of the cystamine accelerate drug release.	[148]
Cisplatin	Redox-responsive	Nanoparticles containing cystamine, as a crosslinker having disulfide bonds, were prepared and a fast drug release was achieved through the reduction of these bonds	[149]
Docetaxel	Enzyme-responsive	Matrix Metalloproteinase-2/9 (MMP-2/9)-responsive micelles were developed and conjugated to an oligopeptide that when exposed to the enzyme led to micelle collapse and drug release	[150]

5.3. Multistimuli-responsive drug delivery systems

Table 3 shows examples of multistimuli-responsive DDSs.

Table 3: Applications of multistimuli-responsive drug delivery systems

Drug and/or carrier	Stimulus	Outcome	Ref.
Micelleplexes	Light/pH	Triblock copolymer has been developed and applied as a carrier for gene delivery in which the release was triggered by the protonation and degradation of micelleplexes	[151]
Dendrimeric nano-assemblies	Enzyme/pH/Redox	Tumor-specific dendrimeric nano-assemblies in which the drug release is activated through multiple stimuli was developed to overcome tumor multidrug resistance	[152]
Micelles	pH/Redox	A biodegradable PEG-based micelles were developed with a particle size that increases after exposure to acidic pH and reactive oxygen species (ROS) in tumor environment leading to drug release	[153]
Curcumin/ Silver nanoparticles	pH/Redox	The release of curcumin was achieved through dual-stimuli-responsive mechanisms (pH and ROS) thus reducing the side effects of non-controlled drug release	[154]
Doxorubicin/ nanoparticles	pH/Redox	Doxorubicin-loaded nanoparticles with pH and GSH dual responsiveness were prepared that exhibited tumor-targeted controlled drug release	[155]

7. Conclusion

In recent years, considerable efforts have been made to create DDSs that can adapt to changes in the environment, whether internal or external, with precision and control. Thanks to major advances in science, stimuli-responsive polymeric carriers have arisen as a promising solution for targeted medication administration. In this work, we have highlighted the unique properties of these carriers and their potential applications in drug delivery.

The article discusses various stimuli-responsive DDSs and provides appropriate examples. These DDSs include temperature-responsive, magnetic-responsive, pH-responsive, photo/light-responsive, redox-responsive, electrical-responsive, ultrasound-responsive, and/or all-in-one dual/multi-responsive DDSs.

Although there has been significant progress in the field of DDSs, there are still many unanswered questions in the biomedical and pharmaceutical industry. When creating drug delivery systems, it is important to consider essential limiting factors such as non-toxicity, biodegradability, biocompatibility, and safe removal of the smart carriers from the biological system. Additionally, the size of the carrier plays a crucial role in facilitating a quick response. Thus, further work is needed to manipulate these factors in order to achieve full control over the developed drug delivery systems.

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- **Conflict of Interest**

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