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Nanotechnology in Targeted Drug Delivery Systems: Recent Advances and Future Perspectives

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Abstract : *Standard pharmaceutical dosage forms often run into serious practical limits, such as poor water solubility, fast enzymatic breakdown, short half-lives in blood, non-specific spread into healthy tissues, and side effects that limit the dose. Over the last twenty years, nanotechnology-based drug delivery systems have drawn strong interest as practical ways to get past these limits by enclosing or chemically linking active pharmaceutical ingredients (APIs) inside nanoscale carriers to shape how the body handles them. This review examines the primary nanocarrier platforms used in targeted delivery—specifically liposomes, polymeric nanoparticles, solid lipid nanoparticles (SLNs), nanostructured lipid carriers (NLCs), polymeric micelles, dendrimers, inorganic nanoparticles, and hybrid constructs. We also discuss passive, active, and stimuli-responsive targeting strategies alongside the physicochemical properties that govern how these systems behave inside the body. Therapeutic applications across oncology, infectious diseases, central nervous system (CNS) disorders, and nucleic-acid delivery are evaluated. Even when nanocarriers improve drug stability and local levels, small particle size by itself does not assure clinical success. Biological obstacles such as protein-corona formation, reticuloendothelial system (RES) clearance, dense tumor stroma, and patient-to-patient disease variability—combined with industrial hurdles in batch consistency, sterilization, and regulatory approval—continue to slow down bench-to-bedside translation. In practice, getting good results in nanomedicine means matching carrier design to drug properties, running thorough analytical checks, and testing against proper comparators in clinical trials.*

Keywords: Nanotechnology; Targeted drug delivery; Nanocarriers; Liposomes; Polymeric nanoparticles; Lipid nanoparticles; Active targeting; Controlled release; Nanomedicine.

Abbreviations: AI: Artificial intelligence; BBB: Blood–brain barrier; EPR: Enhanced permeability and retention; FDA: Food and Drug Administration; LNP: Lipid nanoparticle; NLC: Nanostructured lipid carrier; PEG: Polyethylene glycol; PDI: Polydispersity index; PLGA: Poly(lactic-co-glycolic acid); RES: Reticuloendothelial system; siRNA: Small interfering RNA; SLN: Solid lipid nanoparticle.

I. INTRODUCTION

The primary goal of pharmaceutical drug delivery is to carry an active pharmaceutical ingredient (API) to its intended site of action at an effective concentration and keep it there for the right duration, while limiting exposure to healthy organs. Conventional dosage forms—such as tablets, capsules, and standard intravenous solutions—remain the foundation of everyday clinical practice because their manufacturing is well established, their safety profiles are familiar, and clinicians know how to dose them reliably. Still, many potent drug molecules suffer from poor aqueous solubility, low membrane permeability, rapid metabolic inactivation, and widespread distribution throughout the body.

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These biopharmaceutical limitations frequently force clinicians to administer higher doses, leading to narrow therapeutic windows and dose-limiting toxicities.

Pharmaceutical nanotechnology applies engineered materials and structures typically measuring between 1 and 100 nm (and occasionally extending up to a few hundred nanometres in clinical drug delivery) to work around these constraints. By entrapping, dissolving, adsorbing, or covalently attaching therapeutic agents onto nanoscale vehicles, formulators can alter dissolution rates, shield fragile molecules from early degradation, extend blood circulation time, and modify how cells internalize the drug. Widely studied nanocarrier families include vesicular phospholipid systems (liposomes), biodegradable polymeric nanoparticles, solid and liquid lipid matrices, branched dendrimers, and functional inorganic nanostructures.

Within targeted drug delivery, three main strategies are generally recognized. Passive targeting takes advantage of anatomical and physiological abnormalities in diseased tissues—such as leaky blood vessels in solid tumors—to encourage preferential carrier accumulation. Active targeting attaches surface recognition ligands, including monoclonal antibodies, antibody fragments, peptides, or aptamers, to bind receptors overexpressed on target cells. Stimuli-responsive systems are built to undergo structural changes or release their payload rapidly when exposed to internal disease microenvironments (such as acidic pH or elevated glutathione) or external triggers (such as localized heat or ultrasound). Combining these features sounds good on paper, yet each extra component adds formulation complexity that has to earn its place with clear experimental evidence.

This review provides a structured overview of nanocarrier architectures, targeting mechanisms, physicochemical characterization methods, therapeutic applications, and translational bottlenecks in targeted nanomedicine, keeping a realistic perspective on the gap between laboratory results and clinical practice.

II. AIM, OBJECTIVES, AND REVIEW SCOPE

2.1 Aim

To examine recent progress in nanotechnology-based targeted drug delivery systems, with emphasis on carrier design, targeting mechanisms, clinical applications, biocompatibility, and hurdles to commercial translation.

2.2 Objectives

- To outline the structural features, benefits, and formulation drawbacks of major pharmaceutical nanocarrier classes.
- To compare passive, active, and stimuli-responsive targeting strategies with respect to biological feasibility and selectivity.
- To review representative therapeutic uses in oncology, infectious diseases, central nervous system disorders, and nucleic-acid therapeutics.
- To summarize key physicochemical characterization techniques needed to verify product quality and batch uniformity.
- To evaluate toxicological concerns, scale-up limitations, and regulatory requirements shaping clinical translation.

2.3 Scope and Methodological Note

This paper is organized as a narrative literature review drawing on peer-reviewed research articles and authoritative reviews published mainly between 2024 and 2026 across PubMed/MEDLINE, Scopus, Web of Science, and Crossref databases. Rather than attempting an exhaustive statistical meta-analysis, our discussion focuses on core mechanistic concepts, formulation trade-offs, and practical lessons relevant to contemporary pharmaceutics.

III. FUNDAMENTALS OF NANOCARRIER-BASED DRUG DELIVERY

A pharmaceutical nanocarrier acts as a protective transport vehicle whose performance depends directly on how the carrier structure interacts with the physicochemical nature of the drug. Depending on the platform, an API can be enclosed inside an aqueous core, dispersed within a hydrophobic polymer or lipid matrix, embedded inside lipid

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bilayers, adsorbed onto porous surfaces, or linked chemically through cleavable bonds. Good formulation design requires balancing high drug-loading capacity with tight retention during blood circulation, followed by predictable release at the diseased site and safe clearance of carrier breakdown products.

Physicochemical properties largely dictate what happens to a nanoparticle after administration. Particle size and polydispersity index (PDI) determine renal filtration cut-offs (generally below 5–10 nm), passage across fenestrated blood vessels, and uptake by macrophages of the mononuclear phagocyte system. Surface charge (zeta potential) affects colloidal stability against clumping as well as electrostatic attraction to negatively charged cell membranes and blood proteins. Surface hydrophilicity—most commonly achieved by grafting polyethylene glycol (PEG) chains—forms a hydrated steric barrier that slows opsonization and extends plasma half-life. In addition, particle shape, mechanical stiffness, and surface porosity influence how carriers drift toward vessel walls in blood flow and enter target cells. Because these traits interact in tangled ways, changing one often shifts another, so formulators usually have to optimize several factors together.

Once nanoparticles enter physiological fluids such as blood plasma, circulating proteins, lipids, and metabolites quickly coat their surfaces to form a dynamic "protein corona." This biological layer masks the synthetic surface of the particle and creates a new biological identity, frequently covering up surface-bound targeting ligands and triggering complement activation or macrophage clearance. As a result, drug release and cell uptake tests carried out in simple protein-free buffers often fail to predict in vivo pharmacokinetics, highlighting the importance of testing formulations in serum-containing media.

Drug release from nanocarriers happens through Fickian diffusion, gradual erosion of polymer or lipid matrices, carrier disassembly, surface desorption, or stimulus-triggered bond cleavage. Controlling this release rate is vital: an early "burst" release cancels out the protective benefit of encapsulation and risks systemic toxicity, whereas overly slow release leaves free drug levels at the target site below the minimum effective concentration.

IV. MAJOR NANOCARRIER PLATFORMS

4.1 Liposomes

Liposomes are spherical, self-assembled vesicles made of one or more concentric phospholipid bilayers surrounding an internal aqueous compartment. Their amphiphilic structure lets formulators load water-soluble drugs inside the aqueous core and fat-soluble drugs inside the lipid bilayer simultaneously or separately. Characteristics such as vesicle diameter, number of bilayers, membrane rigidity (adjusted by adding cholesterol), and surface charge can be controlled using established techniques like thin-film hydration, ethanol injection, and microfluidic mixing.

As the first nanocarrier platform to reach routine clinical use, liposomes offer strong biocompatibility, biodegradability, and reduced organ toxicity for potent drugs like doxorubicin and amphotericin B. Even so, chemical breakdown via phospholipid oxidation and ester hydrolysis, physical instability causing vesicle fusion or payload leakage, high raw-material costs, and sterilization difficulties remain persistent drawbacks. While PEGylation extends circulation time, repeated doses of PEG-coated vesicles can trigger anti-PEG IgM antibodies, causing the accelerated blood clearance (ABC) phenomenon and complement activation-related pseudoallergy (CARPA).

4.2 Polymeric Nanoparticles

Polymeric nanoparticles—which include solid matrix nanospheres and reservoir-style nanocapsules—are prepared from synthetic biodegradable polymers like poly(lactic-co-glycolic acid) (PLGA), polylactic acid (PLA), and polycaprolactone (PCL), as well as natural polymers such as chitosan, alginate, and albumin. By varying polymer molecular weight, lactide-to-glycolide ratios, and terminal functional groups, formulators can tune degradation timelines and sustain drug release over days or even months.

Although polymeric carriers provide good mechanical strength and convenient chemical handles for attaching targeting ligands, they present practical manufacturing issues. These include trace toxic organic solvents left over from emulsion-solvent evaporation steps, biphasic release profiles marked by an initial burst phase, local tissue acidity caused by lactic

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and glycolic acid breakdown products, and trouble maintaining narrow particle size distributions during large-scale production.

4.3 Lipid-Based Nanoparticles, Micelles, and Dendrimers

Solid Lipid Nanoparticles (SLNs): Introduced as alternatives to polymeric systems and conventional emulsions, SLNs are built from physiological lipids (such as triglycerides, fatty acids, or waxes) that stay solid at room and body temperatures, stabilized by biocompatible surfactants. They shield sensitive APIs from degradation and allow solvent-free high-pressure homogenization. Their main weakness lies in polymorphic lipid transitions during storage: as lipid molecules pack into tighter crystalline lattices over time, drug molecules get pushed out of the matrix, lowering encapsulation efficiency and causing particle aggregation.

Nanostructured Lipid Carriers (NLCs): NLCs represent second-generation lipid carriers created by mixing solid lipids with spatially incompatible liquid oils. This blend introduces deliberate imperfections into the solid crystal lattice, forming larger molecular spaces that boost drug-loading capacity and prevent drug expulsion on storage. Still, NLC stability depends heavily on lipid-to-surfactant ratios, phase separation risks, and processing temperatures.

Polymeric Micelles: Formed through spontaneous self-assembly of amphiphilic block copolymers above their critical micelle concentration (CMC), polymeric micelles feature a hydrophobic inner core that dissolves poorly water-soluble BCS Class II and IV drugs and a hydrophilic outer shell (usually PEG) that provides steric protection. A major drawback inside the body is thermodynamic instability: when diluted in the bloodstream below the CMC or exposed to plasma lipoproteins, micelles can break apart prematurely and dump their drug cargo into general circulation.

Dendrimers: Dendrimers are hyperbranched, monodisperse synthetic macromolecules growing outward from a central core in concentric generational layers, ending in a dense shell of reactive surface groups (such as polyamidoamine [PAMAM] dendrimers). Their exact molecular weight and multivalent surface allow controlled drug attachment and ligand conjugation. However, multi-step chemical synthesis drives up manufacturing costs, and positively charged surface groups often cause dose-dependent cell toxicity, hemolysis, and membrane damage unless chemically masked.

4.4 Inorganic and Hybrid Nanoparticles

Inorganic nanocarriers—including gold nanoparticles, superparamagnetic iron oxide nanoparticles (SPIONs), mesoporous silica nanoparticles (MSNs), and quantum dots—possess distinctive optical, plasmonic, magnetic, or high-porosity features absent in organic materials. These properties allow external magnetic guidance, photothermal heating, and combined diagnostic imaging. On the downside, inorganic cores resist enzymatic breakdown, raising serious concerns about long-term buildup in the liver and spleen, chronic oxidative stress, and heavy-metal toxicity. Because safety depends heavily on elemental composition and surface coating, broad safety claims cannot be made across all inorganic platforms.

Hybrid nanocarriers combine complementary materials—such as lipid-polymer hybrid nanoparticles (LPHNs) or cell-membrane-coated biomimetic particles—to pair the mechanical stability and controlled release of polymeric cores with the biocompatibility and stealth behavior of lipid shells. Hybrid designs often outperform single-material carriers in animal studies, though multi-step preparation makes quality control, characterization, and regulatory approval harder.

Table 1. Comparative Overview of Major Pharmaceutical Nanocarrier Platforms

Nanocarrier Class	Key Formulation Strengths	Primary Limitations & Risks
Liposomes	Carries both hydrophilic and lipophilic drugs; biocompatible; proven clinical track record.	Phospholipid oxidation/hydrolysis; drug leakage; high raw-material cost; anti-PEG immune responses.
Polymeric Nanoparticles	Tunable biodegradation and sustained release; high structural stability; straightforward ligand attachment.	Residual organic solvents; initial burst release; acidic degradation byproducts; scale-up variability.
SLNs & NLCs	Physiological lipid composition; solvent-free scalable production; improved oral and topical bioavailability.	Polymorphic crystallization and drug expulsion (mainly SLNs); gelation on storage; low hydrophilic drug loading.

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Polymeric Micelles	High solubilization of poorly water-soluble APIs; ultra-small size (<50 nm) aiding deep tissue penetration.	Dissociation upon intravenous dilution below CMC; premature drug loss via plasma protein exchange.
Dendrimers	Monodisperse structure; high density of surface functional groups for multivalent targeting.	Complex multi-step synthesis; cationic surface cytotoxicity and hemolysis; slow biological clearance.
Inorganic & Hybrid Systems	Unique magnetic, optical, or photothermal behavior; theranostic potential; adjustable pore volume.	Poor biodegradability; long-term organ retention; chronic oxidative toxicity; difficult regulatory validation.

V. TARGETING STRATEGIES

5.1 Passive Targeting

Passive targeting relies on structural differences between healthy and diseased tissues rather than specific molecular recognition. In solid tumors and inflamed tissues, rapid blood vessel growth produces defective endothelial gaps (fenestrations typically 100 to 800 nm wide) paired with poor lymphatic drainage. Long-circulating nanocarriers slip through these leaky vessels and accumulate inside the tumor interstitium—a process known as the enhanced permeability and retention (EPR) effect.

Although the EPR effect served as an early cornerstone of cancer nanomedicine, clinical data show that it is far more variable and modest in human tumors than in fast-growing mouse xenograft models. Elevated tumor interstitial fluid pressure (IFP), dense extracellular matrix (ECM) collagen fibers, poorly vascularized necrotic regions, and differing vessel permeability across metastatic sites often limit passive uptake. Consequently, passive targeting by itself rarely delivers uniform drug concentrations throughout a solid tumor.

5.2 Active Targeting

Active targeting modifies the outer surface of a nanocarrier with affinity ligands—such as monoclonal antibodies, Fab' fragments, transferrin, folic acid, RGD peptides, or nucleic-acid aptamers—that bind receptors overexpressed on diseased cells or newly formed tumor blood vessels. Crucially, these ligands do not act like "homing missiles" pulling particles out of circulation toward distant o

rgans; carriers still depend on normal blood flow and passive extravasation to reach the target neighborhood, where ligand-receptor binding improves cellular retention and receptor-mediated endocytosis.

Successful active targeting hinges on ligand density, proper spatial orientation, linker flexibility, and receptor accessibility. Overloading the surface with ligands can block stealth PEG chains, speed up RES clearance, and encourage protein-corona masking. Furthermore, uneven receptor expression within a tumor and receptor downregulation over time can reduce clinical benefit across patient groups.

5.3 Dual and Multi-Modal Targeting

Newer delivery platforms increasingly combine stealth polymers, active targeting ligands, and environment-sensitive release triggers in one construct—such as pH-cleavable PEG coatings that shed inside acidic tumor tissue to uncover cell-penetrating peptides. These designs look clever, yet multi-step carriers run into tough hurdles on the way to clinic: every extra chemical step adds synthesis work, testing demands, batch failure risk, and regulatory review.

VI. STIMULI-RESPONSIVE AND CONTROLLED RELEASE SYSTEMS

Stimuli-responsive ("smart") nanocarriers are engineered to stay intact while circulating in healthy blood vessels, then undergo rapid physical or chemical changes—such as swelling, bond cleavage, membrane disruption, or phase transition—when triggered by pathological tissue signals or externally applied energy.

pH-Responsive Systems: These carriers take advantage of natural pH drops between healthy blood and tissues (pH ~7.4), the extracellular tumor or inflammatory environment (pH 6.5–6.9), and intracellular endosomal or lysosomal compartments (pH 4.5–5.5). Adding acid-labile linkers (such as hydrazones, acetals, or imines) or ionizable polymers

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and lipids prompts carrier disassembly and endosomal escape after cell uptake. A key formulation challenge is tuning sensitivity so release occurs reliably in mildly acidic diseased tissue without leaking prematurely at normal physiological **pH.**

Redox- and Enzyme-Responsive Systems: Intracellular glutathione (GSH) levels (2–10 mM) are vastly higher than extracellular plasma concentrations (~2–20 μM). Nanocarriers cross-linked with disulfide bonds undergo rapid reductive cleavage once inside target cells, releasing their payload intracellularly. In a similar way, enzyme-responsive carriers use peptide or ester linkages cleaved by disease-linked enzymes such as matrix metalloproteinases (MMPs), phospholipases, or cathepsins, though differences in enzyme levels between patients can affect reproducibility.

Exogenously Triggered Systems: External physical triggers—including near-infrared (NIR) light, focused ultrasound, alternating magnetic fields, and localized mild hyperthermia—allow clinicians to control when and where drug release happens. However, shallow tissue penetration (especially for UV/visible and NIR light), specialized hospital equipment needs, and the risk of overheating nearby healthy tissues limit widespread clinical adoption.

It is worth distinguishing controlled release from true spatial targeting: stretching drug release out over 48 hours does not mean the carrier actually concentrates inside diseased tissue. Careful preclinical studies must measure both organ biodistribution and local drug release rates independently.

VII. FORMULATION AND PHYSICOCHEMICAL CHARACTERIZATION

Because small shifts in nanoscale size, surface chemistry, or internal structure can dramatically alter biological behavior, nanomedicines demand thorough physicochemical characterization under a Quality by

Design (QbD) approach. Critical Quality Attributes (CQAs) must be verified using complementary analytical methods rather than relying on a single measurement.

Hydrodynamic diameter and size distribution (reported as PDI) are routinely checked using dynamic light scattering (DLS), while transmission electron microscopy (TEM), scanning electron microscopy (SEM), and atomic force microscopy (AFM) offer direct visual confirmation of particle shape, morphology, and aggregation. Surface electrokinetic charge is measured via zeta potential, which helps predict dispersion stability (values beyond ±30 mV generally support strong electrostatic repulsion) and biological interactions.

Drug loading (% w/w) and encapsulation efficiency (% EE) are quantified by separating free unencapsulated drug via ultrafiltration, ultracentrifugation, or size-exclusion chromatography, followed by validated HPLC or UV-Vis analysis. In vitro release studies should be run in justified biorelevant media under sink conditions to avoid false solubility-limited plateaus. For injectable nanomedicines, compendial quality control also covers pH, osmolality, residual solvents (ICH Q3C), sterility, bacterial endotoxins, and long-term ICH stability testing tracking physical, chemical, and microbiological integrity.

