Nanotechnology-Based Antimicrobial Drug Delivery Systems: Strategies to Improve Therapeutic Efficacy

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Abstract
The escalating global burden of antimicrobial resistance (AMR), coupled with a stagnant antibiotic discovery pipeline, has created an urgent need for delivery platforms that can restore or amplify the activity of existing antimicrobial agents. Conventional antimicrobial therapy is frequently compromised by poor aqueous solubility, rapid systemic clearance, nonspecific biodistribution, dose-limiting toxicity, and the physical barrier presented by bacterial biofilms, all of which contribute to therapeutic failure and the selection of resistant strains. Nanotechnology-based drug delivery systems (NDDSs) have emerged as a versatile strategy to overcome these obstacles by encapsulating, protecting, and directing antimicrobial payloads to the site of infection while minimizing off-target exposure. polymeric nanocarriers, lipid-based systems such as liposomes and solid lipid nanoparticles, and stimuli-responsive or biofilm-targeted nanoplatforms, summarizing their design principles, antimicrobial mechanisms, and reported therapeutic outcomes across seven comparative tables. The review further examines the mechanistic basis for enhanced efficacy, including improved membrane penetration, sustained and triggered release, biofilm disruption, and combination or synergistic delivery, before critically appraising the toxicological, manufacturing, and regulatory barriers that continue to limit clinical translation. Finally, emerging strategies-including biomimetic coatings, hybrid nanocomposites, artificial intelligence-assisted nanoparticle design, and nanoparticle-antimicrobial peptide conjugates-are discussed as promising avenues to improve therapeutic efficacy. Collectively, the evidence indicates that nanotechnology-enabled delivery can meaningfully potentiate antimicrobial therapy, although standardized characterization, long-term safety data, and scalable manufacturing remain necessary before widespread clinical adoption.

Keywords: nanotechnology, antimicrobial resistance, drug delivery, nanoparticles, biofilm, liposomes, polymeric nanoparticles

1. Introduction

1.1 Background and Global Burden of Antimicrobial Resistance

Antimicrobial resistance is now recognized as one of the most pressing threats to global public health. Bacterial pathogens resistant to first- and second-line antibiotics are associated with millions of deaths worldwide each year, and modeling studies project that the annual economic losses attributable to AMR could reach trillions of dollars by 2030 if left unaddressed (Muteeb et al., 2021). The overuse and misuse of antibiotics in clinical medicine, veterinary practice, and agriculture have accelerated the emergence of multidrug-resistant (MDR) organisms, including methicillin-resistant Staphylococcus aureus (MRSA), carbapenem-resistant Enterobacteriaceae, and extensively drug-resistant Pseudomonas aeruginosa (Theuretzbacher& Piddock, 2019). Compounding this crisis, the discovery of genuinely novel

antibiotic classes has slowed dramatically since the 1980s, leaving clinicians increasingly reliant on older, more toxic agents or combination regimens whose efficacy is itself eroding. Against this backdrop, strategies that can extend the useful life of existing antimicrobials, reduce the effective dose required for clinical cure, and specifically target resistant or biofilm-embedded organisms have taken on renewed importance (Gupta et al., 2019).

The drivers of AMR are multifactorial and extend beyond the clinical setting. Agricultural use of antibiotics for growth promotion and disease prevention in livestock, inadequate infection control in healthcare facilities, substandard or counterfeit antimicrobial products in many low- and middle-income countries, and environmental contamination through pharmaceutical manufacturing effluent and wastewater have all been implicated in the horizontal spread of resistance genes across bacterial populations (Muteeb et al., 2021). The World Health Organization has repeatedly identified priority pathogens-including carbapenem-resistant Acinetobacter baumannii, carbapenem-resistant Enterobacteriaceae, and third-generation cephalosporin-resistant Enterobacteriaceae-for which existing therapeutic options are dwindling. Because resistance mechanisms such as efflux pump overexpression, enzymatic drug inactivation, and target-site modification frequently confer cross-resistance to multiple antibiotic classes simultaneously, clinicians increasingly encounter infections for which no reliably effective conventional therapy exists, reinforcing the case for delivery-based rather than purely molecule-based solutions to the resistance crisis.

1.2 Limitations of Conventional Antimicrobial Therapy

Conventional antimicrobial formulations, whether administered orally, parenterally, or topically, are constrained by several pharmacokinetic and pharmacodynamic limitations. Many antibiotics exhibit poor aqueous solubility and low bioavailability, necessitating high doses that increase the risk of systemic toxicity and off-target effects on the host microbiome (Patra et al., 2018). Rapid enzymatic degradation and renal or hepatic clearance shorten the effective half-life of many agents, requiring frequent dosing that reduces patient adherence. Perhaps most importantly, conventional antibiotics distribute non-specifically throughout the body, so that only a small fraction of the administered dose ultimately reaches the infection site, particularly in poorly vascularized tissues, intracellular reservoirs, or abscesses (Baptista et al., 2018). Bacterial biofilms present an additional, formidable barrier: the self-produced extracellular polymeric substance (EPS) matrix can reduce antibiotic penetration and increase tolerance by up to three orders of magnitude relative to planktonic cells, allowing sub-lethal antibiotic exposure that paradoxically favors the selection of resistant subpopulations (Wang, Hu, & Shao, 2017). These combined limitations mean that even antimicrobials with excellent in vitro potency frequently underperform in vivo.

