

Antibacterial Nanoparticles for Biofilm Control in Medical and Food Industries: A Comprehensive Review

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Abstract

Bacterial biofilms are self-assembled, multicellular microbial communities encapsulated within a self-produced matrix of extracellular polymeric substances (EPS). These complex architectures present critical public health hazards and economic burdens across biomedical devices, chronic wound management, and food processing lines due to their extreme resistance to standard antibiotics, sanitizers, and host immune clearing mechanisms. Conventional small-molecule biocides fail to effectively cross the protective EPS shield, promoting the selection of multidrug-resistant (MDR) phenotypes.

Nanotechnology offers a transformative paradigm for anti-biofilm intervention. This comprehensive review systematically evaluates recent breakthroughs in engineered antibacterial nanoparticles (NPs) encompassing metallic, metal oxide, organic polymeric, and lipid-based nanosystems designed to prevent, disrupt, and eradicate biofilms. We provide an in-depth analysis of nano-mediated mechanistic pathways, highlighting shape-dependent EPS diffusion kinetics, dark-catalytic and reactive oxygen species (ROS)-independent degradation pathways in light-restricted industrial lines, and micro-environment-triggered targeted drug release.

Furthermore, this review introduces dedicated sections on bacterial adaptation mechanisms against nanomaterials (e.g., heavy-metal efflux pumps, *Sil* gene clusters, and extracellular sequestration) and food contact material (FCM) regulations, nano-migration limits, and organoleptic considerations. Commercialized products (e.g., Acticoat®, SilvaSorb®, Nanocid®) and standardized quantitative evaluation protocols (including ASTM E2799 MBEC assays and CLSM imaging) are systematically surveyed. Finally, key translational bottlenecks including human cytotoxicity, ecotoxicity, manufacturing scalability, and evolving regulatory frameworks are critically examined alongside future directions in smart theranostic and CRISPR-Cas nano-deliveries.

Keywords: Biofilms; Nanoparticles; Antimicrobial Resistance; Food Safety; Active Packaging; Nano-Migration; Silver Nanoparticles; Chitosan; Smart Nanosystems

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1. Introduction

The transition of bacteria from free-swimming, planktonic entities to surface-attached, organized multicellular communities—known as biofilms—is a primary survival strategy across diverse environments. Biofilms are encapsulated within a self-synthesized matrix composed of extracellular polymeric substances (EPS), including polysaccharides, structural proteins, lipids, and extracellular DNA (eDNA). This complex cross-linked network func-

tions as a physical and chemical barrier, severely restricting the diffusion of conventional antimicrobials and sheltering internal bacterial subpopulations from environmental stress and host immune defenses. Consequently, biofilm-entrenched bacteria exhibit a 100- to 1000-fold increase in tolerance to standard antibiotics compared to their planktonic counterparts (Fig2). The global escalation of antimicrobial resistance (AMR) represents a major threat to public health and economic stability. According to global health metrics, AMR is associated with millions of annual

