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Review Article

EMERGING TRENDS IN STIMULI-SENSITIVE DRUG DELIVERY SYSTEM: A COMPREHENSIVE REVIEW OF CLINICAL APPLICATIONS AND RECENT ADVANCEMENTS

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ABSTRACT

The combination of fields such as applied physics, biology, computational modeling and analysis, pharmaceuticals, chemistry, optics, and material science study has been made easier for the rise of stimuli-sensitive drug delivery systems. This study aimed to overcome the shortcomings of conventional therapeutic approaches by concentrating on the most recent developments in stimuli-sensitive drug delivery systems, which are intended to accomplish the targeted release of drugs in specified areas. This review aims to provide an overview of stimuli-sensitive drug delivery systems and recent advancements between 2015 and 2023 by focusing on their ability to respond to exogenous and endogenous stimuli. In recent years, significant progress has been made in developing innovative stimuli-responsive drug delivery platforms that can trigger various external stimuli, such as light, temperature, magnetic fields, and ultrasound. These exogenous stimuli-responsive systems enable on-demand drug release at specific target sites, allowing for personalized and patient-centric treatment strategies. Notable breakthroughs include photoresponsive nanocarriers, thermosensitive hydrogels, and magnetic nanoparticles, all designed to respond to specific cues for controlled drug delivery.

Keywords: Stimuli-sensitive drug delivery systems, Exogenous stimuli, Endogenous stimuli, Recent advancements

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INTRODUCTION

A stimuli-sensitive drug delivery system is a sophisticated platform designed to respond intelligently to specific triggers from external sources (exogenous stimuli) and internal cues within the body (endogenous stimuli). These triggers include light, temperature, magnetic fields, ultrasound, pH levels, enzymatic activity, and more. By exploiting the potential of these stimuli, stimuli-sensitive drug delivery systems can achieve accurate drug release at specific locations, maximizing therapeutic results and minimizing potential adverse reactions [1].

This article will explore the fascinating world of stimuli-sensitive drug delivery systems. We will focus on two crucial aspects: the diverse range of exogenous and endogenous stimuli that can trigger drug release and the recent ground-breaking advancements that have propelled this field to new heights. By obtaining a comprehensive understanding of the fundamental principles and the latest innovations, we can better appreciate the immense potential of intelligent drug administration systems in revolutionizing patient treatments and ushering in a new era of personalized medicine. So, let us embark on this journey through cutting-edge advancements in drug delivery, where science meets resourcefulness to redefine the panorama of healthcare.

Stimuli-sensitive drug delivery systems

A recent advanced method for drug targeting is the Stimuli-sensitive drug delivery system. In a stimuli-sensitive drug delivery system, the medication is directly delivered to the target site or released whenever necessary, thereby reducing the adverse effects of medication in other tissues [2]. Medication is selectively accumulated in the target site for a prolonged period in a highly controlled manner for enhancing the therapeutic activity in the stimuli-sensitive drug delivery system [3]. An ideal stimuli-sensitive drug delivery system should meet several critical criteria. Firstly, the material used to create the system's matrix should be biocompatible or at least not adversely affect the body. Secondly, the medication should be able to be encapsulated within the system without losing its effectiveness. Thirdly, the release of the drug should be able to be triggered in a non-invasive way without requiring any external devices. Finally, the system should ensure that no medication is released until it is activated or turned on [4].

