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Recent Advances in Nanoparticle-Based Targeted Drug Delivery Systems: A Comprehensive Review

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Abstract

Nanomedicine has transformed the landscape of therapeutic interventions, with nanoparticle-based targeted drug-delivery systems among its most promising advances. Conventional chemotherapy often suffers from poor specificity, leading to severe systemic toxicity and limited efficacy. This comprehensive review synthesizes recent progress in the design and application of engineered Nanoparticles (NPs) that address these limitations through enhanced targeting, improved bioavailability, and controlled drug release. Major classes of nanocarriers ,including lipid-based NPs (Lipid Nanoparticles (LNPs) and liposomes), polymeric and inorganic NPs (such as gold NPs), dendrimers, and exosomes, are systematically categorized and discussed, with emphasis on their physicochemical characteristics and biomedical applications. The review further highlights key targeting strategies, including passive targeting via the Enhanced Permeability and Retention (EPR) effect and active targeting through surface-functionalized ligands such as antibodies, peptides, and aptamers. Special attention is given to stimuli-responsive or "smart" nanocarriers that enable drug release in response to internal (pH, enzymes, redox) or external (light, magnetic field) cues. Advances in multifunctional platforms, combination therapies, and Artificial Intelligence (AI)–assisted nanocarrier design are also discussed, alongside ongoing challenges such as crossing biological barriers, particularly the blood-brain barrier. Finally, the review outlines the translational landscape, regulatory considerations, and future perspectives of nanoparticle-based drug delivery systems, offering insights into the path from bench to bedside.

Keywords: Targeted drug delivery, Nanoparticles, Nanomedicine, Cancer therapy.

1 | Introduction

The pursuit of effective and safe therapeutic modalities remains a central goal in modern medicine. Conventional drug administration, particularly for life-threatening diseases such as cancer, typically relies on the systemic delivery of chemotherapeutic agents. Although this approach can be practical, it is often limited

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by a narrow therapeutic index, in which the effective dose is close to the toxic dose. Consequently, the lack of specificity results in collateral damage to healthy, rapidly dividing cells, leading to severe adverse effects such as nephrotoxicity, cardiotoxicity, and bone marrow suppression. These complications significantly impair patient quality of life and limit the maximum tolerable dose.

The concept of a "magic bullet," first proposed by Paul Ehrlich over a century ago, envisioned a therapeutic agent capable of selectively targeting diseased cells while sparing healthy ones. The advent of nanotechnology in the late twentieth and early twenty-first centuries has brought this vision closer to reality. Nanoparticles (NPs), defined as particulate dispersions or solid particles with dimensions between 1 and 100 nanometers, provide a unique platform for the construction of sophisticated drug delivery vehicles. Their nanoscale size is comparable to that of biological molecules and cellular structures, enabling molecular-level interactions that are not possible in bulk materials.

The rationale for employing NPs in drug delivery is multifaceted. Their large surface area-to-volume ratio enables high drug loading and facile conjugation of targeting ligands. NPs protect encapsulated therapeutic agents, whether small molecules, proteins, or nucleic acids (as demonstrated by Lipid Nanoparticles (LNPs) in mRNA-based COVID-19 vaccines), from premature degradation in the bloodstream. Moreover, they enhance the solubility of hydrophobic drugs and enable sustained or controlled release kinetics, thereby maintaining therapeutic concentrations over extended periods.

The most significant advantage of NPs lies in their ability to achieve targeted drug delivery, which can be broadly categorized into two mechanisms.

I. Passive targeting exploits the distinctive pathophysiology of diseased tissues, substantial tumors, which exhibit leaky vasculature and impaired lymphatic drainage, a phenomenon known as the Enhanced Permeability and Retention (EPR) effect. NPs within a specific size range can preferentially accumulate in tumor tissue while being cleared more slowly.

II. Active targeting involves functionalizing nanoparticle surfaces with biological ligands (e.g., antibodies, folic acid, transferrin, peptides) that bind receptors overexpressed on target cells with high affinity. This ligand–receptor interaction promotes receptor-mediated endocytosis and enhances the intracellular accumulation of therapeutic agents at the intended site of action.