Table 2. Essential Physicochemical Characterization Parameters for Nanocarriers

Parameter / CQA	Pharmaceutical & Biological Relevance	Standard Analytical Methods
Particle Size & PDI	Governs circulation half-life, vascular extravasation, cellular uptake, and batch-to-batch uniformity.	Dynamic light scattering (DLS); nanoparticle tracking analysis (NTA).
Morphology & Structure	Reveals particle shape, lamellarity, core-shell integrity, and physical clumping.	TEM, cryo-TEM, SEM, atomic force microscopy (AFM).
Surface Charge	Predicts colloidal dispersion stability, protein-corona adsorption, and cell membrane interactions.	Electrophoretic light scattering (Zeta potential).

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Drug Loading & % EE	Determines required dose volume, manufacturing efficiency, and unencapsulated free-drug fraction.	Ultrafiltration or ultracentrifugation paired with validated HPLC or LC-MS.
In Vitro Release	Evaluates sustained or stimulus-triggered release kinetics and identifies early burst release.	Dialysis bag diffusion, USP Apparatus IV (flow-through cell).
Purity & Sterility	Confirms safety for parenteral dosing and compliance with pharmacopoeial standards.	GC (residual solvents), LAL assay (endotoxins), compendial sterility testing.

VIII. THERAPEUTIC APPLICATIONS

8.1 Oncology

Oncology remains the most heavily researched clinical area for nanomedicine. Standard cytotoxic chemotherapy drugs suffer from narrow therapeutic indices and severe systemic side effects, including cardiotoxicity, bone marrow suppression, and peripheral neuropathy. Packaging drugs such as doxorubicin, paclitaxel, or irinotecan inside liposomes, polymeric micelles, or albumin-bound nanoparticles shifts their tissue distribution, lowering accumulation in vulnerable organs like the heart while extending plasma residence time.

Nevertheless, clinical trial results show that approved nanocarriers improve patient tolerability and safety more reliably than they extend overall survival. Dense tumor stroma, poor blood flow in hypoxic zones, and uneven vascular permeability hinder deep penetration, often leaving nanoparticles trapped near blood vessel walls. Current studies focus on pairing nanomedicines with stroma-modifying agents, immune checkpoint inhibitors, and companion imaging diagnostics to identify patients most likely to respond.

8.2 Combination Therapy and Theranostics

Nanocarriers make it possible to co-load synergistic drug pairs—such as combining a cytotoxic chemotherapy agent with an efflux-pump inhibitor or siRNA—inside a single carrier to coordinate their pharmacokinetics and deliver fixed drug ratios to target cells. Synchronizing release rates for two drugs with very different solubilities remains a major formulation hurdle. Theranostic platforms combine therapeutic drugs with imaging agents (such as radionuclides, fluorescent probes, or iron oxide cores) to track biodistribution and treatment response in real time, though regulatory approval pathways for dual-purpose products remain complicated.

8.3 Infectious Diseases, CNS Disorders, and Nucleic-Acid Delivery

Infectious Diseases: Growing antimicrobial resistance and intracellular pathogen survival (such as Mycobacterium tuberculosis or deep fungal infections) limit standard antibiotic therapy. Nanocarriers can shield unstable antimicrobials, penetrate bacterial biofilms, and target phagocytic immune cells harboring intracellular microbes. Liposomal amphotericin B stands as a classic clinical example showing substantially lower kidney toxicity than conventional deoxycholate injections.

Central Nervous System (CNS) Disorders: The blood–brain barrier (BBB), fortified by tight endothelial junctions and active efflux pumps like P-glycoprotein, blocks over 98% of small-molecule drugs and virtually all large biologics from entering brain tissue. Approaches using receptor-mediated transcytosis ligands (targeting transferrin, insulin, or lipoprotein receptors) and nose-to-brain intranasal nanocarriers are being explored for glioblastoma, Alzheimer's disease, and Parkinson's disease. Importantly, preclinical studies must prove that intact active drug—not merely a detached fluorescent dye—crosses the endothelial barrier into target neural cells.