Graphical Abstract

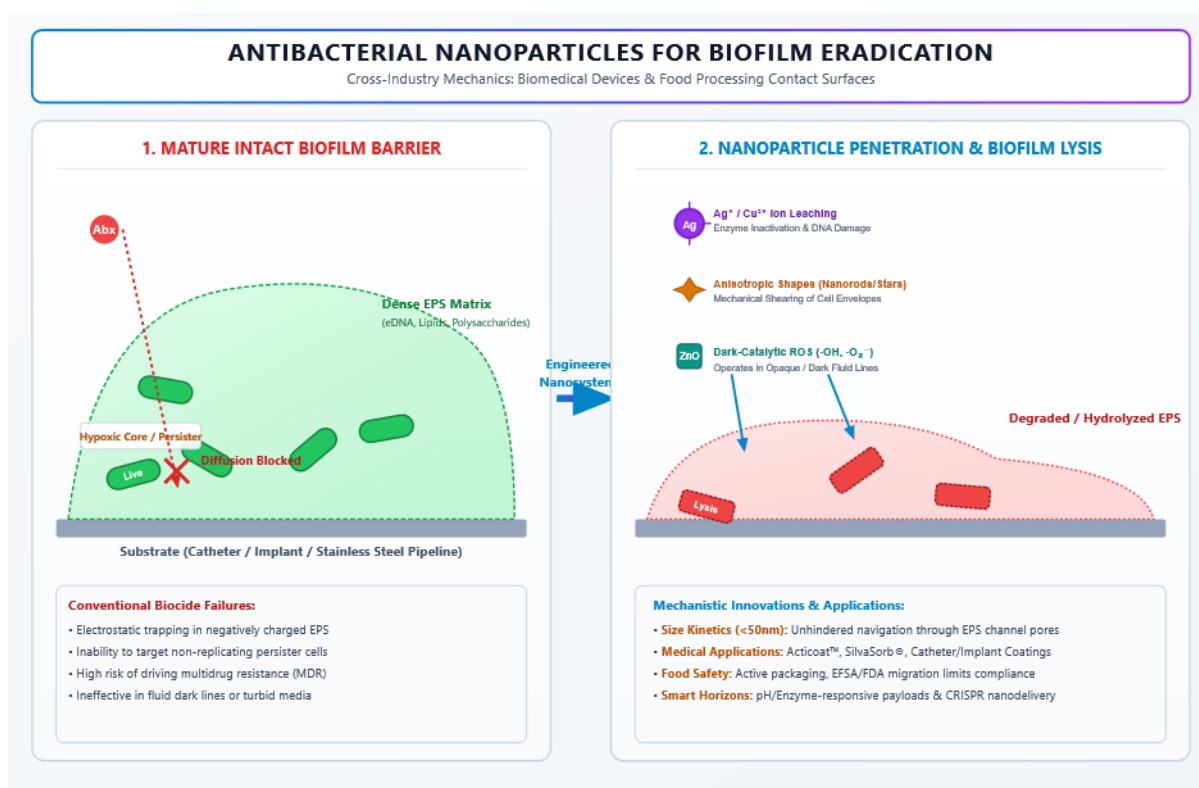


Figure 1: Mechanistic pathways of biofilm eradication by antibacterial nanoparticles. (A) Mature biofilm EPS matrix sterically and electrostatically impedes standard antibiotics, leaving persister cells in the hypoxic core intact. **(B)** Engineered nanosystems 50 nm) penetrate EPS channels to drive biofilm lysis via metallic ion leaching Cu^{2+} , mechanical envelope shearing (anisotropic nanorods/stars), and dark-catalytic ROS generation ZnO. Applications span medical device coatings and active food packaging, with emerging utility in stimulus-responsive and CRISPR nanodelivery.

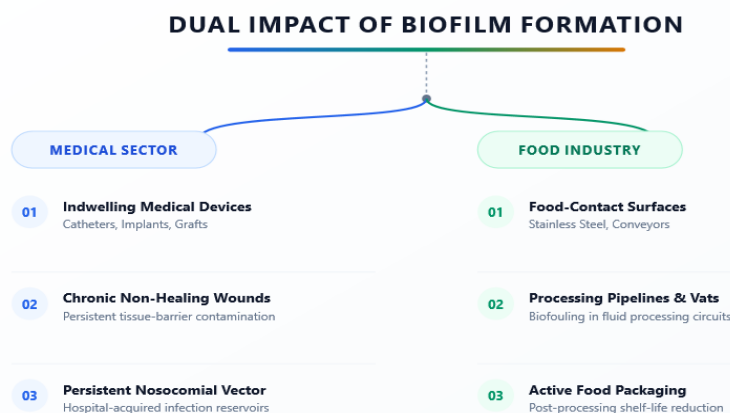


Figure 2. Comparative overview of the dual impact of biofilm formation across sectors. Highlighting key contamination sites, biofouling targets, and persistent infection vectors in both clinical healthcare environments and industrial food processing operations.

deaths, driven significantly by persistent biofilm-mediated infections that serve as hotbeds for horizontal gene transfer (HGT) and mobile resistance elements.

As traditional small-molecule antibiotics and chemical sanitizers encounter rising bacterial resistance, nanotechnology provides an adaptable toolkit to circumvent these defensive barriers. Nanoparticles (NPs), defined as materials engineered within the 1–100 nm size regime, possess unique physico-chemical properties—including high surface-area-to-

volume ratios, tailorable surface charges, anisotropic geometries, and multi-target mechanisms of action—that make spontaneous bacterial resistance development extremely difficult.

This review critically evaluates current progress in antibacterial nanotechnology for biofilm eradication across medical and food sectors, examining structural life cycles, shape-dependent penetration mechanics, dark-catalytic mechanisms, bacterial nano-resistance pathways, regulatory migration limits in food contact materials, standardized testing protocols, and future stimuli-responsive smart nanosystems.

2. Biofilm Architecture, Dynamics, and Resistance Mechanics

2.1 Biofilm Life Cycle and Matrix Composition

Biofilm assembly follows a tightly coordinated, five-stage developmental program:

1. **Reversible Attachment:** Planktonic cells approach a substrate via Brownian motion, fluid

flow, or flagellar motility. Initial surface contact relies on weak, reversible physical forces, including van der Waals forces, hydrophobic interactions, and electrostatic attraction.

2. **Irreversible Adhesion:** Bacteria deploy specialized structural appendages (such as type IV pili, curli fibers, and fimbriae) to solidify attachment, upregulating adhesin proteins and initiating preliminary EPS secretion.
3. **Microcolony Formation & EPS Synthesis:** Attached cells proliferate rapidly while secreting large volumes of EPS (exopolysaccharides, eDNA, lipopeptides, and structural proteins). Population-density signaling through Quorum Sensing (QS) triggers coordinated group behavior.
4. **Biofilm Maturation:** The matrix matures into a complex three-dimensional architecture characterized by mushroom- or tower-like structures integrated with fluid-filled interstitial channels. These channels facilitate nutrient influx and metabolic waste removal. Pronounced microenvironmental gradients form, creating distinct aerobic exterior zones and severely hypoxic or anaerobic core regions.
5. **Active Dispersion:** In response to local nutrient depletion, accumulation of toxic metabolites, or chemical triggers, bacteria secrete matrix-degrading enzymes (such as alginate lyase, dispersin B, and DNases) to hydrolyze the EPS, releasing planktonic cells to colonize new sites.