Given these advantages, recent research has increasingly focused on developing advanced nanoparticle-based drug delivery systems that combine precision targeting, controlled release, and biocompatibility. This comprehensive review systematically explores recent advances in the design and application of such systems, encompassing various nanocarrier platforms, targeting mechanisms, and intelligent stimuli-responsive approaches. Furthermore, it discusses emerging multifunctional and combination strategies and addresses the translational challenges of converting laboratory innovations into clinically viable therapies.

2 | Major Classes of Nanoparticle Drug Carriers

The selection of nanocarrier materials is a critical determinant of drug-loading capacity, release kinetics, biocompatibility, and overall pharmacokinetic behavior. Based on recent literature, NPs used in targeted drug delivery can be systematically classified into the following primary categories.

2.1 | Lipid-Based Nanoparticles

LNPs have gained significant prominence, particularly following their successful application in mRNA-based COVID-19 vaccines, which significantly accelerated their clinical translation [1]. These systems are highly biocompatible as they are typically composed of physiological or physiologically similar lipids.

2.1.1 | Liposomes

Liposomes are spherical vesicles consisting of one or more concentric phospholipid bilayers enclosing an aqueous core. This dual structure enables the encapsulation of both hydrophilic and hydrophobic drugs.

Liposomes have been extensively studied for decades, and several formulations have already received clinical approval [2]. Their surfaces can be modified with polymers such as Polyethylene Glycol (PEG) to impart "stealth" properties, thereby prolonging circulation time and minimizing clearance by the Mononuclear Phagocyte System (MPS) [2], [3].

2.1.2 | Solid lipid nanoparticles and next-generation lipid nanoparticles

Solid Lipid Nanoparticles (SLNs) were developed as an alternative to liposomes and polymeric NPs, providing a solid lipid matrix at physiological temperatures that enhances stability and enables controlled drug release [4], [5]. They typically consist of triglycerides, partial glycerides, or waxes. The evolution from SLNs to next-generation LNPs led to systems incorporating ionizable lipids, phospholipids, cholesterol, and PEG-lipids. Ionizable lipids are particularly important for nucleic acid delivery, as they acquire a positive charge at low pH, facilitating complexation with negatively charged Ribonucleic Acid (RNA) or Deoxyribonucleic Acid (DNA) and promoting endosomal escape [1], [6]. Tenchov et al. [1] provide a comprehensive overview of this transition from traditional liposomes to mRNA-delivering LNPs [1].

2.2 | Polymeric Nanoparticles

Polymeric NPs offer exceptional versatility owing to the wide range of synthetic and natural polymers available, enabling precise control over physicochemical and biological properties.

2.2.1 | Synthetic polymers

Poly Lactic-co-Glycolic Acid (PLGA) is among the most widely used biodegradable polymers approved by the Food and Drug Administration (FDA). It degrades by hydrolysis into lactic and glycolic acids ,both natural metabolic intermediates that ensure biocompatibility. The degradation rate, and hence the release kinetics, can be tuned by varying the lactic-to-glycolic acid ratio [7], [8]. Other notable polymers include Poly ε-Caprolactone (PCL) and Polyethyleneimine (PEI), with PEI being particularly effective for gene delivery due to its high cationic charge density.

2.2.2 | Natural polymers

Chitosan, alginate, and albumin are representative natural polymers valued for their biodegradability, low toxicity, and inherent bioactivity. A prominent clinical example is albumin-bound paclitaxel (Abraxane®), which exploits albumin's natural transport pathways to enhance tumor targeting [9], [10].

2.2.3 | Dendrimers

Dendrimers are a distinct class of synthetic polymers with a well-defined, highly branched, and monodisperse three-dimensional structure. Their architecture offers numerous surface groups for ligand attachment and a hydrophobic core for drug encapsulation. The stepwise synthesis of dendrimers enables precise control of molecular size and weight [11–13]. Recent studies highlight their utility not only as independent carriers but also as surface modifiers that improve the functionality of inorganic NPs [12],[13].

2.3 | Inorganic Nanoparticles

Inorganic NPs exhibit unique optical, magnetic, and electronic properties, making them attractive for both therapeutic and diagnostic ("theranostic") purposes.

