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Smart Nanotechnology-Based Drug Delivery Systems: Recent Advances and Future Prospects in Stimuli-Responsive Targeted Therapy

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ABSTRACT

Drug Delivery System based on smart nanotechnology allow stimuli-responsive and spatiotemporally regulated therapeutic release, which is a revolutionary development in precision medicine. When compared to traditional drug formulations, engineered nanocarriers, such as liposomes, polymeric nanoparticles, dendrimers, micelles, solid lipid nanoparticle NPs, and hybrid inorganic platforms, display improved bioavailability, reduced off-target toxicity, and superior pharmacokinetic performance. Therapeutic payloads can be released site-specifically and on demand thanks to these nano systems ability to react to endogenous cues (pH, redox gradients, enzymatic activity, and hypoxia) or exogenous stimuli (temperature, light, ultrasonic, magnetic, and electric fields). Their selectivity and biological performance are further enhanced by the incorporation of targeted ligands, surface modifications, and biocompatible materials across intricate pathophysiological barriers, such as the blood–brain barrier and the tumour microenvironment. In cancer, neurodegenerative, cardiovascular, and infectious illnesses, smart nanocarriers have shown encouraging efficacy. They have also opened the door for sophisticated theragnostic applications that combine therapy and diagnostics. Translational issues such as large-scale repeatability, long-term stability, immunogenicity, and regulatory uniformity still exist despite tremendous advancements. These obstacles should be addressed by the confluence of artificial intelligence, 3D/4D printing, and nanorobotics, which will hasten the clinical translation of next-generation intelligent nanomedicines toward tailored and flexible therapy paradigms.

Keywords: ***Smart Nanocarriers, Stimuli-Responsive Drug Delivery, Targeted Therapy, Controlled Drug Release, Nanomedicines, Personalized Medicine.***

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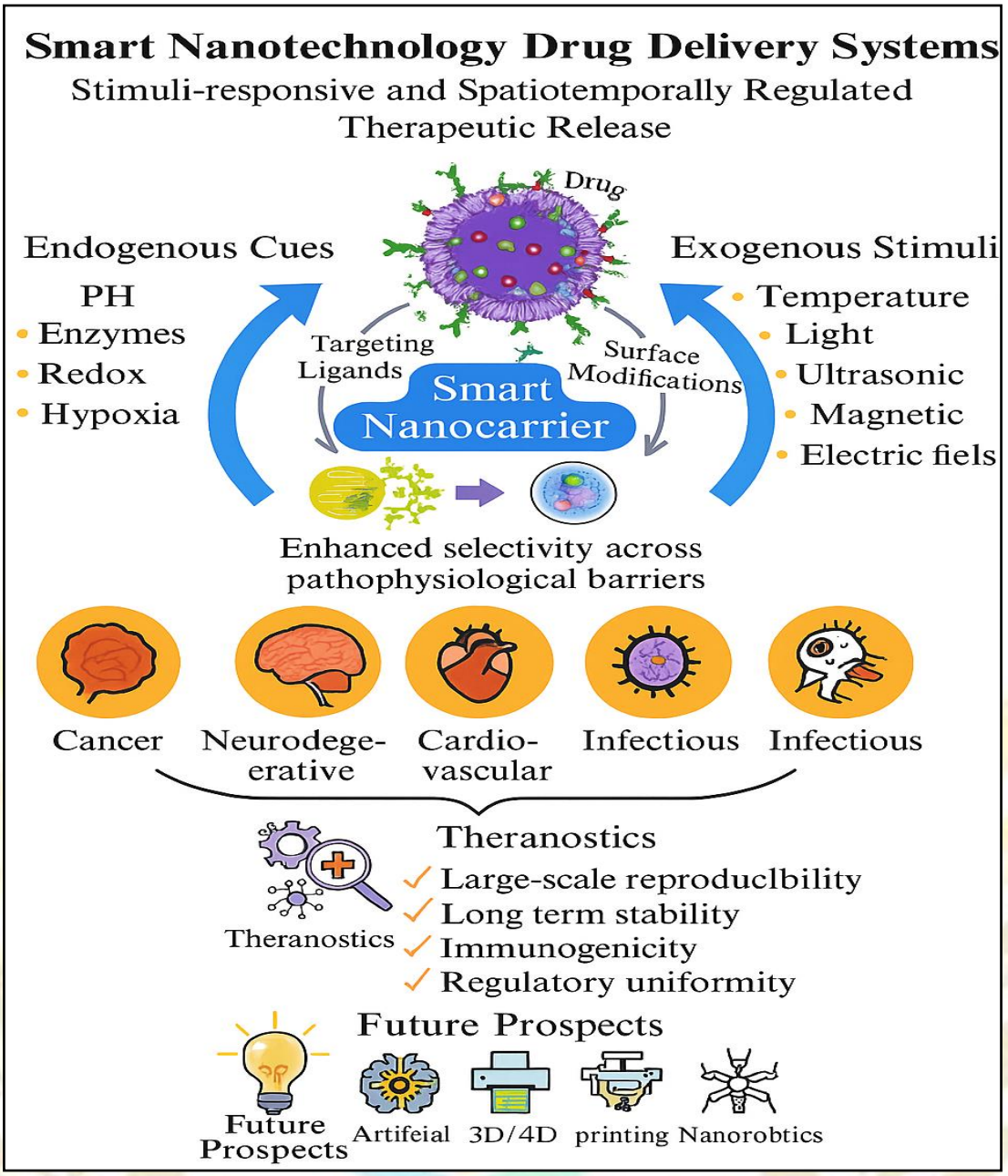
Graphical Abstract: Stimuli-responsive smart nanocarriers for targeted and controlled drug delivery.



Introduction

Nanotechnology has changed drug delivery in a big way by making it possible to make nanoscale carriers that can do better than traditional formulations [1]. Materials at the nanoscale (1–100 nm) have unique physical and chemical properties that make them great for biomedical uses. These properties include a high surface-to-volume ratio, different sizes, surface functionality, and better solubility. NPs can encapsulate medications, protect them from damage, improve pharmacokinetics, and make forms that release drugs over a longer period of time because of these properties [2]. A variety of nanocarriers have been developed for different therapeutic purposes, including liposomes, solid lipid NPs, micelles, dendrimers, polymeric NPs, and inorganic nanostructures [3].Lipid-based mRNA vaccines and liposomal doxorubicin formulations are two well-known examples of nanomedicines in action. Many of these carriers have been shown to work in clinical settings. NPs can also improve targeted specificity by recognizing over expressed receptors on sick cells better when they are engineered on their surfaces with targeting ligands like aptamers, peptides, and antibodies. Passive targeting, which is the increased permeability and retention EPR effect, also helps nanocarriers build up in tumour tissues more than other types of tissues [4]. Nanotechnology has shown effectiveness in treating cancer as well as neurological disorders, inflammatory diseases, immunotherapy, and infectious diseases [5]. Nanomedicines take theragnostic to the next level by combining imaging probes with therapeutic delivery. Theragnostic is the idea of combining diagnosis and therapy on one platform. Nanotechnology has made DDSs more accurate and flexible, going from simple transport systems to