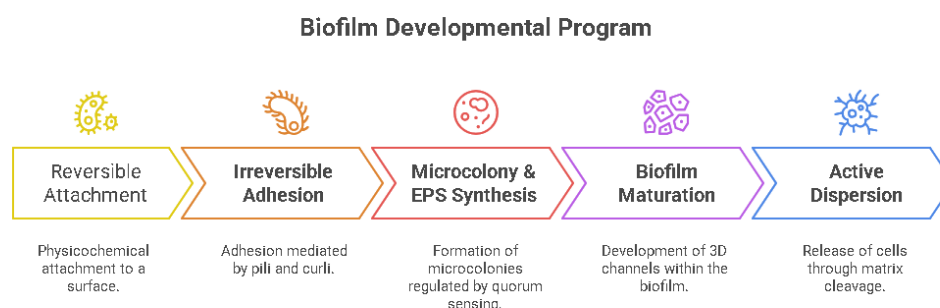


Figure3: Biofilm Developmental Program

Physicochemical Drivers of Nano-Penetration

Driver	Size & Pore Radius	Surface Charge	Geometry / Aspect Ratio
Mechanism	Sub-100 nm particles move through EPS pores (20-50 nm)	Cationic charge promotes binding; PEGylation aids deep core diffusion via neutral stealth kinetics	Anisotropic shapes (nanorods/stars) offer higher kinetic propulsion and membrane disruption rates

Figure 4: Physicochemical drivers of Nano-penetration

EPS functional groups (carboxylates, uronic acids, and phosphates) bind and sequester cationic biocides, preventing deep penetration.

Metabolic Heterogeneity & Persister Subpopulations: Steep oxygen and nutrient gradients within mature biofilms force core-dwelling cells into slow-growing or non-replicative metabolic states. Because most conventional antibiotics target active cellular processes (cell wall synthesis, protein translation, or DNA replication), these dormant *persister cells* survive high-dose antibiotic treatments and re-establish the infection once treatment ceases.

Upregulation of Efflux Systems: Embedded sessile cells frequently upregulate multidrug efflux pumps, actively extruding internal therapeutic molecules.

Enhanced Horizontal Gene Transfer (HGT): Dense cell packing within the EPS matrix increases the rate of plasmid conjugation, transfor-

mation, and transduction, accelerating the dissemination of resistance factors.

2.3 Physicochemical and Shape-Dependent Kinetics of Nanoparticle Penetration

The ability of engineered nanoparticles to penetrate the EPS matrix depends strongly on their physicochemical characteristics and geometric design(Fig4):

Size Dynamics: Pore diameters within typical EPS matrices range from 20 to 50 nm. Nanoparticles under 50 nm diffuse efficiently through interstitial fluid channels, whereas larger particles (100nm) often become trapped near the outer surface.

Surface Charge Modulation: While cationic nanoparticles bind strongly to the negatively charged outer EPS layer via electrostatic attraction, excessive positive charge can trap particles at the periphery through an "adsorption-barrier" effect.

2 Classical Mechanisms of Biofilm Antimicrobial Tolerance

The enhanced tolerance of biofilms to antimicrobial agents stems from several physical, physiological, and genetic mechanisms:

Diffusion and Charge Barriers: The highly hydrated, cross-linked EPS matrix physically retards the diffusion of large molecules. Negatively charged

Geometric & Aspect-Ratio Kinetics: Anisotropic nanoparticles—such as nanorods, nanostars, and triangular nanoplatelets—demonstrate distinct transport mechanics compared to isotropic spherical particles. High-aspect-ratio nanorods experience directional rotational diffusion that can facilitate passage through polymeric networks. Furthermore, sharp-edged geometries (e.g., nanostars or nanoplatelets) generate localized physical stress, mechanically shearing cell membranes and damaging EPS structural polymers.

3. Classification and Mechanistic Pathways of Anti-Biofilm Nanoparticles

Antibacterial nanoparticles can be categorized into inorganic (metallic and metal oxides) and organic (polymeric and lipid-based) platforms.

3.1 Inorganic Metallic and Metal Oxide Nanosystems

3.1.1 Silver (AgNPs) and Copper Nanoparticles (CuNPs)

Silver nanoparticles remain among the most widely studied inorganic antimicrobials. AgNPs release silver ions (Ag^+) upon oxidative dissolution. These free ions bind strongly to thiol, carboxyl, and phosphate groups in bacterial proteins and nucleic acids, deactivating respiratory enzymes, inhibiting DNA replication, and triggering cell death. Similarly, copper nanoparticles (CuNPs) release Cu^{2+} ions that drive Fenton-like redox reactions, generating reactive species that disrupt cell wall integrity and induce double-strand DNA breaks (Fig5).