2.3.1 | Gold nanoparticles

Gold Nanoparticles (AuNPs) are highly tunable in terms of size, shape (spheres, rods, shells), and surface chemistry. Their strong Surface Plasmon Resonance (SPR) enables light absorption and conversion into heat, which is exploited in photothermal therapy and light-triggered drug release [14], [15].

2.3.2 | Mesoporous silica nanoparticles

Mesoporous Silica Nanoparticles (MSNs) possess a high surface area and tunable pore sizes, enabling high drug-loading efficiency. Their surfaces can be modified via silane chemistry, and the pores can be capped with stimuli-responsive gatekeepers for controlled release [7].

2.3.3 | Magnetic nanoparticles (e.g., Iron Oxides)

Superparamagnetic Iron Oxide Nps (SPIONs) can be guided to specific sites using external magnetic fields (magnetic targeting). They also act as MRI contrast agents, enabling real-time imaging and tracking of the delivery system [7], [16].

2.4 | Biomimetic and Hybrid Nanoparticles

Recent research has focused on mimicking biological systems or combining multiple materials to achieve synergistic performance.

2.4.1 | Exosomes

Exosomes are natural extracellular vesicles (30–150 nm) secreted by cells that play essential roles in intercellular communication. They exhibit intrinsic homing capabilities, low immunogenicity, and the natural ability to cross biological barriers such as the blood–brain barrier [17], [18]. Engineered exosomes are now being explored as next-generation drug carriers through cargo loading and membrane surface modification [17]

2.4.2 | Cell membrane-coated nanoparticles

This biomimetic approach involves cloaking synthetic nanoparticle cores (e.g., PLGA) with membranes derived from natural cells—such as red blood cells, leukocytes, or cancer cells. These coatings endow the particles with the surface proteins and biological functions of the source cells, enhancing circulation time and target specificity [19].

2.4.3 | Hybrid nanoparticles

Hybrid systems integrate components from multiple classes to combine their advantages. For instance, lipid–polymer hybrid NPs may feature a polymeric core for drug loading surrounded by a lipid shell for improved stability and biocompatibility [7], [20].

A schematic overview of the significant classes of nanoparticle drug carriers is presented in *Fig. 1*, highlighting lipid-based, polymeric, inorganic, and emerging biomimetic or hybrid systems, along with representative examples and their key applications. *Fig. 1* provides a concise visual summary to complement the detailed descriptions provided in the text.

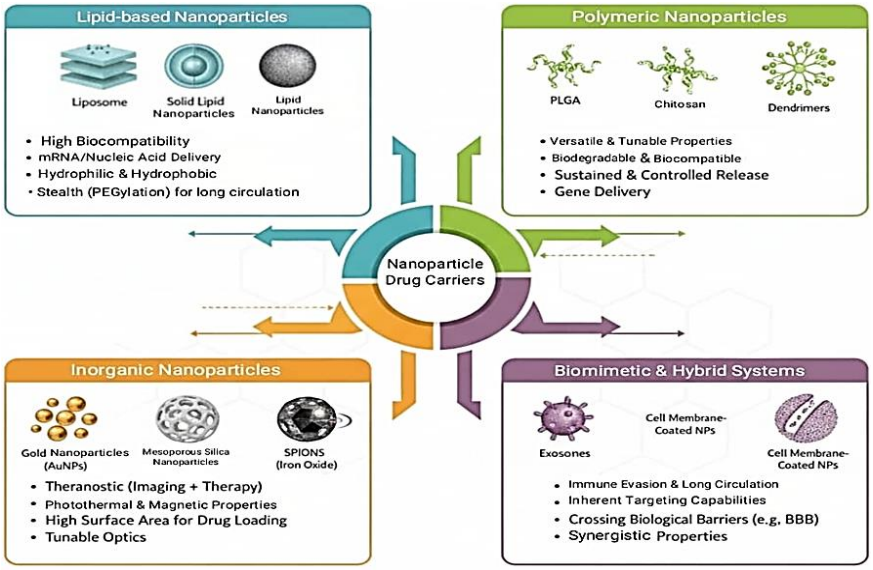

Fig. 1. Schematic classification of major nanocarriers: lipid-based (e.g., LNPs), polymeric (e.g., PLGA), inorganic (e.g., AuNPs), and biomimetic/hybrid systems (e.g., exosomes, membrane-coated NPs).