Nucleic-Acid Delivery: Therapeutic nucleic acids, including mRNA, siRNA, and antisense oligonucleotides, break down rapidly in blood via nucleases and cannot cross negatively charged cell membranes passively due to their large molecular size and polyanionic charge. Ionizable lipid nanoparticles (LNPs)—built from an ionizable cationic lipid, helper phospholipid, cholesterol, and PEG-lipid—have transformed this field, as seen in approved siRNA drugs

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(patisiran) and mRNA vaccines. Ionizable lipids stay neutral at blood pH to limit toxicity, gain a positive charge inside acidic endosomes to disrupt the endosomal membrane, and release nucleic acids into the cytoplasm. Active research continues to tackle extrahepatic targeting, repeat-dose immune reactions, and ultra-cold storage constraints.

IX. CLINICAL TRANSLATION AND APPROVED NANOMEDICINES

Moving a nanocarrier from an academic bench prototype to a commercial medicine requires proving reproducible manufacturing, acceptable long-term safety, and meaningful therapeutic advantage over standard treatments. Clinically approved nanomedicines—including liposomal doxorubicin (Doxil/Caelyx),
liposomal amphotericin B (AmBisome), albumin-bound paclitaxel (Abraxane), liposomal irinotecan (Onivyde), and LNP-based siRNA/mRNA products—confirm the practical value of diverse carrier designs.

Still, high failure rates in Phase II and III clinical trials point to persistent translational gaps. Many candidates fail because animal tumor models poorly mimic human disease structure, or because the high manufacturing cost of a complex carrier is not justified by modest clinical gains over generic drugs. Core principles for successful translation include:

- Choosing the simplest carrier design capable of solving a clearly defined biopharmaceutical problem.
- Validating scalable, Good Manufacturing Practice (GMP)-compliant production processes early in development.
- Establishing solid in vitro–in vivo correlations (IVIVC) and orthogonal bioanalytical assays to separate encapsulated from free drug in plasma and tissues.
- Designing clinical trials with appropriate active comparators and clinically meaningful endpoints (such as overall survival, progression-free survival, or reduced Grade 3/4 adverse events).

X. SAFETY, TOXICITY, AND BIOCOMPATIBILITY

Nanomaterial biocompatibility depends heavily on route and context rather than being a fixed property of a raw material: a polymer or lipid safe for oral or topical use can trigger acute hypersensitivity or organ accumulation when injected intravenously. Comprehensive nanotoxicology testing must evaluate the intact carrier, the encapsulated API, carrier degradation products, and residual manufacturing excipients.

Major safety risks include complement activation-related pseudoallergy (CARPA), acute infusion reactions, hemolysis, blood clot formation, oxidative stress driven by reactive oxygen species (ROS), and prolonged retention inside clearance organs (liver Kupffer cells, splenic macrophages, and kidneys). Non-degradable inorganic nanoparticles carry heightened risks of chronic inflammation and tissue fibrosis upon repeated administration. Because routine cell-culture viability assays often miss systemic immune and blood-compatibility reactions, tiered safety testing combining hemocompatibility panels, immunotoxicity assays, and repeat-dose in vivo toxicokinetic studies is necessary.

XI. KEY CHALLENGES AND LIMITATIONS

Biological Barriers: Beyond blood vessel walls, nanocarriers encounter mucus layers in oral and inhaled routes, dense extracellular matrices in solid tumors, rapid mucociliary clearance, and phagocytic uptake by the RES. Surface traits engineered to cross one barrier (such as positively charged or mucoadhesive coatings) frequently hinder passage across the next barrier.

Manufacturing and Scale-Up: Bench-scale preparation methods such as probe sonication, thin-film hydration, or small-volume solvent injection often show poor batch-to-batch consistency when scaled up to commercial batch sizes. Shifts in fluid shear, mixing energy, temperature gradients, and raw-material polydispersity can alter particle diameter and encapsulation efficiency. Continuous manufacturing systems, including microfluidic mixing and high-pressure homogenization paired with inline Process Analytical Technology (PAT), are increasingly used to maintain tight CQA control.