Classification is based on the mechanism by which drug release

Endogenous stimulus

The term "endogenous stimulus," also called intrinsic stimulus, pertains to a scenario wherein the triggering signal originates within the body. This signal is generated explicitly by factors such as the internal pH level, redox activity, and enzyme activity. These drug delivery systems initiate the administration of medications by controlling the conditions within the tissues, increasing the activity of particular enzymes, facilitating the interaction between antibodies and antigens, and identifying specific configurations of host-guest molecules [5].

pH-responsive drug delivery system

pH-susceptible polymers are a kind of polymers that demonstrate a reply to fluctuations in the encompassing pH levels. These polymers can be sorted into two categories: (A) polymers with ionizable functional groups and (B) polymers containing acid-degradable bonds. The ionization of the connected acidic or fundamental groups is prompted by the change in environmental pH, which causes cross-linking and modifications to the polymer's swelling properties [6]. To demonstrate, when subjected to a low pH environment, polyacid polymers undergo a decrease in size, whereas, in a high pH environment, they encounter an extension due to the protonation of their acidic components [7]. Combining pH-sensitive drug-release systems with other stimuli, redox, or temperature triggers enhances the accuracy and efficacy of these systems in responding to multiple parameters. For example, PEG-grafted PMAAc demonstrates notable sensitivity to changes in pH levels. For instance, To achieve specific delivery of 5-Fluorouracil (5-FU) to the colon, researchers developed a method utilizing citrus pectin nanoparticles (E-CPNs) coated with Eudragit S100 [8]. Polymers that respond to changes in pH

commonly encompass chitosan, albumin, gelatin, interpenetrating networks of poly(acrylic acid) (PAAc) and chitosan, poly(methacrylic acid-g-ethylene glycol) [P(MAA-g-EG)], poly(ethylene imine) (PEI), poly(N, N-dialkylamino ethyl methacrylates) (PDAAEMA), and poly(lysine). Table 1 shows the pH valves of different fluids in the body.

Table 1: pH valves of different fluids in the body

Site	pH value	Reference
Small intestinal fluid	7.5–8.0	[9]
Gastric juice	1.0–3.5	[9]
Bile	7.8	[9]
Plasma	7.38–7.42	[9]
Saliva	6.0–7.0	[9]
Golgi apparatus	6.0–6.7	[9]
Pancreatic juice	8.0–8.3	[9]
Lysosome	4.5–5.0	[9]
Coliform fluid	5.5–7.0	[9]
Tumor microenvironment	6.5–6.8	[9]
Endosome	4-7	[9]

Redox-responsive drug delivery systems

Compared to normal cells, the environment inside tumor tissues is distinguished by a substantial decrease in its circumstances, frequently called a reducing environment. It is essential to incorporate redox-sensitive chemical elements into the formulation of the drug distribution systems for utilizing the tumor cells' reducing environment for accurate drug distribution. Redox-sensitive chemical elements such as Sulfur Bonds, Amide-Thioether Linkage, Tetrasulfur Bonds, Platinum Conjugation, and the chemical substances responsible for the reduction microenvironment are glutathione [10]. The intracellular levels of Glutathione Sulfhydryl (GSH) in normal cells typically range from 1 to 10 mmol, while the extracellular GSH levels are significantly lower, ranging from 2 to 20 μM. However, GSH levels are more than four times higher in tumor cells than in healthy cells. GSH demonstrates remarkable antioxidant properties [11]. NADPH, along with its oxidized form NADP+, is an additional biomolecule that enhances the reducing capacity of tumor cells [12].