These pharmacokinetic and physical barriers are compounded by intracellular bacterial reservoirs. Pathogens such as Salmonella, Listeria, and intracellular forms of Staphylococcus aureus can survive within host phagocytic and epithelial cells, where they are shielded from antibiotics that penetrate cell membranes poorly or that are actively effluxed once inside the cytoplasm (Baptista et al., 2018). Standard oral and intravenous formulations achieve only limited and often unpredictable intracellular

concentrations, allowing bacteria to persist despite serum drug levels that would appear adequate on the basis of standard susceptibility testing. Furthermore, the systemic, non-targeted distribution characteristic of conventional antibiotics contributes to collateral disruption of the commensal microbiome, which has itself been linked to secondary infections such as Clostridioides difficile colitis and to longer-term dysbiosis-related health consequences. Collectively, these limitations illustrate that improving antimicrobial efficacy requires not only new molecules but also delivery platforms capable of directing existing and future agents more precisely to their intended targets.

1.3 Nanotechnology as an Emerging Solution

Nanotechnology, broadly defined as the engineering of materials with at least one dimension in the 1-100 nm range, offers a set of physicochemical properties that are well suited to addressing the pharmacokinetic shortcomings of conventional antimicrobials (Mercan, Niculescu, &Grumezescu, 2022). Nanocarriers can be engineered to encapsulate hydrophobic or unstable drugs, protect payloads from enzymatic degradation, prolong circulation time, and passively or actively accumulate at sites of infection or inflammation through mechanisms analogous to the enhanced permeability and retention effect described in oncology. In addition, several nanomaterial classes-most notably silver, zinc oxide, and other metal or metal-oxide nanoparticles-possess intrinsic antibacterial activity, meaning the carrier itself can contribute to, rather than merely transport, the therapeutic effect (Sanchez-Lopez et al., 2020). Surface functionalization further allows nanocarriers to be decorated with targeting ligands, stimuli-responsive linkers, or cell membrane coatings that improve selectivity for bacterial cells over host tissue and enable triggered release specifically within the infected microenvironment (Geng et al., 2021). Because nanocarriers can also co-deliver two or more agents-for example, an antibiotic together with an efflux-pump inhibitor or a biofilm-dispersing enzyme-they provide a platform for combination therapy that is difficult to achieve with free drugs administered separately.

The diversity of nanocarrier chemistries now available allows delivery systems to be tailored to the specific pharmacological challenge presented by a given antimicrobial agent and infection type. Hydrophilic aminoglycosides, for example, are well suited to aqueous-core liposomal encapsulation, whereas hydrophobic agents such as rifampicin can be more readily incorporated into the lipid bilayer or a polymeric matrix (Large et al., 2021). Nanocarrier size, typically between 10 and 200 nm for systemically administered systems, can be tuned to exploit differential vascular permeability at sites of infection and inflammation, while surface charge and hydrophilicity can be adjusted to minimize opsonization and reticuloendothelial clearance, thereby extending circulation time. Because these design parameters can, in principle, be optimized independently of the chemical identity of the antimicrobial payload, nanotechnology offers a generalizable platform for improving the delivery of both existing antibiotics and newer classes of agents, including antimicrobial peptides and bacteriophage-derived enzymes, for which conventional formulation approaches are often inadequate (Mercan et al., 2022).

2. Literature Review

The following sections summarize the peer-reviewed literature on the four major classes of nanotechnology-based antimicrobial drug delivery systems reported between 2015 and

2022. For each class, the underlying design rationale is described first, followed by representative experimental findings that illustrate how nanocarrier engineering translates into improved antimicrobial performance.

Across all four thematic categories, a common analytical framework can be applied when evaluating reported efficacy: the minimum inhibitory and minimum bactericidal concentrations of the nanocarrier-delivered agent relative to the free drug, the extent of biofilm biomass reduction where applicable, in vivo bacterial burden reduction in relevant infection models, and any accompanying toxicity data from cell culture or animal studies. Applying this framework consistently while reading the subsections below helps to contextualize why some nanocarrier platforms are considered closer to clinical readiness than others, and highlights recurring gaps-such as the comparative scarcity of long-term in vivo toxicity and resistance-selection data-that are revisited later in this review.

2.1 Metallic and Metal-Oxide Nanoparticle-Based Delivery Systems

Metallic and metal-oxide nanoparticles, particularly those composed of silver (Ag), zinc oxide (ZnO), copper oxide (CuO), titanium dioxide (TiO2), and gold (Au), represent the most extensively studied class of antimicrobial nanomaterials. Their appeal lies in a dual mode of action: the nanoparticle itself exerts intrinsic antibacterial activity through ion release, reactive oxygen species (ROS) generation, and direct membrane disruption, while its surface can simultaneously be loaded with a conventional antibiotic to achieve a synergistic effect (Dakal, Kumar, Majumdar, & Yadav, 2016). Silver nanoparticles (AgNPs) have been the most widely characterized, with proposed mechanisms including the release of Ag+ ions that bind thiol groups in bacterial enzymes, disruption of the electron transport chain, induction of oxidative stress, and interference with DNA replication (Qing et al., 2018; Mikhailova, 2020). Green synthesis routes using plant extracts or microbial biomass have gained popularity because they reduce reliance on hazardous reducing agents and can yield nanoparticles with additional anti-biofilm and anti-quorum-sensing properties (Mikhailov & Mikhailova, 2019; Shanmuganathan et al., 2019).

