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Nanotechnology for efficient drug loading and delivery: A comprehensive review of nanocarriers, loading strategies, therapeutic applications, and translational challenges

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Abstract

Nanotechnology has revolutionized pharmaceutics by enabling the entrapment of bioactive molecules in carriers that enhance their aqueous solubility, chemical stability, pharmacokinetics and tissue-specificity. Nanocarrier-based delivery system can entrap small molecules, peptides, proteins, nucleic acids and imaging probes with the additional benefits of controlled release and diminished systemic toxicity. This updated review covers high efficiency loading and delivery of drugs with focus on the impact of the nanocarrier structure and physicochemical characteristics, formulation processing, biological interaction and manufacturing approach on drug encapsulation efficiency, loading capacity, drug retention, drug release, and therapeutic effect [1-4],[9-18]. Several classes of nanocarriers: liposomes, lipid nanoparticles (LNPs), polymeric nanoparticles, polymeric micelles, dendrimers, mesoporous silica nanoparticles, inorganic nanoparticles, nanogels and exosome-like systems are discussed and compared in relation to their structure, loading mechanisms, advantages and limitations [18-21]. Emphasis on passive loading, active/remote loading, microfluidic production, flash nanoprecipitation, protein corona formation, passive/active targeting, stimuli-responsive release, characterization, and medically approved nanomedicines is provided [22-28,51-58]. Lastly, translation bottlenecks such as poor in vivo delivery efficiency, scale-up, sterilization, regulatory requirements, and long-term safety, are critically discussed along with potential solutions including biomimetic design, in silico prediction, artificial intelligence-guided formulation, quality-by-design manufacturing [8,9,24],[27-30],[59,60].

Keywords: Nanotechnology; Drug Delivery; Drug Loading; Encapsulation Efficiency; Lipid Nanoparticles; Liposomes.

1. Introduction

Conventional drug delivery mechanisms are often hindered by its hydrophobic nature, rapid elimination from body, instability, low bioavailability, toxicity at doses needed for effect, and poor accumulation in target tissue. These barriers are particularly daunting when it comes to anticancer, nucleic acid, peptide therapeutics and central nervous system drugs. Nanotechnology resolves many of these issues since nanometer-sized carriers can entrap active molecules, shield them from degradation, extend circulation time, alter biodistribution, and control spatiotemporal release [1-4,9]. The modern view underlying nanomedicine is not simply miniaturization. Instead, it relies on the rational manipulation of size, morphology, surface chemistry, elasticity, and interfacial interactions to tailor interactions with proteins, cells, tissues, and biological barriers [7-9,25]. Depending on the formulation, nanoparticles may enhance solubility and stability of drugs, reduce off target effect, cross some biological barriers or deliver multiple therapeutic or imaging agents [10-12,22-24]. High drug loading is at the heart of this area. A nanocarrier has clinical relevance only if it fulfills a series of prerequisites involving the ability to contain a sufficient amount of drug, retain its cargo during processing and storage, avoid premature leakage while in circulation, and deliver the payload at the desired site under that expected conditions [13-18]. Therefore, drug-loading science integrates materials chemistry, formula engineering,

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interface biology, and pharmacological performance. In this review, a general and broad narrative synthesis of nanotechnology-based drug delivery is provided with a focus on carrier classes, loading strategies, encapsulation efficiency influencers, targeting strategy, characterization instruments, therapeutic application, approved products, manufacturing issues, protein corona influences, and future computational directions [19-24].

2. Literature Search Strategy and Review Design

This article has been written as a narrative review to which quantitative data synthesis was applied. It was not intended as systematic review or meta-analysis, thus there is no pooled effect size calculation, PRISMA flow diagram and/or formal risk of bias rating. To enhance transparency, reproducibility, and coverage of the literature, a structured search strategy was implemented. We searched the literature in PubMed/MEDLINE, Scopus, Google Scholar, and Web of Science. The following search terms were combined with Boolean operators: nanotechnology OR nanomedicine OR nanocarrier OR nanoparticle drug delivery; drug loading OR encapsulation efficiency OR loading capacity OR controlled release; liposomes OR lipid nanoparticles OR polymeric nanoparticles OR PLGA nanoparticles OR polymeric micelles OR dendrimers OR nanogels OR mesoporous silica nanoparticles; protein corona OR biomolecular corona; targeted delivery OR EPR effect OR receptor-mediated uptake; microfluidics OR flash nanoprecipitation OR scale-up OR quality by design; and in silico OR molecular dynamics OR machine learning OR artificial intelligence formulation optimization. The review focused104 on landmark studies from 1986, and placed particular emphasis on those published between 2010 and 2025. Earlier seminal reports were the basis of how to understand the EPR effect, liposomal remote loading, nanoprecipitation, and flash nanoprecipitation [5,6,51-54]. Inclusion criteria were peer-reviewed English language articles, they must have been directly related to nanocarrier drug loading, release, targeting, characterization, manufacturing, toxicity or clinical translation, and were required to make a very clear contribution to either formulation science or biomedically relevant interpretations. The exclusion criteria were: repeated records, non-peer-reviewed publications, articles not directly related to drug delivery, and papers on non-nanoscale-based formulations lacking a nanotechnology element.

To avoid excessive dependence on review literature, the synthesis deliberately combines high-impact reviews with original research and clinically influential studies. Original studies were prioritized when discussing remote loading in liposomes, nanoprecipitation of polymeric nanocapsules, microfluidic production of lipid nanoparticles, flash nanoprecipitation, protein-corona-mediated loss of targeting, and clinically validated nanomedicines [35-37,51-58].

3. Why Nanotechnology Improves Drug Delivery

Nanocarriers enhance the delivery of drugs via several mechanisms, which are not mutually exclusive. To begin with, they have the potential to raise the apparent solubility of a poorly water-soluble drug by molecular dispersion, by partitioning into hydrophobic domains, or by encapsulation within nanoscale cores and pores [10,14,15]. Secondly, they shield the cargo molecules from hydrolysis, oxidation, enzymatic digestion and fast renal excretion [3,9,12]. In addition, adsorption of proteins and circulation time can be modulated by surface functionalization with polyethylene glycol (PEG), zwitterions, polysaccharides, peptides, or cell membranes [7,25,55-58]. With nanotechnology, pharmacokinetic control can be enhanced as well. The particles size and composition can be modified to influence the biodistribution, tropism of organs, intracellular trafficking, and release-profile of [17,25] the [8,16] drug delivery platform. For instance, liposomes may transport hydrophilic as well as lipophilic agents, controlled release in matrix form from polymeric nanoparticles is feasible, and mesoporous silica nanoparticles enable adsorption-based loading accompanied by gatekeeper-controlled release [20,21]. Targeted delivery to a diseased site is yet another major benefit. Nanoparticles are hypothesized to accumulate in diseased tissues via the enhanced permeability and retention (EPR) effect or active receptor-mediated targeting [5,6,26-28]. Yet analyses giving it a quantitative treatment – such as that by Wilhelm et al. [8] – reveal an often low and very variable delivery efficiency, and thus EPR should be viewed as a probabilistic advantage, rather than a universal guarantee.