Enzyme-responsive drug delivery system

Enzyme-reactive systems offer a captivating approach for forming responsive drug carriers due to the potential irregularities in enzyme levels within the microenvironment of diseased sites [13]. Smart carriers or binders equipped with drug payloads will facilitate the targeted liberation of drugs at specific locations through enzymatic splitting. This splitting can occur between encapsulation or covalent linkage between the carriers/binders and the drug. The action of varied enzymes initiates the liberation of the drug. Different materials are employed in systems that respond to enzymes, with proteases, kinases, phosphatases, and endonucleases being among the most commonly utilized enzyme categories [14]. In reality, diseases frequently show the imbalance or disturbance of one or multiple enzymatic functions. Precisely, tumor tissues often exhibit increased levels of proteases, which aid in the invasion and spread of tumor cells. This makes proteases an appealing focus for delivering drugs selectively. By comprehending the structural characteristics necessary for targeting a specific enzyme, it becomes possible to create modified medicine carriers that release the medication specifically within tumor microenvironments [15]. When creating enzyme-reactive materials, several crucial factors are typically considered to ensure their effectiveness [16]. These factors include considering (a) the chemical and physical properties of the material, (b) the enzyme concentration in the substrate or material, and (c) how the substrate is attached or fixed to the material [17]. For instance, an eight-amino acid string known as the Gly-Pro-Leu-Gly-Ile-Ala-Gly-Gln (GPLGIAGQ) sequence was developed by Torchilin and coworkers as a sensitive connector for attaching long-chain PEG to liposomes and containing the cell-penetrating peptide TATp. MMP2's octapeptide GPLGIAGQ breakdown exposed TATp, which improved tumor cells' ability to absorb liposome particles [18]. Fig. 1 illustrates the Enzyme-dependent drug release profile of the Enzyme-responsive drug delivery system.

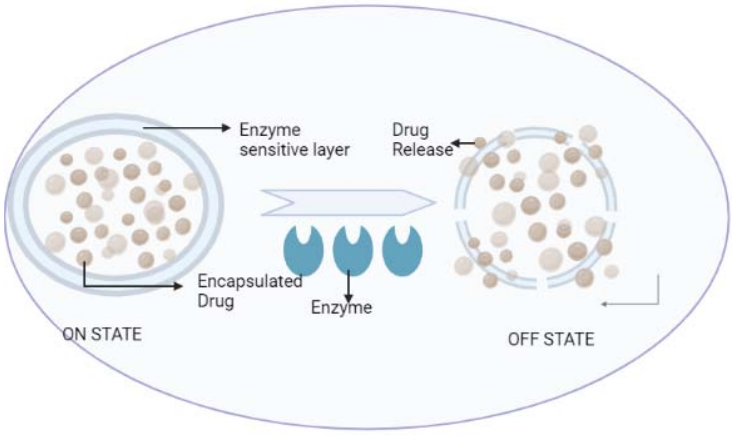

Fig. 1: Represents the mechanism of the enzyme-responsive drug delivery system

Exogenous stimulus

An external stimulus refers to an outside signal applied to Nanocarriers to provoke the liberation of the drug, such as a heat change, sound waves, magnetism field, or electrical field [19].

Temperature stimulus drug delivery system

Temperature can function as a stimulus in two ways: External when the temperature is applied from outside the body, or internal when certain illness conditions lead to a natural increase in body

temperature [20]. In water, thermosensitive polymer solutions exhibit a phenomenon called the Lower Critical Solution Temperature (LCST). The polymer solution remains in a singular phase when the temperature is beneath this threshold. However, when the temperature surpasses the LCST, the polymer chains collapse and gather, leading to phase separation, where water is expelled from the solution [21]. This specific quality has been utilized in the design of temperature-responsive nanocarriers, mainly based on this property. Some frequently used PNIPAAm, poly(N-vinylalkylamide), poly(N-vinyl caprolactam), poly(N, N-diethyl acrylamide), electronics, Pluronic's, phosphorene derivatives, and polysaccharide derivatives are examples of thermosensitive polymers. When establishing the phase transition temperature (Tp) of thermosensitive nanocarriers, it is crucial to consider certain factors. (a) The Tp (transition temperature) should be near the body's typical temperature (around 37 °C), avoiding temperatures lower than this. By doing this, medication release before the application of local hyperthermia is prevented or reduced. (b) The Tp should fall within a relatively small temperature range (about 4-5 °C) and be below the body's acceptable temperature. (c) When approaching the Tp, the architecture of thermosensitive nanocarriers should experience considerable changes that enable faster release and maximize efficiency. For instance, Phase-Change Materials (PCMs) are Temperature-responsive drug delivery systems to create a new method for releasing drugs in response to changes in temperature. They specifically employed two PCMs: 1-tetradecane, which liquefies at 38-39 °C, and dodecanoic acid, which liquefies at 43-46 °C [22]. To construct this system, they embedded small particles containing FITC-dextran (a fluorescent dye) into a matrix composed of the PCM. These particles were shaped like spheres or rods. When the temperature was beneath the liquefaction point of the PCM, nothing occurred because the PCM was hydrophobic (repelled water). Nonetheless, when the temperature increased beyond the liquefaction point, the PCM commenced melting, causing the particles to be released and eventually enabling FITC-dextran to be discharged from them [23]. Table 2 states that thermosensitive polymer and their LCST.