Table1: Classification and Mechanistic Pathways of Anti-Biofilm Nanoparticles

Nanoparticle Category	Representative Examples	Primary Anti-Biofilm Mechanism	Major Advantages	Key Translational Limitations
Inorganic Metallic	AgNPs, CuNPs, AuNPs	$\text{Ag}^+/\text{Cu}^{2+}$ ion leaching, physical membrane tearing, genomic damage	High thermal stability, broad-spectrum bactericidal action	Potential eukaryotic cytotoxicity, tissue accumulation
Metal Oxides	ZnO, TiO_2 , MgO, CuO	Photocatalytic & dark-catalytic ROS, lipid peroxidation	Low production cost, durable surface coatings	Variable activity in opaque/dark industrial systems
Organic Polymeric	Chitosan, PLGA, PCL	Electrostatic envelope disruption, sustained payload release	Excellent biocompatibility and biodegradability	Lower intrinsic bactericidal potency
Lipid-Based	Liposomes, SLNs, NLCs	Membrane fusion, targeted core delivery of lipophilic drugs	Encapsulates diverse payloads, high biocompatibility	Susceptible to thermal and physical degradation

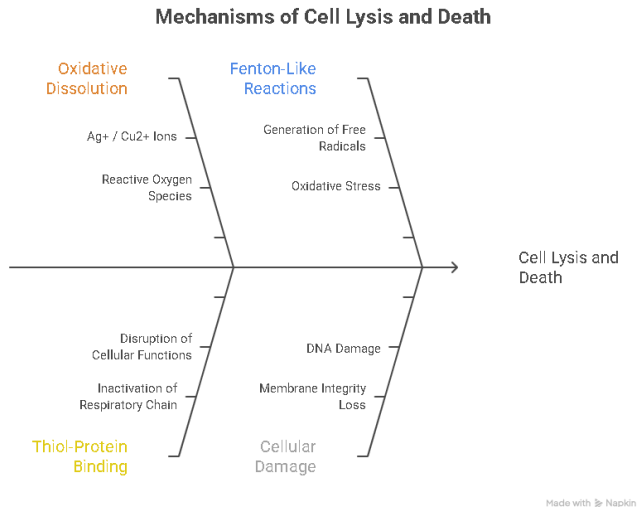
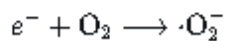
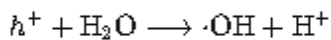
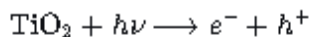


Figure 5: Mechanism of cell lysis and death

3.1.2 Photocatalytic vs. Dark-Catalytic Pathways in Metal Oxides ZnO TiO₂

When exposed to light energy exceeding their bandgap, metal oxide nanoparticles such as ZnO and TiO₂ generate electron-hole pairs (e^-/h^+). These photogenerated charge carriers subsequently react with adsorbed water molecules and molecular oxygen to produce reactive oxygen species (ROS), including hydroxyl radicals (OH) and superoxide anions (O_2^-), through the following reactions:



While this photocatalytic mechanism is highly effective on illuminated surfaces, its practical utility is substantially constrained in dark or optically opaque environments. Such conditions are prevalent in real-world applications, including turbid dairy fluid streams, dark food processing pipelines, and deep internal tissue wounds, where light penetration is severely limited. This inherent limitation underscores the need for alternative activation strategies or the development of visible-light-responsive photocatalysts to broaden the applicability of metal oxide nanoparticles in biofilm control.

To operate effectively without light activation, advanced metal oxide nanosystems exploit dark-catalytic and ROS-independent pathways:

Defect-Engineered Surface Vacancies: Doping metal oxides with transition metals (e.g., Fe, Mn, or Ag) creates surface crystal lattice defects that generate ROS directly through ambient chemical reactions without requiring photon irradiation.

Direct Surface Charge Neutralization: Highly basic or acidic surface sites on nano-MgO or nano-ZnO can alter localized pH microenvironments and disrupt bacterial membrane potentials on contact, causing cell death without light input.

3.2 Organic and Polymeric Nanosystems

Organic nanoparticles offer high biocompatibility, structural adaptability, and controlled drug-release capabilities.

Chitosan Nanoparticles (ChNPs): Derived from deacetylated chitin, chitosan contains abundant protonated amino groups NH_3^+ under acidic-to-neutral conditions. These cationic charges interact electrostatically with negatively charged bacterial cell envelopes, destabilizing the outer membrane and inducing cytoplasmic leakage. Furthermore, hybrid systems like varepsilon-poly-L-lysine conjugated chitosan nanoparticles (ChNP-PL) have demonstrated strong synergy in disrupting polymicrobial biofilms of *Listeriaceae* and *Pseudomonadaceae*.

PLGA and Synthetic Polymeric Vehicles: Poly(lactic-co-glycolic acid) (PLGA) and polycaprolactone (PCL) nanoparticles serve as biodegradable carrier platforms. They protect delicate antimicrobial payloads (such as essential oils or enzymes) from premature degradation and deliver controlled, sustained doses directly into the biofilm core.

