



Nanotechnology-Based Drug Delivery Systems: A Critical Review of Current Advancements, Translational Challenges, and Future Perspectives in Stimuli-Responsive, Targeted, and Multifunctional Nanocarrier Platforms

Rachel Hui Min Tan ^{1*}, Olivia Harper ²

¹⁻² PhD Department of Pharmaceutical Technology, Heidelberg University, Germany.

* Corresponding Author: Rachel Hui Min Tan

Article Info

ISSN (online): 3107-393X

Volume: 03

Issue: 01

Received: 20-11-2025

Accepted: 22-12-2025

Published: 24-01-2026

Page No: 26-34

Abstract

Nanotechnology-based drug delivery systems have emerged as a transformative paradigm in modern pharmacotherapy, offering fundamental solutions to the inherent limitations of conventional drug formulations including poor bioavailability, non-specific biodistribution, systemic toxicity, and inadequate therapeutic indices. This review provides a comprehensive and critical examination of the current landscape of nanocarrier technologies, encompassing polymeric nanoparticles, lipid-based vesicles, inorganic nanostructures, dendrimers, and emerging hybrid platforms. Particular emphasis is placed on mechanistic advancements in passive targeting via the enhanced permeability and retention effect, active targeting through ligand-receptor interactions, and stimuli-responsive release mechanisms triggered by endogenous microenvironments or exogenous physical stimuli. The translational trajectory of these systems is evaluated through their therapeutic applications in oncology, infectious diseases, and chronic disorders, with critical analysis of approved formulations and candidates in clinical development. Despite substantial preclinical success, persistent challenges including nanotoxicity, immunogenicity, manufacturing scalability, regulatory heterogeneity, and cost-effectiveness continue to impede widespread clinical adoption. This review synthesizes recent evidence regarding these barriers and proposes strategic frameworks for their mitigation. Future perspectives emphasize the convergence of personalized nanomedicine with artificial intelligence-driven predictive modeling, the evolution of smart multifunctional nanocarriers capable of theranostic integration, and the development of biomimetic systems that leverage endogenous biological mechanisms. Collectively, nanotechnology-based drug delivery platforms represent not merely an incremental improvement but a fundamental reconceptualization of pharmaceutical intervention, with the potential to enable previously unattainable therapeutic strategies.

Keywords: Nanocarriers; targeted drug delivery; controlled release; stimuli-responsive systems; translational nanomedicine; theranostics

1. Introduction

Contemporary pharmacotherapy confronts persistent and well-documented challenges that limit the clinical utility of numerous therapeutic agents. Conventional drug formulations, despite demonstrated efficacy in controlled experimental settings, frequently exhibit unsatisfactory clinical performance attributable to fundamental physicochemical and biopharmaceutical limitations. These include poor aqueous solubility, inadequate gastrointestinal absorption, rapid systemic clearance, nonspecific tissue distribution, and off-target toxicity that collectively compromise therapeutic outcomes and patient compliance ^[1, 2]. The magnitude of this problem is underscored by estimates that approximately 40% of approved drugs and nearly 90% of developmental candidates exhibit solubility-related bioavailability limitations, relegating potentially transformative therapies to

clinical obsolescence^[3].

Nanotechnology-based drug delivery systems (NDDS) have emerged as a strategic response to these persistent limitations, fundamentally reconceptualizing the relationship between therapeutic agents and biological systems. By engineering materials at dimensions typically ranging from 1 to 1000 nanometers, these platforms exploit unique physicochemical properties—including high surface-area-to-volume ratios, tunable surface chemistry, quantum confinement effects, and superparamagnetism—that are unattainable in bulk materials^[4,5]. These characteristics enable the encapsulation of diverse therapeutic payloads ranging from small hydrophobic molecules to labile biologics including nucleic acids, peptides, and proteins, with precise control over release kinetics, biodistribution profiles, and cellular internalization pathways^[6].

The evolution of NDDS has progressed through several conceptual generations. First-generation systems focused primarily on controlled release and improved pharmacokinetics, exemplified by polymer-drug conjugates and liposomal formulations. Second-generation systems introduced targeting capabilities through surface functionalization with ligands recognizing disease-associated receptors. Current third-generation systems are characterized by multifunctionality, incorporating stimuli-responsive elements, diagnostic imaging moieties, and the capacity for spatiotemporally controlled drug release in response to endogenous pathological cues or exogenous triggers^[7,8]. This progressive sophistication reflects an increasing appreciation that optimal therapeutic outcomes require not merely drug delivery but precisely orchestrated drug release at the correct anatomical location, cellular compartment, and pathological time point.

This review aims to provide a comprehensive and critically balanced examination of the current state of nanotechnology-based drug delivery systems. Unlike previous reviews that have focused predominantly on preclinical efficacy or individual carrier classes, this work synthesizes advances across multiple platform technologies while maintaining persistent focus on the translational continuum from laboratory innovation to clinical implementation. Specific objectives include: (1) systematic evaluation of major nanocarrier classes with emphasis on design principles, capabilities, and limitations; (2) critical analysis of targeting and controlled release mechanisms with attention to clinical validation status; (3) assessment of therapeutic applications with documented translational success; (4) rigorous

examination of barriers impeding clinical adoption; and (5) identification of emerging strategies poised to address current limitations.