4. Major Nanocarrier Platforms

A wide variety of nanoscale carriers have been developed, each with distinct chemical architecture and loading behavior. Their selection depends on the physicochemical properties of the drug, administration route, desired release profile, target tissue, biological medium, and manufacturability [9-18]. Table 1 summarizes the main classes.

Table 1 Comparison of major nanocarrier platforms used for drug loading and delivery.

Platform	Typical composition	Main loading mode	Key advantages
Liposomes	Phospholipid bilayers + cholesterol	Aqueous-core loading, bilayer partitioning, remote loading	Biocompatible; carry hydrophilic and lipophilic drugs; clinically established
Lipid nanoparticles	Ionizable/solid lipids, helper lipids, PEG-lipids	Electrostatic complexation and rapid self-assembly	Excellent for RNA; scalable microfluidics; potent intracellular delivery
Polymeric nanoparticles	PLGA, PLA, PCL, chitosan, alginate, gelatin	Matrix entrapment, adsorption, conjugation	Controlled release; biodegradability; versatile chemistry
Polymeric micelles	Amphiphilic block copolymers	Core solubilization of hydrophobic drugs	Improve solubility; small particle size
Dendrimers	Branched macromolecules	Entrapment, electrostatic complexation, conjugation	High functional density; precise architecture
Nanogels	Cross-linked hydrophilic polymer networks	Swelling-based entrapment and ionic interaction	Soft, water-rich, stimuli-responsive
Mesoporous silica nanoparticles	Porous silica	Pore adsorption and gatekeeper-controlled release	High surface area; tunable pores
Inorganic nanoparticles	Gold, iron oxide, quantum dots	Surface adsorption and conjugation	Theranostic magnetic/optical functions

4.1. Liposomes and lipid nanoparticles

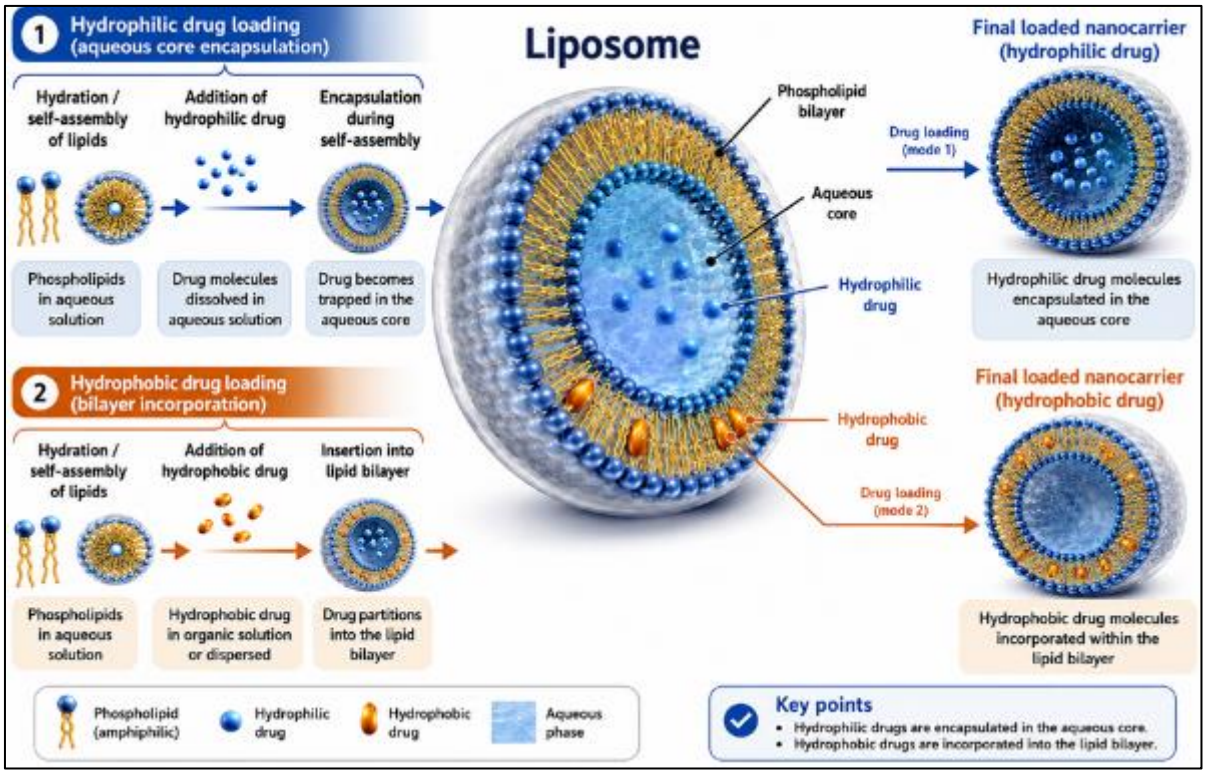

Figure 1 Schematic illustration of drug loading into a liposome, showing encapsulation of hydrophilic drugs in the aqueous core and incorporation of hydrophobic drugs into the phospholipid bilayer.

Liposomes are multi-layered spherical vesicles made of phospholipids, which encapsulate a watery core. Due to their dual-chamber design, hydrophilic agents can be encapsulated within the core, while lipophilic agents can be dissolved into the bilayer [10,11]. Traditional benefits including biocompatibility, lower toxicity and the ability for remote loading with transmembrane ion or pH gradients. The ammonium-sulfate-gradient method is a paradigm which may be applied to attain both high and stable drug encapsulation of amphipathic weak bases like anthracyclines [11,35,51]. Lipid nanoparticles (LNPs), particularly ionizable lipid-based systems, are the predominant platforms for nucleic acid delivery. They complex negatively charged nucleic acids, shield them from nucleases degradation, and mediate endosomal escape [12,13,39,40]. The success of LNP-enabled vaccines has spurred interest in scalable lipidic nanomedicines and process-controlled RNA delivery [12,39,40,53].