4. Bacterial Adaptation and Resistance to Antimicrobial Nanoparticles

While nanoparticles are less prone to inducing classical resistance compared to single-target antibiotics, accumulating evidence demonstrates that bacteria can develop adaptive resistance mechanisms under persistent, sublethal nanoparticle exposure (Fig6):

4.1 Genotypic and Phenotypic Resistance Pathways

Upregulation of Heavy-Metal Efflux Pumps: Exposure to sublethal concentrations of silver or copper nanoparticles can select for strains that overexpress specialized cation efflux pumps. For example, the *Sil* gene cluster (*silCFPBAER*) encodes membrane pumps that actively export Ag ions from the cytoplasm and periplasm to the extracellular

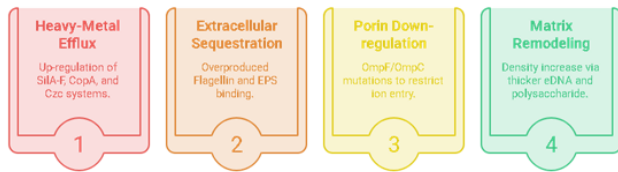


Figure 6: Bacterial Adaptation Mechanism to Nanoparticle

environment, preventing toxic intracellular ion buildup.

Porin Down-Regulation & Outer Membrane Alterations: Mutational down-regulation or structural alteration of outer membrane porins (such as OmpF and OmpC in Gram-negative organisms) reduces passive ionic diffusion, restricting the uptake of leached metal ions.

4.2 Matrix-Mediated Trapping and Extracellular Sequestration

Flagellin-Mediated Aggregation: Under nanoparticle-induced stress, certain bacteria upregulate flagellin production. Secreted flagellin proteins bind directly to metallic nanoparticles, causing them to aggregate outside the cell and reducing their ability to penetrate the biofilm matrix.

EPS Compositional Remodeling: Resistant biofilms alter their matrix composition by increasing the ratio of negatively charged exopolysaccharides and eDNA. This creates an extracellular electrostatic sink that traps cationic nanoparticles near the surface, preventing them from reaching deeper bacterial subpopulations.

5. Industrial and Clinical Applications

5.1 Biomedical Deployments and Commercial Formulations

Nanoparticles have been integrated into several clinical products to prevent device-associated infections and accelerate chronic wound healing (Fig7):

Indwelling Device Coatings: Incorporating AgNPs, ZnO NPs, or chitosan coatings into the inner and outer surfaces of urinary catheters, endotracheal tubes, and vascular grafts suppresses initial bacterial adhesion, reducing the incidence of catheter-associated urinary tract infections (CAUTIs) and ventilator-associated pneumonia (VAP).

Implantable Materials: Surface modification of titanium orthopedic implants with nano-copper or

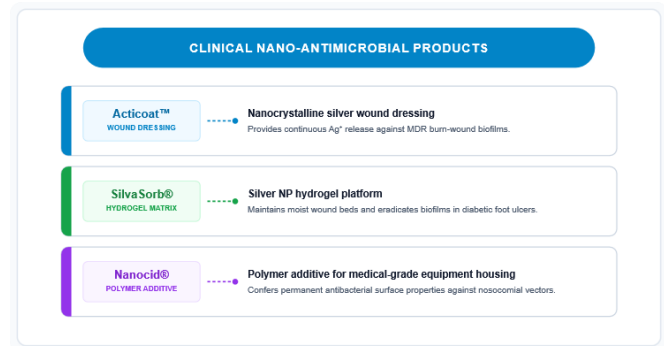


Figure 7: Clinical Nano-Antimicrobial Products

nano-zinc coatings promotes osseointegration while preventing periprosthetic joint infections.

5.2 Food Industry Applications, Active Packaging, and Equipment Coatings

Biofilm formation on food-contact surfaces presents continuous contamination hazards for pathogens such as *Listeria monocytogenes*, *Salmonella enterica*, and *Escherichia coli* O157:H7.

Surface Modification of Processing Lines: Applying nanocomposite coatings (e.g., silver-silica or copper-polymer blends) to stainless steel tanks, cutting surfaces, and conveyor systems creates anti-fouling barriers that reduce bacterial attachment.

Active Food Packaging Films: Incorporating organic and inorganic nanoparticles (such as essential oil-loaded chitosan NPs or ZnO nanocomposites) directly into polymeric packaging matrices enables active, sustained release of antimicrobial agents onto food surfaces, extending product shelf life and preventing pathogen growth(8).

5.3 Food Contact Materials (FCM), Nano-Migration Limits, and Organoleptic Impact

The use of nanomaterials in food contact applications requires careful consideration of safety thresholds and product quality:

Regulatory Nano-Migration Limits: Regulatory agencies including the European Food Safety Authority (EFSA) and the U.S. Food and Drug Administration (FDA) enforce strict limits on nanoparticle migration from packaging materials into food matrices. Standard migration assays use food simulants (e.g., 10% ethanol, 3% acetic acid, or vegetable oils) to measure particle leaching via Inductively Coupled Plasma Mass Spectrometry (ICP-MS). Migration of engineered nanomaterials must remain well below specific migration limits (SMLs) to prevent consumer exposure.