3 | Targeting Strategies: Passive and Active Approaches

The ability to deliver therapeutic agents specifically to the disease site is a cornerstone of nanomedicine. Targeting strategies can be broadly classified into two complementary mechanisms: passive and active targeting.

3.1 | Passive Targeting

Passive targeting exploits the distinctive pathophysiological features of diseased tissues, most notably solid tumors, without relying on specific molecular recognition.

The enhanced permeability and retention effect

This is the most widely recognized mechanism for passive targeting. Tumor tissues often exhibit aberrant, leaky vasculature with wide fenestrations, resulting from rapid, poorly organized angiogenesis. Simultaneously, lymphatic drainage is typically impaired. This combination allows NPs within a specific size range (typically 10–200 nm) to extravasate into the tumor interstitium more readily than into healthy tissues and remain there for extended periods [3], [9], [20]. Consequently, nanocarriers selectively accumulate in the tumor microenvironment.

The role of nanoparticle physicochemistry

The efficiency of passive targeting largely depends on the physicochemical properties of the NPs. Size is critical: particles must be large enough to avoid rapid renal clearance yet small enough to traverse vascular gaps in tumors. Surface charge is also essential; near-neutral or slightly negative surfaces are generally preferred, as highly positive charges tend to induce non-specific interactions with serum proteins and cell membranes, leading to rapid clearance by the MPS [3], [16]. PEGylation, the covalent attachment of PEG, is a widely employed strategy to create a "stealth" layer around NPs, reducing opsonization and prolonging circulation half-life, thereby maximizing opportunities for the EPR effect [1], [21].

3.2 | Active Targeting

While passive targeting facilitates initial accumulation in tumors, active targeting enhances cellular uptake by specific cell types through molecular recognition. This is achieved by conjugating targeting ligands (also called

homing ligands) to the nanoparticle surface, which bind with high affinity to receptors overexpressed on target cells (e.g., cancer cells).

Ligand-Receptor Interactions: Binding of ligand-functionalized NPs to their cognate receptors typically triggers receptor-mediated endocytosis, enabling the internalization of the nanoparticle-drug complex. This mechanism significantly increases intracellular drug concentration at the target site while minimizing exposure to non-target cells [19], [20], [22].

3.3 | Commonly Used Targeting Ligands

3.3.1 | Antibodies and antibody fragments

These ligands offer high specificity. Monoclonal antibodies (e.g., anti-HER2 for breast cancer) or their fragments (e.g., single-chain variable fragments, scFv) can be employed. This approach is often referred to as immuno NPs [9], [22].

3.3.2 | Peptides and proteins

Peptides such as Arg-Gly-Asp (RGD) target αvβ3 integrins, which are overexpressed on tumor endothelial cells. Proteins like transferrin, an iron-transporting protein, bind to transferrin receptors, which are highly expressed on many cancer cells due to their elevated metabolic demands [16], [19].

3.3.3 | Vitamins

Folic acid (vitamin B9) is a small, stable, and cost-effective ligand that binds to folate receptors, which are overexpressed in various cancers, including ovarian and lung cancers [7], [8].

3.3.4 | Aptamers

Aptamers are short, single-stranded DNA or RNA oligonucleotides that fold into specific three-dimensional structures, allowing them to bind target molecules with antibody-like affinity. They are synthetically produced and exhibit low immunogenicity [3].

3.3.5 | Immune cell targeting

An advanced application of active targeting involves directing NPs to specific immune cells to modulate the immune response, a key strategy in cancer immunotherapy. NPs can be designed to target T cells, dendritic cells, or tumor-associated macrophages to enhance anti-tumor immunity or suppress protumorigenic activity [22], [23]. It is important to note that active targeting complements, rather than replaces, passive targeting. Initial accumulation in the tumor via the EPR effect is often a prerequisite for effective ligand-receptor interactions[3], [16].