4.2. Polymeric nanoparticles and polymeric micelles

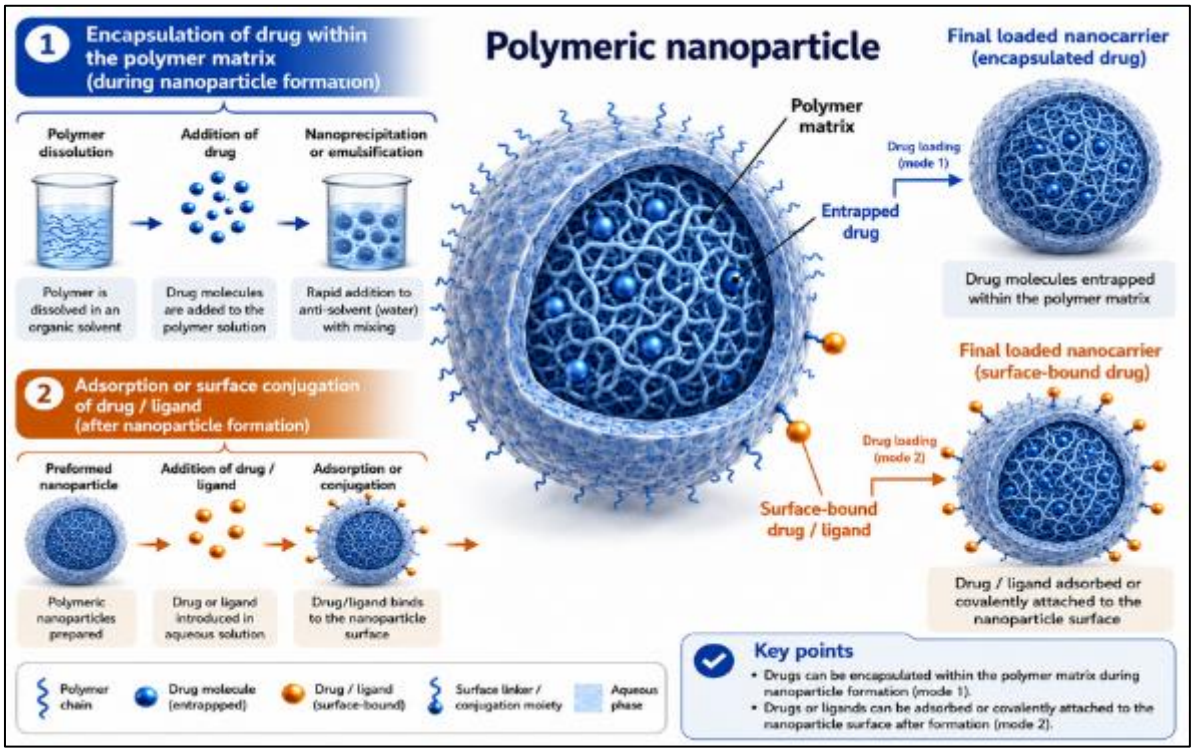

Figure 2 Three-dimensional schematic illustration of drug loading into a polymeric nanoparticle, showing matrix entrapment during nanoparticle formation and post-synthesis surface adsorption or conjugation**.**

Polymeric nanoparticles are generally synthesized from biodegradable polymers such as polylactic-co-glycolic acid (PLGA), polylactic acid (PLA), polycaprolactone (PCL), chitosan, alginate, gelatin, and copolymers synthetically engineered [14,15,32]. Drug moieties may be solubilized, dispersed, adsorbed or covalently bonded to the polymer matrix. Their structural flexibility, adjustable degradation and long-term sustained release make them excellent candidates for application in formulation research [14]. The conventional solvent-displacement/nanoprecipitation technique, described by Fessi et al, is still essential to produce polymeric nanocapsules and nanospheres [52]. Polymeric micelles are self-assembled colloids composed of amphiphilic block copolymers. Their hydrophobic core acts as a nanoreservoir for the hydrophobic drugs whereas their hydrophilic corona renders a good stability of the formulation in aqueous medium [15,41]. Micelles are effective for chemotherapeutics and combination treatments, although two concerns persist, dilution-induced destabilization and poor loading of certain drugs [41].

4.3. Dendrimers, nanogels, and biomacromolecular carriers

Dendrimers are branched nanosized macromolecules with well-defined 3D geometry and possess numerous terminal functional groups. Drugs may be trapped in internal cavities, conjugated with end groups, or ionically complexed [18]. Their precision and functional density allow flexible engineering, however, cationic Dendrimers may be toxic if not appropriately modified [18]. Nanogels are cross-linked hydrophilic polymer networks in the range of nanometers which can load drugs by swelling, ionic interaction or chemical bonding, or solvents of drugs (Fig. They are also highly suitable for osteoinductive biomacromolecules and stimuli-responsive release as a result of their soft nature and extreme high water content [16,17]. Nanoparticles and nanogels based on chitosan are of special interest, as they are mucoadhesive,

biodegradable, and can be loaded by a ionotropic gelation-based method [32]. Biomacromolecular and exosome-inspired vectors play host to biological membranes and in principle enhance immune, and tissue communications. Exosomes and cell membrane coated nanoparticles emerge as two rapidly evolving platforms for biomimetic drug delivery, though scalable isolation and cargo standardization continue to be daunting challenges [49].

4.4. Inorganic and hybrid nanocarriers

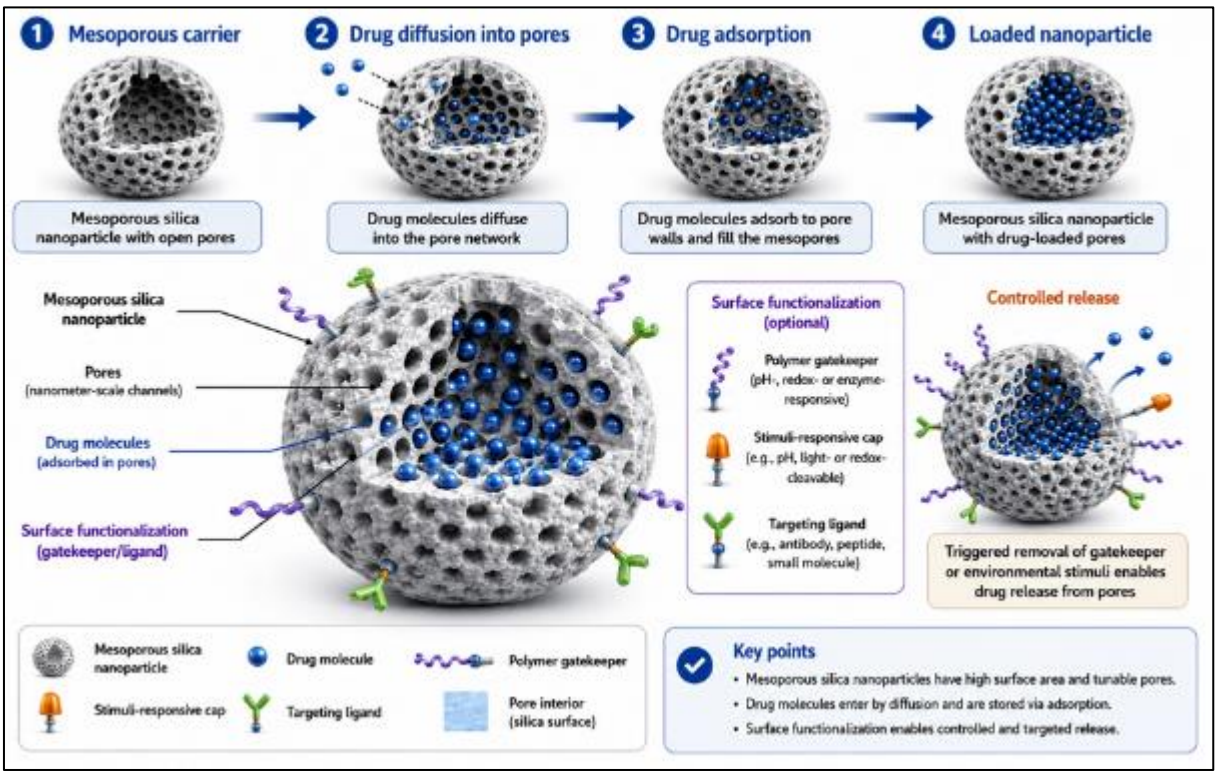

Figure 3 Schematic illustration of drug loading into a mesoporous silica nanoparticle, showing diffusion into nanopores, adsorption inside the pore network, surface functionalization, and controlled release.

Mesoporous silica nanoparticles are one of the most flexible inorganic systems, with potential for a wide range of applications, owing to their large pore volume, adjustable pore size, high surface area, and easy surface modification [20,21]. Drugs can be incorporated through adsorption inside the pores, and the release occurs via diffusion or by opening of the pores with stimulus-responsive gatekeepers. These particles hold promise for the delivery of poorly soluble molecules and for combination therapies. Gold nanoparticles, iron oxide nanoparticles, quantum dots, and other inorganic systems achieve optical, magnetic, or catalytic properties, thereby diversifying the possibilities of theranostics [19,41]. Nevertheless, long-term biodegradation, tissue accumulation, and regulatory approval are more challenging compared to many soft organic nanocarriers. Hybrid systems of lipids, polymers, and inorganic cores have been developed to provide a balance between loading efficiency and multi-functionality [19,41].

5. Drug Loading: Concepts, Metrics, and Mechanisms

An efficient loading of drugs is to maximizing the incorporated active agent while maintaining the colloidal stability, safety and release profile. The most widely used quantitative descriptors are encapsulation efficiency (EE%) and loading capacity or drug loading (LC% or DL%). The drug loading content (LC) indicates how much drug is encapsulated in each unit mass of nanoparticle, while the encapsulation efficiency (EE) shows how much of the initially added drug was encapsulated into the nanoparticle [16,17]. Both are required for a satisfactory explanation. A very high EE% formulation can have low LC% if the amount of excipient is very high. On the other hand, very high drug loading can render colloids unstable, leading to increased aggregation and/or burst release. An informative optimization thus entails a tradeoff of drug payload, particle stability, manufacturability, and release behavior, not maximization of any single metric [14,16,31]. Drug loading can be achieved by physical entrapment, hydrophobic partitioning, electrostatic complexation, hydrogen bonding, metal coordination, host-guest inclusion, or covalent conjugation. The relative contributions of these mechanisms are influenced by both the cargo properties and the chemistry of the carrier [15-18,20,21].

5.1. Passive loading

Passive loading is accomplished during particle synthesis or by incubation following carrier formation. It is also typical in nanoprecipitation, emulsification-solvent evaporation, lipid film hydration, thin-film dispersion and self-assembly techniques [10,14,15,52]. According to solubility, polarity and affinity, the drug is partitioned into the nascent core or matrix. This method is straightforward and versatile but could result in moderate loading or burst release when the drug is loosely associated [14,15].

5.2. Active or remote loading

Active loading uses transmembrane gradients, pH differences, ion pairing, or affinity interactions to drive drug molecules into preformed nanoparticles. Remote loading in liposomes is a classic example and can produce high loading efficiencies and strong retention for amphipathic weak bases such as doxorubicin [11,35,51]. Similar principles are being explored through host-guest chemistry, boronate ester formation, selective complexation, and stimuli-cleavable conjugation [16,17].

5.3. Determinants of loading efficiency

Loading efficiency is influenced by drug hydrophobicity, molecular weight, pKa, crystallinity, and chemical stability, as well as by carrier composition, polymer-to-drug ratio, lipid packing, pore diameter, solvent selection, stirring or mixing rate, ionic strength, and processing temperature [16,17,20,21,31]. Figure 4 summarizes these relationships and clarifies that the formulation outcome depends on the combined effects of drug properties, carrier architecture, processing variables, interfacial interactions, stabilization strategy, and biological medium.

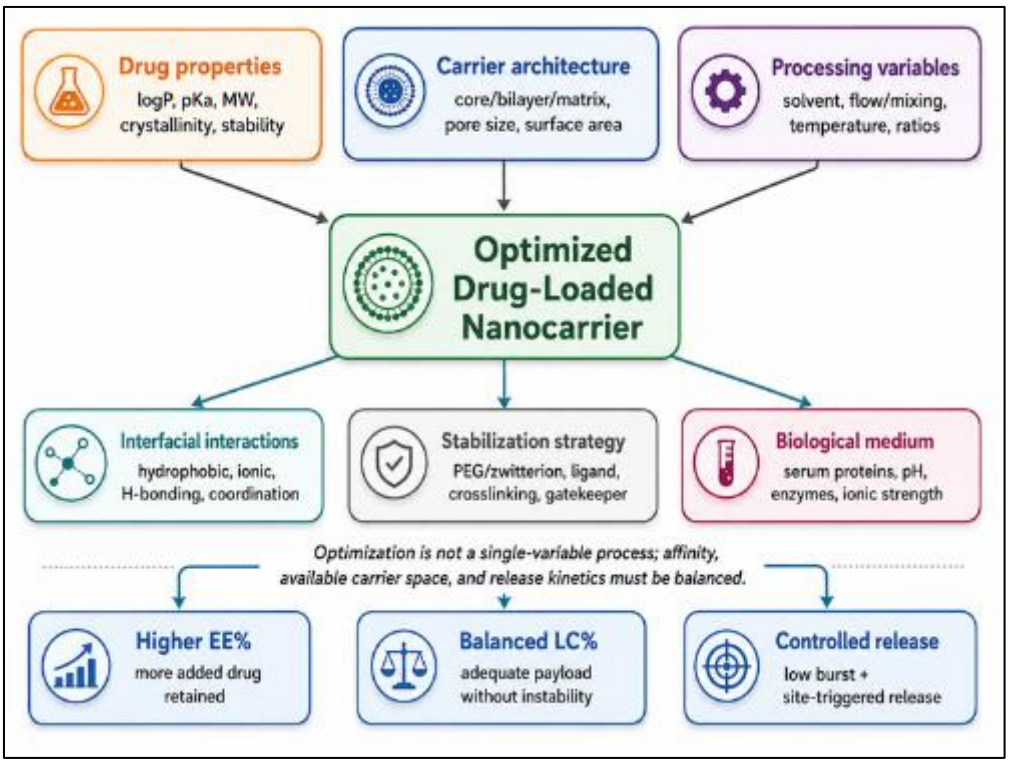

Figure 4 Drug loading routes and major determinants of encapsulation efficiency, loading capacity, retention, and release in nano drug delivery systems.

Hydrophobic drugs are typically loaded more efficiently into nonpolar cores or bilayers, whereas hydrophilic and ionizable molecules often require aqueous cores, ionic complexation, porous hydrophilic environments, or gradient-based loading [10,15,51]. For nucleic acids, ionizable lipids and cationic polymers are especially important because electrostatic condensation drives encapsulation and protects the cargo [12,13,39].

Surface area and internal volume are also crucial. Smaller particles may increase external surface adsorption but can reduce internal payload when the core volume becomes too small. In porous systems, the match between molecular

size and pore architecture strongly determines uptake and release [20,21]. In every case, the best formulation is obtained by optimizing affinity, available carrier space, and release kinetics together.

Table 2 Drug loading strategies and the main factors that influence encapsulation efficiency**.**

Strategy	Typical systems	Mechanism	Important variables
Passive loading during formulation	Liposomes, polymeric nanoparticles, micelles	Drug partitions into a forming nanostructure	Drug solubility, polymer/lipid ratio, solvent choice
Remote / active loading	Liposomes	pH or ion gradient drives drug inward	Gradient magnitude, temperature, membrane permeability
Electrostatic complexation	LNPs, chitosan nanoparticles, dendrimers	Opposite charges condense cargo	pKa, ionic strength, N/P ratio
Pore adsorption	Mesoporous silica	Drug adsorbs into porous network	Pore size, surface functionality, solvent
Covalent conjugation	Polymer-drug conjugates, dendrimers	Cleavable chemical linkage	Linker chemistry, cleavage trigger, drug activity
Microfluidic self-assembly	LNPs and hybrid lipid/polymer systems	Rapid controlled mixing of organic and aqueous streams	Flow-rate ratio, total flow rate, solvent composition, lipid/RNA ratio
Flash nanoprecipitation	Hydrophobic drug nanoparticles and polymer-stabilized particles	Rapid supersaturation after solvent/antisolvent mixing	Mixing time, stabilizer/drug ratio, supersaturation, solvent-to-antisolvent ratio

6. Targeting Strategies and Controlled Release

Effective delivery requires not only loading the drug but also transporting it to the appropriate site and releasing it at the right time. Targeting and release are therefore inseparable aspects of nanocarrier design [7,16,17,26-28]. Figure 5 presents the main steps from administration and circulation to tissue accumulation, receptor-mediated uptake, endosomal trafficking, stimuli-responsive release, and intracellular action.

6.1. Passive targeting

Passive targeting refers to nanoparticle accumulation driven by physiological and anatomical features of diseased tissues. In tumors and inflamed regions, abnormal vasculature and impaired lymphatic drainage may facilitate extravasation and retention of appropriately sized particles [5,6]. Although this EPR-based concept has supported many nanomedicine designs, its magnitude varies substantially across animal models, tumor types, and human patients [8,26,27]. Therefore, passive targeting should not be presented as a guaranteed mechanism of tumor delivery.

6.2. Active targeting

Active targeting is achieved by decorating nanoparticle surfaces with ligands such as antibodies, aptamers, peptides, sugars, folate, transferrin, or small molecules that bind overexpressed receptors on target cells [2,7,9,28]. Active targeting can improve cellular uptake and internalization, especially after nanoparticles have reached the vicinity of diseased tissue. However, surface ligands do not automatically overcome poor pharmacokinetics and may be masked by the protein corona in biological fluids [7,25,57,58].

6.3. Stimuli-responsive release

Stimuli-responsive nanocarriers release cargo in response to endogenous or exogenous triggers such as pH, redox potential, enzymes, temperature, light, magnetic fields, or ultrasound [16,17]. Tumor tissues and endolysosomal compartments are attractive because they often display acidic pH and altered redox conditions. Labile bonds, swelling components, gatekeepers, and phase-transition materials can reduce premature leakage and increase release within the target microenvironment [16,17,20].

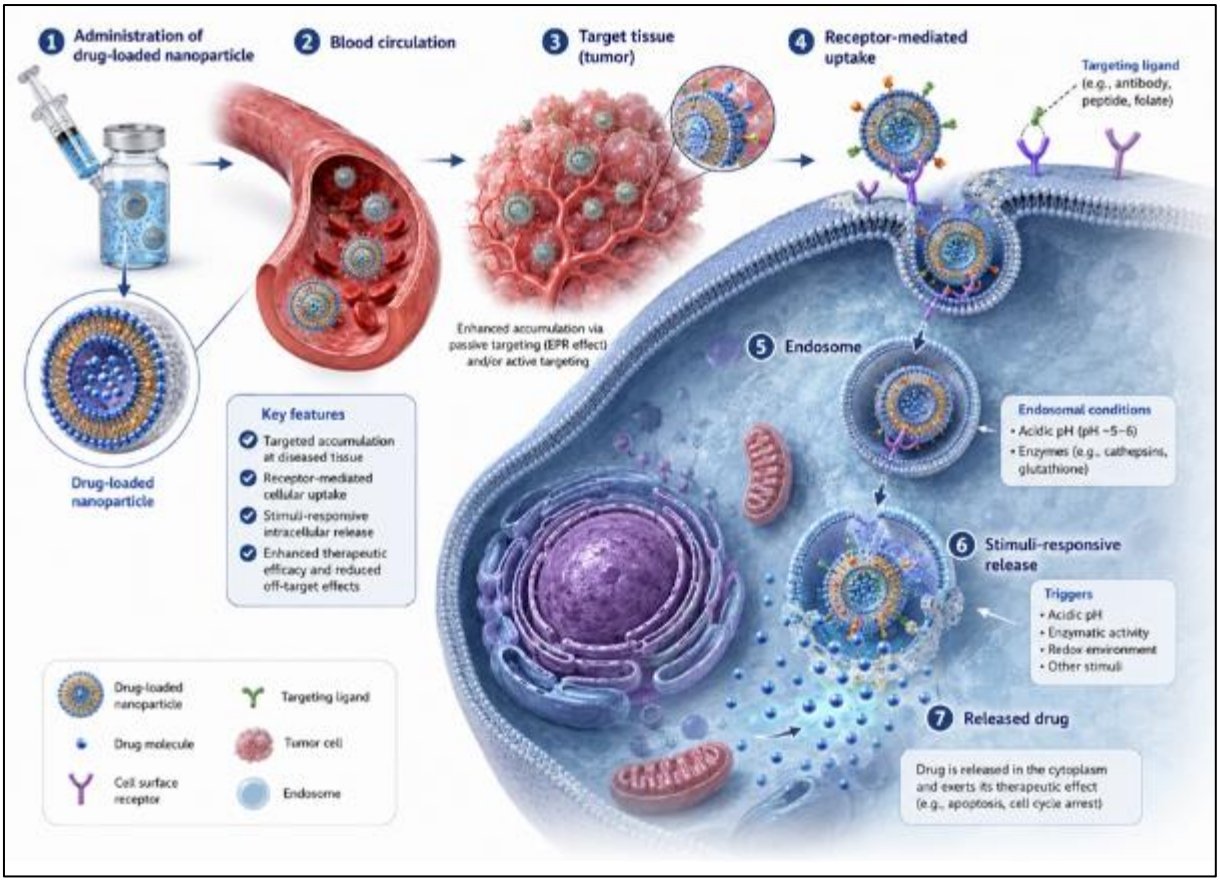

Figure 5 Three-dimensional schematic illustration of targeted nano drug delivery and intracellular release, showing systemic administration, tumor accumulation, receptor-mediated uptake, endosomal trafficking, stimuli-responsive release, and intracellular drug action.

Table 3 Targeting and controlled-release strategies in nanomedicine**.**

Approach	Representative tools	Main benefit	Limitation
Passive targeting	Size optimization and long circulation	Exploits leaky vasculature or inflamed tissue	Highly heterogeneous in patients
Active targeting	Antibodies, peptides, folate, transferrin, aptamers	Improves cell-specific binding and internalization	Does not overcome poor pharmacokinetics by itself
pH-responsive release	Acid-labile linkers, protonatable groups	Releases cargo in tumor/endosomal acidity	May release prematurely in some tissues
Redox-responsive release	Disulfide-containing carriers	Triggered in glutathione-rich environments	Requires sufficient intracellular redox difference
Enzyme-responsive systems	Protease-cleavable coatings	Disease-specific release	Enzyme expression can vary
Light/heat/ultrasound-responsive	Photothermal agents, thermosensitive lipids	External spatiotemporal control	Needs device support and penetration-depth consideration

7. Characterization of Nano Drug Delivery Systems

Rigorous characterization is essential due to the fact that even minor variation in size distribution, surface charge, crystallinity, morphology, or surface chemistry can have profound effects on loading, stability and biological fate [25,31,33]. Dynamic light scattering is the most popular technique for the determination of hydrodynamic size and polydispersity while electron microscopy enable direct observation of morphology [10,14,20]. Zeta potential is a parameter which provides information regarding colloidal stability and interfacial charge; DSC, XRD and FTIR are techniques to investigate the solid state and the interaction among the drug and the carrier [14,20,21,31]. The drug loading is usually determined by UV-visible spectroscopy, HPLC, LC-MS, fluorescence analysis or by elemental methods depending on the nature of the drug [15,16]. Drug release tests are commonly performed by dialysis or sample-and-separate techniques or diffusion cells and kinetic modeling of the data [24-26]. Additional testing of sterility, endotoxin level, residual solvent, hemocompatibility, protein corona formation and storage stability will be required for the translational formulations [22-24,50,55-58].

Table 4 Core characterization methods used for nano drug delivery systems**.**

Technique	Main output	Why it matters
Dynamic light scattering (DLS)	Hydrodynamic diameter, PDI	Particle size affects biodistribution, uptake, and stability
Zeta potential	Surface charge	Indicates colloidal stability and biological interaction tendency
TEM/SEM	Morphology and direct size visualization	Confirms shape, aggregation state, and shell structure
AFM	Surface topography and nanomechanics	Useful for soft nanoparticles and biomimetic systems
HPLC/UV/LC-MS	Drug content, EE%, LC%	Quantifies encapsulated and free drug
FTIR/Raman	Chemical interactions	Reveals drug-carrier interaction or surface functionalization
XRD/DSC	Crystallinity and thermal behavior	Shows drug physical state and matrix organization
Release testing	Release profile and kinetics	Essential for controlled-release assessment
Stability studies	Shelf-life, aggregation, leakage	Critical for translation and regulatory approval

8. Therapeutic Applications

The application landscape of nano-enabled drug delivery is broad and continuously expanding. The strongest clinical and preclinical presence remains in oncology, but important advances also exist in infectious diseases, inflammation, gene therapy, vaccination, neurological disorders, and localized delivery [19,22-24,33,40]. Table 5 emphasizes established or broadly supported application areas rather than isolated early-stage reports.

8.1. Cancer therapy

Cancer has Traditionally been the largest application area for nanomedicine due to inadequateselectivity and high toxicity of many chemotherapeutics [19,2,4]. Liposomal doxorubicin, albumin-bound paclitaxel, and liposomal irinotecan provide examples of how nanocarriers can enhance the therapeutic index by changing biodistribution and limiting certain toxicities [35-37]. Nanoparticles enable co-delivery of drugs, photosensitizers, immunomodulators and nucleic acidsfor combination therapy [19,28,42]. Although advancements have been made, an average low percentage of injected nanoparticles actually reach solid tumours. Wilhelm etal. [8] is of particular importance as it has put into question overly positive interpretations EPR-mediated accumulation and foster more realistic patient stratifications, microenvironment-responsive design and inmunologically aware formulations [8,27,28,50].

8.2. Delivery across biological barriers and to the central nervous system

Crossing the blood-brain barrier remains a major challenge for neurological therapy. Nanocarriers may improve delivery through receptor-mediated transcytosis, adsorption-mediated transport, cell membrane mimicry, or intranasal administration strategies [43,48]. Lipidic, polymeric, and biomimetic nanoparticles are being explored for neurodegenerative diseases, glioma, and brain inflammation, but these applications should be interpreted as emerging rather than broadly established clinical standards [43,48,49].

8.3. Anti-inflammatory, antimicrobial, and localized therapy

Nanocarriers are increasingly used to improve local retention of anti-inflammatory, antimicrobial, and wound-healing agents. Chitosan-based systems, silver-containing nanocomposites, lipid nanocarriers, and nanogels can enhance mucosal adhesion, increase residence time, and provide sustained release [32,41]. Localized delivery to the lungs, eye, skin, and intra-articular spaces is promising because it may reduce systemic adverse effects while increasing site-specific concentrations.

8.4. Nucleic acid delivery and vaccines

Nucleic acid delivery is a landmark success of nanotechnology. Lipid nanoparticles have become leading nonviral platforms for mRNA and siRNA because they package fragile polyanions, support cellular uptake, and facilitate endosomal escape [12,13,39,40,53]. This area transformed nanotechnology from a mainly experimental concept into an enabling pharmaceutical technology with global public health impact.

Table 5 Representative therapeutic applications of nanotechnology-enabled drug delivery.

Therapeutic area	Typical cargo	Frequently used nanocarriers	Main goals
Cancer therapy	Doxorubicin, paclitaxel, irinotecan, siRNA	Liposomes, polymeric nanoparticles, micelles, dendrimers, MSNs	Reduce toxicity, improve tumor exposure, enable combination therapy
Gene delivery / vaccines	mRNA, siRNA, plasmid DNA	LNPs, cationic polymers, hybrid nanoparticles	Protect nucleic acids, support cellular uptake and endosomal escape
Neurological disorders	Small molecules, peptides, nucleic acids	LNPs, polymeric nanoparticles, biomimetic carriers	Improve brain exposure and barrier transport; still largely emerging
Anti-inflammatory therapy	NSAIDs, steroids, biologics	Nanogels, liposomes, polymeric nanoparticles	Prolong local residence and lower systemic dose
Antimicrobial delivery	Antibiotics, peptides, metal-based agents	Lipid nanoparticles, chitosan nanoparticles, nanocomposites	Improve local delivery and overcome selected resistance-related barriers
Ocular, pulmonary, dermal, localized delivery	Small molecules and proteins	Mucoadhesive nanoparticles, nanogels, liposomes	Increase retention and site-specific exposure

9. Clinically Approved Nanomedicines and Translational Lessons

Several marketed products have validated the nanomedicine concept, including Doxil/Caelyx, AmBisome, Abraxane, Onivyde, Patisiran, and lipid nanoparticle-based mRNA vaccines [22-24,35-40]. These products differ in material composition and indication, yet they share common formulation principles: clinically meaningful payload, adequate physical and chemical stability, reproducible large-scale manufacturing, and a demonstrated therapeutic advantage.

A major translational lesson is that clinical success does not always require extreme structural complexity. Robust and scalable systems may outperform highly sophisticated laboratory constructs if the latter do not solve a specific clinical

bottleneck [22,23,50]. Regulatory translation also depends strongly on physicochemical characterization, batch-to-batch reproducibility, and control of critical quality attributes.

Table 6 Selected clinically used or clinically influential nanomedicines and lessons from them.