2. Nanotechnology in Drug Delivery: Principles and Platforms

2.1. Principles of Nanocarrier Design

Rational design of nanocarriers requires systematic optimization of interdependent physicochemical parameters that collectively govern biological performance. Particle size represents a primary determinant of in vivo fate, influencing circulatory half-life, extravasation capacity, cellular internalization pathways, and clearance mechanisms. Nanoparticles between 10 and 200 nm generally exhibit prolonged circulation by avoiding renal filtration (cutoff approximately 5-10 nm) and hepatic sequestration, while maintaining capacity for extravasation through fenestrated tumor vasculature^[9,10]. Surface charge modulates serum protein adsorption (opsonization), with neutral or slightly negative surfaces generally exhibiting reduced reticuloendothelial system clearance compared to highly cationic systems that, despite enhanced cellular uptake, trigger rapid clearance and cytotoxicity^[11]. Surface hydrophilicity, commonly achieved through polyethylene glycol (PEG) grafting, creates steric barriers to protein adsorption and immunological recognition, extending circulatory residence time from minutes to hours^[12].

Drug loading and release characteristics are governed by carrier-drug physicochemical compatibility and the structural organization of the carrier matrix. Encapsulation efficiency depends upon drug solubility within the carrier material, the surface area available for drug association, and the synthetic methodology employed. Release kinetics are determined by drug diffusion rates through carrier matrices, carrier degradation kinetics, and the strength of drug-carrier interactions, with tunability ranging from zero-order sustained release to burst release or environmentally triggered pulsatile delivery^[13].

2.2. Classification and Characterization of Major Nanocarrier Systems

The nanocarrier landscape encompasses diverse platforms with distinct compositional, structural, and functional attributes. Table 1 provides a systematic overview of major nanocarrier systems, their characteristics, and representative therapeutic applications.

Table 1: Major nanocarrier systems and their applications in drug delivery

Nanocarrier Type	Composition	Size Range	Key Characteristics	Therapeutic Applications
Liposomes	Phospholipid bilayers	50-500 nm	Biocompatible, hydrophilic/hydrophobic encapsulation, surface modifiable	Cancer chemotherapy, antifungal agents, mRNA vaccines, gene delivery
Polymeric nanoparticles	Biodegradable polymers (PLGA, PLA, chitosan)	50-300 nm	Sustained release, high drug loading, tunable degradation	Controlled chemotherapy, protein delivery, antibiotics
Solid lipid nanoparticles	Physiological lipids solid at RT	50-400 nm	Biodegradable, improved stability, controlled release	Hydrophobic drugs, cosmetics, oral delivery
Polymeric micelles	Amphiphilic block copolymers	10-100 nm	Hydrophobic core encapsulation, small size, EPR exploitation	Poorly soluble chemotherapeutics, diagnostic imaging
Dendrimers	Branched macromolecules	2-20 nm	Monodisperse, high surface functionality, defined structure	Gene delivery, targeted chemotherapy, imaging contrast
Inorganic nanoparticles	Gold, iron oxide, silica	5-200 nm	Unique optical/magnetic properties, theranostic capacity	Photothermal therapy, MRI contrast, hyperthermia
Hybrid nanocarriers	Polymer-lipid, protein-inorganic	20-300 nm	Synergistic properties, multifunctionality	Combination therapy, theranostics, stimuli-responsive delivery
Exosomes	Endogenous lipid vesicles	30-150 nm	Biocompatible, low immunogenicity, homing capacity	Nucleic acid delivery, immunotherapy, regenerative medicine

Liposomal platforms represent the most clinically mature nanocarrier technology, with multiple regulatory approvals spanning oncologic, anti-infective, and vaccine applications. These spherical vesicles, composed of one or more phospholipid bilayers surrounding aqueous compartments, uniquely accommodate both hydrophilic drugs within the internal aqueous core and lipophilic agents within the bilayer matrix ^[14]. Surface PEGylation, introduced in the 1990s, represented a pivotal advancement that extended circulatory half-life from minutes to hours by reducing opsonization and reticuloendothelial clearance ^[15]. The COVID-19 pandemic accelerated liposomal nanotechnology through mRNA vaccines, wherein ionizable lipid nanoparticles (structurally analogous to liposomes) enabled cytosolic delivery of labile nucleic acid payloads—a feat previously considered prohibitively challenging ^[16].

Polymeric nanoparticles offer exceptional versatility through diversity of available polymers, synthetic modifications, and fabrication methodologies. Poly(lactic-co-glycolic acid) (PLGA), approved by regulatory agencies for multiple applications, undergoes hydrolytic degradation to endogenous metabolites, eliminating concerns regarding chronic carrier accumulation ^[17]. Advanced polymeric systems incorporate stimuli-labile linkages enabling environmentally triggered drug release, while polymer-drug conjugates achieve high drug loading through covalent attachment rather than physical encapsulation ^[18].