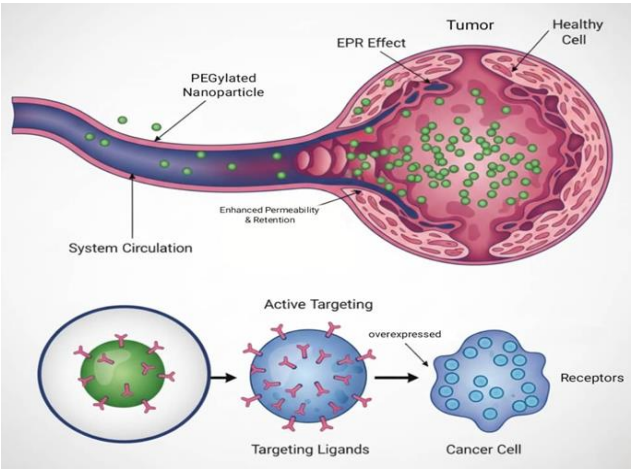

Fig. 2. Overview of nanoparticle-based targeted drug delivery strategies.

Fig. 2 illustrates passive targeting via the EPR effect, where PEGylated NPs preferentially accumulate in tumor tissue due to leaky vasculature. The bottom panel depicts active targeting, in which NPs are functionalized with targeting ligands that specifically bind to overexpressed receptors on cancer cell surfaces, thereby facilitating cellular uptake.

4 | "Smart" Stimuli-Responsive Nanoparticles

To achieve greater spatial and temporal control over drug release, "smart" or stimuli-responsive NPs have been developed. These systems remain stable in circulation but undergo physicochemical transformations such as degradation, disassembly, or pore opening, releasing their payload specifically at the disease site in response to internal (endogenous) or external (exogenous) stimuli [24–26].

4.1 | Internally Triggered (Endogenous) Systems

These systems exploit the unique biochemical characteristics of the disease microenvironment.

I. pH-Responsive systems: the tumor microenvironment and intracellular compartments (endosomes, lysosomes) are more acidic (pH 6.5–7.0 and 4.5–5.0, respectively) than blood and normal tissues (pH 7.4). NPs can be engineered using pH-sensitive bonds (e.g., hydrazone, acetal) or polymers (e.g., poly(histidine)) that destabilize or become protonated under acidic conditions, triggering drug release [24], [27].

II. Enzyme-responsive systems: certain enzymes, such as Matrix Metalloproteinases (MMPs), cathepsins, and phospholipases, are overexpressed in tumors. NPs can incorporate enzyme-cleavable linkers (e.g., MMP-2-sensitive peptide sequences), either within the nanoparticle structure or as a "gatekeeper" for mesoporous silica NPs. Enzymatic cleavage compromises the nanoparticle integrity, enabling drug release [25], [27].

III. Redox-responsive systems: the intracellular environment contains a much higher concentration of reducing agents, such as Glutathione (GSH), compared to the extracellular space. This gradient is even more pronounced in cancer cells. NPs containing disulfide bonds (-S-S-) remain stable extracellularly but rapidly cleave in the reducing intracellular milieu, triggering drug release [24], [25].

4.2 | Externally Triggered (Exogenous) Systems

These systems respond to externally applied physical stimuli, providing high spatial and temporal control over drug release.

4.2.1 | Thermoresponsive systems

NPs, often composed of polymers such as poly N-isopropylacrylamide (pNIPAAm), undergo a phase transition (swelling or collapse) at a specific temperature. When combined with a localized external heat source (e.g., Near-Infrared (NIR) light or ultrasound), they release their payload in a defined area [25].

4.2.2 | Photo-responsive systems

Light, especially NIR light due to its superior tissue penetration, can trigger drug release via photothermal heating or cleavage of photolabile chemical groups (e.g., o-nitrobenzyl esters), as previously described for gold NPs [14], [24].

4.2.3 | Magnetic-responsive systems

SPIONs can be used not only for targeting but also for triggering. Under an alternating magnetic field, these NPs generate heat, thereby inducing drug release from a thermosensitive matrix and enabling combined hyperthermia and chemotherapy [7], [16].

The development of these intelligent, externally triggered systems represents a significant step toward truly precision nanomedicines, capable of releasing their therapeutic cargo on demand, at the exact time and location required.