Product	Platform	Drug/cargo	Clinical significance / lesson
Doxil / Caelyx	PEGylated liposome	Doxorubicin	Reduced cardiotoxicity and altered pharmacokinetics; landmark remote-loading success
AmBisome	Liposomal formulation	Amphotericin B	Reduced nephrotoxicity versus conventional amphotericin B
Abraxane	Albumin-bound nanoparticle	Paclitaxel	Solvent-free delivery and improved administration profile
Onivyde	Liposomal formulation	Irinotecan	Enhanced exposure and prolonged circulation
Patisiran	Lipid nanoparticle	siRNA	Demonstrated clinical maturity of RNA nanomedicine
mRNA LNP vaccines	Lipid nanoparticle	mRNA	Validated LNPs as scalable and globally deployable delivery platforms

10. Toxicological, Regulatory, and Manufacturing Challenges

Despite progress, nanotechnology-based delivery still faces major barriers. Toxicological concerns include immunogenicity, complement activation, oxidative stress, organ accumulation, off-target interactions, and uncertainty regarding long-term biodegradation, especially for inorganic materials [19,22-24,50]. Even biocompatible lipids and polymers may trigger unexpected biological responses once assembled into nanoparticles and exposed to complex protein-rich fluids.

10.1. Protein corona and biological identity

The protein corona is the dynamic adsorption layer formed when nanoparticles encounter biological media such as plasma, serum, interstitial fluid, or cell culture media. This layer can redefine the biological identity of the nanocarrier by changing apparent size, surface charge, receptor availability, cellular uptake route, immune recognition, and biodistribution [25,55,56,58]. Consequently, results obtained in serum-free or simplified in vitro media may not fully predict in vivo behavior.

Protein corona effects are particularly important for targeted nanocarriers. Salvati et al. [57] showed that transferrin-functionalized nanoparticles can lose targeting capability after corona adsorption, illustrating that surface ligands may be masked by biomolecules in realistic biological environments. Therefore, ligand density and affinity should be evaluated not only on freshly prepared particles but also after exposure to relevant biological fluids.

Table 7 Protein corona effects on loading, targeting, and in vitro-in vivo translation.

Nanoparticle feature	Likely corona-related effect	Impact on loading/targeting interpretation	Practical recommendation
Small size / high curvature	Different protein composition and dynamic exchange compared with larger particles	May alter apparent hydrodynamic size and cellular uptake measured in vitro	Test in serum/plasma and report post-corona size, PDI, and zeta potential
Cationic surface	Strong adsorption of anionic plasma proteins, possible complement activation	Enhanced uptake in vitro may reflect nonspecific interaction rather than true targeting	Use charge shielding, optimize N/P ratio, and evaluate hemocompatibility

PEGylated or zwitterionic surface	Reduced but not eliminated protein adsorption	Stealth behavior may be incomplete and ligand accessibility may still change	Quantify corona composition and ligand availability after incubation
Hydrophobic surface	Albumin, apolipoprotein, or opsonin enrichment may occur	May increase macrophage recognition or change biodistribution	Increase surface hydration and control hydrophobic domains
Porous nanocarrier such as MSN	Proteins may block pores or modify gatekeeper function	In vitro release in buffer may overestimate release in protein-rich fluids	Compare release in buffer, serum-containing media, and relevant simulated fluids
Ligand-decorated active-targeting system	Corona can mask ligand-receptor recognition	Loss of specificity may occur despite preserved total uptake	Perform receptor-competition assays after corona formation

10.2. Manufacturing and scale-up challenges

Production is not a terminal engineering step, but is integrated into the design of nanomedicines. Scale-up can change patterns of mixing, solvent exchange, heat transfer, nucleation, growth, and aggregation kinetics of particles. These modifications influence the particle size, zeta potential, encapsulation efficiency, loading capacity, and release profile PDI, residual solvent. Microfluidics enables controlled mixing on small length scales, which is particularly critical for lipid nanoparticles and hybrid particles. The total flow rate, the flow rate ratio between the organic and aqueous streams, the solvent type and composition, the lipid concentration, the N/P ratio, the temperature, and the device geometry are essential parameters included [12,39,53]. These factors have a significant impact on particle size, nucleic acid encapsulation, batch reproducibility, and scale-up via parallelization. Flash nanoprecipitation is particularly adapted to hydrophobic actives. In this method, an organic phase carrying drug and stabilizer is mixed quickly with an antisolvent to induce supersaturation, nucleation, and stabilization of nanoparticles [54].

Table 8 Manufacturing methods and process variables that influence drug loading and critical quality attributes.

Manufacturing approach	**Main use**	**Critical process variables**	**Effect on EE%, LC%, and product quality**
Microfluidic mixing	LNPs, hybrid nanoparticles, polymer/lipid systems	Flow-rate ratio, total flow rate, channel geometry, solvent ratio, temperature	Controls nucleation and self-assembly; affects size, PDI, nucleic acid encapsulation, and reproducibility
Flash nanoprecipitation	Hydrophobic drugs and polymer-stabilized particles	Mixing time, supersaturation, drug/stabilizer ratio, solvent/antisolvent ratio	Fast mixing can increase payload and narrow size distribution; insufficient stabilization causes aggregation
Emulsion-solvent evaporation	Polymeric nanoparticles and nanocapsules	Emulsifier type, homogenization energy, solvent removal rate	Affects entrapment of hydrophobic drugs and residual solvent
Thin-film hydration + extrusion	Liposomes	Hydration medium, lipid composition, extrusion pore size, temperature	Influences lamellarity, size, leakage, and remote-loading performance
Aseptic processing / sterilization	Clinical-grade formulations	Filter size, pressure, heat exposure, irradiation dose	Can cause leakage, aggregation, or drug degradation if not optimized
Lyophilization	Long-term storage	Cryoprotectant type, freezing rate, residual moisture	Improves shelf-life but may affect redispersion, size, and release if poorly controlled

Key factors are mixing time, solvent-to-antisolvent ratio, drug-to-stabilizer ratio, concentration, and stabilizer type. Uncontrolled deterioration of these factors can reduce EE %, broaden the particle size distribution or increase the burst

release. Sterilization and storage-related are other translational limitations. Filtration (potentially) eliminates or rounds aggregations, heat sterilization destabilizes liposomes and polymeric nanoparticles, and gamma irradiation (possibly) impacts polymer integrity. Lyophilization, cryoprotectants, aseptic production, process analytical technology and quality-by-design constructs are therefore necessary for robust development [24,39,50].

Table 9 Major challenges in nano drug delivery and practical mitigation strategies.

Challenge	Why it matters	Mitigation strategy
Low in vivo delivery efficiency	Reduces therapeutic impact	Better targeting logic, patient selection, biomimetic designs
Protein corona formation	Alters biological identity and targeting	Surface engineering, corona-aware testing, serum/plasma assays
Scale-up and reproducibility	Affects batch quality and regulatory approval	Microfluidics, flash nanoprecipitation, QbD, critical quality attribute control
Premature leakage or burst release	Lowers effective dose and raises toxicity	Active loading, stronger affinity interactions, gatekeeper designs
Sterilization and storage instability	Impairs shelf-life and safety	Lyophilization optimization, cryoprotectants, aseptic processing
Long-term safety uncertainty	Limits regulatory confidence	Extended biodistribution, biodegradation, and toxicology studies

11. Future Perspectives

The future of nano drug delivery will likely be shaped by precision design, smarter biological interfacing, and translational realism. Instead of pursuing increasingly complicated architectures without clinical rationale, the field is moving toward fit-for-purpose platforms that directly address specific therapeutic bottlenecks [9,19,27,28].

Emerging directions include biomimetic coatings, extracellular-vesicle-inspired carriers, patient-specific targeting, theranostic systems, quality-by-design manufacturing, and computationally guided formulation [44-49,59,60]. Figure 6 summarizes key opportunities and bottlenecks governing clinical translation.