complex platforms [6]. Even though oral pills, capsules, and injectables remain the foundation of current therapy, the site-specific, safe, and predictable drug delivery that they provide is often compromised [7]. Low bioavailability is one of the oldest and most persistent issues. Due to their low solubility and fast first-pass effects, many compounds are hydrophobic agents, in particular, minimizing systemic exposure, and require higher dosing [8]. Non-specific dispersion is another disadvantage. Typical drug-delivery methods have no way of differentiating between diseased and normal tissues [9]. Drugs then end up being distributed all through the body as a result, causing lowered therapeutic index, dose-limiting toxicities, as well as off-target adverse effects. It is quite relevant when one is under chemotherapy because the systemic exposures to the cytotoxic chemicals have the potential to cause grave adverse effects [10]. The efficiency of traditional approaches is also impaired by the ready clearance and short circulatory half-life [11]. High-rapidity metabolism, degradation, or excretion of the majority of therapeutic compounds prevents them from achieving efficacious levels at the site of the drug's action. In addition, enzymatic degradation and limited membrane permeability are two more complications that hydrophilic bio-molecules, like proteins, peptides, and nucleic acids, must contend with and that traditional systems cannot cope with effectively [12]. Drug release from the traditional systems is not controlled in most cases, and the outcome is frequently burst release and variable plasma levels [13]. Such modifications can decrease the patient's compliance, increase the toxicity, and put the loss of efficacy at risk. These systems fail when treating complex and multifactorial diseases that need combination, adaptive, and targeted medicine, such as chronic inflammation, Neurological Disorders, and Cancer [14].

2. Fundamentals of Smart Nanotechnology-Based Drug Delivery System

Smart nanotechnology-based drug delivery represents a significant advancement in therapeutics by enabling precise, controlled, and targeted delivery of medications [15]. These platforms are engineered to optimize drug efficacy, minimize side effects, and increase patient compliance through innovations in carrier design, material selection, and stimulus-triggered release mechanisms [16]. Biocompatibility and biodegradability serve as core requirements for these materials. They make sure the substances interact safely with biological systems [17]. They also break down into byproducts that cause no harm. Stability in physiological conditions matters just as much. This feature lets nanocarriers hold their structure intact across various body environments. They stay solid until arriving at the target location. Drug loading capacity needs to be high for real efficiency. It supports strong encapsulation or attachment of therapeutic agents. In turn, this delivers the right dose levels and boosts overall treatment results. Controlled release properties come into play for better outcomes [18]. They extend time in circulation and focus delivery right at the disease area. Off-target issues drop, and dose levels stay steady without big swings. Surface modification boosts nanocarriers performance in key ways. Hydrophilic polymers like PEG work well to limit immune system clearance. Targeting elements like antibodies or peptides aids in precise uptake by specific cells. Scalability for industry and reliable manufacturing processes round out the essentials. They promote consistent results and keep costs in check. Plus, they align with regulatory rules, which opens doors for nanomedicines to succeed in clinical settings [19]. Different nanomaterial systems offer diverse physical, chemical, and biological properties to address specific therapeutic needs. Among them, liposomes, composed of phospholipids bilayers forming vesicular structures, are widely used as drug carriers. They can encapsulate hydrophilic drugs within their aqueous core and hydrophobic drugs within the lipid membrane, ensuring efficient drug delivery, protection from degradation, and controlled release [20]. Owing to their biocompatibility and structural similarity to biological membranes, liposomes provide a versatile and safe platform for therapeutic applications. Furthermore, surface modification with PEG and targeting ligands enhances their circulation time and enables site-specific delivery, thereby improving therapeutic efficacy and reducing off-target effects [21]. Created from biodegradable polymers like as PLGA, PLA, and PEG-based copolymers, polymeric NPs provide versatile platforms for controlled and sustained release of both hydrophilic and hydrophobic drugs. Their structure allows for physical encapsulation of chemical conjugation of therapeutics, and they may include stimuli-responsive segments for triggered release. Surface engineering with ligands enables active targeting of disease sites [22]. These are highly branched macromolecules with a tree-like projection and a high density of surface functional groups for drug attachment or encapsulation [23]. Dendrimers offer tunable size, high drug-loading capacity, and the ability to deliver multiple-therapeutics simultaneously. Smart dendrimers often include stimuli-sensitive linkers for controlled release and can be modified to enhance biocompatibility and targeting [24]. These are self-assembled nanostructures formed from amphiphilic molecules in aqueous solution. They feature a hydrophobic core for loading water-insoluble drugs and a hydrophilic shell for stability. Micelles are particularly suited for delivering poorly soluble therapeutic agents and can be designed to release drugs in response to

environmental triggers like Temperature shift and pH [25]. It includes mesoporous silica, gold NPs, iron oxide, and other metal-based systems. These carriers exhibit unique optical, electronic, magnetic, and structural properties that are useful for target delivery, imaging, and stimulus-responsive release [26]. Drug releases from nanocarriers can utilize the two principles of paradigms. Examples like Magnetic NPs allow for external guidance to specific tissues, while mesoporous silica offers high surface area and tunable pore size for drug loading and controlled release [27]. This method relies on the natural physiological environment of diseased tissues to enhance the permeability and retention effects in tumours. Nanocarriers with appropriate size surface properties preferentially accumulate in target sites due to leaky vasculature and compromised lymphatic drainage, resulting in increased contraction of the drug where needed. The passive system may release drug slowly or upon encountering local conditions like pH or enzyme contraction, distinctive to diseased tissues [28]. This may involve functionalizing nanocarrier surfaces with ligands that bind to specific markers on target cells of inflamed tissues or over expressed receptors of cancer cells [29]. This strategy promotes receptor-mediated uptake and ensures more accurate delivery. Moreover, the smart system utilizes internal stimuli such as enzymes, pH shift, and redox gradients and external triggers such as ultrasound, heat, light, and magnetic fields, to initiate controlled, on-demand drug release at the disease site. For example, pH-sensitive carriers may disassemble in the acidic microenvironment of a tum our or heat-sensitive liposomes may release their contents upon local hyperthermia induced by external devices [30].

3. Stimuli-Responsive Mechanisms

Through site-specific, on-demand release of medications, stimuli-responsive nanotechnology is a viable solution to the limitations posed by traditional approaches [31]. Even though they are developed to remain stable under systemic circulation, intelligent nanocarriers respond to external stimuli such as light, temperature, ultrasound, or magnetic fields, or endogenous stimuli such as acidic pH, elevated glutathione. Such systems are valuable for over expressed enzymes or hypoxia. In their ingenious response, harm to normal tissues is minimized, and therapy accuracy is enhanced on multiple fronts [32]. First, through the validation that medications are solely released under ill microenvironments, they enhance the accuracy and safety of therapy while reducing the systemic toxicity and boosting efficacy. Second, through the shifting of their physicochemical properties in response to stimuli, they facilitate the evasion of biological filter [33].

In the process, NPs can adjust their size or charge such that the uptake is increased at the cellular level, and penetration through the tumour is enhanced. Lastly, combination therapies are enabled through the existence of wise nanocarriers, through which chemotherapeutic medications can be administered concurrently with immunomodulators, gene therapies, or photosensitizes such that mutually beneficial effects accrue. Many stimuli-responsive devices allow theragnostic uses through the combination of medications with imaging moieties, allowing, in real-time, the observation of the response towards therapy as well as drug bio-distribution. Such devices are very vital in the next-generation healthcare due to their capability to aid precision and personalized therapy [34]. When subjected to certain environmental conditions, stimuli-responsive nanocarriers, a next-generation variant of drug delivery vehicles, can switch their response [35]. Because nanocarriers have the capability of achieving geographic as well as temporal control over the release of therapy, especially in diseases like cancer whose microenvironment is incredibly distinct from normal tissue, they play a significant role in approaches towards targeted therapy. There are two broad classes into which stimuli-responsive nanocarriers can be broadly categorized: intra- and exterior stimuli-responsive systems. In this article, we discuss the methods, components, and biological significance of these two sets [36]. Responsive nanocarriers that are triggered by internal stimuli are formulated such that they will respond based on intrinsic physicochemical gradients or alterations at the level of the cell or the tissue. Spontaneous changes in the tumour microenvironment, inflammatory tissues, or certain organelles due to disease serve as endogenous stimuli that enhance the target specificity, reduce the off-target effects, and trigger drug release [37]. The mild to major differences in acidity from healthy tissues to diseased areas are exploited by the pH-responsiveness of nanocarriers [38]. In this case, because of enhanced glycolytic metabolism, tumours usually have an acidic extracellular pH (6.2–6.8) compared to the normal physiological pH of 7.4. Intracellular organelles like lysosomes and late endosomes that are engaged in endocytic transit keep the environment considerably acidic. Lower pH causes protonation, instability, or hydrolysis of pH-sensitive polymers, including poly (L-histidine), polyaniline, and those containing acid-labile links (hydrazone, cis-aconityl), which disrupts the structure or solubility of the nanocarrier and releases the payload. Gene carriers with endosomal escape capabilities, regulated administration of chemotherapy medications to solid tumours, and combination imaging-therapeutic agents are examples of successful uses [39].

Another indicator of sick tissues or specific sub-cellular locations is enzymatic activity. During the inflammation and infection, this may increase the levels of phospholipases or esterases in tumour tissues, which frequently over express the matrix of metalloproteinases (MMPs), catharsis, or other proteases [40]. The carrier can be designed to destabilize upon enzymatic cleavage by including chemical motifs (peptides, glycosidic linkages, and esters) or enzyme-cleavable sequences into the nanocarrier design [41]. At locations with high enzyme concentrations, this procedure can either release the therapeutic substances or activate prodrugs. By enabling the customization for different disease pathologies and enhancing the safety profile of powerful treatments, like enzyme-responsive systems, offers a route toward precision medicine [42].

Redox-sensitive nanocarriers are formulated such that they can take advantage of the unique redox microenvironment that exists inside the cells, particularly the high levels of reducing equivalents, such as GSH, that exist in the cytoplasm inside cancer cells compared to inside plasma. The framework of the carrier is made up of disulfide, Di selenide, and other chemical bonds that have redox-active linker moieties, or the carrier and the pharmaceutical payload are attached [43]. Those linkages are cleaved quickly through the high GSH that is found intracellularly when the drug is transported into the cells, causing the breakdown of the carrier or the release of the drug that is conjugated. By facilitating differential release inside the cells, the method reduces the likelihood of undue premature systemic drug exposure as well as enhances drug delivery therapeutically into cancerous cells. Multidrug resistance can be overcome, and targeted distribution of proteins, nucleic acids, or small-molecule therapeutics can be obtained using the redox-sensitive systems [44].

The rate of cell growth outpaces that of angiogenesis, hypoxic microenvironments are prevalent in the majority of aggressive cancers [45]. By utilizing chemical moieties that undergo bio-reduction (e.g., nitroimidazoles) or cleave under hypoxic conditions, hypoxia can be utilized as a drug-delivery trigger. It can cause the degradation of the nanocarrier or activation of the contents. Hypoxia-responsive nanoplatforms have been investigated as imaging agents, as promoters of immunogenic cell death, and as drug-delivery vehicles that release chemotherapy agents. They have the potential for site-specifically treating previously difficult tumour histologies and decreasing the cytotoxicity toward healthy, well-oxygenated tissue that is inherent with nonspecific distribution [46]. When the body undergoes chemical or physical changes brought about by medical devices or exogenous stimuli, responsive nanocarriers respond. By achieving non-invasive and site-specific drug release at specific sites, the process ensures temporal as well as spatial control in one additional dimension [47]. The controlled heat at sites is exploited by temperature-sensitive (thermo-responsive) nanocarriers, a property that is particularly advantageous in drug treatments for tumour hyperthermia. Certain examples of material that have critical solution temperatures, in which the permeability or physical properties of the material undergo transformation, include certain lipid membranes, poly (N-isopropyl acrylamide) and elastin-like polypeptides. They are stable at body temperatures (about 37°C) but open up when exposed to raise temperatures, causing the release of the drug. In combination with localized external heat sources (such as ultrasound-based heat or laser infra-red), this enables localized, on-demand drug dosing to deep sites in tissues with low systemic effect [48]. Materials or chemical bonds that are selectively responsive to light are utilized in light-responsive nanoplatforms. Carriers are degraded through bond cleavage, heat, or structural photochemical conversion when treated with specialized wavelengths (UV, visible, or more often near-infrared due to increased depth penetration) and release the drug as a result [49]. Because the light is so spatially precise, treatments can be focused back towards superficial treatments of cancers that remain accessible or can be used as a guide towards imaging-guided treatments with lower risk delivered towards neighbouring healthy tissues [50]. To assist with tracking, localization, or heating with the aid of external magnetic fields, the magnetic-responsive nanocarriers contain magnetic NPs, including super paramagnetic iron oxide. Static magnets can be employed to focus these carriers at the tumour site after systemic delivery; alternating magnetic fields can induce localized hyperthermia or release the payload when the payload is too hot [51].

The formulation ingredients, such as gases, gas-generating moieties, or mechano-sensitive polymers, can be designed to vary their permeability or cause physical degradation in the presence of focused or ultrasound pulses. Increased intracellular uptake, permeability changes in tissues, and local drug concentrations can all be achieved through this non-invasive process. Another advantage of ultrasound is the simultaneous imaging capability [52]. When electric or electro-magnetic fields are applied, permeability, surface charge, or conformation of electric field-responsive nanocarriers change. In active modes such as electrophoretic migration, electrically controlled pore formation, or through passive approaches, the carriers can potentially attain controlled drug release [53]. Electric-field devices have been considered possible devices that can be

used for transdermal drug delivery, neurostimulation, and electro chemotherapy of superficial or easily reached cancers, although much less often translated [54].

Figure 1 Illustrates smart nanocarriers responsive to internal stimuli (pH, enzymes, redox and hypoxia) and external stimuli (light, heat, magnetic field, and ultrasound) for controlled drug release. These multi-stimuli systems, built from liposomes, polymers, MOFs, and inorganic NPs, enhance targeted delivery, though challenges in safety and scalability remain for clinical translation [55].

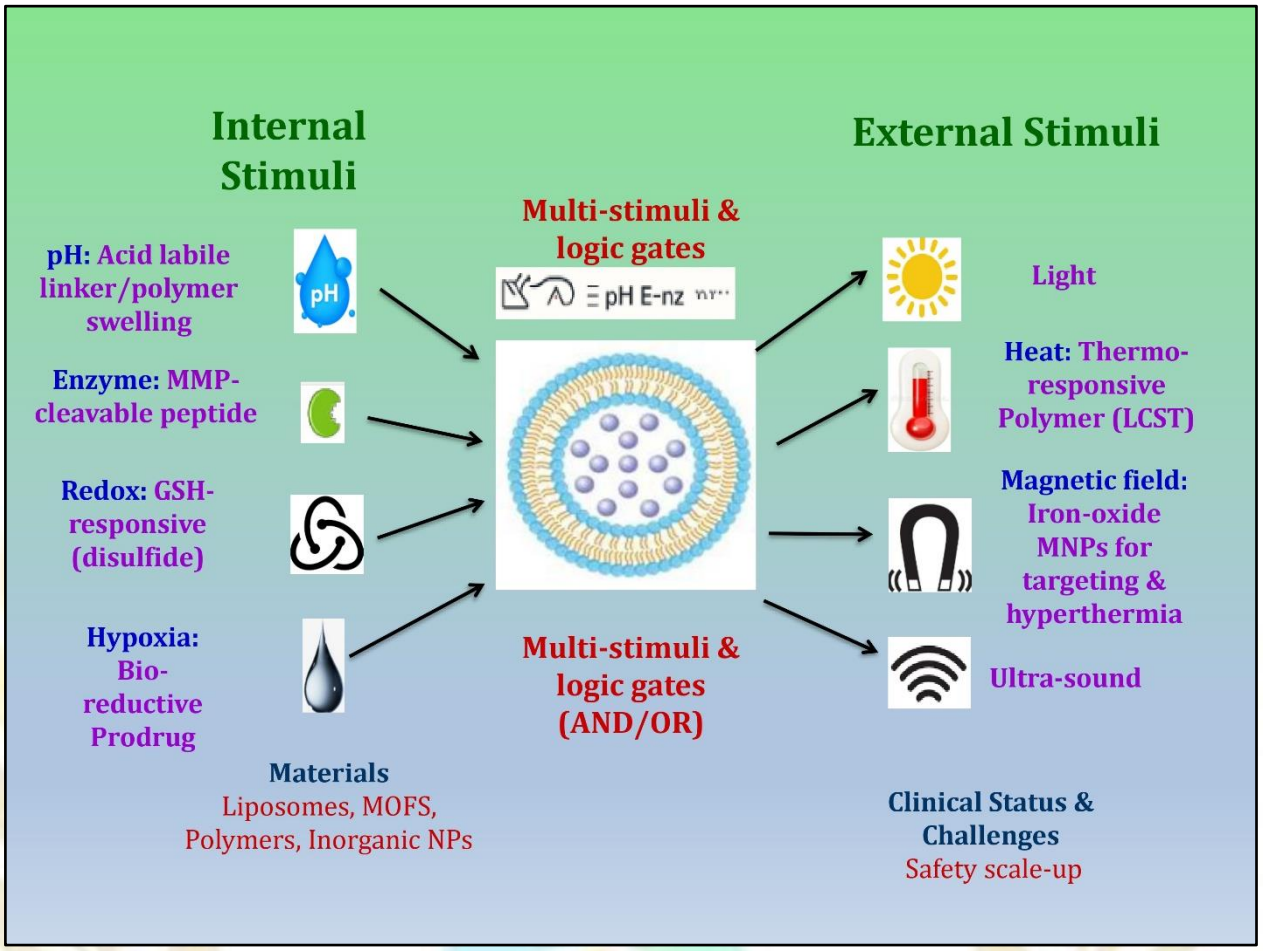


Figure 1: Overview of multi-stimuli–responsive nanocarriers integrating internal and external triggers for controlled drug release.

Schematic representation of internal (pH, enzyme, Redox, hypoxia) and external (light, heat, magnetic field, ultrasound) stimuli governing smart nanotechnology-based DDSs with targeting ligands for site-specific therapeutic release.

4. Recent Advance in Smart Nanocarriers

Hybrid nanocarriers form dynamic platforms that have the ability to address difficult biological problems through the integration of organic and inorganic components or numerous functional modules. Typically constructed as core-shell structures, hybrids integrate the biocompatibility and drug-loading flexibility of organic shells (e.g., polymers and lipids) with the mechanical robustness and imaging capabilities of inorganic cores (e.g., silica and magnetic NPs) [56]. Design strategies focus on merging multiple features into one construct, i.e., controlled release, stimulus responsiveness, targeted distribution, and diagnostic imaging. Targeting ligands and stealth moieties can be immobilized through surface engineering to optimize cellular contact and bio-distribution. Mesoporous silica NPs with stimuli-responsive polymer capping for pH- or enzyme-triggered controlled release of drugs are two such examples, as are polymer-coated magnetic NPs for magnetically directed drug delivery with simultaneous MRI monitoring. Such multi-functional platforms are indeed the best examples of the future generation of nanomedicines, where individualized treatment regimens and synergistic therapy protocols can be implemented [57].

Biomimetic NPs can be used to target tumour cells by cloaking nanocarriers with natural cell membrane (derived either erythrocytes, leukocytes, tumour cells or platelets), which causes the homotypic maintenance of immune evasion, prolonged systemic circulation and tumour cells recognition [58]. An

example is NPs coated with tumour cell membranes (CCM -NPs), which recapitulate endogenous tumour antigens and allows selective attachment to and ingestion by homologous tumour tissue and evades the immune system clearance by macrophages. These systems would hence improve biocompatibility, reduce off-target toxicity and offer options in combinatorial regimens that include chemotherapy, photothermal therapy, and immunotherapy. Inflamed or tumour-associated microenvironment stimulates again in the case of biomimetic carriers to assist precision in oncology through targeted release as well as immune modulation [59]. With the development of CRISPR/Cas9, responses The state of CRISPR/Cas9 has triggered the design of responsive nanocarriers that transport gene-editing cargos with precision and few off-target effects [60].