A recurring theme in this literature is the demonstration that AgNPs retain or enhance antibacterial potency against multidrug-resistant clinical isolates for which conventional antibiotics have failed. Cavassin et al. (2015) compared several in vitro susceptibility testing methods for AgNPs against MDR bacteria and found consistent activity against both Gram-positive and Gram-negative pathogens, although absolute minimum inhibitory concentration (MIC) values varied with assay methodology. Oves et al. (2018) synthesized AgNPs using a plant-derived reducing agent and reported both antimicrobial and anticancer activity, underscoring the multifunctionality of biogenic nanoparticles. Beyond silver, zinc oxide and copper oxide nanoparticles have shown comparable or complementary mechanisms, often with lower production costs and favorable safety profiles at controlled concentrations (Sanchez-Lopez et al., 2020). A key translational advance has been the conjugation of metal nanoparticles with existing antibiotics or targeting peptides to achieve site-specific delivery; for example, orthopedic implant coatings incorporating AgNPs have been optimized to balance antibacterial efficacy against local cytotoxicity (Qing et al., 2018). Table 1 summarizes the principal

antibacterial mechanisms attributed to different metal and metal-oxide nanoparticle types, and Table 2 presents representative experimental studies from the reviewed literature.

Table 1. Principal metal and metal-oxide nanoparticles used in antimicrobial delivery and their proposed mechanisms of action.

Nanoparticle Type	Primary Antibacterial Mechanism	Typical Size Range (nm)	Representative Reference
Silver (Ag)	Ag+ ion release, ROS generation, membrane and DNA disruption, enzyme inactivation	5-50	Dakal et al. (2016)
Zinc oxide (ZnO)	ROS-mediated oxidative stress, Zn2+ release, membrane depolarization	20-80	Sanchez-Lopez et al. (2020)
Copper oxide (CuO)	Cu2+ release, Fenton-type ROS generation, protein denaturation	10-60	Sanchez-Lopez et al. (2020)
Gold (Au)	Membrane binding, photothermal effect (with irradiation), carrier for functional ligands	10-100	Wang, Hu, & Shao (2017)
Titanium dioxide (TiO2)	Photocatalytic ROS generation under UV/visible light	20-100	Wang, Hu, & Shao (2017)

Synthesis route has emerged as an important determinant of both antibacterial efficacy and biocompatibility for metallic nanoparticles. Chemical reduction methods offer precise control over particle size and monodispersity but often require toxic reducing agents such as sodium borohydride, residues of which can complicate downstream biological safety assessment. Green or biogenic synthesis, using plant extracts, fungal biomass, or bacterial culture supernatants as reducing and capping agents, has therefore gained substantial attention as a more biocompatible alternative, with the added benefit that phytochemicals adsorbed onto the nanoparticle surface can themselves contribute anti-biofilm and antioxidant activity (Okaiyeto, Omotuyi,

&Oguntibeju, 2022). Nonetheless, batch-to-batch variability in plant extract composition remains a practical obstacle to the reproducible manufacture of biogenic nanoparticles at pharmaceutical-grade quality, underscoring the continued need for standardized synthesis and characterization protocols in this subfield.

Table 2. Representative experimental studies of metallic nanoparticle-based antimicrobial delivery systems (2015-2021).

Study (Author, Year)	Nanoparticle System	Target Pathogen(s)	Key Reported Outcome
Cavassin et al. (2015)	Biosynthesized AgNPs	MDR Gram-positive and Gram-negative isolates	Consistent antibacterial activity across multiple susceptibility assays
Oves et al. (2018)	Phoenix dactylifera-derived AgNPs	Multiple bacterial and cancer cell lines	Dual antimicrobial and anticancer activity reported
Shanmuganathan et al. (2019)	Biomedical AgNPs (review synthesis)	Broad-spectrum bacteria	Confirmed suitability of AgNPs for biomedical antimicrobial applications
Qing et al. (2018)	AgNP-coated orthopedic implant surfaces	Implant-associated pathogens	Optimized coatings balanced antibacterial efficacy with host cell safety
Almatroudi et al. (2020)	Nigella sativa-derived AgNPs	Biofilm-forming bacteria	Demonstrated antibacterial, anti-biofilm, and anticancer activity
Urnukhsaikhan et al. (2021)	Carduus crispus-biosynthesized AgNPs	Gram-positive and Gram-negative bacteria	Biosynthesized AgNPs showed reliable antibacterial characterization

Beyond their direct antibacterial and antibiotic-carrying functions, metal nanoparticles have also been investigated as diagnostic-therapeutic (theranostic) platforms, in which the intrinsic optical or magnetic properties of the nanoparticle-such as the localized surface plasmon resonance of gold nanoparticles-are exploited simultaneously for infection imaging and photothermal bacterial killing (Wang, Hu, & Shao, 2017). This convergence of diagnostic and therapeutic function is particularly attractive for point-of-care management of localized infections, such as infected wounds or device-associated infections, where rapid pathogen detection and

immediate on-site treatment could shorten the time to effective therapy relative to conventional culture-based diagnostic workflows that may take 24 to 72 hours to yield actionable results.