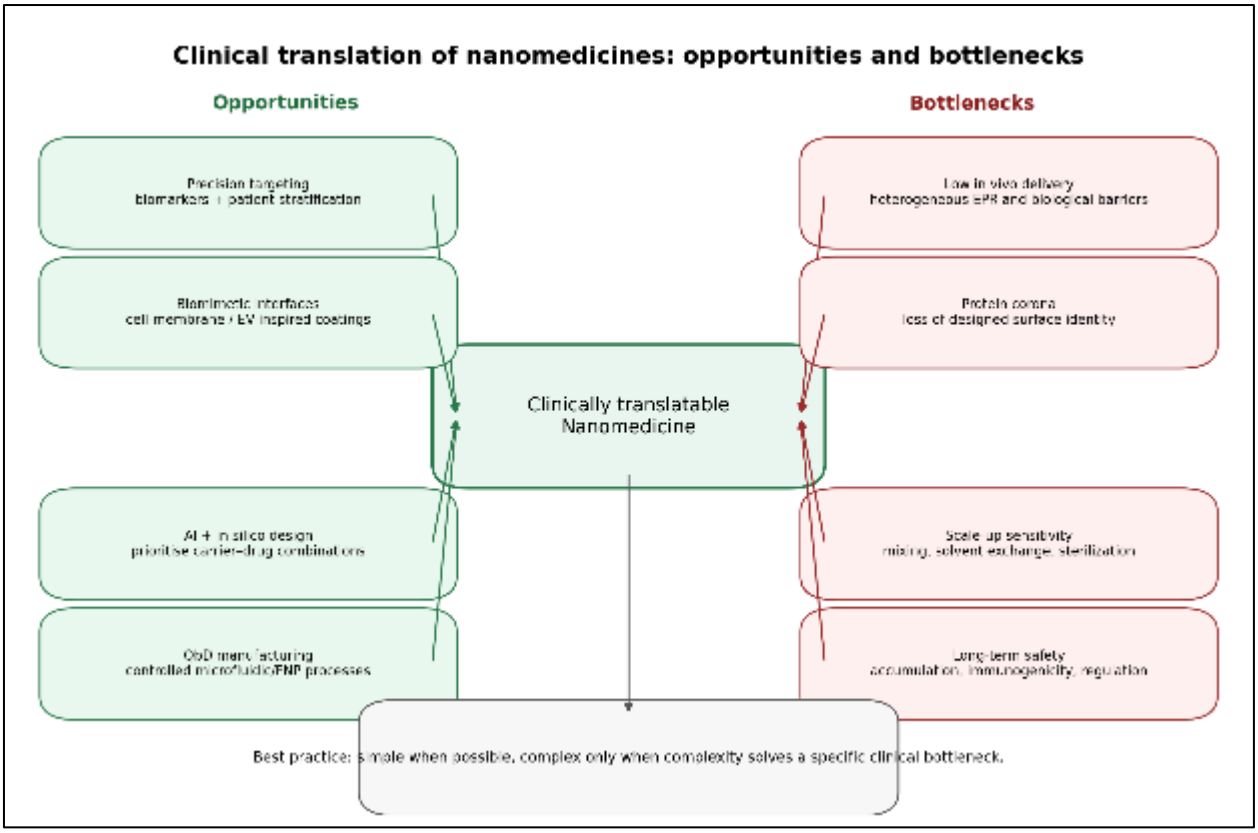

Figure 6 Main opportunities and bottlenecks governing the clinical translation of nanomedicines**.**

11.1. In silico modeling, artificial intelligence, and predictive formulation

In silico methods are increasingly relevant because experimental formulation optimization is expensive, time-consuming, and high-dimensional. Molecular dynamics, coarse-grained simulations, quantitative structure-property relationships, physiologically based pharmacokinetic modeling, and machine learning can help predict drug-carrier affinity, drug location within a carrier, release behavior, protein-corona tendencies, pharmacokinetic behavior, and potential toxicity before extensive laboratory work [59,60].

For drug loading, computational approaches can screen candidate polymers, lipids, surfactants, and solvents; estimate drug partitioning between aqueous, lipidic, polymeric, and interfacial domains; and prioritize formulations likely to produce high EE% and stable retention. For safety, in silico toxicology and pharmacokinetic models may guide early risk assessment, but they should be used as decision-support tools rather than replacements for experimental validation.

Table 10 In silico and AI-based approaches that can support nanocarrier design**.**

Approach	Predicted or optimized feature	Use in formulation development	Caution
Molecular dynamics / coarse-grained simulation	Drug-carrier affinity, membrane interaction, drug location	Screens carrier composition and explains loading/release mechanisms	Requires validated force fields and realistic model conditions
QSPR / nano-QSAR	Size, surface charge, toxicity or uptake trends	Links molecular descriptors to formulation behavior	Limited by dataset quality and applicability domain
Machine learning models	EE%, LC%, particle size, release rate, stability	Reduces trial-and-error and guides formulation selection	Needs standardized, high-quality training datasets

PBPK / biodistribution modeling	Organ exposure, clearance, dose translation	Supports translational planning and dose selection	Must be calibrated with in vivo data
Digital twin / QbD integration	Critical process parameters and quality attributes	Connects manufacturing variables to clinical product performance	Regulatory acceptance requires transparency and validation

In parallel, improved disease models, rigorous reporting standards, and realistic benchmarking against existing therapies are needed. Nanotechnology should not be evaluated only by whether it can load a drug, but by whether it improves clinically meaningful outcomes relative to established treatment options.

Abbreviations

- BBB, blood-brain barrier;
- EE, encapsulation efficiency;
- EPR, enhanced permeability and retention;
- FNP, flash nanoprecipitation;
- LC, loading capacity;
- LNP, lipid nanoparticle;
- MSN, mesoporous silica nanoparticle;
- PDI, polydispersity index;
- QbD, quality by design.

12. Conclusion

Nanotechnology has become a cornerstone of advanced drug delivery because it addresses fundamental pharmaceutical limitations including poor solubility, instability, systemic toxicity, and inadequate tissue selectivity. However, the practical value of any nanocarrier depends strongly on efficient drug loading, stable cargo retention, biological identity in realistic fluids, and controlled release at the target site [1-3],[16,17],[55-58].

Liposomes, lipid nanoparticles, polymeric nanoparticles, micelles, dendrimers, nanogels, mesoporous silica, inorganic systems, and biomimetic vesicles provide distinct opportunities for cargo incorporation and therapeutic optimization [10-21]. The success of approved nanomedicines demonstrates the power of this approach, while persistent barriers such as low in vivo delivery, protein corona formation, manufacturing sensitivity, sterilization, and regulatory expectations show that biological complexity and process control cannot be ignored [22-24,35-40,50].

Overall, the field is transitioning from proof-of-concept nanomaterials toward disciplined, application-driven pharmaceutical engineering. Continued progress will depend on integrating materials chemistry, interface science, pharmacology, manufacturing, computation, and clinical insight to create nanomedicines that are not only elegant in design but also effective, safe, reproducible, and translatable.

Compliance with ethical standards

Disclosure of conflict of interest

The author declares no conflict of interest.

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