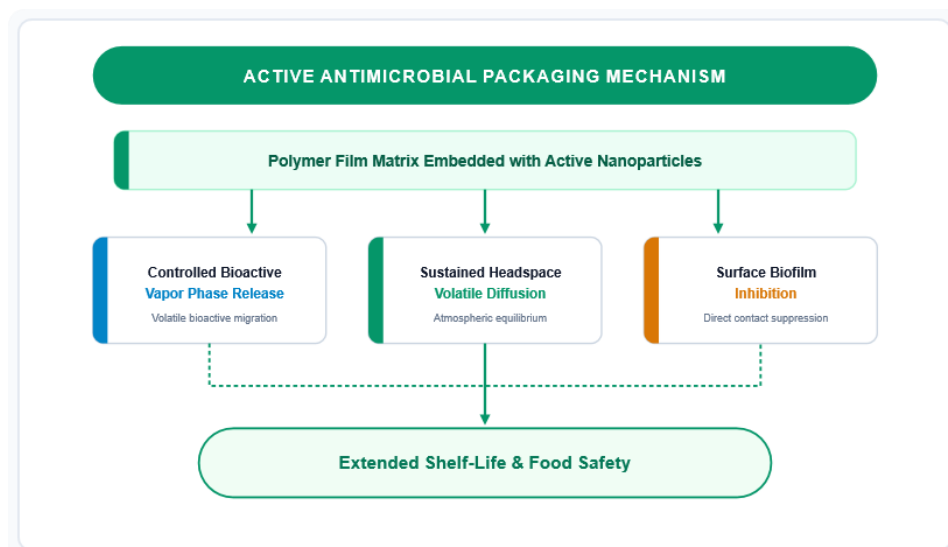


Figure 8: Active antimicrobial packaging Mechanism

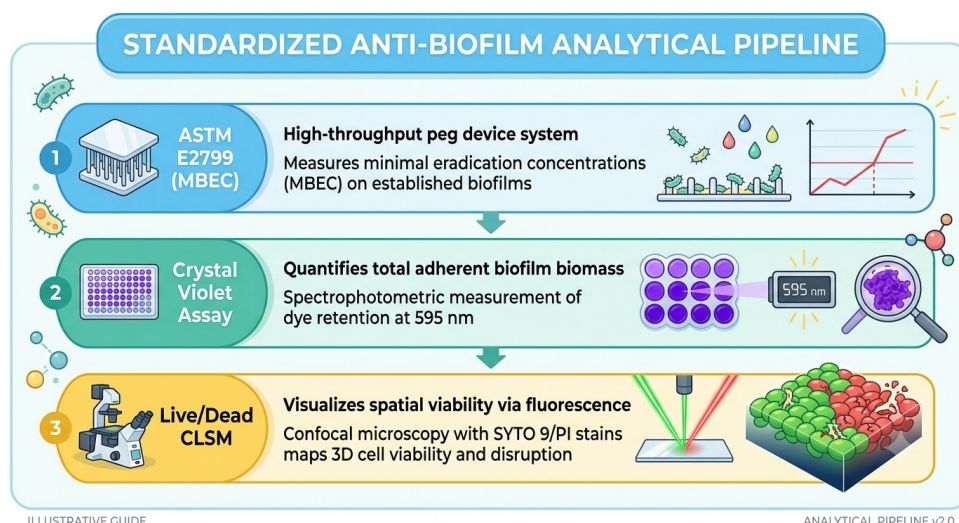


Figure 9: Standardized Anti-Biofilm Analytical Pipeline

Organoleptic and Quality Considerations: Leaching of metallic ions or active compounds can alter food flavor, color, texture, or odor profiles. For example, excessive migration of copper or silver ions can accelerate lipid oxidation in high-fat foods, leading to rancidity and off-flavors. Active packaging systems must be designed to maintain antimicrobial efficacy while preserving food sensory qualities.

6. Standardized Evaluation Protocols and Analytical Workflows

To accurately quantify anti-biofilm efficacy, research and industrial testing rely on standardized protocols (Fig 9):

6.1 Calgary Biofilm Device and MBEC Quantification (ASTM E2799)

The Calgary Biofilm Device consists of a microtiter lid fitted with 96 pegs that extend into standard microplate wells. Biofilms form on the pegs under controlled shear conditions. The peg lid is then transferred to a challenge plate containing sequential dilutions of the test nanoparticles.

Following treatment, the lid is moved to a recovery plate and subjected to sonication to release surviving biofilm cells. Plate counts are used to establish the Minimum Biofilm Eradication Concentration (MBEC), providing a reproducible metric for anti-biofilm efficacy.

6.2 Microplate Biomass and EPS Assays

Crystal Violet Staining: Quantifies total biofilm biomass (cells and matrix). Biofilms grown in micro-

plates are fixed, stained with crystal violet dye, washed, and solubilized using acetic acid or ethanol. Absorbance measured at 595 nm correlates with total biomass.

Congo Red Assay: Evaluates changes in exopolysaccharide synthesis. Biofilms cultured in the presence of sub-inhibitory nanoparticle concentrations are incubated with Congo Red dye; reductions in dye binding reflect inhibition of EPS matrix production.

6.3 Microscopic and Spectroscopic Profiling (CLSM, SEM, Live/Dead)

Confocal Laser Scanning Microscopy (CLSM) paired with fluorescent viability staining (SYTO 9 for green live cells; propidium iodide for red membrane-compromised dead cells) allows three-dimensional visualization of structural disruption, matrix thickness, and spatial cell mortality within intact biofilms. Scanning Electron Microscopy (SEM) provides high-resolution imaging of cell membrane damage and matrix degradation.