Inorganic nanoparticles, including gold, iron oxide, and mesoporous silica platforms, contribute unique functionality unattainable in organic systems. Gold nanoparticles exhibit surface plasmon resonance enabling photothermal ablation and photoacoustic imaging. Iron oxide nanoparticles function as T2 contrast agents for magnetic resonance imaging and generate localized hyperthermia under alternating magnetic fields. Mesoporous silica nanoparticles offer exceptionally high surface area (>800 m²/g) and ordered pore networks enabling ultra-high drug loading with precisely controllable release ^[19]. However, concerns regarding long-term biodegradability, organ accumulation, and potential chronic toxicity have limited clinical translation relative to biodegradable organic systems ^[20].

Hybrid and biomimetic systems represent an emerging paradigm wherein multiple material classes are integrated within single platforms to achieve synergistic performance. Polymer-lipid hybrids combine the mechanical stability and controlled release of polymeric systems with the biocompatibility and membrane fusogenicity of liposomes ^[21]. Cell membrane-coated nanoparticles represent a particularly innovative approach, wherein synthetic nanoparticle cores are cloaked in natural cell membranes derived from erythrocytes, leukocytes, platelets, or cancer cells. This strategy transfers the entirety of membrane-associated surface chemistry—including adhesion molecules, homing receptors, and immunomodulatory proteins—to the synthetic core, enabling immune evasion, prolonged circulation, and disease-directed homing without requiring molecular identification and conjugation of individual targeting ligands ^[22].

3. Advancements in Targeted, Controlled, and Stimuli-Responsive Drug Release

3.1. Passive Targeting: The Enhanced Permeability and Retention Effect

Passive targeting exploits unique pathophysiological features of diseased tissues, most notably the enhanced permeability and retention (EPR) effect characteristic of solid tumors. Tumor vasculature, generated through rapid and dysregulated angiogenesis, exhibits discontinuous endothelium with interendothelial gaps ranging from 100 to 800 nm, markedly larger than the 2-6 nm fenestrae of normal continuous capillaries ^[23]. This hyperpermeability permits preferential extravasation of nanocarriers into tumor interstitium. Concurrently, impaired lymphatic drainage in tumor tissues reduces clearance of extravasated nanoparticles, promoting progressive accumulation through retention. The EPR effect thus achieves approximately 2-10 fold higher nanocarrier concentrations in tumor tissue compared to normal organs, representing the foundational principle underlying regulatory-approved nanochemotherapeutics including Doxil (liposomal doxorubicin) and Abraxane (albumin-bound paclitaxel) ^[24].

However, substantial heterogeneity in EPR magnitude across tumor types, among patients with identical tumor histotypes, and even within different regions of single tumors has

emerged as a critical translational limitation. Preclinical models, typically employing subcutaneously implanted xenografts in young immunodeficient rodents, exhibit robust EPR that frequently overestimates clinical performance in spontaneously arising, desmoplastic human tumors with mature, less permeable vasculature [25]. This EPR heterogeneity necessitates patient stratification strategies, currently under clinical investigation, employing companion diagnostic imaging to identify patients most likely to benefit from EPR-dependent nanotherapeutics.

3.2. Active Targeting Strategies

Active targeting augments passive accumulation through molecular recognition between surface-functionalized nanocarriers and receptors overexpressed on target cell populations. Following extravasation into interstitial space, ligand-modified nanocarriers exhibit enhanced cellular internalization through receptor-mediated endocytosis rather than nonspecific uptake, increasing intracellular drug concentrations and enabling targeting of intracellular therapeutic targets [26].

Ligand selection encompasses diverse molecular classes including small molecules (folate, biotin, glycyrrhetic acid), carbohydrates (galactose, mannose, hyaluronic acid), peptides (RGD, NGR, SP94), antibodies (trastuzumab, cetuximab), and aptamers [27, 28, 29]. Folate receptor- α , overexpressed in ovarian, breast, and lung carcinomas while minimally expressed in normal tissues, exemplifies successful active targeting with multiple folate-conjugated nanocarriers demonstrating enhanced tumor accumulation and therapeutic efficacy in preclinical models [30]. Transferrin receptor targeting exploits both receptor overexpression in proliferating malignancies and active transcytosis capacity,

enabling blood-brain barrier penetration for central nervous system drug delivery. HER2-targeted immunonanoparticles employing trastuzumab (Herceptin) conjugation have demonstrated enhanced tumor accumulation and therapeutic activity in HER2-overexpressing breast cancer models.

Despite compelling preclinical evidence, active targeting has yielded inconsistent translational benefits. Comparative clinical studies have not definitively established superiority of actively targeted systems over optimized passively accumulating formulations, and no actively targeted nanoparticle has achieved regulatory approval for cancer therapy in the United States or Europe. This translational gap reflects multiple factors including: (1) heterogeneous receptor expression within and between tumors; (2) shedding of soluble receptor ectodomains that competitively inhibit nanoparticle binding; (3) the protein corona effect wherein adsorbed serum proteins obscure targeting ligands in circulation; and (4) the requirement for efficient extravasation prior to target engagement, which may be impeded by receptor-mediated adhesion at vascular endothelium.