Table 2: Represents different thermosensitive polymer

Type of thermosensitive micelle	Composition of thermosensitive micelles	Encapsulated drug	LCST (◦C)	References
Thermo-responsive shell	Poly(butyl methacrylate)	Adriamycin	32.5	[24]
	P(NIPAAm-co-HMAAm) with poly(D,L-lactide)	Adriamycin	37–42.5	[25]
	Poly(ε-caprolactone) with P(NIPAAm-co-HMAAm)	Cinnarizine	29.5–35.2	[26]
Thermo-responsive core	pHPMAmDL-b-PEG	Methotrexate	41	[27]
	P(IPAAm-co-HMAAm)-biotin-PEG	Paclitaxel	10–65	[28]

Light-responsive drug delivery system

Systems for delivering photoresponsive drugs can adapt their structure and composition in response to exposure to light. Light is an easily accessible, effective, and non-intrusive external stimulus that can be effortlessly acquired and controlled by adjusting various factors such as brightness, wavelength, exposure duration, and beam size [29]. This allows for accurate concentration and management of the light stimulus. Ultraviolet (UV), observable light, and Near-Infrared (NIR) are commonly employed light sources. Three major categories can be used to categorize light-manipulated medication delivery systems: those relying on photoisomerization, photochemistry, and photothermal effects to release medications. In photoisomerization-based systems, the hydrogels undergo structural shifts from straight to bent when exposed to light [30]. In photochemical-based systems, light-triggered reactions modify the hydrogel's network structure and configuration, facilitating drug release. On the contrary, the photothermal reaction utilizes materials capable of converting light into heat energy. This heat energy subsequently disrupts the drug carrier's sensitivity to temperature changes [31]. Numerous photo-sensitive polymers containing azobenzene or spirogyra, such as PAA, PHPM Am, and PNIPAM, have been documented in the literature [32].

Magnetic-responsive drug delivery system

Magnetic drug directing involves using outer magnetic fields to control the motion of magnetic medicine transporters within the body, guiding them toward the desired position. For magnetic medicine directing to be efficient, a dependable magnet system is necessary for steering the drug transporters toward the intended target [33]. Pharmaceutical applications have extensively studied the use of Superparamagnetic Iron Oxide Nanoparticles (SPIONs). Superparamagnetism occurs when the size of ferrimagnetic or ferromagnetic particles diminishes below a certain threshold, resulting in the display of magnetic properties. Superparamagnetic iron oxide nanoparticles, including magnetite (Fe_3O_4) and maghemite (γ-Fe_2O_3), possess significant potential in nanomedicine. The regulated motion of SPIONs in the bloodstream relies on a dynamic equilibrium between the magnetic and hydrodynamic forces acting upon them [34]. PVA and alginate-dispersed magnetic microspheres are some polymers that show magnetic-responsive drug delivery. Fig. 2 illustrates the magnetic-responsive drug delivery system's magnetic stimuli-dependent drug release profile.