7. Bottlenecks, Toxicity, and Regulatory Frameworks

7.1 Cytotoxicity and Dermal/Systemic Accumulation

A major challenge facing metallic and metal oxide nanoparticles is potential toxicity toward mammalian cells. High intracellular concentrations of silver, copper, or zinc ions can induce host oxidative stress, mitochondrial dysfunction, and DNA damage in dermal fibroblasts and keratinocytes, potentially delaying wound healing. Systemic absorption of non-biodegradable nanoparticles can lead to accumulation

in liver, kidney, and spleen tissues. Surface modification with biocompatible polymers (e.g., PEG, hyaluronic acid) or green synthesis using plant extracts can help mitigate host toxicity.

7.2 Ecotoxicity and Environmental Fate

Industrial runoff containing metallic nanoparticles poses risks to aquatic and terrestrial ecosystems. Persistent nanoparticles entering waterways can alter natural microbial communities, disrupt nutrient cycling, and bioaccumulate in aquatic food chains. Developing fully biodegradable organic nanoparticles and efficient wastewater recovery systems represents an important area of ongoing research.

7.3 Scalability, Quality Control, and Regulatory Approvals

Scaling up nanoparticle synthesis from laboratory settings to industrial manufacturing presents technical challenges:

Batch-to-Batch Reproducibility: Maintaining consistent particle size distribution, morphology, and surface chemistry across large production batches requires tight process control.

Regulatory Ambiguity: Regulatory frameworks specific to nanomaterials continue to evolve. The lack of standardized safety and toxicity testing protocols can complicate regulatory submission and approval pathways for new nano-enabled products (Fig 10).

8. Smart Nanosystems and Future Horizons

Next-generation anti-biofilm strategies focus on intelligent, multi-functional nanosystems designed for targeted action(fig11):