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Sterilization and Storage Stability: Terminal heat sterilization (autoclaving) frequently melts lipid cores or degrades heat-sensitive polymers, while gamma irradiation can generate free radicals that break polymer chains or oxidize phospholipids. Sterile filtration through 0.22 µm membranes is standard practice but becomes impractical for particles larger than ~200 nm or viscous dispersions. Additionally, liquid nanosuspensions are vulnerable to hydrolysis, Ostwald ripening, and particle clumping, often requiring freeze-drying (lyophilization) with cryoprotectants like trehalose or sucrose to achieve an acceptable shelf life.

Regulatory Complexity: Nanomedicines often fall under complex regulatory categories ("non-biological complex drugs") where minor changes in manufacturing can shift clinical pharmacokinetics and safety. Agencies such as the US FDA and European Medicines Agency (EMA) require detailed physicochemical comparability data, immunogenicity testing, and product-specific bioequivalence protocols for follow-on ("nanosimilar") products.

XIII. FUTURE PERSPECTIVES

Next-generation nanomedicine research is moving away from overly elaborate, trial-and-error particle designs toward rational, mechanism-guided engineering. Biomimetic carriers—such as nanoparticles cloaked with natural red blood cell, platelet, leukocyte, or tumor cell membranes—use native surface proteins (like CD47 "do-not-eat-me" markers) to evade macrophage uptake and achieve homotypic targeting, though donor sourcing, batch standardization, and sterility remain practical hurdles.

Artificial intelligence (AI) and machine learning tools are increasingly used for high-throughput formulation screening, modeling structure–activity links between ionizable lipid structures, protein-corona profiles, and organ tropism. Getting reliable predictions from these models depends on standardized, transparent experimental datasets rather than fragmented literature reports.

Finally, personalized nanomedicine aims to match targeted carriers with diagnostic biomarkers—such as quantitative imaging of tumor vessel permeability or receptor density—to select responsive patient subgroups prior to treatment, alongside growing interest in green synthesis and biodegradable polymers to reduce environmental impact.

XIII. DISCUSSION

A critical look at recent literature shows that while nanotechnology provides versatile ways to improve drug solubility, stability, and tissue distribution, carrier engineering must stay grounded in practical pharmaceutics. A recurring trap in lab nanomedicine papers is treating higher cell uptake in vitro or brighter bulk fluorescence in animal organs as proof of true targeting. Fluorescent dyes can leak out of carriers and distribute on their own, while receptor-targeted particles may bind outer tumor cells without reaching poorly perfused tumor cores.

In the same way, relying too heavily on the EPR effect without accounting for human tumor variability has led to several clinical setbacks. Active targeting and stimuli-responsive release mechanisms can boost intracellular delivery and local drug availability, provided their added chemical complexity does not hurt manufacturing reproducibility or trigger unwanted immune reactions. Going forward, standardized reporting of physicochemical attributes, direct head-to-head comparisons against standard clinical formulations, and rigorous pharmacokinetic–pharmacodynamic (PK/PD) modeling will be critical to closing the translational gap.

XIV. CONCLUSION

Nanotechnology-based targeted drug delivery systems have reshaped modern pharmaceutics by enabling the protection, controlled release, and tailored biodistribution of difficult drug molecules, spanning poorly soluble small molecules to fragile nucleic acids. Platforms including liposomes, polymeric nanoparticles, SLNs, NLCs, polymeric micelles, dendrimers, and hybrid constructs each bring distinct strengths alongside characteristic physicochemical and biological drawbacks. While passive, active, and stimuli-responsive strategies offer valuable design frameworks, true clinical translation depends on overcoming biological barriers, ensuring scalable GMP manufacturing, verifying long-term biocompatibility, and proving clear therapeutic superiority over conventional dosage forms. Practical, purpose-driven

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formulation—backed by reliable analytical testing and realistic clinical comparisons—will decide how far targeted nanomedicine goes.

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