Polymeric carriers that are stimuli-responsive have been designed to deliver plasmid DNA or ribonucleoprotein complexes in response to tumour specific signals being exposed to pH, redox gradient or enzymatic activity. In a study, hyper branched polymeric NPs have been used to deliver Cas9 plasmids in vitro with efficiency to knock out genes and low cytotoxicity. Combining gene editing and specific nanocarriers expands the therapeutic approaches to include targeting oncogenic drivers with or silencing resistance genes, which has the potential to transform cancer therapy [61].

Nano gels and hydrogels are cross-linked polymer networks on a nanoscale that offer highly tuneable drug reservoirs through which they can respond to intrinsic or extrinsic stimuli (temperature, pH, redox, light) and provide sustained, localized therapy [62]. An example is the thermo-responsive nanogel depot that was used in the orthotropic ovarian cancer models and generated an in situ gel and significantly reduced tumour volume compared to the conventional micellar formulations. The latter facilitates also high drug loading and penetration of dense tumoural stroma as well as inhibition of burst release, thus overcoming a significant challenge of drug delivery in solid tumours. In the field, the future of smart nanogels is seen in combination regimens, i.e. chemotherapy with immunotherapy or individualised delivery based on tumour micro-environmental cues [63].

Figure 2 illustrate the highlights recent advancements in multifunctional nanocarriers across three major platforms biomimetic, hybrid, and gene delivery systems. It depicts how each platform enhances therapeutic precision through mechanisms such as immune evasion, multimodal treatment, magnetic or photo-thermal targeting, and advanced gene delivery tools like mRNA and CRISPR. Key technological innovations for each platform are summarized to showcase their role in next-generation drug delivery [64].

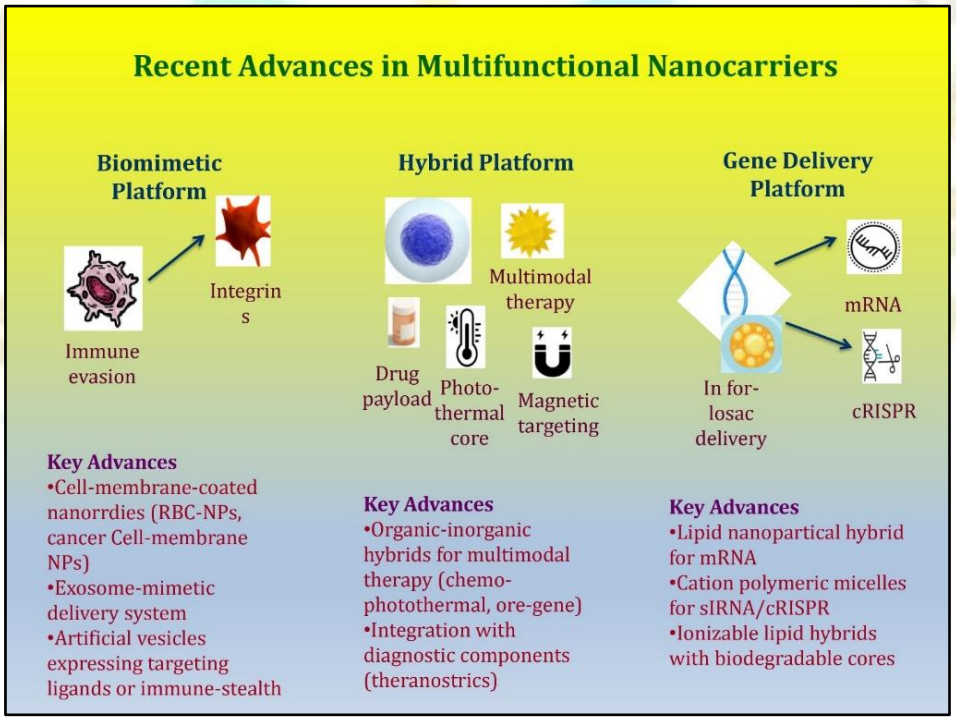


Figure 2: *Recent advances in multifunctional nanocarriers highlighting biomimetic platforms for immune evasion, hybrid platforms enabling multimodal therapy and targeted delivery, and gene delivery platforms designed for mRNA and CRISPR transport, along with key technological advancements in each category.*

5. Application in target therapy

Intelligent nanocarrier-based target therapies have greatly improved the treatment of diseases in all of oncology, neurology, cardiology, infectious disease, and the growing field of personalized medicine. While an overview of these applications is described, it emphasizes the clinical significance and design methodologies [65]. In the treatment of cancer, the target nanocarriers are converted by increasing the specificity of drug delivery and reducing the destruction of healthy tissue. These carriers have been fabricated to take advantage of the specific properties of tumour cells, such as over expression of protein and distorted microenvironment [66]. By functionalizing the surface using targeted ligands such as antibodies and peptides, nanocarriers selectively bind to cancer cells and deliver chemotherapeutic and genetic material directly into tumours. This decreases the systemic toxicity and enhances the accumulation of the drug within the tumour site. In addition, the stimulus-responsive nanocarriers release their carrier upon response to local triggers such as a change in pH, specific enzyme, and temperature [67]. Recently, the advanced nanocarrier also comprised the co-delivery of several agents in a single application, which allows combinational therapies such as delivering the chemotherapy with the gene-silencing molecules as siRNA. Nanocarriers are also utilized for photothermal and photodynamic therapy, which involve light and heat that trigger the treatments that further increase the destruction of tumour cells while avoiding healthy tissue [68]. Drug delivery through the BBB is a major problem in the treatment of neurological disorders like Alzheimer's and Parkinson's. Smart nanocarriers address this by being designed for size, surface properties, and inclusion of targeting ligands that allow for transport through the blood-brain barrier. Examples such as the binding of transferrin or peptide to the surface of the nanocarrier promote receptor-mediated uptake by brain endothelial cells, allowing for direct delivery of therapeutic agents into affected neurons [69]. Nanocarriers encapsulate neuroprotective drugs, gene therapies, or molecules that are targeted to reduce abnormal protein aggregation. Controlled or stimuli-responsive release mechanisms provide assurance that drugs are released only upon arrival at the targeted brain regions, maximize efficacy, and minimize peripheral side effects [70]. In cardiovascular diseases, nanocarriers enhance therapeutic efficacy by providing targeted delivery of the drug into inflamed, injured, and atherosclerotic areas. They could be modified using antibodies or peptides that selectively identify markers of vascular inflammation or injury. When present at the site of the disease, nanocarriers deliver anti-inflammatory, anti-thrombotic, and plaque-stabilizing agents, promoting tissue repair and avoiding further tissue damage [71]. Based on stimuli-responsive characteristics, some nanocarrier systems have been integrated on the basis of enzyme- and pH-triggered release to ensure that therapeutic agents are only deployed where and when they are required. This reduces the risk of systemic bleeding or other drug-induced side effects and facilitates more effective intervention after occurrences like myocardial infarction or angioplasty [72]. Increasingly, intelligent nanocarriers are used to enhance the targeting and efficiency of antimicrobial therapy. They can increase a drug's accumulation in infection sites, improve host cell penetration, and shield the antibiotics or antiviral drugs from premature degradation. Nanocarrier surfaces can be modified through coating with molecules that interact with bacterial- or viral-specific markers [73]. In addition, these nanocarriers may also provide controlled or sustained drug release, which sustains drug concentrations effectively for extended periods and aids in fighting resistant pathogens. Co-delivery systems are also under development to deliver combinations of antimicrobial agents, which act at several stages of pathogen-like cycles or boost immune responses [74]. Modular nanocarrier design facilitates their tailoring to the specific needs of each patient, underlying the concept of personalized medicine. With proper material selection, surface ligands, and release mechanisms, nanocarriers can be tailored to a given patient's genetic, molecular, or pathological profile. It allows optimal drug and dosage selection for each patient, optimizing therapeutic impact and limiting adverse effects [75]. The theragnostic nanocarriers that combine therapeutic and diagnostic capabilities enable real-time monitoring of drug delivery and response to treatment. This feedback facilitates the dynamic modulation of therapy, enabling truly personalized and adaptive care [76].