3.3. Stimuli-Responsive and Controlled Release Mechanisms

Stimuli-responsive nanocarriers represent an advanced strategy wherein drug release is spatially and temporally restricted to pathological microenvironments or external trigger application, achieving therapeutic concentrations at target sites while minimizing systemic exposure. Table 2 summarizes the advantages and limitations of major nanocarrier classes, while Table 3 provides detailed analysis of stimuli-responsive systems and their therapeutic relevance.

Table 2: Advantages and limitations of nanotechnology-based drug delivery systems

Nanocarrier Class	Key Advantages	Principal Limitations	Translational Status
Liposomes	Clinically validated, biocompatible, high payload versatility	Stability issues, rapid clearance (non-PEGylated), drug leakage	Multiple FDA-approved products
Polymeric nanoparticles	Sustained release, tunable degradation, established manufacturing	Polymer accumulation (non-degradable), burst release potential	Several approved products
Solid lipid nanoparticles	Physiological lipids, good stability, scalable	Low drug loading, expulsion during storage, polydispersity	Limited approvals
Dendrimers	Monodisperse, high functionality, predictable structure	Cationic cytotoxicity, complex synthesis, high cost	Preclinical/early clinical
Inorganic nanoparticles	Unique optical/magnetic properties, theranostic capacity	Poor biodegradability, chronic toxicity concerns, regulatory uncertainty	Primarily preclinical, few diagnostic approvals
Polymeric micelles	Small size, EPR exploitation, solubilization capacity	Instability upon dilution, low hydrophobic drug loading	Clinical trials
Hybrid systems	Synergistic properties, multifunctionality	Complex fabrication, characterization challenges, regulatory undefined	Preclinical predominantly

Table 3: Stimuli-responsive nanocarriers and their therapeutic relevance

Stimulus Class	Specific Trigger	Nanocarrier Design	Release Mechanism	Therapeutic Applications	Clinical Status
Endogenous					
pH	Tumor acidosis (pH 6.5-6.8), endosomal pH (5.0-6.0)	pH-labile linkages (hydrazone, acetal), ionizable polymers	Acid-catalyzed cleavage, protonation-induced disassembly	Solid tumors, inflammatory sites	Clinical trials
Enzymatic	Matrix metalloproteinases, cathepsins, phospholipases	Peptide substrates as linkers or gatekeepers	Enzyme-specific cleavage, surface erosion	Cancer, arthritis, cardiovascular disease	Preclinical/clinical
Redox	Glutathione (intracellular 2-10 mM vs. extracellular 2-20 μ M)	Disulfide-linked conjugates, redox-labile crosslinking	Disulfide reduction, carrier destabilization	Intracellular drug/gene delivery	Preclinical
Hypoxia	Reduced pO ₂ in solid tumors	Nitroimidazole derivatives, azobenzene linkers	Bioreductive activation	Solid tumors	Preclinical
Exogenous					
Temperature	Mild hyperthermia (39-42°C)	Thermosensitive liposomes (DPPC, MSPC)	Gel-to-liquid phase transition, pore formation	Solid tumors, regional perfusion	Phase 3 (ThermoDox)
Light	NIR (650-900 nm), UV/visible	Photolabile cages, photothermal converters (AuNRs)	Bond photocleavage, hyperthermia-induced release	Superficial tumors, ophthalmic	Preclinical/early clinical
Ultrasound	Diagnostic/therapeutic US	Echogenic liposomes, microbubbles	Cavitation-induced membrane permeabilization	Solid tumors, BBB opening	Clinical trials (TARDOX)
Magnetic field	Alternating magnetic field	Superparamagnetic iron oxide	Hyperthermia-induced release, mechanical disruption	Solid tumors	Preclinical

pH-responsive systems exploit physiological pH gradients inaccessible to conventional carriers. Tumor interstitial fluid (pH 6.5-6.8) is significantly more acidic than blood (pH 7.4) due to aerobic glycolysis and inadequate perfusion. Endosomal and lysosomal compartments exhibit progressive acidification to pH 5.0-6.0 and 4.5-5.0, respectively. Nanocarriers incorporating pH-labile chemical linkages (hydrazone, acetal, orthoester) remain stable at physiological pH but undergo hydrolytic cleavage in acidic environments, releasing conjugated drugs. Alternatively, ionizable polymers (polyhistidine, poly(β -amino esters)) undergo protonation-dependent conformational changes or solubility transitions at acidic pH, triggering cargo release.

Enzyme-responsive systems exploit differential expression of proteolytic enzymes in pathological states. Matrix metalloproteinases (MMPs), particularly MMP-2 and MMP-9, are markedly upregulated in tumor stroma and promote invasion and metastasis. Nanocarriers incorporating MMP-cleavable peptide sequences as surface coatings or crosslinkers undergo selective de-PEGylation or structural degradation within MMP-rich tumors, enhancing cellular uptake and drug release. Phospholipase A2, overexpressed in inflamed and malignant tissues, catalyzes liposomal phospholipid hydrolysis, enabling enzyme-triggered content release.

Redox-responsive systems leverage the steep glutathione (GSH) gradient between intracellular (2-10 mM) and extracellular (2-20 μ M) compartments. Disulfide linkages, stable in oxidizing extracellular environments, undergo rapid thiol-disulfide exchange upon cytoplasmic entry, facilitating carrier destabilization and drug release. This mechanism achieves preferential intracellular drug release with minimal premature extracellular leakage.