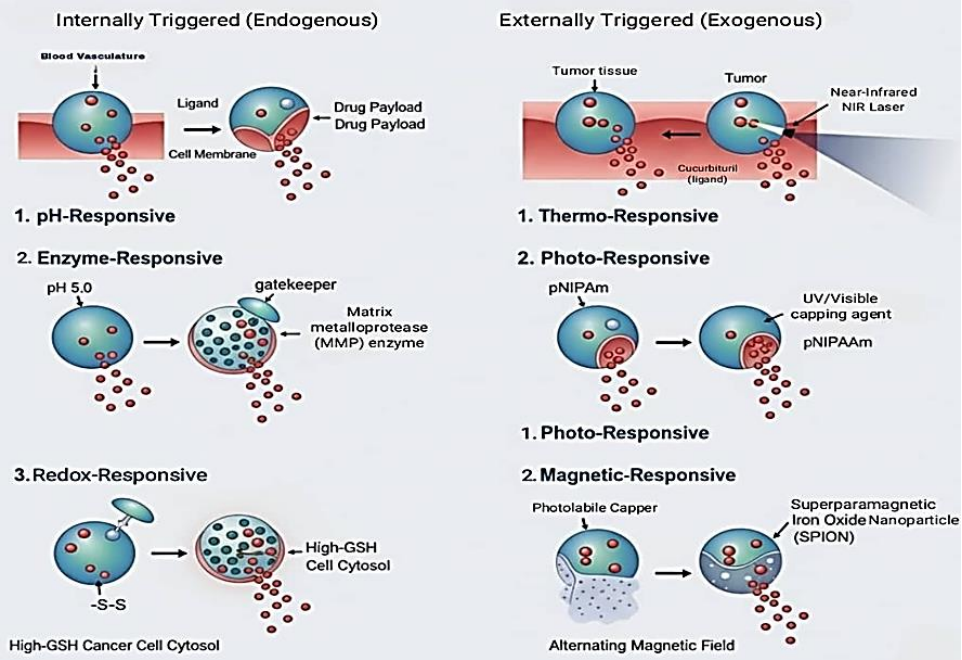

Fig. 3. Schematic representation of "smart" stimuli-responsive nanocarriers for on-demand drug release.

As shown in *Fig. 3*, the diagram distinguishes between internally triggered (endogenous) systems, which exploit tumor microenvironment features such as pH, enzymes, and redox gradients, and Externally Triggered (exogenous) systems, which utilize external physical stimuli, thermo, photo, or magnetic responsive mechanisms for localized and controlled payload release.

5 | Advanced Applications and Combination Strategies

The full potential of nanoparticle-based drug delivery emerges in advanced applications that extend beyond simple, single-drug delivery. These sophisticated systems are designed to address the complex, multifactorial nature of diseases, such as cancer.

5.1 | Multifunctional and Combination Therapy Nanoparticles

Monotherapy often leads to drug resistance in cancer. To overcome this, combination therapies targeting multiple disease mechanisms are highly effective, and NPs provide an ideal platform for implementing such strategies.

I. Co-delivery of therapeutic agents: NPs can be engineered to deliver multiple drugs with complementary mechanisms of action simultaneously. For example, a single nanocarrier can transport a chemotherapeutic drug alongside a chemosensitizer or an anti-angiogenic agent, ensuring that both drugs reach the same cell simultaneously. This synergy often produces effects greater than the sum of individual treatments [20]. Li et al. [20] highlight platforms combining drugs with Small Interfering Ribonucleic Acid (siRNA) to silence resistance genes, effectively suppressing drug efflux pumps [20].

II. Theranostics: integrating therapy and diagnosis: the term theranostics refers to the integration of therapy and diagnostic imaging within a single agent. Inorganic NPs are particularly well-suited for this purpose. For instance, SPIONs can function as both MRI contrast agents and drug carriers. Similarly, gold NPs can be

employed for Computed Tomography (CT) imaging and photothermal therapy. This approach allows real-time monitoring of drug distribution to the target site and assessment of treatment efficacy [7], [14].

6 | Overcoming Biological Barriers

A significant challenge in drug delivery is navigating the body's formidable biological barriers. NPs offer innovative strategies to bypass these defenses.