Table 1 presents a comparative summary of various stimuli-responsive nanocarriers, highlighting their triggering mechanisms, design materials, and therapeutic applications [77]. It categorizes systems based on internal stimuli such as pH, redox, enzyme, and hypoxia, as well as external stimuli like temperature, light, magnetic field, ultrasound, and electric field. Each stimulus type is associated with specific nanocarrier designs (e.g., polymeric micelles, liposomes, dendrimers, metallic (NPs)) and mechanisms of action that enable controlled and site-specific drug release. The table also outlines recent advancements, including dual or multi-stimuli-responsive platforms, which enhance precision, therapeutic efficacy, and safety, underscoring their potential in cancer therapy, infection control, and tissue regeneration [78].

Table 1. Comparative summary of Stimuli-Responsive Nanocarrier, their triggering mechanisms, and therapeutic applications

S. No	Stimulus Type	Representative Trigger	Nanocarrier Design / Material	Mechanism of Action	Therapeutic Applications	Recent Advancements	References
	pH-responsive	Acidic tumour microenvironment, endosomal pH (≈5–6)	Polymeric micelles (PAA, PEG-b-PLA), liposomes with pH-sensitive lipids	Protonation or hydrolysis causes carrier disassembly and drug release	Tumour-targeted chemotherapy, infection sites	Dual pH/redox-responsive hydrogels and metal–organic frame works (MOFs) for precision release	[79]
	Redox-responsive	Elevated intracellular GSH levels	Disulfide-linked polymeric NPs, dendrimers	Cleavage of disulfide bonds triggers payload release	Anticancer drugs, gene delivery	Di selenide and thioether linkers enabling tenable redox thresholds	[80]
	Enzyme-responsive	Matrix metalloproteinases (MMPs), esterase, hyaluronidase	Peptide-modified liposomes, polymer–peptide conjugates	Enzymatic cleavage of linkers exposes active sites or triggers drug release	Cancer therapy, tissue regeneration, and inflammation	Smart enzyme-labile peptide linkers integrated with targeting ligands	[81]
	Hypoxia-responsive	Low oxygen levels in solid tumours	Nitroimidazole -modified polymeric NPs	Bio-reduction of nitro groups leads to nanoparticle degradation	Hypoxic tumour therapy	Co-delivery of hypoxia-activated prodrugs with oxygen carriers	[82]
	Temperatu re-responsive	Local hyperthermia (40–43 °C)	Poly(N-isopropylacryl amide) (PNIPAM) nanogels, lipid vesicles	Phase transition induces structural collapse and release	Cancer thermotherapy, infection control	Hybrid thermos sensitive–magnetic NPs for controlled heating	[83]
	Light-responsive	UV, visible, or NIR light	Gold nanorods, graphene oxide, azobenzene-conjugated polymers	Photo-isomerization or photo-thermal heating enables on-demand release	Photothermal therapy, gene activation	NIR-II responsive nanocarriers for deep-tissue activation	[84]
	Magnetic field-responsive	Alternating magnetic field	Superparamag netic iron oxide NPs (SPIONs), magnetic–polymer hybrids	Magnetic heating or mechanical vibration induces release	Hyperthermia, targeted drug delivery, imaging	MRI-guided magneto-theragnostic platforms integrating dual-drug delivery	[85]
	Ultrasoun d-responsive	Focused ultrasound (FUS), acoustic cavitation	Echogenic liposomes, polymer microbubbles	Acoustic cavitation disrupts carrier structure for release	Targeted chemotherapy, gene transfection	Ultrasound-triggered phase-change nanodroplets for spatiotemporal control	[86]
	Electric field-responsive	External electrical pulses	Conductive polymeric NPs, carbon-based systems	Electric potential induces conformational or permeability change	Localized neural drug delivery, wound healing	Electrically controlled nanogels for on-demand peptide delivery	[87]
	Multi-stimuli-responsive	Combination (pH/redox/light/ma gnetic)	Hybrid polymer–inorganic composites, MOFs, liposome–SPION hybrids	Sequential or synergistic response to multiple triggers	Smart combination therapy, precision oncology	4D nanocarriers integrating sensing, release, and real-time monitoring functions	[88]

6. Challenges and Limitation

There are certain encouraging benefits for the disease treatment via applying smart nanotechnology-based drug delivery, but they also introduce a series of considerable challenges and limitations that need to be