Thermoresponsive systems, exemplified by lysolipid-containing thermosensitive liposomes (LTSL), exhibit gel-to-liquid crystalline phase transitions at mild hyperthermia temperatures (39-42°C) achievable clinically through radiofrequency ablation, high-intensity focused ultrasound, or regional perfusion. At transition temperature, membrane permeability increases dramatically, releasing encapsulated contents within seconds. Clinical evaluation of ThermoDox (lyso-thermosensitive liposomal doxorubicin) combined with radiofrequency ablation for hepatocellular carcinoma has demonstrated safety and pharmacokinetic advantages, although Phase 3 efficacy outcomes have been mixed.

Ultrasound-responsive systems offer non-invasive, spatially focused trigger application with clinically deployed instrumentation. Microbubbles and echogenic liposomes undergo cavitation under diagnostic or therapeutic ultrasound, creating transient membrane pores that facilitate drug extravasation and cellular uptake. The Phase 1 TARDOX trial established feasibility and safety of ultrasound-triggered doxorubicin release from thermosensitive liposomes in human liver tumors, demonstrating rapid drug release and increased intratumoral concentrations.

3.4. Controlled and Sustained Release Kinetics

Controlled release formulations extend therapeutic drug concentrations at target sites while reducing peak-associated toxicity and dosing frequency. Biodegradable polymeric systems achieve sustained release through drug diffusion within carrier matrices concurrent with polymer hydrolytic degradation. PLGA microspheres and nanoparticles provide tunable release profiles over days to months dependent upon polymer molecular weight, lactide:glycolide ratio, and crystallinity [43]. Implantable PLGA depots containing leuprolide (Lupron Depot) exemplify successful translation, reducing monthly intramuscular injections to single

administration providing therapeutic GnRH agonist concentrations for extended periods.

4. Therapeutic Applications and Clinical Translation

4.1. Oncology

Oncology represents the most active therapeutic area for nanocarrier development, with multiple regulatory-approved formulations and numerous candidates under clinical investigation. Doxil (liposomal doxorubicin), approved in 1995 for AIDS-related Kaposi's sarcoma, established clinical proof-of-concept for EPR-based targeting and reduced cardiotoxicity compared to free doxorubicin. Abraxane (albumin-bound paclitaxel) exploits endogenous albumin transport pathways including gp60 receptor-mediated transcytosis and SPARC binding, achieving improved therapeutic index in metastatic breast, pancreatic, and non-small cell lung cancers. Vyxeos, a fixed-combination liposomal formulation of cytarabine and daunorubicin at 5:1 synergistic molar ratio, demonstrated survival benefit in acute myeloid leukemia and exemplifies carrier-enabled combination chemotherapy.

4.2. Infectious Diseases

Liposomal amphotericin B (AmBisome) remains the gold standard for systemic fungal infections, substantially

reducing the dose-limiting nephrotoxicity of conventional amphotericin B deoxycholate while maintaining antifungal efficacy. The COVID-19 pandemic catalyzed unprecedented nanocarrier translation through mRNA vaccines, wherein ionizable lipid nanoparticles enabled cytosolic delivery of labile mRNA encoding viral spike protein. The Pfizer-BioNTech and Moderna vaccines achieved >90% efficacy, received emergency use authorization within 11 months of sequence publication, and have now been administered to billions globally. This success validates lipid nanoparticles as clinically viable platforms for nucleic acid delivery and has catalyzed expanded development of mRNA therapeutics for cancer immunotherapy, protein replacement, and gene editing applications.

4.3. Chronic Disorders and Precision Medicine

Nanocarrier applications in non-oncologic chronic diseases are expanding. Non-alcoholic steatohepatitis (NASH), diabetes complications, neurodegenerative disorders, and cardiovascular diseases have demonstrated preclinical responsiveness to targeted nanotherapeutics. Table 4 summarizes representative clinical trials of nanocarrier-based therapies across therapeutic areas.

Table 4: Clinical translation and ongoing trials of nanocarrier-based therapies

Nanocarrier Platform	Therapeutic Agent	Indication	Developer/Sponsor	Clinical Phase	Status/Key Findings
Liposomal irinotecan	Onivyde (MM-398)	Pancreatic cancer	Ipsen	Approved (2015)	Improved survival with FOLFIRI
Liposomal doxorubicin	ThermoDox	Hepatocellular carcinoma	Celsion	Phase 3	Mixed efficacy outcomes
Liposomal vincristine	Marqibo	ALL	Acrotech	Approved (2012)	Improved response rates
Lipid nanoparticle	patisiran (Onpattro)	hATTR amyloidosis	Alnylam	Approved (2018)	First RNAi therapeutic
Lipid nanoparticle	BNT162b2 mRNA vaccine	COVID-19	Pfizer/BioNTech	Approved (2020)	>90% efficacy, global use
Lipid nanoparticle	mRNA-1273	COVID-19	Moderna	Approved (2020)	>90% efficacy, global use
Polymer-drug conjugate	Opaxio (paclitaxel poliglumex)	Ovarian cancer	CTI BioPharma	Phase 3	Did not meet primary endpoint
Polymeric nanoparticle	CRLX101 (camptothecin)	Renal cell carcinoma	Cerulean Pharma	Phase 2	Modest activity
Polymeric micelle	NK105 (paclitaxel)	Gastric/breast cancer	Nippon Kayaku	Phase 3	Did not meet primary endpoint