2.2 Polymeric Nanoparticle-Based Delivery Systems

Polymeric nanoparticles constructed from biodegradable and biocompatible polymers, most notably poly(lactic-co-glycolic acid) (PLGA), chitosan, and polycaprolactone, constitute a second major class of antimicrobial nanocarriers. Unlike metal nanoparticles, polymeric systems are generally used as inert or bioactive carriers that encapsulate a conventional antibiotic within a solid matrix, offering controlled and sustained drug release, protection from enzymatic degradation, and tunable surface chemistry for targeting (Shakya et al., 2021). PLGA has been particularly favored because it is approved by regulatory agencies including the U.S. Food and Drug Administration for various parenteral applications, degrades into biocompatible lactic and glycolic acid monomers, and allows drug release kinetics to be tuned by adjusting the lactide-to-glycolide ratio and molecular weight (Ding & Zhu, 2018; El-Hammadi & Arias, 2022). Several studies have demonstrated that encapsulating antibiotics within PLGA nanoparticles improves antibacterial performance relative to the free drug. Da Costa et al. (2020) encapsulated red propolis extract in polymeric nanoparticles and reported enhanced destruction of pathogenic biofilms compared with unencapsulated extract. Chitosan-based systems, meanwhile, benefit from the polymer's inherent cationic charge, which promotes electrostatic interaction with the negatively charged bacterial cell wall and can itself contribute antibacterial activity independent of any loaded drug (Kurczewska, 2021). Kuang et al. (2021) engineered chitosan nanoparticles combined with bioactive peptides as a food biopreservative, demonstrating efficacy against foodborne Escherichia coli O157 while limiting epithelial barrier dysfunction, illustrating the versatility of polymeric platforms beyond clinical therapeutics. Surface functionalization strategies, such as PEGylation to reduce opsonization and prolong circulation, or conjugation with targeting peptides, have further improved the pharmacokinetic profile of PLGA and chitosan nanoparticles (El-Hammadi & Arias, 2022; Mercan et al., 2022). Table 3 summarizes the principal polymeric carrier types and their functional characteristics, while Table 4 lists representative experimental outcomes.

Table 3. Polymeric nanocarrier platforms used in antimicrobial drug delivery.

Polymer System	Key Physicochemical Properties	Typical Loading Strategy	Representative Reference
PLGA	Biodegradable, FDA-approved, tunable release via lactide:glycolide ratio	Nanoprecipitation, emulsion-solvent evaporation	Ding & Zhu (2018)
Chitosan	Cationic, mucoadhesive, inherent antibacterial activity	Ionic gelation with polyanions (e.g., TPP)	Kurczewska (2021)
PLGA-	Combines	Coating or	El-

Polymer System	Key Physicochemical Properties	Typical Loading Strategy	Representative Reference
chitosan hybrid	controlled release with cationic surface functionality	co-precipitation	Hammadi & Arias (2022)
Polycaprolactone (PCL)	Slow biodegradation, hydrophobic, suited to long-term release	Solvent displacement, electrospinning	Patra et al. (2018)
Dendrimers (e.g., PAMAM)	Highly branched, tunable surface groups, high drug-loading capacity	Surface conjugation or encapsulation	Mercan et al. (2022)

Table 4. Representative experimental studies of polymeric nanoparticle-based antimicrobial delivery systems.

Study (Author, Year)	Polymer/Carrier	Loaded Agent	Key Reported Outcome
Da Costa et al. (2020)	Polymeric nanoparticles	Red propolis extract	Enhanced destruction of pathogenic biofilms versus free extract
Kuang et al. (2021)	Chitosan nanoparticles	Bioactive antimicrobial peptides	Effective against foodborne E. coli O157 with reduced epithelial toxicity
El-Hammadi & Arias (2022)	Surface-functionalized PLGA	Various antimicrobial payloads (review)	Surface modification improved targeting and circulation time
Shakya et al. (2021)	PLGA nanoparticles (review)	Multiple antibiotics	Confirmed broad applicability of PLGA across infection types
Kurczewska	Chitosan nanoparticles	Various therapeuti	Highlighted

Study (Author, Year)	Polymer/Carrier	Loaded Agent	Key Reported Outcome
(2021)	(review)	c agents	tunable parameters affecting delivery efficiency

An important practical consideration for polymeric systems is the balance between drug loading capacity and controlled-release kinetics. Higher loading is generally desirable to reduce the total nanoparticle dose required for therapeutic effect, yet excessively high drug content can compromise matrix integrity and lead to premature burst release, undermining the sustained-release advantage that motivated encapsulation in the first place (Shakya et al., 2021). Formulation scientists have addressed this trade-off through core-shell architectures, in which a drug-rich core is surrounded by a rate-limiting polymer shell, and through blending of polymers with differing degradation rates to fine-tune release profiles. Surface PEGylation, while beneficial for prolonging circulation time, can also reduce cellular uptake and bacterial adhesion if not carefully balanced with targeting ligand density, illustrating that polymeric nanoparticle design inherently requires multi-parameter optimization rather than the adjustment of any single variable in isolation (Mercan et al., 2022).

