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Development of Nanoparticle-Based Drug Delivery Systems Against Multidrug-Resistant (MDR) Bacteria

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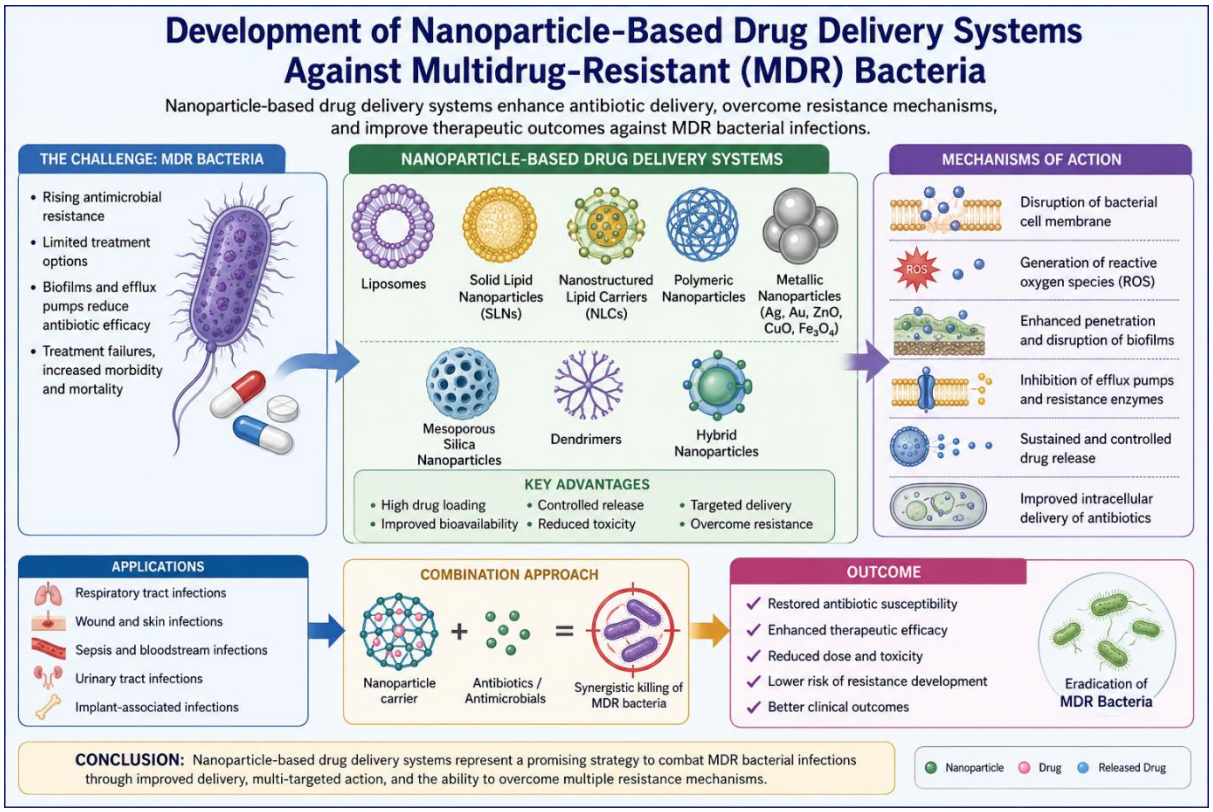
ABSTRACT

Nanoparticle-based drug delivery systems (NDDSs) have attracted considerable interest as a potential method to effectively treat multidrug-resistant (MDR) bacterial infections, which pose increasing risks to the global community's health. With the emergence of MDR bacteria, the antimicrobial resistance (AMR) phenomenon results in diminished efficacy of current traditional antibiotics and increases in morbidity, mortality, and cost of healthcare services. The accelerated global spread of resistance mechanisms such as, but not limited to, enzymatic degradation of the drug molecules, increased expression of efflux pumps, biofilm development/formation, and modification of the target site have created a pressing need for new therapeutic options. NPs give the potential unique opportunity to combat MDR bacterial infections due to their nanoscale size, high surface area, ability to be chemically modified to create uniquely tunable set of physical and chemical properties, and the ability to encapsulate a broad spectrum of antimicrobial agents. NPs can also provide enhanced stability through improved control over the interaction of the drug with the patient and/or environment. The variety of NDDS types, such as liposomes, well-defined polymeric NPs, solid lipid NPs, nanostructured lipid carriers, metallic NPs, dendrimers, and mesoporous silica NPs have been shown to possess significant antibacterial activity against clinically relevant MDR pathogens, including MRSA, carbapenem-resistant A. baumannii, PdR P. aeruginosa, K. pneumoniae, and E. coli. There are several mechanisms through which NPs can provide therapeutic benefits to combat antibiotic resistance (AMR), including disrupting bacterial cellular membranes, aiding in the penetration of antibiotics into microbial biofilms, inhibiting efflux pumps, producing reactive oxygen species (ROS), and achieving targeted intracellular delivery of the therapeutic. This review presents recent advances in the development and use of NDDS for the treatment of MDR bacterial infections, as well as their mechanisms of action, therapeutic applications, current challenges, and future directions. The combination of nanotechnology with personalized medicine, artificial intelligence (AI), and intelligent NDDS will likely facilitate the speedier development of the next generation of antimicrobial agents to address the public health threat of global AMR due to the emergence of MDR bacteria, and that innovative approaches to manage the ever-increasing problem of MDR bacteria are essential.
Keywords: Nanoparticles; NDDS; MDR bacteria; AMR; Liposomes; Polymeric NPs; Solid Lipid NPs; Nanomedicine.