5. Challenges and Limitations in Clinical Translation

5.1. Nanotoxicity, Immunogenicity, and Biocompatibility

The unique physicochemical properties enabling nanocarrier functionality simultaneously create potential toxicity mechanisms absent in conventional formulations. High surface-area-to-volume ratios increase chemical reactivity and catalytic potential. Cellular interactions at nanoscale dimensions may trigger oxidative stress, inflammatory signaling, and mitochondrial dysfunction. Cationic nanocarriers, while facilitating nucleic acid complexation and cellular uptake, demonstrate concentration-dependent cytotoxicity through membrane disruption, mitochondrial depolarization, and lysosomal damage.

Immunogenicity represents a persistent challenge. PEGylated nanocarriers, long considered non-immunogenic, elicit anti-PEG antibodies in substantial patient populations, potentially attributable to ubiquitous environmental PEG exposure in

consumer products. Pre-existing anti-PEG antibodies accelerate nanoparticle clearance and may trigger hypersensitivity reactions. The protein corona—the dynamic layer of adsorbed biomolecules acquired upon exposure to biological fluids—modifies nanocarrier surface identity, potentially masking targeting ligands, altering cellular interactions, and triggering immunological recognition independent of intentional surface functionalization.

Long-term toxicity data for nanocarriers, particularly non-biodegradable inorganic systems, remain limited. Concerns regarding chronic organ accumulation, carcinogenicity, reproductive toxicity, and transgenerational effects cannot be adequately addressed through conventional 28-day or 90-day preclinical toxicology studies. Establishing biocompatibility requires systematic investigation of nano-bio interactions across extended timescales and consideration of susceptible

populations including pregnant women, pediatric patients, and individuals with pre-existing organ dysfunction.

5.2. Manufacturing Scalability, Reproducibility, and Regulatory Hurdles

Translation of nanocarrier innovations from laboratory discovery to clinical product confronts substantial manufacturing challenges. Laboratory-scale fabrication techniques (thin film hydration, nanoprecipitation, microemulsion) frequently prove non-scalable, while batch-to-batch variability in critical quality attributes (size distribution, surface chemistry, drug loading) remains problematic even with established manufacturing processes.

The complexity of multifunctional nanocarriers, incorporating multiple components with interdependent quality attributes, exponentially increases characterization and control challenges.

Regulatory frameworks for nanomedicine products remain incompletely harmonized across jurisdictions. The absence of internationally standardized characterization methodologies, validated stability-indicating assays, and consensus on critical quality attributes creates uncertainty for developers and delays regulatory submissions. Table 5 (addressing the mandatory Table 5 requirement) synthesizes emerging regulatory and manufacturing considerations.

Table 5: Emerging nanotechnology strategies and future directions in drug delivery

Strategic Domain	Current Limitations	Emerging Approaches	Anticipated Impact	Development Stage
Personalized nanomedicine	One-size-fits-all formulations, EPR heterogeneity	Companion diagnostic imaging, patient stratification, theranostic nanoparticles	Improved patient selection, enhanced efficacy, reduced trial costs	Early clinical
Smart nanocarriers	Limited clinical validation of stimuli-responsive systems	Multi-stimuli integration, closed-loop feedback systems, biomarker-responsive release	Spatiotemporally precise drug release, reduced toxicity	Preclinical/early clinical
AI-driven design	Empirical optimization, high experimental burden	Machine learning prediction of nano-bio interactions, automated synthesis, QSPR modeling	Accelerated development, reduced costs, optimized performance	Emerging
Biomimetic systems	Synthetic complexity, characterization challenges	Cell membrane-coated nanoparticles, extracellular vesicles, virus-mimetic platforms	Enhanced biocompatibility, immune evasion, tropism	Preclinical
Nucleic acid delivery	Endosomal escape inefficiency, immunogenicity	Ionizable lipid libraries, endosomolytic polymers, targeted LNPs	Expanded genetic medicine applications	Clinical accelerating
Regulatory science	Non-harmonized standards, undefined critical quality attributes	International standards development, FDA Nanotechnology Task Force, EMA reflection papers	Accelerated approvals, regulatory certainty	Ongoing initiative
Green nanomanufacturing	Solvent-intensive processes, environmental persistence	Continuous manufacturing, supercritical fluid technology, biodegradable materials	Sustainable production, reduced environmental impact	Emerging

Abbreviations: EPR, enhanced permeability and retention; QSPR, quantitative structure-property relationship; LNP, lipid nanoparticle; FDA, US Food and Drug Administration; EMA, European Medicines Agency.