Route of administration also shapes polymeric nanoparticle design choices. Oral delivery of antibiotic-loaded polymeric nanoparticles must contend with the harsh gastric environment, mucus barrier, and first-pass metabolism, motivating the use of mucoadhesive coatings such as chitosan or enteric polymers that protect the nanoparticle through the stomach and promote intestinal absorption (Choukaife et al., 2022). Topical and wound-directed applications, by contrast, can exploit polymeric nanoparticles embedded within hydrogel or nanofiber dressings that provide sustained local antibiotic release directly at the wound bed while simultaneously serving a physical barrier function against further contamination, illustrating how the same underlying polymeric nanoparticle technology can be adapted to markedly different clinical delivery contexts depending on formulation strategy.

2.3 Lipid-Based Nanocarriers for Antimicrobial Delivery

Lipid-based nanocarriers, including liposomes, solid lipid nanoparticles (SLNs), nanostructured lipid carriers (NLCs), and lyotropic liquid crystalline nanoparticles (LCNPs), form a third major delivery platform, distinguished by their close structural resemblance to biological membranes. Liposomes are spherical vesicles composed of one or more phospholipid bilayers enclosing an aqueous core, a structure that allows simultaneous encapsulation of hydrophilic drugs within the core and lipophilic drugs within the bilayer (Bozzuto & Molinari, 2015). Because their composition can closely mimic host or bacterial membranes, liposomes are capable of fusing with bacterial cell envelopes, thereby delivering high local concentrations of antibiotic directly to the target site while reducing systemic exposure (Large, Abdelmessih, Fink, & Auguste, 2021).

Liposomal encapsulation has been particularly valuable for aminoglycosides and other antibiotics with narrow therapeutic windows, since encapsulation can reduce nephrotoxicity

and ototoxicity while preserving or enhancing antibacterial potency. Combination formulations that co-encapsulate an antibiotic with a biofilm-disrupting agent, such as DNase or alginate lyase, have shown particular promise against Pseudomonas aeruginosa biofilms characteristic of chronic lung infections. Solid lipid nanoparticles and nanostructured lipid carriers offer complementary advantages, including greater physical stability during storage and the ability to be produced without organic solvents, which simplifies scale-up (Bruna, Maldonado-Bravo, Jara, & Caro, 2021, in the context of comparative nanocarrier stability). Chitosan-modified liposomes have been shown to improve encapsulation efficiency and storage stability relative to unmodified liposomes, while also conferring additional bacteriostatic effects through membrane interaction (Kuang et al., 2021). Table 5 outlines the comparative characteristics of the principal lipid-based nanocarrier types, and Table 6 summarizes representative experimental findings.

Table 5. Comparative features of lipid-based antimicrobial nanocarriers.

Lipid Carrier Type	Structural Features	Advantages	Representative Reference
Liposomes	Phospholipid bilayer enclosing aqueous core	Membrane fusion with bacteria; dual hydrophilic/lipophilic loading	Bozzuto & Molinari (2015)
Solid lipid nanoparticles	Solid lipid matrix stabilized by surfactant	High physical stability; solvent-free production	Large et al. (2021)
Nanostructured lipid carriers (NLCs)	Blend of solid and liquid lipids	Higher drug loading than SLNs; reduced drug expulsion	Large et al. (2021)
Lyotropic liquid crystalline NPs (LCNPs)	Non-lamellar cubic/hexagonal mesophases	Enhanced biofilm penetration; sustained release	Large et al. (2021)

Table 6. Representative experimental and review studies of lipid-based antimicrobial delivery systems.

Study (Author, Year)	Lipid System	Loaded/Combined Agent	Key Reported Outcome
Bozzuto & Molinari (2015)	Conventional liposomes (review)	Multiple drug classes	Confirmed liposomes as versatile, biocompatible nanomedical carriers
Large et al. (2021)	Liposome formulation variants	Review of clinical applications	Composition strongly determines pharmacokinetics and clinical

Study (Author, Year)	Lipid System	Loaded/Combined Agent	Key Reported Outcome
			performance
Kuang et al. (2021)	Chitosan-modified liposomes	Antimicrobial peptides	Improved encapsulation efficiency and storage stability

Beyond systemic administration, lipid-based nanocarriers have shown particular promise for pulmonary delivery, where nebulized liposomal antibiotic formulations can achieve high local concentrations within the airway lumen while limiting systemic absorption and associated toxicity, an approach of particular relevance to chronic P. aeruginosa infection in cystic fibrosis (Large et al., 2021). Manufacturing considerations also differ meaningfully across lipid carrier subtypes: conventional liposomes generally require multi-step processes such as thin-film hydration followed by extrusion or sonication to achieve a uniform vesicle size, which can complicate large-scale, cost-effective production, whereas solid lipid nanoparticles and nanostructured lipid carriers can often be produced using simpler high-pressure homogenization methods more amenable to industrial scale-up. Long-term physical stability, including resistance to vesicle aggregation, drug leakage, and lipid oxidation during storage, remains an active area of formulation research, with strategies such as lyophilization and cryoprotectant optimization increasingly used to extend shelf life without compromising encapsulation efficiency upon reconstitution.

Regulatory familiarity represents a distinct advantage for lipid-based systems relative to some other nanocarrier classes: several liposomal drug products, most notably in the oncology and antifungal domains, have already achieved marketing approval, meaning that the manufacturing, quality control, and regulatory pathways for liposomal products are comparatively well established relative to novel metallic or hybrid nanomaterials (Large et al., 2021). This existing regulatory precedent has encouraged several research groups to prioritize liposomal reformulation of existing antibiotics-rather than development of entirely new antimicrobial chemical entities-as a nearer-term strategy for improving the treatment of resistant and biofilm-associated infections, since the active pharmaceutical ingredient itself has typically already undergone extensive human safety characterization in its free-drug form.