The Blood-Brain Barrier is a highly selective barrier that protects the brain but blocks over 98% of small-molecule drugs. NPs can be designed to cross the BBB via ligand-mediated transcytosis, using surface functionalization with ligands such as transferrin or lactoferrin [28]. Wu et al. [28] provide a comprehensive analysis of BBB structure and advanced nanocarrier strategies for treating neurological disorders and brain tumors [28].

7 | The Convergence with Artificial Intelligence

Designing and optimizing NPs is a complex, multi-parameter problem. Artificial Intelligence (AI) and Machine Learning (ML) are emerging as transformative tools in nanomedicine.

Accelerated design and prediction

AI algorithms can analyze large datasets to predict relationships between nanoparticle properties (size, charge, lipid composition) and biological outcomes (efficacy, toxicity, biodistribution). This significantly reduces the time and cost of experimental trial-and-error [26]. Das et al. [26] discuss how AI can integrate with nanomedicine to enable personalized nanomedicine, optimizing carrier properties for individual patient profiles [26].

8 | Clinical Translation and Regulatory Landscape

The journey of a nanoparticle-based therapeutic from bench to bedside is long and complex. Despite extensive preclinical research, only a fraction of nanomedicines reach the market.

Key challenges

I. Scalable and reproducible manufacturing: producing NPs with consistent size, composition, and drug loading on a large scale. Good Manufacturing Practice (GMP) is challenging [9], [10].

II. Robust characterization: understanding the physicochemical properties and stability of the final product is critical for regulatory approval.

III. Safety and toxicology: long-term toxicity and potential immunogenic responses (e.g., accelerated blood clearance against PEG) must be carefully assessed [29], [30].

IV. Demonstrating clinical advantage: new nanomedicines must show significant improvements over existing therapies, not just equivalence, to justify development costs and regulatory hurdles [9].

V. Notable successes —liposomal Doxorubicin (Doxil®), Abraxane®, and the mRNA COVID-19 vaccines based on LNPs — illustrate the potential for rapid development and large-scale deployment of nanoparticle technology [1], [22].

VI. Regulatory pathways and clinical trials :regulatory approval, governed by agencies like the FDA and European Medicines Agency (EMA), requires filing an Investigational New Drug (IND) application followed by phased clinical trials (Phase I: safety, Phase II: efficacy and dosing, Phase III: large-scale efficacy) [29]. Younis et al. [31] provide a detailed overview of the clinical translation process and the FDA's perspective on nanomedicines [29]. Understanding this pathway is crucial for translating laboratory innovation into real-world therapies.

9 | Conclusion and Future Perspectives

This comprehensive review has synthesized recent advances in nanoparticle-based targeted drug delivery systems, focusing on publications from 2020 to 2025. We have navigated from the fundamental building blocks to the major classes of nanocarriers, including lipidic, polymeric, and inorganic NPs, to the sophisticated targeting strategies that confer specificity through both passive (EPR effect) and active (ligand-receptor) mechanisms. The discussion progressed to "smart" stimuli-responsive systems, which enable precise spatiotemporal control of drug release, and finally to the advanced frontiers of the field, including multifunctional theranostics, AI-driven design, and the critical challenges of clinical translation. The field is dynamic and rapidly evolving. Future research will likely focus on several key areas:

Enhanced biomimicry

Leveraging biological components such as exosomes and cell membrane coatings to improve biocompatibility and inherent targeting capabilities [17–19].

Personalized nanomedicine

Integrating diagnostics with therapy (theranostics) and AI-driven design to tailor treatments to individual patients' genetic, proteomic, and pathophysiological profiles [26].

Overcoming immunological hurdles

Understanding and mitigating immune responses to nanocarriers, including anti-PEG immunity, will be crucial for next-generation formulations [29].

9.4 | Tackling Biological Complexity

Designing systems that account for tumor heterogeneity and the dynamic nature of biological barriers to improve delivery efficiency.

In conclusion, nanoparticle-based targeted drug delivery systems represent a paradigm shift in therapeutics. For undergraduate chemistry students, this field exemplifies how fundamental chemical principles, such as synthesis, self-assembly, surface functionalization, and triggered release, can be harnessed to address profound biological and medical challenges. The journey from a chemical structure to a life-saving medicine is long. Still, the continued convergence of chemistry, materials science, biology, and medicine promises a future where the "magic bullet" becomes a standard tool in the clinical arsenal.

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