tackled for the effective and safe clinical results [89]. One of the main challenges in nanocarrier design is to make sure that these materials are non-toxic and biocompatible. Depending on size, shape, surface chemistry, and degradation products, NPs may contain unwanted immune responses, oxidative stress, or inflammation. Some NPs may build up unwantedly in critical organs such as the lungs, liver, and kidneys, causing toxicity. The size-dependent toxicity has been seen, where certain particle size show augmented adverse effects [90]. Though nanocarriers are the hope for laboratory levels, their large-scale manufacture poses a technical hurdle. To obtain the reproducibility, scalability, and batch-to-batch uniformity of nanocarriers of defined size, shape, drug loading, and surface properties is complicated. During manufacturing it should be economical and adhere to GMP regulatory standards. Further, controlling the purity and stability of raw materials and intermediates can be challenging. Complexities related to multi-component system, such as those surface alterations and stimuli-responsive components, compound the manufacturing challenges [91]. The approval of nanomedicines restricted with limited standardized guidelines specific to the agency demands full data on pharmacokinetics, bio-distribution, toxicity, and environmental in distinct properties. The variety in the nanocarrier compositions, behaviour within the biological system, and therapeutic actions make it difficult to assess safety and efficacy. The regulatory conditions, which generally require long, time-consuming investigations [92]. The ethical issue also arises due to the possible long-term health and environmental impact of nanomaterials, especially regarding bioaccumulation and waste management of NPs. Despite this, price and consent problems crop up in theragnostic use, where diagnostic as well as therapeutic activities are integrated into a single platform. Addressing these issues needs concerted action among scientists, policymakers, and industry to make the standardized guidelines for responsive use and development of nanomedicines [93]. Physical and chemical stability of nanocarriers is important to provide safety and efficacy during storage, transport, and administration. Most nanoparticle formulations aggregate, oxidize, or hydrolyse over time, so consequently, there is structural breakdown and drug leakage before time [94]. Lipid-based systems such as liposomes and solid lipid NPs are particularly susceptible to temperature variation and humidity, whereas polymeric and metal NPs can undergo surface degradation or alterations in charge distribution. In order to enhance the stability of nanocarrier lyophilization's, freezing and drying techniques are usually used; additionally, such processes would change particle size distribution or damage functional coating. Formulation development that maintains the stability for long-term storage, along with proper packaging and environmental control, is still a critical step in maintaining the clinical reliability and shelf life of drug [95].

Table 2 summarizes the major challenges and future strategies for translating smart nanotechnology-based DDSs into clinical use. It addresses key issues such as toxicity, manufacturing scalability, stability, targeting efficiency, and regulatory barriers, while suggesting strategies like biodegradable materials, standardized production, improved stability, and AI-driven design to enhance safety, efficacy, and clinical applicability [96].

Table 2: Challenges and Future Strategies in developing clinically translatable smart nanotechnology based drug delivery.

S. No	Challenge	Description	Impact on Translation	Potential Short-term Strategies	Future/Research Directions	References
1.	Biocompatibility & Toxicity	Uncertain acute and chronic toxicity, immunogenicity, and off-target effects of nanomaterials.	Safety concerns delay or prevent clinical trials and regulatory approval.	Use biodegradable materials; systematic in vitro/in vivo toxicity screening; dose optimization.	Develop predictive in silico toxicology models; long-term safety studies; safer-by-design nanomaterials.	[97]
2.	Scale-up & Manufacturing Reproducibility	Difficulties in producing consistent batches at an industrial scale with controlled size, surface properties.	Batch variability undermines reproducibility, regulatory approval, and commercialization.	Adopt GMP-compatible scalable processes; inline monitoring; process analytical technologies (PAT).	Continuous manufacturing, modular micro-fluidic production platforms, standardized SOPs.	[98]
3.	Stability & Storage	Aggregation, payload leakage, and	Reduced shelf-life, cold-chain requirements, and	Optimize formulation (lyophilization, stabilizers), packaging,	Design inherently stable carriers (biodegradable yet	[99]

		loss of activity during storage and transport.	logistical hurdles.	and storage conditions.	shelf-stable); room-temperature stable LNPs.	
4.	Targeting Specificity &Tumour Heterogeneity	Variable expression of targets across patients and within tumours (intra-tumoural heterogeneity).	Reduced efficacy and variable patient responses.	Use multi-ligand targeting, patient stratification biomarkers, and companion diagnostics.	Develop adaptive/logic-gated multi-stimuli carriers and personalized nanomedicine approaches.	[100]
5.	Immune Clearance & RES Uptake	Rapid opsonization and clearance by the mononuclear phagocyte system (MPS/RES).	Short circulation half-life and low tumour accumulation.	Stealth coatings (PEG alternatives), biomimetic membranes, dosing strategies.	Immune-tolerant surface chemistries, transient immune modulation, targeted RES evasion.	[101]
6.	Controlled Release Reproducibility	Ensuring predictable, repeatable stimulus-response behavior in complex biological environments.	Inconsistent therapeutic windows and unpredictable pharmacodynamics.	Robust in vitro/in vivo validation across models; standardized stimulus protocols.	Smart feedback-enabled carriers with sensing and closed-loop release control.	[102]
7.	Regulatory & Translation Pathways	Lack of clear regulatory frameworks for complex multifunctional nanomedicines.	Unclear approval requirements slow clinical translation and investment.	Early regulatory engagement, standardized characterization data packages, and clear comparators.	Harmonized international guidelines for nanomedicines; regulatory science research programs.	[103]
1.	Bio-distribution & Off-target Effects	Non-specific accumulation in organs (liver, spleen) and potential long-term retention.	Safety liabilities and reduced therapeutic index.	Optimize size/charge, active targeting, and biodegradable components.	Real-time imaging-guided delivery and clearance-promoting designs (renal-clearable NPs).	[104]
2.	Clinical Trial Design & Endpoints	Selecting appropriate endpoints, dosing, and patient selection for nanomedicine trials.	Misleading efficacy signals or underpowered studies impede approval.	Adaptive trial designs, use of biomarkers, and translational PK/PD modelling.	Patient-tailored trials, companion diagnostics, and surrogate endpoints for faster readouts.	[105]
3.	Cost-effectiveness &Accessibility	High production and development costs limit accessibility in lower-resource settings.	Limited adoption and inequitable access to advanced therapies.	Cost-reduction via scalable manufacturing, simpler formulations, and public-private partnerships.	Affordable-by-design platforms and decentralized manufacturing strategies.	[106]
4.	Standardization & Characterization	Lack of standardized assays for physicochemical and biological characterization	Difficult cross-study comparisons and regulatory uncertainty.	Adopt community-accepted standards (size, surface chemistry, payload), and inter-laboratory studies.	Automated high-throughput characterization and open data repositories for benchmarking.	[107]
5.	Long-term Safety & Clearance	Incomplete understanding of long-term	Potential chronic toxicity and regulatory barriers.	Extended preclinical pharmacokinetic and bio-distribution studies;	Design for complete biodegradation, renal-clearable	[108]

		fate, biodegradation, and excretion pathways.		biodegradable chemistries.	architectures, and post-market surveillance.	

7. Future Perspectives

Intelligent nanotechnology in DDSs continues to develop at a fast rate, propelled by innovations that increase the precision, safety, and individualization. The amalgamation of computational tools, hybrid materials, and biomedical engineering is revolutionizing therapeutic strategies and bringing revolutionary technologies for clinical applications [109]. In AI and ML, the redefined nanocarrier optimization and discovery are done. These systems use predictive algorithms to analyse the vast experimental data and thereby facilitate the detection of optimal material composition, particle size, and surface modification for a given therapeutic application. AI-driven models have replaced conventional trial-and-error design strategies by offering the in-silico screening of nanocarrier formulations, which enhances the research and minimizes the cost [110]. Recent research showed the AI research design of lipid NPs for delivery of the gene and mRNA, tuning their composition for selective organ cell type targeting. Likewise, AI-based simulations are enhanced to understand the correlation between nanoparticle shape, charge, ligand density, and bio-distribution, and to identify the safety and effective formulations more effectively. Despite this, the development of AI has a critical function to predict the pharmacokinetics, dose optimization, and monitoring of therapy, facilitating an adaptive feedback system in personalized nanomedicine [111]. It is the platform that merges the therapy and diagnostic imaging, which are one of the most promising frontiers in the development of nanomedicine. These dual-function nanocarriers are engineered to deliver therapeutic agents in real time as well as image the bio-distribution, treatment response, and biological response. Polymeric and metallic NPs have proven an exceptional challenge in cancer Thera gnostic [112]. For example, drug-loaded polymer NPs conjugated with imaging molecules allow physicians to visualize tumour localization, track drug release kinetics, and dynamically modify treatment plans. The real-time visualization of nanoparticle bio-distributions makes it possible to achieve accurate dose control, reduce systemic toxicity, and increase patient safety. For future theranostic nanocarrier amine development to merge the multi-functionality with biocompatibility and provide integrated diagnosis, personalized therapy feedback, and adaptive treatment methods, particularly in oncology and neurodegenerative disease management [113]. Ahead, 3D/4D bio printing is transforming the production of precision DDSs. Nanomaterial integration with 3D printing has potential for customized fabrication of drugs, scaffolds, and tissue constructs specifically to fit individual patient anatomy and pathology. Nanoparticle incorporation in printed matrices enables controlled and sustained drug delivery, especially for neurological and regenerative medicine [114]. While 4D printing is an extension of 3D printing, it makes stimuli-responsive materials with the ability to change shape or release drugs actively upon environmental stimuli such as light, pH, and temperature. The advancement facilitates the development of adaptive drug delivery devices that respond dynamically to physiological changes of patients. Nanorobotics are programmable nanoscale devices made of magnetic and biodegradable materials that present the potential for navigable and targeted drug delivery directly to intracellular locations. Such "smart" nanobots may one day conduct minimally invasive drug delivery or local tissue repair with the direction of external fields or microsensors [115]. The translation of smart nanomedicines to the clinic is still in its infancy. Certain ongoing and recent clinical trials reflect the progress, particularly the nanoparticle-enhanced immunotherapy and the gene delivery system. The progress includes lipid nanoparticle (LNP)-mediated CAR-T and CAR-NK treatments that are now in the early phase of trials for solid and hematologic cancers [116]. These trials demonstrate the nanocarriers ability to enhance the targeted immune cell modification and therapeutic index with reduced systemic side effects. To fully realize the translational potential, there should be interdisciplinary collaboration between material scientists, physicians/doctors, and regulatory authorities. Future efforts must also be aimed at developing the standardized evaluation models in order to enhance large-scale reproducibility and the incorporation of real-time imaging and a few AI analytics data in the course of clinical testing. Through combining all these efforts, nanocarrier-based systems can develop from promising laboratory tools to dependable patient-centred medical technologies for clinical deployment [117].

Conclusion

Smart nanotechnology-based DDSs have emerged as a critical component in the growth of modern treatments, bridging the gap between traditional pharmacology and precision medicine. These intelligent nano systems, designed to respond to internal (pH, redox, enzyme, hypoxia) and exterior (light, temperature, ultrasonic, magnetic, and electric field) stimuli, provide unprecedented control over drug

release kinetics, bio-distribution, and target specificity. They achieve selective accumulation at diseased areas, improve treatment efficacy, and reduce systemic adverse effects by combining biocompatible materials, surface functionalization, and multi-stimuli responsiveness. The introduction of multifunctional nanocarriers with theranostic capabilities enables simultaneous diagnosis, real-time monitoring, and therapeutic intervention on a single platform, hastening the development of personalized medicine. Despite great progress, issues such as immunogenicity, large-scale production, stability, and regulatory inconsistency continue to impede clinical translation. To address these restrictions, an interdisciplinary strategy that combines material science, pharmacogenomics, regulatory innovation, and bioinformatics is required. The introduction of artificial intelligence and machine learning into nanocarrier design, combined with upcoming 3D/4D printing and nanorobotic systems, has the potential to transform the landscape of targeted therapy by increasing precision, adaptability, and safety. Finally, the convergence of these technologies will allow for the rational design of next-generation nanomedicines with dynamic, patient-specific therapeutic modulation, ushering in a new age of intelligent, responsive, and translationally practical drug delivery platforms.

In summary, smart nanotechnology-based DDSs offer precise, stimuli-responsive, and targeted therapy by integrating biocompatible materials and multifunctional design. They enhance drug release control, efficacy, and safety while enabling theragnostic applications. Despite challenges in scalability, stability, and regulation, advancements in AI, 3D/4D printing, and nanorobotics promise the development of next-generation intelligent and personalized nanomedicines.

Abbreviation

DDS = Drug delivery system (DDS)
NPs = Nanoparticles (NPs)
SLNs = Solid Lipid Nanoparticles (NPs)
NLCs = Nanostructured Lipid Carriers
MSNs = Mesoporous Silica Nanoparticles (NPs)
SPIONs = Superparamagnetic Iron Oxide Nanoparticles (NPs)
PEG = Polyethylene Glycol
PLGA = Poly(lactic-co-glycolic acid)
PLA = Polylactic Acid
PCL = Polycaprolactone
PAMAM = Poly (amidoamine) Dendrimer
EPR = Enhanced Permeability and Retention
BBB = Blood–Brain Barrier
GSH = Glutathione
MMPs = Matrix Metalloproteinases
PNIPAAm = Poly(N-isopropyl acrylamide)
AI = Artificial Intelligence
ML = Machine Learning
LNP = Lipid Nanoparticle
MOF = Metal Organic Framework
RES = Reticuloendothelial System
MRI = Magnetic Resonance Imaging
UV = Ultraviolet
NIR = Near-Infrared
PK/PD = Pharmacokinetics / Pharmacodynamics
GMP = Good Manufacturing Practice
ROS = Reactive Oxygen Species
RNA = Ribonucleic Acid
DNA = Deoxyribonucleic Acid
siRNA = Small Interfering RNA
CAR-T = Chimeric Antigen Receptor T-cell
CAR-NK = Chimeric Antigen Receptor Natural Killer Cell
QDs = Quantum Dots
AI-Nano = Artificial Intelligence–Driven Nanotechnology
3D/4D = Three-/Four-Dimensional Printing Technologies

Author Contribution

F.A. Data Analysis and interpretation, P.C Data collection and Conceptualization, A.S. Visualization, M.T Writing the paper, S.A Study concept or design Z.A. Visualization.

Conflict of Interest

The authors declare no conflict of interest.

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