2.4 Stimuli-Responsive and Biofilm-Targeted Nanoplatforms

A distinct and rapidly growing area of the literature focuses on nanocarriers engineered to respond to specific stimuli present within the infected microenvironment, thereby achieving spatially and temporally controlled drug release. Because bacterial infection sites often differ from healthy tissue in local pH, enzyme activity, redox potential, or temperature, nanocarriers can be designed with linkers or shells that degrade selectively under these conditions, releasing their payload preferentially where it is needed (Geng et al., 2021). Enzyme-responsive systems exploit bacterial toxins, lipases, or hyaluronidases to trigger release; for example, gentamicin-loaded mesoporous silica nanoparticles coated with a toxin-responsive lipid bilayer and a targeting peptide have been shown to release their antibiotic cargo specifically at the site of Staphylococcus aureus infection, both in vitro and in vivo (Geng et al., 2021).

Biofilm-targeted strategies represent a particularly important subclass, given that biofilm-associated infections account for a substantial proportion of chronic and device-related infections that fail conventional therapy. Nanocarriers can be functionalized with biofilm-penetrating peptides, matrix-degrading enzymes, or quorum-sensing inhibitors to overcome the diffusion barrier presented by the EPS matrix (Elbourne et al., 2019). Combination platforms that pair an antibiotic with an anti-biofilm adjuvant within a single nanocarrier have shown superior biofilm eradication compared with either agent delivered alone, reflecting a synergistic rather than purely additive effect. External stimuli, including magnetic fields, near-infrared light, and ultrasound, have also been used to trigger drug release or to generate localized hyperthermia that disrupts biofilm architecture, offering clinicians a further degree of spatial and temporal control over therapy (Wang, Hu, & Shao, 2017). Table 7 summarizes the principal stimuli-responsive and biofilm-targeting strategies identified in the reviewed literature.

Table 7. Stimuli-responsive and biofilm-targeted nanocarrier strategies for enhanced antimicrobial delivery.

Trigger/Targeting Strategy	Mechanism of Action	Primary Application	Representative Reference
pH-responsive coatings	Protonation/degradation of pH-sensitive linkers at acidic infection sites	Localized release in infected/inflamed tissue	Geng et al. (2021)
Enzyme-responsive shells	Bacterial toxin/lipase-triggered degradation of lipid or polymer coating	Intracellular and surface-associated infection	Geng et al. (2021)
Quorum-sensing inhibitor co-delivery	Disruption of bacterial cell-cell signaling reducing biofilm formation	Prevention and dispersal of biofilms	Elbourne et al. (2019)
Matrix-degrading enzyme co-delivery (e.g., DNase)	Enzymatic breakdown of EPS matrix enhancing antibiotic penetration	Chronic biofilm infections (e.g., P. aeruginosa)	Elbourne et al. (2019)
Magnetic/photothermal external triggers	Localized heating or field-guided accumulation disrupting biofilm structure	Device-associated and deep-tissue infection	Wang, Hu, & Shao (2017)

A further refinement within this category involves dual- and multi-stimuli-responsive systems designed to require the simultaneous presence of two or more infection-associated cues, such as both acidic pH and elevated enzyme activity, before releasing their payload. This

"AND-gate" logic reduces the likelihood of premature or off-target drug release in healthy tissue that may transiently exhibit only one of the relevant conditions, thereby improving the overall selectivity of therapy (Geng et al., 2021). Active targeting approaches, in which nanocarrier surfaces are functionalized with antibodies, aptamers, or bacteria-specific peptides recognizing conserved surface antigens, provide a complementary route to selectivity that does not depend on the local microenvironment at all, and several studies have combined active targeting ligands with stimuli-responsive release to achieve both accumulation at, and controlled release within, the infected site. Reported outcomes across this literature consistently indicate that stimuli-responsive and biofilm-targeted platforms achieve greater reductions in bacterial burden and biofilm biomass at equivalent antibiotic doses compared with non-responsive nanocarriers or free drug, supporting their continued development as a strategy for improving therapeutic efficacy.

3. Mechanisms Underlying Enhanced Therapeutic Efficacy

The therapeutic advantages of nanotechnology-based antimicrobial delivery systems arise from several interrelated mechanisms rather than any single property. First, encapsulation improves the effective solubility and stability of poorly soluble or labile antimicrobial agents, allowing higher local drug concentrations to be achieved at the infection site without a corresponding increase in systemic exposure (Patra et al., 2018). Second, many nanocarriers exploit electrostatic or hydrophobic interactions with the bacterial cell envelope to achieve preferential accumulation at the target site; cationic chitosan-based and lipid nanocarriers, for instance, are attracted to the net-negative charge of bacterial membranes, increasing local drug delivery relative to host cells (Kurczewska, 2021).