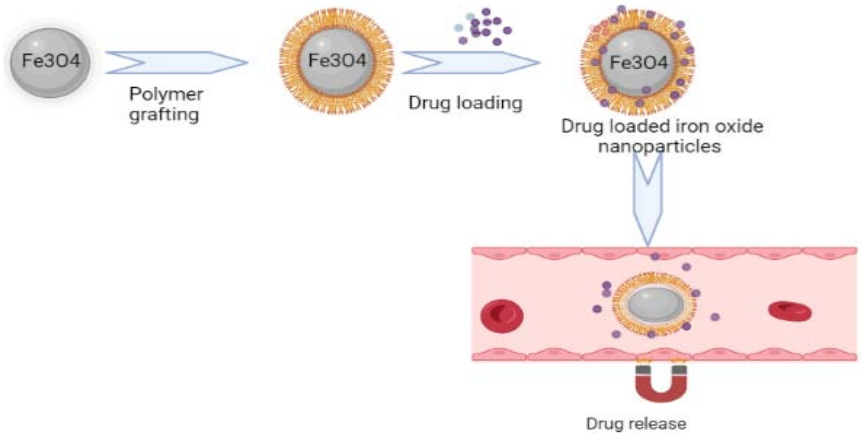

Fig. 2: Represents magnetic responsive drug delivery system

Ultrasound-responsive drug delivery system

Ultrasound signals are a kind of mechanical signals that have elevated frequencies (≥20 kHz) [35]. These signals can be directed and transmitted through specific substances or mediums. Two primary impacts of ultrasound are believed to contribute to this procedure: thermal and non-thermal impacts. The thermal impact of ultrasound involves transforming sound energy into heat, increasing the temperature within the targeted tissue [36]. This temperature elevation can disturb the cell membrane and enhance the permeability of blood vessels. In cancer treatment, this effect has been harnessed to trigger the release of drugs from temperature-sensitive liposomes, microbubbles, or polymeric micelles. The non-thermal effect of ultrasound is mainly linked to a phenomenon known as cavitation. Cavitation can occur when small or tiny bubbles within the tissue respond to ultrasound signals [37]. Two categories of cavitation exist: non-inertial and inertial. Non-inertial cavitation comprises a continuous cycle of bubbles expanding and contracting, which can be intensified by agents that respond to ultrasound. On the other hand, inertial cavitation involves the forceful collapse of bubbles, producing high-speed microstreams and free radicals [38]. PLA poly(lactic acid), PAH poly(allylamine hydrochloride), a polymer which responsive to ultrasound, are PFC perfluorocarbon, PVA polyvinyl alcohol, PLGA poly(lactic-co-glycolic acid), PFO-PLLA perfuoroctanol-poly(lactic acid) [39].

Electro-responsive drug delivery system

The utilization of electric field shocks has the potential to magnify the permeability of cellular membranes. The electrical potential disparity generated by employing an electric field is responsible for the aimed discharge of medications by producing a differentiation between the internal and external potentials of the cell [40]. Utilizing an electric field to the cell membrane causes alterations in polarity, ionic potency, and pH, leading to variations in the overall osmotic pressure within polymers (recognized as electro-osmosis) [41]. This, consequently, triggers flexing, expansion, contraction, or disintegration of the polymer, resulting in the discharge of the active component. For several reasons, electric fields are preferred over alternate external stimuli [42]. Primarily, they provide the benefit of being effortlessly manageable and applicable. Secondly, they do not necessitate intricate and elaborate instruments. Lastly, they can be smoothly integrated into the progression of chip-based apparatus. Polypyrrole ferrocene and carbon nanotubes are commonly encountered as typical examples of electro-responsive materials used in pharmaceutical delivery applications [43].