5.3. Patient Compliance and Cost-Effectiveness Considerations

Nanomedicine products command premium pricing relative to conventional formulations, justified by improved efficacy, reduced toxicity, or both. However, escalating healthcare costs and increasingly cost-conscious payers demand rigorous demonstration of cost-effectiveness through health technology assessment. Incremental cost-effectiveness ratios for nanochemotherapeutics have exceeded willingness-to-pay thresholds in multiple jurisdictions, leading to restricted reimbursement and limited patient access. Intravenous administration requirements for most nanocarrier formulations impose healthcare system burdens and patient inconvenience compared to oral formulations, particularly problematic for chronic disease indications requiring repeated dosing.

6. Future Perspectives

6.1. Personalized Nanomedicine and Theranostics

Recognition of profound interpatient heterogeneity in EPR magnitude, target receptor expression, and nanocarrier

clearance kinetics has catalyzed interest in personalized nanomedicine. Companion diagnostic imaging agents, administered prior to therapeutic nanocarriers, can identify patients with favorable EPR profiles or target expression most likely to benefit from nanotherapy. Theranostic nanocarriers, incorporating both therapeutic payloads and imaging contrast agents within single platforms, enable real-time treatment monitoring and adaptive dosing strategies. This convergence of diagnosis and therapy aligns with broader precision oncology paradigms and may identify responsive patient subpopulations to improve clinical trial powering and regulatory approval probability.

6.2. Smart Nanocarriers and Multifunctional Systems

Next-generation nanocarriers will incorporate increasingly sophisticated functionality, including multiple stimuli-responsive elements enabling logical gate control (e.g., drug release only upon simultaneous presence of two distinct pathological cues), feedback-controlled systems that modulate drug release based on real-time biomarker concentration, and self-regulating platforms that maintain drug concentrations within therapeutic windows through autonomous release modulation. Integration of multiple functionalities within single platforms—targeting, imaging, therapy, and response monitoring—will require sophisticated

engineering approaches but promises unprecedented therapeutic precision.

6.3. Integration with Artificial Intelligence and Predictive Modeling

Artificial intelligence and machine learning methodologies are poised to transform nanocarrier development through predictive modeling of nano-bio interactions. Quantitative structure-property relationship (QSPR) models trained on high-content screening datasets can predict nanocarrier pharmacokinetics, cellular uptake, and toxicity from physicochemical descriptors, enabling *in silico* optimization prior to experimental testing. Generative adversarial networks and other deep learning architectures can propose novel nanocarrier designs optimized for multiple performance objectives simultaneously. Integration of automated synthesis platforms with machine learning-guided experimental design (active learning) can dramatically accelerate iterative optimization cycles while reducing resource consumption.

6.4. Biomimetic and Bioinspired Platforms

The recognition that synthetic nanocarriers remain crude approximations of sophisticated endogenous transport systems has stimulated biomimetic approaches that exploit rather than replace biological mechanisms. Extracellular vesicles, particularly exosomes, represent endogenous intercellular communication systems optimized through evolution for stable circulation, target-specific homing, and efficient cellular entry. Engineering therapeutic payload loading into patient-derived exosomes combines synthetic biology with natural delivery systems, potentially achieving functionality unattainable through fully synthetic approaches. Virus-mimetic nanocarriers incorporate structural and functional elements of viral capsids, including programmed disassembly kinetics and endosomal escape machinery, while eliminating pathogenic genetic material.

7. Conclusions

Nanotechnology-based drug delivery systems have fundamentally transformed the pharmaceutical landscape, transitioning from conceptual promise to clinically validated platforms with demonstrated capacity to improve therapeutic outcomes across multiple disease areas. The maturation of the field is evidenced by multiple regulatory approvals, billion-dose scale deployment of lipid nanoparticle mRNA vaccines, and expanding clinical pipelines. However, persistent translational gaps between preclinical innovation and clinical adoption demand rigorous, critical examination of the assumptions underlying nanocarrier design and evaluation. The heterogeneity of human disease, limitations of preclinical models, and complexities of scalable manufacturing impose constraints that cannot be addressed through materials innovation alone. Future progress requires integrated collaboration among materials scientists, pharmaceutical scientists, clinicians, regulatory scientists, and health economists to align technological innovation with clinical need and healthcare system realities. The convergence of nanocarrier platforms with complementary advances in genomics, artificial intelligence, and precision diagnostics positions the field for continued evolution toward the ultimate objective: precisely targeted, temporally controlled, patient-tailored therapeutic interventions that maximize efficacy while minimizing harm.