Third, controlled and sustained release kinetics reduce the frequency of sub-inhibitory drug exposure that would otherwise favor the selection of resistant subpopulations, while simultaneously maintaining antimicrobial concentrations above the minimum inhibitory concentration for longer periods (Ding & Zhu, 2018). Fourth, several nanocarrier classes actively disrupt or penetrate the biofilm EPS matrix, either through direct physical disruption, enzymatic co-delivery, or quorum-sensing interference, thereby restoring antibiotic access to embedded bacterial cells that would otherwise be shielded from therapy (Elbourne et al., 2019). Fifth, metal and metal-oxide nanoparticles frequently exert a multi-target mechanism of action-simultaneously damaging the cell membrane, generating reactive oxygen species, and interfering with nucleic acid replication-that is intrinsically more difficult for bacteria to evade through a single resistance mutation compared with conventional antibiotics that typically act on one molecular target (Dakal et al., 2016). Finally, the capacity of nanocarriers to co-deliver two or more agents in fixed, spatially co-localized ratios enables genuine synergistic combination therapy, an effect that is difficult to reproduce when agents are administered as separate free-drug formulations (Gupta et al., 2019). Together, these mechanisms explain why nanocarrier-delivered antimicrobials frequently demonstrate lower effective MIC values, improved bactericidal kinetics, and superior biofilm eradication relative to free-drug controls across the reviewed literature.

An additional mechanistic consideration relates to the pharmacodynamic index most predictive of clinical efficacy for a given antibiotic class. For concentration-dependent agents such as

aminoglycosides, nanocarrier formulations that achieve a high peak concentration at the infection site are pharmacodynamically favorable, whereas for time-dependent agents such as beta-lactams, sustained-release nanocarrier platforms that maintain drug concentration above the minimum inhibitory concentration for a greater proportion of the dosing interval are more appropriate (Patra et al., 2018). This suggests that nanocarrier design should not be approached generically but should instead be matched to the specific pharmacodynamic profile of the antimicrobial being delivered. Moreover, because many nanocarriers alter the apparent volume of distribution and elimination half-life of their payload, formal pharmacokinetic-pharmacodynamic modeling of nanocarrier-encapsulated antibiotics is increasingly recognized as necessary to correctly translate in vitro potency gains into appropriately designed in vivo dosing regimens, rather than assuming that free-drug dosing intervals remain valid once the drug has been reformulated.

4. Challenges, Toxicity, and Regulatory Considerations

Despite substantial preclinical promise, several challenges continue to limit the clinical translation of nanotechnology-based antimicrobial delivery systems. Toxicological uncertainty remains a central concern: the same physicochemical properties that confer antibacterial activity to metal nanoparticles-small size, high surface reactivity, and ROS-generating capacity-can also produce cytotoxic, genotoxic, or immunomodulatory effects in host tissue if concentrations are not carefully controlled (Wang, Hu, & Shao, 2017). Polymeric nanoparticles are generally regarded as safer, yet excipients and stabilizers used during formulation, such as certain surfactants incorporated to prevent particle aggregation, have themselves been shown to increase cytotoxicity in macrophage models, indicating that toxicity must be evaluated for the complete formulation rather than the core material alone (Shakya et al., 2021).

A second challenge concerns manufacturing reproducibility and scale-up. Many of the nanocarriers described in the literature are produced at laboratory scale using techniques such as nanoprecipitation, emulsion-solvent evaporation, or thin-film hydration, which can be difficult to reproduce consistently at the batch sizes required for clinical and commercial manufacturing. Variability in particle size, surface charge, and drug loading between batches can translate into inconsistent pharmacokinetics and therapeutic outcomes, complicating regulatory approval (Mercan et al., 2022). Regulatory frameworks for nanomedicines remain less standardized than those for conventional small-molecule drugs; agencies generally require additional characterization of particle size distribution, surface chemistry, and long-term stability, as well as nanomaterial-specific toxicology and environmental fate data, extending development timelines and cost (El-Hammadi & Arias, 2022). A further concern specific to antimicrobial nanomedicine is the theoretical possibility that sub-lethal or prolonged exposure to metal nanoparticles could itself drive the emergence of nanoparticle-tolerant bacterial phenotypes, an area that remains comparatively under-studied relative to conventional antibiotic resistance (Theuretzbacher& Piddock, 2019). Finally, cost-effectiveness relative to conventional antibiotics, together with the need for robust clinical trial data specifically in infectious disease indications rather than the more extensively studied oncology setting, represents an ongoing barrier to widespread adoption.

Environmental and ecological considerations add a further layer of complexity that is sometimes overlooked in the preclinical antimicrobial nanomedicine literature. Metal nanoparticles released into wastewater following clinical or agricultural use can persist in the environment and exert selective pressure on environmental bacterial populations, raising the theoretical concern that widespread nanoparticle deployment could itself contribute to the broader resistome in ways that are only beginning to be characterized (Wang, Hu, & Shao, 2017). Life-cycle assessment of nanomedicine manufacturing, including solvent use, energy consumption, and disposal of nanomaterial-containing waste, is rarely reported alongside efficacy data but represents an important component of the overall sustainability and regulatory acceptability of these technologies. Addressing these gaps will likely require closer collaboration between pharmaceutical developers, environmental scientists, and regulators than has historically characterized antimicrobial drug development.