Table 3: Represents the recent advancements in stimuli-sensitive drug delivery systems

Stimulus	Product name	Drug loaded	Mechanism	Targeting area	Reference
Temperature-responsive drug delivery system	DOX@PAM AND DOX@PIPAM	Doxorubicin (DOX)	This depolarization negatively affected the electrostatic interactions between the positively charged nanoparticles and mitochondrial membranes, thereby hindering mitochondrial targeting.	Lung Cancer Mitochondria-targeted delivery	[44]
	Poly(N-isopropyl acrylamide-co-acrylic acid) nanofiber	Crystal violet (CV) or gentamicin	The nanofibers showed responsive behavior to changes in temperature and pH, with the ability to swell and release their loaded contents between 31 and 34 °C.	Wound healing	[45]
	(PNIPAM-FPA-DMA) copolymer-based hydrogel with PEO90 dihydrazone as cross-linker	Doxorubicin (DOX)	Enhanced matrix mobility beyond the LCST of PNIPAM, inducing coil-to-globule transitions, facilitates drug release.	Cancer cells	[46]
	Chitosan grafted PNIPAM-based nano gel assembly.	Curcumin	The enhanced mobility of the matrix due to the coil-to-globule transition of PNIPAM, occurring above its LCST (lower critical solution temperature), facilitates the release of drugs.	Controlled release	[47]
Light-responsive drug delivery system	NP [CPP]	Doxorubicin (DOX)	The caging group of DEACM is eliminated through photo-cleavage using UV light at 400 nm, 50 mW cm^-2, for a duration of 1 min.	Choroidal neovascularization CNV	[48]
	AKBA@ZnO nanoparticles	Acetyl-11-keto-β-boswellic acid (AKBA).	Zinc oxide (ZnO) nanoparticles loaded with AKBA (acetyl-11-keto-β-boswellic acid) and designed for UV-controlled drug release.	Polymorphous Light Eruption (PLE)	[49]
	Gelatin PAD and Alginate	5-fluorouracil (5-FU)	3D printed scaffolds for accurate structure control and drug release	Breast cancer	[50]
Ultrasonic responsive drug delivery system	Bioelectrets	Curcumin	Ultrasonic stimulation at 90% power (Pmax = 1200 W) produced a current of 0.472 nA. This current produces the heat that makes carnauba wax melt and releases drugs.	Sustained release for chronic inflammatory diseases	[51]
	MSN: MSN-Ce6	Doxorubicin (DOX)	Drug-loaded mesoporous silica nanoparticles (MSN-DOX-Ce6) entered the bloodstream, passively targeting tumors through the EPR effect, releasing DOX and Ce6 to enhance drug concentration around tumor cells, with subsequent sonication-triggered activation leading to combined antitumor effects of DOX and Ce6.	Breast Cancer	[52]
	LPs (MFL)+MBs: DMPC|DOTAP|DSPE-MPEG2k+ SonoVue	DTX	MFLs are efficiently fused with the cell membrane for drug delivery within cells. MB+FUS induced sonoporation in vascular cells, enhancing the EPR effect.	Breast Cancer	[53]