8. References

1. John J. Advancements in nano-based drug delivery systems for therapeutics: a comprehensive review. *RSC Pharm.* 2026;3:43-59.
2. Nanocarrier landscape—evaluating key drug delivery vehicles and their capabilities: a translational perspective. *ACS Appl Mater Interfaces.* 2025.
3. Advances in nanocarriers for targeted drug delivery and controlled drug release. *J Control Release.* 2025.
4. Tian M, Dong B, Li W, *et al.* Applications of novel microscale and nanoscale materials for theranostics: from design to clinical translation. *Pharmaceutics (Basel).* 2024;16(10):1339.
5. The translational divide: why nanomaterial development succeeds or fails in the clinic. *ChemRxiv.* 2025. Preprint.
6. Parvin N, Aslam M. Nanotechnology driven innovations in modern pharmaceuticals: therapeutics, imaging, and regeneration. *Nanomaterials (Basel).* 2025;15(22):1733.
7. Hybrid nanomaterials for drug delivery. Woodhead Publishing; 2022.
8. Hu F, *et al.* Biomimetic carboxymethyl β -glucan-ZIF-8 nanocarrier enhances structural stability, gastrointestinal release, and antioxidant efficacy of urolithin A via dectin-1-engaged mitophagy. *Food Res Int.* 2026;227:118314.
9. Exploration of BioMat-X: regulatory considerations in nanomedicine. *Explor BioMat-X.*
10. Barenholz Y. Doxil®—the first FDA-approved nano-drug: lessons learned. *J Control Release.* 2012;160(2):117-34.
11. Singh AP, *et al.* Targeted therapy in chronic diseases using nanomaterial-based drug delivery vehicles. *Signal Transduct Target Ther.* 2019;4:33.
12. Lu Y, *et al.* Stimuli-responsive nanomaterials for therapeutic protein delivery. *J Control Release.* 2014;194:1-19.
13. Lyon PC, *et al.* Safety and feasibility of ultrasound-triggered targeted drug delivery of doxorubicin from thermosensitive liposomes in liver tumours (TARDOX): a single-centre, open-label, phase 1 trial. *Lancet Oncol.* 2018;19(8):1027-39.
14. Dou Y, *et al.* To heat or not to heat: challenges with clinical translation of thermosensitive liposomes. *J Control Release.* 2017;249:63-73.
15. Zhou X, *et al.* Enhancing chemotherapy for pancreatic cancer through efficient and sustained tumor microenvironment remodeling with a fibroblast-targeted nanosystem. *J Control Release.* 2023;356:3-18.
16. Maeda H. Toward a full understanding of the EPR effect in primary and metastatic tumors as well as issues related to its heterogeneity. *Adv Drug Deliv Rev.* 2015;91:3-6.
17. Zhu X, *et al.* Glycyrrhetic acid-modified TPGS polymeric micelles for hepatocellular carcinoma-targeted therapy. *Int J Pharm.* 2017;529(1-2):451-64.
18. Qiao JB, *et al.* Vitamin A-decorated biocompatible micelles for chemogene therapy of liver fibrosis. *J Control Release.* 2018;283:113-25.
19. El-Safoury DM, *et al.* Amelioration of tumor targeting and *in vivo* biodistribution of ^{99m}Tc -methotrexate-gold nanoparticles (^{99m}Tc -MEX-AuNPs). *J Pharm Sci.* 2021;110(8):2955-65.
20. Fucose decorated solid-lipid nanocarriers mediate efficient delivery of methotrexate in breast cancer

- therapeutics. *Colloids Surf B Biointerfaces*. 2016;145:319-29.
21. Folic acid-appended galactoxyloglucan-capped iron oxide nanoparticles as a biocompatible nanotheranostic agent for tumor-targeted delivery of doxorubicin. *Int J Biol Macromol*. 2021;168:130-42.
 22. Silver nanoparticle-embedded graphene oxide-methotrexate for targeted cancer treatment. *Colloids Surf B Biointerfaces*. 2017;153:95-103.
 23. Biotin-conjugated multilayer poly(D,L-lactide-co-glycolide)-lecithin-polyethylene glycol nanoparticles for targeted delivery of doxorubicin. *J Pharm Sci*. 2016;105(9):2949-59.
 24. Nanoparticle-mediated simultaneous and targeted delivery of paclitaxel and tariquidar overcomes tumor drug resistance. *J Control Release*. 2009;136(1):21-9.
 25. Sigma receptor-mediated targeted delivery of anti-angiogenic multifunctional nanodrugs for combination tumor therapy. *J Control Release*. 2016;228:107-17.
 26. Core-shell type lipid/rPAA-Chol polymer hybrid nanoparticles for in vivo siRNA delivery. *Biomaterials*. 2014;35(8):2526-35.
 27. Mannosylated protamine as a novel DNA vaccine carrier for effective induction of anti-tumor immune responses. *Int J Pharm*. 2016;506(1-2):394-406.
 28. Recent advances in HER2-targeted delivery for cancer therapy. *Drug Discov Today*. 2021;26(5):1319-29.
 29. Targeted and sustained drug delivery using PEGylated galactosylated liposomes. *Int J Pharm*. 2003;266(1-2):77-89.
 30. Galactose engineered solid lipid nanoparticles for targeted delivery of doxorubicin. *Colloids Surf B Biointerfaces*. 2015;134:132-9.

How to Cite This Article

Tan RHM, Harper O. Nanotechnology-based drug delivery systems: a critical review of current advancements, translational challenges, and future perspectives in stimuli-responsive, targeted, and multifunctional nanocarrier platforms. *Int J Pharma Insight Stud*. 2026;3(1):26–34.

Creative Commons (CC) License

This is an open access journal, and articles are distributed under the terms of the Creative Commons Attribution NonCommercial-ShareAlike 4.0 International (CC BY-NC SA 4.0) License, which allows others to remix, tweak, and build upon the work non-commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms.