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Nanotechnology-Based Smart Drug Delivery Systems for Controlled and Targeted Therapeutic Applications

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Abstract

Nanotechnology has revolutionized modern drug delivery by enabling the development of smart delivery systems capable of achieving controlled drug release, targeted therapeutic delivery, and improved treatment efficacy. Unlike conventional drug administration methods, nanotechnology-based smart drug delivery systems enhance the bioavailability, stability, and site-specific accumulation of therapeutic agents while minimizing systemic toxicity and adverse side effects. This review paper examines recent advances in nanotechnology-based smart drug delivery systems for controlled and targeted therapeutic applications. The study explores a wide range of nanocarriers, including liposomes, polymeric nanoparticles, dendrimers, solid lipid nanoparticles, nanogels, micelles, mesoporous silica nanoparticles, and metallic nanoparticles, highlighting their physicochemical properties and biomedical applications. Furthermore, the review discusses active and passive targeting strategies, stimulus-responsive drug release mechanisms, and surface functionalization techniques that improve therapeutic precision. Emerging applications in cancer therapy, infectious diseases, cardiovascular disorders, neurological diseases, and gene delivery are also critically evaluated. Despite significant progress, challenges related

to nanotoxicity, large-scale manufacturing, long-term biocompatibility, regulatory approval, and clinical translation continue to impede widespread implementation. This review synthesizes current developments and emphasizes the potential of nanotechnology-based smart drug delivery systems to advance precision medicine by improving therapeutic outcomes and patient safety.

1. Introduction

Traditional therapeutic strategies are often limited by the unfavorable physicochemical and pharmacokinetic properties of conventional small-molecule drug agents. A major clinical challenge is that most conventional drug molecules possess poor aqueous solubility and are moderately lipophilic, as described by Lipinski's rule of five (Sivadasan et al., 2021). This limited solubility, combined with poor biological stability, rapid systemic clearance, and an inability to cross biological membranes, often results in low bioavailability and requires high and frequent dosing regimens (Shakhakarmi et al., 2023). Consequently, conventional systemic administration is frequently characterized by a rapid initial burst of drug release immediately after administration, leading to transient toxic concentrations in the blood, followed by a rapid decline below the therapeutic threshold (Doroudian et al., 2021). Furthermore, the lack of tissue selectivity in traditional therapies leads to nonspecific drug distribution, resulting in severe off-target systemic toxicities that limit the therapeutic index of highly potent agents, particularly in oncology, cardiology, neurology, and immunology (Cheng et al., 2023).

The integration of nanotechnology with pharmaceutical and medical sciences, termed nanomedicine, has emerged as a promising strategy to address these systemic limitations (Pushpamalar et al., 2021). The concept of using nanomaterials in medicine was first conceptualized by Dr. Richard P. Feynman in his famous 1959 lecture, where he envisioned manipulating matter at the atomic level to create microscopic mechanical devices (Mu et al., 2020). In the context of drug delivery, smart nanocarriers are engineered sub-micron particles, typically ranging from 10 to 100 nanometers in diameter, designed to isolate, protect, transport, and release therapeutic payloads precisely at targeted pathological sites (Sun et al., 2023).

Operating at this scale provides structural advantages. Nanocarriers exhibit a massive surface area-to-volume ratio, enabling high-density drug loading and surface functionalization with targeting ligands or protective coatings (Haggag et al., 2023). Moreover, encapsulating delicate payloads such as small-molecule inhibitors, proteins, peptides, or fragile nucleic acids shields them from premature enzymatic degradation, chemical hydrolysis, and rapid renal filtration (Rostami, 2020). By shifting the pharmacokinetic profile away from the inherent properties of the drug itself and toward the engineered features of the nanocarrier, smart drug delivery systems can dramatically extend circulation time, optimize bio-distribution, and provide spatial and temporal control over therapeutic release (Yetisgin et al., 2020).

2. Structural Classification of Advanced Nanocarriers

A wide variety of organic, inorganic, and hybrid nanomaterials have been developed as drug delivery platforms, each offering unique structural properties and drug-loading capabilities (Zhuo et al., 2024).

2.1. Organic Nanocarriers

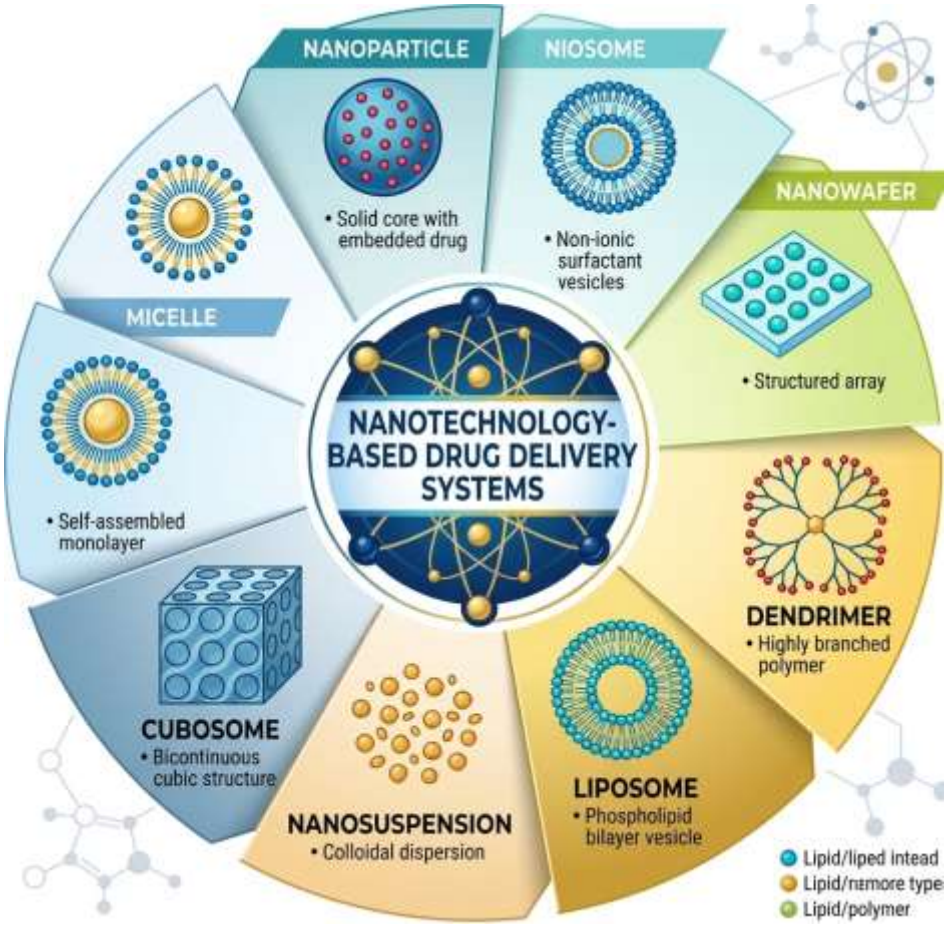
Organic and polymeric nanocarriers are highly valued for their excellent biocompatibility, structural flexibility, and minimal long-term systemic toxicity (Afzal et al., 2022).

- **Liposomes:** Liposomes are spherical vesicles composed of one or more concentric lipid bilayers enclosing an aqueous core. Constructed from amphiphilic phospholipids and stabilized with cholesterol, they possess the

unique ability to co-deliver multiple payloads. Hydrophilic drugs can be entrapped within the central aqueous core, while hydrophobic molecules are embedded within the lipophilic domain of the lipid bilayer (Khan et al., 2022).

- **Polymeric Micelles:** Polymeric micelles are self-assembled supramolecular structures formed by amphiphilic block copolymers in aqueous solution (Shi et al., 2023). When the copolymer concentration exceeds the critical micelle concentration (CMC), the hydrophobic blocks orient inward to minimize thermodynamic exposure to water, creating a dense hydrophobic core that acts as a reservoir for poorly soluble drugs. Simultaneously, the hydrophilic blocks extend outward to form a protective shell that ensures structural stability (Yadav et al., 2024).
- **Dendrimers:** Dendrimers are highly branched, symmetric macromolecules featuring well-defined three-dimensional architectures. They grow outward from a central core through sequential reaction steps, resulting in distinct generations. Dendrimers possess a high density of surface functional groups that can be used to conjugate targeting ligands or drugs, alongside internal cavities that can physically trap guest molecules (Emeihe et al., 2024).

Figure 1. Structural classification and morphological diversity of lipid- and polymer-based nanocarriers for smart drug delivery systems.



2.2. Inorganic Nanocarriers

Inorganic nanocarriers are widely utilized for their unique optical, electronic, magnetic, and structural properties, making them excellent platforms for diagnostic imaging and combination therapies (Ezike et al., 2023).

- **Gold Nanoparticles (AuNPs):** Gold nanoparticles display strong Localized Surface Plasmon Resonance (LSPR), allowing them to convert absorbed light into localized heat for photothermal therapy (PTT) while serving as robust platforms for surface conjugation (Hari et al., 2023).
- **Magnetic Iron Oxide Nanoparticles (SPIONs):** Superparamagnetic iron oxide nanoparticles can be guided to specific tissues using external magnetic fields and serve as contrast agents for Magnetic Resonance Imaging (MRI) (Tang et al., 2021).
- **Mesoporous Silica Nanoparticles (MSNs):** MSNs feature highly ordered, tunable porous networks with a massive internal surface area, enabling exceptionally high drug loading and predictable diffusion-controlled release (Adepu & Ramakrishna, 2021).

The structural characteristics, advantages, and limitations of these diverse nanocarrier classes are compared in Table 1 (Das, 2023).

Table 1: Structural Comparison of Advanced Nanocarrier Classifications

Nanocarrier Class	Core Structural Composition	Average Diameter (nm)	Primary Drug Loading Mechanism	Core Biomedical Advantage	Key Operational Limitation
Liposomes	Amphiphilic phospholipid bilayers around an aqueous core	80–150	Core encapsulation (hydrophilic) and lipid bilayer intercalation (hydrophobic)	High biocompatibility; simultaneous delivery of multiple payloads	Susceptible to premature leakage and mechanical disruption
Polymeric Micelles	Self-assembled amphiphilic block copolymers	10–100	Physical entrapment within the inner hydrophobic core	Excellent solubilization of poorly soluble drugs; long blood circulation	Rapid structural disassembly if diluted below the critical micelle concentration
Dendrimers	Highly branched, symmetric	2–10	Covalent surface conjugation	Monodisperse structure; precise	High-generation lines can

	synthetic macromolecules		or physical trapping within internal cavities	control over surface functional groups	induce charge-dependent cellular toxicity
Gold Nanoparticles	Solid metallic crystalline gold cores	5–50	Chemical absorption via sulfur-gold bonds on the surface	Unique optical properties (LSPR) for imaging and photothermal therapy	Non-biodegradable; risk of long-term tissue bioaccumulation
Mesoporous Silica	Ordered amorphous silicon dioxide porous networks	50–200	Physical adsorption within stable internal honeycomb pores	Exceptionally high drug loading capacity; tunable pore sizes	Difficult to achieve consistent, large-scale uniform synthesis

3. Mechanisms of Targeted Bio-distribution

To maximize therapeutic efficacy and prevent off-target toxicity, nanocarriers are engineered to navigate complex biological environments and accumulate selectively at targeted pathological sites through passive or active targeting pathways (Bhia et al., 2021).

3.1. Passive Targeting and the Enhanced Permeation and Retention (EPR) Effect

Passive targeting relies entirely on the unique physiological features of diseased tissues, such as solid tumors or sites of chronic inflammation. Rapid, uncontrolled blood vessel growth (angiogenesis) in solid tumors produces structural defects in the endothelial lining, resulting in large intercellular gaps that typically range from 100 to 800 nanometers. Furthermore, developing tumors frequently lack functional lymphatic drainage networks (Ciftci et al., 2025).

This combination of highly permeable blood vessels and impaired lymphatic clearance creates the Enhanced Permeation and Retention (EPR) effect. Long-circulating nanocarriers within the optimal size range of 10 to 200 nanometers can selectively extravasate through these leaky endothelial gaps and accumulate within the tumor tissue over time (Hoseini-Ghahfarokhi et al., 2020). However, passive targeting is limited by physiological barriers, including structural variations in tumor blood vessels and high internal fluid pressure, which can prevent uniform drug distribution (Ma et al., 2020).

3.2. Active Targeting and Receptor-Mediated Endocytosis

Active targeting addresses the limitations of passive accumulation by functionalizing the outer surface of the nanocarrier with specific targeting ligands. These ligands are selected to bind with high affinity to receptors that are uniquely overexpressed on the plasma membranes of diseased cells compared to healthy tissues (Mahmoud & Deambrogi, 2025).

When the surface-bound ligands bind to these target receptors, they initiate receptor-mediated endocytosis, triggering the cell membrane to invaginate and engulf the nanocarrier into an intracellular vesicle (Djayanti et al., 2023). Common targeting strategies include conjugating small molecules like folic acid to target folate receptors

overexpressed in epithelial cancers, or using monoclonal antibodies and aptamers to target specific surface markers such as Human Epidermal Growth Factor Receptor 2 (HER2) or vascular endothelial growth factor (VEGF) (Hosseini, 2021).

4. Pharmacokinetics and the Surface-Engineering Frontier

When nanocarriers enter blood circulation, they instantly interface with complex biological systems. Unmodified nanoparticles face immediate opsonization, a process where blood plasma proteins rapidly adsorb onto the high-energy surface of the nanoparticle to form a protein corona (Chehelgerdi et al., 2023). This protein corona masks the engineered targeting ligands and acts as a flag for recognition by circulating macrophages, leading to rapid clearance by the mononuclear phagocyte system (MPS), primarily in the liver and spleen (Deng et al., 2020).

To prevent opsonization and extend blood circulation time, nanocarriers undergo surface engineering to create a protective, hydrophilic steric barrier. The most widely used approach is PEGylation, the covalent grafting of polyethylene glycol (PEG) chains onto the nanoparticle surface. The conformation of these grafted polymer chains dictates their biological performance (Li et al., 2023):

- **Mushroom Conformation:** Occurs at low grafting densities, where the PEG chains remain relaxed and folded, providing incomplete surface coverage that allows plasma proteins to interact with the core (Mall et al., 2024).

- **Brush Conformation:** Occurs at high grafting densities, where steric repulsion forces adjacent PEG chains to extend outward into a rigid, highly aligned brush layout. This dense polymer brush coordinates a stable shell of water molecules that physically prevents opsonization, reduces macrophage clearance, and extends blood circulation half-life from minutes to hours (Avval et al., 2020).

However, repeated clinical administration of PEGylated nanocarriers can trigger the production of anti-PEG antibodies, leading to accelerated blood clearance (ABC) and potential hypersensitivity reactions, driving ongoing research into alternative hydrophilic polymers like polyoxazolines and zwitterionic coatings (Edis et al., 2021).

5. Controlled Release Kinetics and Mathematical Modeling

The clinical success of an advanced drug delivery platform relies on its ability to maintain controlled, predictable drug release kinetics over an extended therapeutic window, preventing dangerous concentration spikes or drops. Drug release from polymer matrices is governed by several mass transport mechanisms, including (Chandrakala et al., 2022):

- **Fickian Diffusion:** Where the drug dissolves and moves down a concentration gradient through the polymer matrix (Fam et al., 2020).

- **Matrix Erosion:** Where the polymer scaffold gradually degrades via chemical hydrolysis or enzymatic cleavage (Sun et al., 2021).

- **Swelling-Controlled Transport:** Where water penetrates a hydrogel network, expanding the polymer mesh to accelerate drug diffusion (Masoudi Asil et al., 2020).

To accurately evaluate these transport mechanisms, breeders and biomedical engineers utilize semi-empirical mathematical frameworks to fit experimental release data. The primary model used is the Korsmeyer-Peppas power-law equation (Luo et al., 2021):

$$\frac{M_t}{M_\infty} = kt^n$$

In this equation (Yan et al., 2020):

- The term M_t divided by M_∞ represents the cumulative fractional release of the drug at any given time t (Zong et al., 2022).
- The variable k is the structural release rate constant that incorporates the structural and geometric features of the nanocarrier (Yusuf et al., 2023).
- The variable n is the transport exponent used to identify the underlying release mechanism based on the geometry of the system (Jia et al., 2021).

For a spherical nanoparticle (Manzari-Tavakoli et al., 2024):

- An exponent value of $n = 0.43$ indicates pure Fickian diffusion (Chen et al., 2024).
- An exponent value exactly equal to $n = 0.85$ signifies **Case II transport**, where release is entirely controlled by the zero-order relaxation and swelling of the polymer chains (Bajracharya et al., 2022).
- An exponent value falling between these limits ($0.43 < n < 0.85$) indicates **anomalous transport**, where drug release is driven by a simultaneous combination of both diffusion and polymer matrix erosion (Zhu et al., 2026).

6. Stimuli-Responsive Dynamic Engineering

"Smart" drug delivery systems go beyond simple passive diffusion by incorporating stimuli-responsive components that remain structurally stable in normal physiological conditions, but undergo rapid chemical or structural changes when exposed to specific internal or external triggers (Satapathy et al., 2021).

6.1. Endogenous Stimuli-Responsive Systems

Endogenous systems exploit the natural physical and chemical gradients that exist between healthy tissues and pathological microenvironments (Su & Kang, 2020).

- **pH-Responsive Delivery:** Healthy blood plasma maintains a strict pH of 7.4, whereas solid tumor tissues and sites of bacterial infection are inherently acidic (pH 6.5 to 6.2) due to anaerobic glycolysis and lactic acid accumulation (Osman et al., 2022). Furthermore, when nanocarriers are internalized via endocytosis, they enter endosomes and lysosomes, which are highly acidic intracellular compartments (pH 5.0 to 4.5) (Sharma & Mukhopadhyay, 2024). pH-responsive nanocarriers exploit this gradient by incorporating acid-labile linkages (such as hydrazone, acetal, or imine bonds) that remain stable at pH 7.4 but undergo rapid hydrolysis in acidic environments, releasing the active payload selectively inside the target cell (Dang & Guan, 2020).
- **Redox-Responsive Delivery:** The intracellular environment of mammalian cells maintains a highly reductive potential due to high concentrations of glutathione (GSH, approximately 2 to 10 millimolar), compared to the oxidative environment of blood plasma and extracellular fluids (where GSH concentrations are low, approximately 2 to 20 micromolar) (Wu et al., 2023). Smart nanocarriers can incorporate disulfide bonds into their polymer backbones or crosslinked shells. These disulfide linkages remain intact in circulation but are rapidly cleaved via reduction upon entering the glutathione-rich cytoplasm, triggering structural collapse of the carrier and rapid intracellular drug release (Zhang et al., 2021).

- **Enzyme-Responsive Delivery:** Pathological tissues frequently overexpress specific enzymes, such as matrix metalloproteinases (MMPs) in tumors or elastases at inflammatory sites. Nanocarriers can be engineered with protective coatings held together by short, enzyme-cleavable peptide sequences, allowing the payload to be released only in the presence of the target enzyme (Hong et al., 2023).

The main endogenous and exogenous stimuli-responsive operational triggers are structured and compared in Table 2 (Mi et al., 2021).

Figure 2. Schematic overview of the integrated biomedical platform: from nanoparticle architecture synthesis to translational applications and organ-system biologically-responsive targeted delivery.

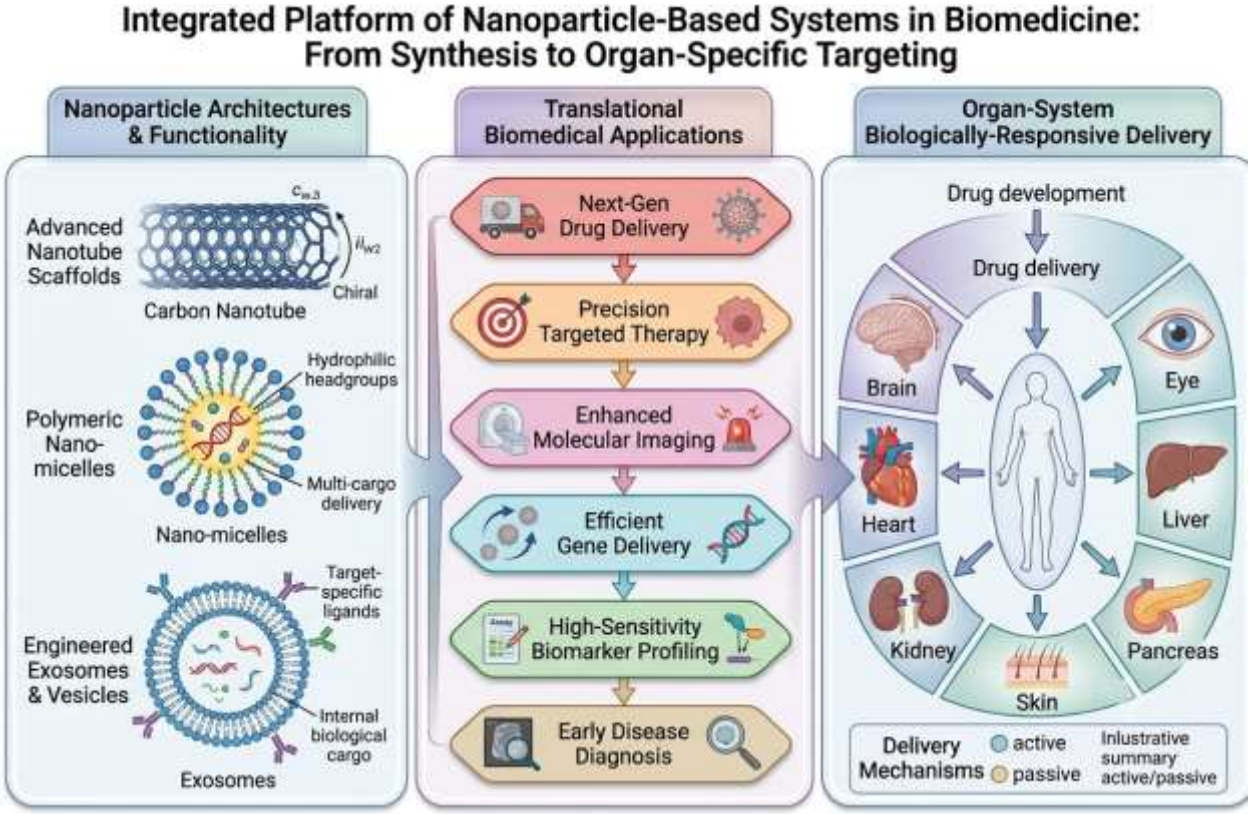


Table 2: Stimuli-Responsive Nanocarrier Triggering Configurations

Stimulus Category	**Specific Operational Trigger**	**Microenvironmental Shift or External Source**	**Core Structural Release Mechanism**	**Typical Clinical Target**
Endogenous	pH-Responsive	Endosomal/lysosomal acidification (pH 4.5–5.5) or tumor extracellular acidity	Rapid acid-catalyzed hydrolysis of cleavable chemical linkages (hydrazones, acetals)	Intracellular chemotherapeutic delivery; localized antibiotic targeting

Endogenous	Redox-Responsive	Intracellular glutathione (GSH) concentration gradient (2–10 mM intracellular versus 2–20 micro-M extracellular)	Cleavage of disulfide bonds via reduction, causing structural matrix disassembly	Targeted intracellular gene, siRNA, and highly potent molecular delivery
Endogenous	Enzyme-Responsive	Upregulated pathological enzymes (Matrix Metalloproteinases, Cathepsin B)	Direct enzymatic cleavage of specific peptide sequences within the polymer shell	Selective drug release in solid tumors and sites of chronic inflammation
Exogenous	Thermo-Responsive	External localized heating or focused microwave hyperthermia	Triggers a sharp phase transition (LCST) in polymers, causing shell collapse and drug ejection	Combination thermal ablation and highly localized photochemotherapy
Exogenous	Light-Responsive	External Ultraviolet, Visible, or Near-Infrared (NIR) laser irradiation	Photo-isomerization, reversible structural rearranging, or localized photolytic cleavage	Superficial tumor treatment; targeted skin and ophthalmological therapies
Exogenous	Magnetic-Responsive	External alternating magnetic field (AMF)	Induces physical rotation or thermal heating in core SPIONs, disrupting the shell	Deep-tissue tumor targeting; synchronized diagnostic imaging and therapy

7. Real-Time Tracking via Nanoparticle Surface Energy Transfer (NSET)

A major advancement in theranostic medicine is the ability to track nanocarrier trafficking and monitor real-time drug release inside living cells. This can be achieved by engineering systems that leverage Nanoparticle Surface Energy Transfer (NSET) (Hsu et al., 2021). NSET is a non-radiative physical phenomenon that operates similarly to classic Fluorescence Resonance Energy Transfer (FRET), but replaces the organic molecular acceptor with a noble metal nanoparticle core, such as gold or silver (Quispe et al., 2022).

To utilize this mechanism, a fluorescent drug or molecular probe is chemically conjugated to the nanoparticle surface via a stimuli-responsive linker (such as an acid-cleavable hydrazone bond) (Liu et al., 2023). When the drug payload is securely bound and in close proximity to the metallic surface, the excited-state electronic energy of the fluorophore undergoes highly efficient, non-radiative transfer directly to the conduction band electrons of the metal core. This results in complete quenching of the drug's fluorescence, representing the **NSET-On / Fluorescence-Off** state (Tian et al., 2023).

Once the nanocarrier is internalized into an acidic endosome or lysosome, the acid-labile linkers are cleaved. As the liberated drug molecules diffuse away from the metallic surface, the distance between the fluorophore donor and the metal core increases, exceeding the functional threshold for energy transfer (Chindamo et al., 2020). This suppresses the NSET effect, allowing the drug molecules to recover their full fluorescent signal, representing the **NSET-Off / Fluorescence-On** state. By monitoring this switchable fluorescence via confocal microscopy, researchers can visually track cellular internalization and map drug release kinetics in real-time in living systems (Naeem et al., 2020).

8. Clinical Translation, Toxicological Safety, and Manufacturing Challenges

Despite the significant therapeutic advantages demonstrated by smart drug delivery systems in preclinical research, their translation into routine clinical practice faces substantial regulatory, safety, and manufacturing hurdles (Vega-Vásquez et al., 2020).

8.1. Nanotoxicology and Bioaccumulation Risks

The unique physical and chemical properties of nanomaterials that make them effective for drug delivery can also introduce unexpected toxicological profiles (Ma et al., 2024). A primary concern is the **"Endosomal Trojan Horse"** toxicity mechanism. When non-biodegradable inorganic nanoparticles (such as certain gold, silver, or silica formulations) enter cells via endocytosis, they are exposed to harsh, acidic lysosomal environments (Sivadasan et al., 2023). This acidity can accelerate the oxidative dissolution of metallic cores, releasing high concentrations of toxic metal cations directly into the cytoplasm (Nie et al., 2020). This localized ion release can disrupt mitochondrial membranes, inhibit essential cellular enzymes, and generate excessive reactive oxygen species (ROS), leading to severe oxidative stress, DNA damage, and cell death (Wei et al., 2021).

Furthermore, non-biodegradable inorganic nanocarriers are resistant to rapid metabolic clearance, leading to long-term bioaccumulation in the reticuloendothelial system, particularly within the kupffer cells of the liver and the macrophages of the spleen. This persistence poses a risk of chronic systemic toxicity and organ dysfunction (Nsairat et al., 2022). Even with organic polymers like polyethylenimine (PEI), a high density of positive surface charge can cause dose-dependent toxicity by interacting non-specifically with negatively charged mammalian cell membranes, causing cell lysis and erythrocyte aggregation (Liu et al., 2023).

8.2. The Preclinical-to-Clinical Translation Gap

A significant gap exists between therapeutic efficacy in animal models and outcomes in human clinical trials. Small-animal tumor models (such as mice with subcutaneous xenografts) grow rapidly and exhibit highly leaky tumor blood vessels, resulting in an

artificially pronounced EPR effect. Human tumors, however, are highly heterogeneous, show variable vascular leakiness, and have areas of high interstitial fluid pressure that limit passive nanoparticle delivery (Zorkina et al., 2020).
Consequently, several clinical studies have shown that the systemic accumulation of target-directed nanoparticles in human solid tumors is frequently less than 1% of the administered dose (Grewal & Salar, 2024). Furthermore, the complexity of these multi-component formulations makes industrial scale-up under Good Manufacturing Practice (GMP) standards exceptionally difficult (Ruman et al., 2020). Controlling critical quality attributes such as particle size, polydispersity, surface charge, and drug encapsulation efficiency with high batch-to-batch reproducibility represents a major technical hurdle for industrial-scale manufacturing (Yang et al., 2024).

Conclusion

In conclusion, nanotechnology-based smart drug delivery systems have emerged as transformative platforms for achieving controlled and targeted therapeutic delivery across a wide range of medical applications. Their ability to enhance drug stability, improve bioavailability, provide site-specific targeting, and enable controlled release significantly increases therapeutic efficacy while reducing systemic toxicity and adverse effects. Advances in nanocarrier design, surface engineering, and stimulus-responsive technologies have expanded their applications in cancer treatment, infectious disease management, cardiovascular therapy, neurological disorders, and gene delivery. However, several challenges, including nanotoxicity, biodegradability, manufacturing scalability, regulatory approval, and long-term clinical safety, remain obstacles to routine clinical implementation. Future research should focus on developing highly biocompatible nanomaterials, optimizing multifunctional nanocarriers, integrating artificial intelligence for nanomedicine design, and conducting extensive preclinical and clinical evaluations. Overall, nanotechnology-based smart drug delivery systems represent a promising frontier in precision medicine, offering innovative solutions for safer, more effective, and personalized therapeutic interventions.

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