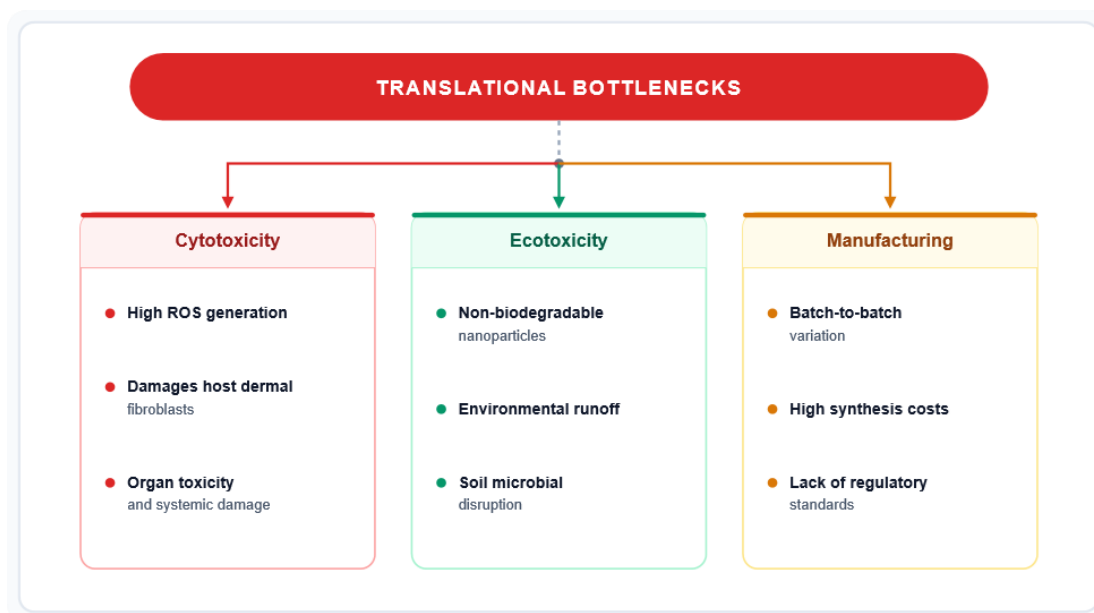


Figure 10: Translational Bottlenecks

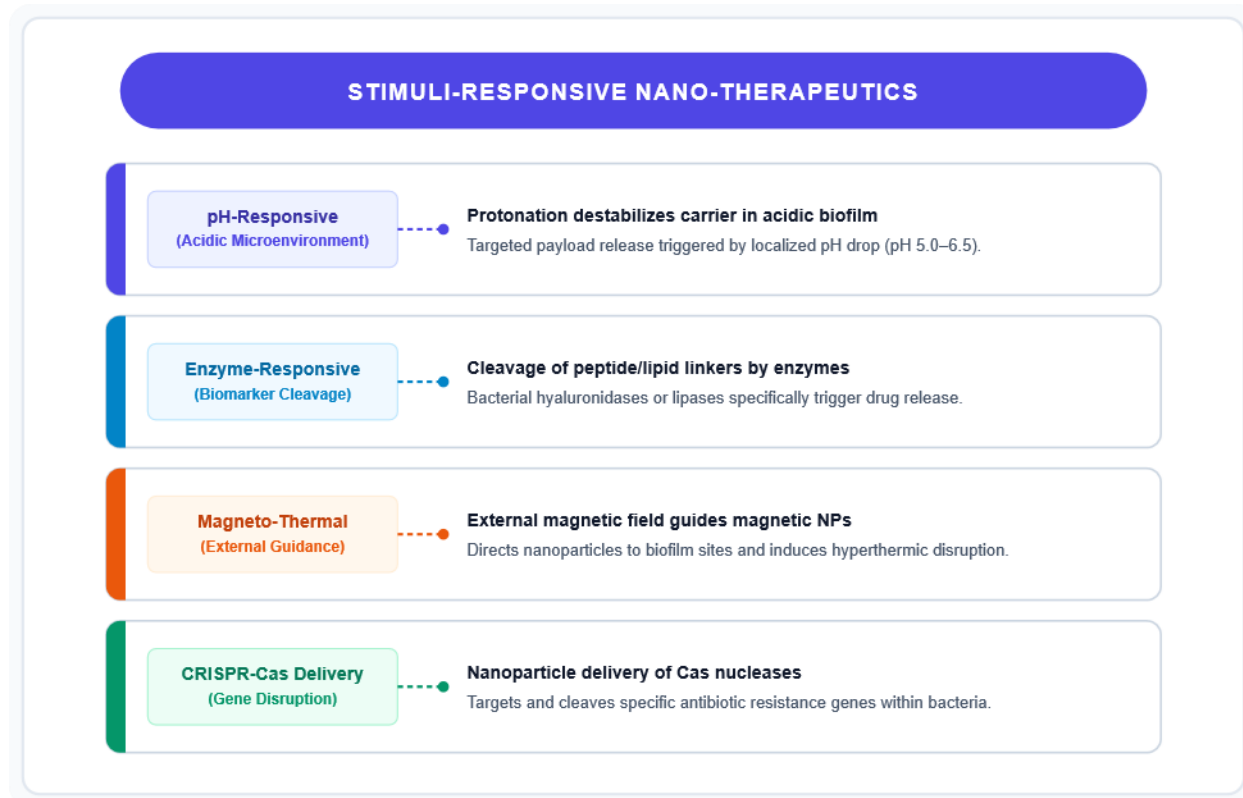


Figure 11: Stimuli-Responsive Nano-Therapeutics

8.1 Stimuli-Responsive Targeted Delivery

Smart nanosystems remain inert during transport and release their active payload selectively upon encountering biochemical triggers specific to the biofilm microenvironment:

pH-Triggered Release: Fermentative bacterial metabolism often lowers the local pH within biofilms to 5.0–6.5. Acid-labile nanoparticles undergo structural changes or bond cleavage in these acidic conditions, releasing therapeutics directly at the infection site while preserving surrounding healthy tissue.

Enzyme-Responsive Delivery: Nanoparticles functionalized with substrates sensitive to bacterial enzymes (such as gelatinases, lipases, or hyaluronidases) release their payload specifically in the presence of active biofilm infections.

8.2 CRISPR-Cas Nanodelivery and Theranostic Integration

CRISPR-Cas Gene-Editing Delivery: Polymer and lipid nanoparticles are being developed to deliver CRISPR-Cas machinery into biofilm-residing bacteria. By targeting specific resistance genes or virulence factors, these systems can reverse antibiotic resistance or kill target pathogens selectively.

Theranostic Platforms: Integrating diagnostic imaging agents (e.g., quantum dots or iron oxide cores) with therapeutic payloads enables simultaneous real-time imaging of biofilm locations and monitoring of treatment response.

9. Conclusions

Antibacterial nanoparticles offer effective strategies to combat persistent bacterial biofilms across biomedical and industrial settings. By combining physical membrane disruption, reactive oxygen species generation, and targeted payload delivery, engineered nanomaterials can penetrate protective EPS matrices and eradicate resistant bacterial communities. Key conclusions from this review include:

Multi-Target Mechanisms: Nanoparticles exert antibacterial effects through multiple concurrent pathways, reducing the likelihood of rapid resistance development compared to single-target antibiotics.

Cross-Industry Utility: Anti-biofilm nanotechnology provides valuable solutions for both clinical applications (wound dressings, implant coatings) and food industry needs (active packaging, surface sanitization).

Addressing Key Challenges: Translating promising laboratory formulations into commercial products

requires resolving ongoing challenges related to mammalian cytotoxicity, environmental fate, manufacturing scalability, and regulatory frameworks.

Emerging Technologies: The development of stimuli-responsive nanosystems, CRISPR-Cas delivery platforms, and theranostic systems offers promising directions for targeted, effective biofilm control.

Continued interdisciplinary research across chemistry, microbiology, materials science, and toxicology will be essential to advance safe, high-performance nano-antimicrobials from concept to commercial adoption.

Declaration of AI Usage

During the preparation of this manuscript, the authors used AI-assisted language tools (Grammarly and ChatGPT) solely for language editing, grammar refinement, and formatting assistance. Graphical figure also used AI-assisted (Napkin and pipeline). All scientific analyses, interpretations, literature synthesis, and conclusions were performed and verified independently by the authors.

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