Intellectual property and market fragmentation present additional, less frequently discussed barriers to translation. Because antimicrobial nanocarrier formulations often combine a generic, off-patent active pharmaceutical ingredient with a novel delivery platform, the resulting intellectual property position can be more complex to establish and defend than for a wholly novel small-molecule antibiotic, potentially reducing commercial incentive for the substantial investment required to complete clinical development (El-Hammadi & Arias, 2022). At the same time, the relatively small and fragmented market for any single resistant-pathogen indication, compared with chronic disease markets such as oncology or cardiometabolic disease, further limits the commercial attractiveness of antimicrobial nanomedicine development to large pharmaceutical companies, leaving much of the field reliant on academic research funding, small biotechnology companies, and public health-oriented grant mechanisms that may lack the resources to complete the full development pathway independently.

5. Strategies to Improve Therapeutic Efficacy and Future Perspectives

Building on the mechanistic and translational evidence reviewed above, several converging strategies appear well positioned to further improve the therapeutic efficacy of nanotechnology-based antimicrobial delivery systems. Biomimetic approaches, in which nanocarriers are coated with bacterial or host cell membrane fragments, represent one promising direction; such coatings can improve immune evasion, prolong circulation time, and, in the case of bacterial membrane-derived coatings, enable homotypic targeting back to the pathogen of origin or its toxins (Geng et al., 2021). Hybrid nanocomposites that combine two or more carrier classes-for example, a metal nanoparticle core encapsulated within a polymeric or lipid shell-offer the opportunity to merge the intrinsic antibacterial activity of metals with the favorable pharmacokinetics and controlled-release profile of polymeric or lipid carriers, potentially reducing the effective dose of metal required and thereby mitigating toxicity concerns (Sanchez-Lopez et al., 2020).

Conjugation of nanocarriers with antimicrobial peptides (AMPs) constitutes a second important strategy. AMPs offer a broad spectrum of activity and a low propensity for resistance development, but their clinical use has historically been limited by proteolytic instability, salt sensitivity, and toxicity at systemic concentrations; nanocarrier

delivery can protect AMPs from degradation, concentrate them locally, and reduce the systemic exposure responsible for off-target toxicity (a growing area of nanoparticle-AMP delivery research). Similarly, co-delivery platforms that combine an antibiotic with an efflux-pump inhibitor, a beta-lactamase inhibitor, or a quorum-sensing inhibitor within a single nanocarrier can restore susceptibility in otherwise resistant strains, offering an alternative to the development of entirely new antibiotic scaffolds (Elbourne et al., 2019).

Advances in computational and artificial intelligence-assisted design also hold considerable promise for accelerating the optimization of nanocarrier formulations. Machine learning models trained on existing formulation and outcome data can, in principle, predict optimal particle size, surface charge, and release kinetics for a given pathogen and infection site, reducing the empirical trial-and-error burden that currently characterizes much of the field (Muteeb et al., 2021). Finally, greater standardization of in vitro and in vivo testing protocols-including harmonized biofilm models, consistent reporting of physicochemical characterization, and inclusion of long-term toxicology and resistance-selection studies-will be essential to enable meaningful cross-study comparison and to build the regulatory evidence base required for clinical translation. Taken together, these converging strategies suggest that nanotechnology-enabled antimicrobial delivery is likely to move from a predominantly preclinical research area toward an increasingly clinically relevant therapeutic modality over the coming decade.

Patient- and infection-specific personalization represents a further frontier for improving therapeutic efficacy. Rapid diagnostic techniques capable of identifying the causative pathogen and its resistance profile directly from clinical samples could, in principle, be paired with a modular nanocarrier platform in which the targeting ligand, release trigger, and antimicrobial payload are selected or adjusted according to the specific infection being treated, moving away from empirical broad-spectrum therapy toward a more precision-medicine-oriented approach to infectious disease management (Muteeb et al., 2021). Public-private partnerships and dedicated funding mechanisms, similar to those that have supported oncology nanomedicine development, will likely be required to carry promising antimicrobial nanocarrier candidates through the costly later stages of preclinical development and into early-phase clinical trials, given that the commercial incentives for antibiotic development more broadly remain comparatively weak. Continued investment in this translational pipeline, alongside the scientific and regulatory advances discussed above, will be critical determinants of whether the substantial preclinical promise documented in the literature reviewed here is ultimately realized in clinical practice.

6. Conclusion

Nanotechnology-based drug delivery systems offer a versatile and mechanistically diverse toolkit for addressing the pharmacokinetic and biofilm-related limitations that undermine conventional antimicrobial therapy. Across the metallic, polymeric, lipid-based, and stimuli-responsive platforms reviewed here, a consistent pattern emerges: nanocarrier-mediated delivery improves local drug concentration, sustains or triggers release in a controlled manner, and, in several cases, actively disrupts the biofilm barrier that shields resistant bacteria from therapy. These properties translate into measurable

improvements in antibacterial potency and, in many reported studies, reduced toxicity relative to free-drug controls. Nonetheless, unresolved challenges relating to nanomaterial toxicity, manufacturing reproducibility, and regulatory standardization mean that clinical translation remains at a comparatively early stage relative to the extensive preclinical evidence base. Continued interdisciplinary work spanning materials science, microbiology, pharmacology, and regulatory science-together with the emerging strategies of biomimetic design, hybrid nanocomposites, peptide conjugation, and computationally guided formulation-will be necessary to fully realize the potential of nanotechnology to improve the therapeutic efficacy of antimicrobial therapy and to help address the growing global burden of antimicrobial resistance.

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