Stimulus	Product name	Drug loaded	Mechanism	Targeting area	Reference
	LPs (Enzyme sensitive, ES)+MBs: POPC|CHOL|PCL+ SonoVue	Doxorubicin (DOX)	PEG cleavage of coated LPs by MMP enzymes resulted in higher intracellular uptake than NES-LPs. However, the VIR: Doxil-like>ES>NES. Tumor growth was reduced by 58%, 39%, and 21%, respectively.	Prostatic cancer	[54]
Electric responsive drug delivery system	Smart skin bandage acrylamide and polyethylene glycol dimethyl acrylate	Curcumin Graphene oxide (GO), gelatin, or trypsin	The water affinity and release profiles of curcumin, Slow and fast release profiles were achieved at 0 V and 24 V, respectively, while intermediate kinetics were observed at 12 V and 48 V	Wound healing	[55]
	Chiston-gold nanocomposite fluorouracil (CGNC-FU)	5-fluorouracil (5-FU).	The CGNC encapsulates the drug molecules within its 3D network at higher pH levels. It undergoes a reversible gel-to-sol transition upon exposure to lower pH conditions, releasing the drug.	Cancer cells	[56]
	Electro-conductive hydrogels (ECHs)-Poly(ethyleneimine) (PEI) and 1-vinylimidazole (VI) polymer	Indomethacin	Volumes of poly(ethyleneimine) above 2.6 ml and 0.7 ml achieved optimal electro-responsive drug release (0.8 mg) for indomethacin, with swelling levels ranging from 25% to 45%.	Controlled personalized drug delivery	[57]
	Macroporous polypyrrole (PPy) thin films	Dexamethasone	Macroporous polypyrrole (PPy) thin films sowed better electrical responsiveness and released more of the drug.	Posterior uveitis	[58]
	Nanocomposite film	Polypyrrole/graphene oxide nanocomposite film Acrylamide and N, N0-ethylene bisacrylamide	Electrochemical reduction The application of an electric voltage results in the quicker release of anionic drugs, whereas cationic drugs are released more slowly	Dexamethasone	[59]
Magnetic responsive drug delivery system	Fe3O4@carbon(C)/ZnO-doxorubicin (DOX)-folic acid (FA) nanoparticles	Doxorubicin (DOX)	The ZnO "gatekeeper" component could degrade in the acidic tumor microenvironment, resulting in controlled drug release that responds to changes in pH. The carbon shell of the nanocomposites can convert light into heat, enabling photothermal therapy.	Cancer cell	[60]
	Paclitaxel loaded in Pluronic F-68	Paclitaxel	Magnetic hyperthermia causes the lipid layer to melt, facilitating drug release.	Targeted drug delivery	[61]
	Manganese ferrite ($MnFe_2O_4$)-chitosan and alginate sodium	Curcumin	Magnetic hyperthermia	Tumor cells	[62]
Redox responsive drug-responsive system	Xyl-SS-Cur/5-FUSA	Curcumin and 5-FU	When there is a high glutathione concentration, the nanoparticles release the drugs more efficiently.	Cancer cell	[63]
	DOX@MSNs-CAIX particles	Doxorubicin hydrochloride (DOX)	Doxorubicin hydrochloride (DOX) released the drug in response to glutathione (GSH), a molecule found in high levels in cancer cells.	Breast cancer cells	[64]
	MP3/ACPP/AE105@NPs	Metal complex	Nanotherapeutics enhanced reactive oxygen species (ROS) production by suppressing TrxR (thioredoxin reductase) activity and modulating metastasis-associated proteins. by inhibiting FAK (focal adhesion kinase)	Breast cancer	[65]
	Chitosan/stearic acid nanoparticles (CSSA NPs)	Curcumin and doxorubicin	Under the influence of redox stimuli from cancer cells, the substance degrades specifically at the tumor site.	Colorectal cancer	[66]

CONCLUSION

This article briefly overviews the unique features shown by responsiveness-triggered polymeric carriers. Moreover, it emphasizes their encouraging abilities in the domain of aimed medication transportation. Before designing Drug Delivery Systems (DDS), it is pivotal to consider diverse vital factors like biocompatibility, biodegradability, non-toxicity, and safe elimination. These factors enforce notable restrictions that necessitate conscientious evaluation. Despite many products undergoing clinical trials, intelligent pharmaceutical delivery systems reveal noteworthy potential. They are actively employed in various fields, such as illness detection, molecular visualization, and precise administration of cancer-fighting medicines to tumors. The recent advancements in stimuli-sensitive drug delivery systems have demonstrated immense potential in revolutionizing healthcare and personalized medicine. However, challenges related to scalability, cost-effectiveness, and regulatory approval remain to be addressed. Continued research and collaboration between academia, industry, and regulatory bodies will be crucial to unlock the full potential of these transformative technologies for patient benefit. Furthermore, in the upcoming years, the fusion of knowledge in focused medication transportation and progressions in intelligent medication transportation systems should give importance to the namely, molecular visualization and focused distribution of anticancer medications to tumors.

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AUTHORS CONTRIBUTIONS

All the authors have contributed equally.

CONFLICTS OF INTERESTS

The authors declare no conflict of interest

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