1. INTRODUCTION

Antimicrobial resistance (AMR) is becoming one of the serious risks to global health care because current antibiotics are not working very well for people's bacterial infections and the number of treatment options is low for these types of infections. The overuse and misuse of antibiotics (for example, during clinical practices, veterinary medicine, agriculture, and aquaculture) have accelerated the development of multidrug-resistant (MDR), extensively drug-resistant (XDR) and pan-drug-resistant (PDR) bacterial pathogens. These resistant microorganisms cause longer hospital stays, increased costs for the health care system, inability to treat patients properly, answer for millions of deaths worldwide each year. Most clinically significant MDR pathogens, which exist today, are methicillin-resistant Staphylococcus aureus (MRSA), carbapenem-resistant Acinetobacter baumannii, multidrug-resistant Pseudomonas aeruginosa, vancomycin resistant Enterococcus faecium, Klebsiella pneumoniae and Escherichia coli. The ever-increasing number of these organisms means that we urgently need to find new methods to treat infection with antimicrobials other than simply developing new antibiotics [1].

Bacteria resist the actions of antimicrobials through a variety of different mechanisms of resistance, including the enzymatic destruction of antibiotics (via β-lactamases and carbapenemases), modification of the antibiotic target site(s), decreased bacterial membrane permeability, overexpression of efflux pumps for removing drugs, and biofilm formation. Biofilm formation is particularly troubling given that many bacteria are embedded in an extracellular polymeric matrix, which provides a much higher degree of tolerance of embedded bacteria to antibiotics and host immune responses than free-living bacteria in a planktonic or floating state. Therefore, the conventional antibiotic treatment of chronic infections associated with biofilms is often unsuccessful, resulting in recurrent infections as well as additional development of antibiotic resistance [2].

One emerging and innovative approach to overcoming this significant public health issue is through the development of nanotechnology. More specifically, nanoparticle-based drug delivery systems (NDDSs) are engineered agents that are typically 1 – 1000 nm in size that can facilitate the therapeutic effects of antimicrobial agents. The unique physical and chemical characteristics of nanoparticles, including high surface area to volume ratio, ability to alter particle size, charge density of nanoparticles, and ease of functionalization, allow for the efficient encapsulating of drugs, enable targeted drug delivery, enable controlled drug release, and to enhance the penetration of antimicrobial agents into bacteria and/or biofilms [3].

Nanoparticles exert their antibacterial activity through various, complementary mechanisms that differ from the way conventional antibiotics do so. For example, application of nanoparticles increases the intracellular accumulation of antibiotics; improve the stability of the drug against enzymatic destruction; facilitate the permeability of the

bacterial membranes; disrupt the formation of biofilms by bacteria; generate ROS; and provide targeted delivery of drugs to sites of infection. Therefore, these multiple mechanisms associated with the use of nanoparticles greatly lower the likelihood that antibiotic resistance can develop and consequently increase the effectiveness of conventional antibiotic therapies. In addition, nanoparticles can co-deliver antibiotics as well as antimicrobial peptides, phytochemicals, nucleic acids, and immunomodulatory agents, which may all have a positive effect on the development of an even higher level of antimicrobial protection [4].

A variety of nanoparticle platforms have been evaluated as potential candidates for antimicrobial use, including liposomal nanoparticles, polymeric nanoparticles, solid lipid nanoparticles (SLN), nanostructured lipid carriers (NLC), metal-based nanoparticles (silver, gold, zinc oxide or copper oxide), dendrimers, mesoporous silica nanoparticles, and a hybrid nanoparticle delivery system. Many of these NDDS systems have demonstrated strong antibacterial activity against MDR bacterial pathogens in vitro and/or in vivo.

This review article will provide a general summary of current and potential NDDS for the prevention and/or treatment of infections caused by MDR bacteria. It will discuss the various NDDS platforms available, their various mechanisms of antibacterial activity, the advancements that have been made in the field of nanomedicine, the present barriers to the application of NDDS, and the future potential for the application of NDDS in clinical settings.

2. NANOPARTICLE-BASED DRUG DELIVERY SYSTEMS FOR MULTIDRUG-RESISTANT BACTERIA

NLNT is the most effective form of drug therapy for MDR bacterial infections by utilizing colloidal nanoparticles for drug delivery within the 1 nm - 1000 nm size range. Compared to conventional pharmaceutical formulations of the same drug, nanoparticles offer various advantages such as: Improved solubility of the active ingredient; increased stability of the active ingredient; extended half-life of the active ingredient; observable sustained/release of the active ingredient over time; delivery of the active ingredient specifically to target tissues; decreased toxicity to the active ingredient; and/or improved cellular/internalization of the active ingredient [5].

Nanoparticles can also be categorized into six classes determined by their composition and shape: i) Lipid-based carriers; ii) Polymer-based carriers; iii) Inorganic carriers (metal); iv) Silicon carriers; v) Dendrimers; and vi) Hybrid carriers. Nanoparticles are uniquely able to transport and deliver drugs effectively due to the specific properties of each class of nanoparticle carrier as determined by physical (e.g., size) and chemical properties (e.g., solubility) and will help improve drug delivery system delivery capabilities.

Lipid-based carriers have received much attention as possible nanoparticle carriers in the context of antimicrobial drug delivery because they possess high biocompatibility, high biodegradability, and high biocompatibility.

Lipid-based carriers (liposomes) continue to be the most widely recognized and utilized form of lipid-based carriers.The configuration of liposomes is typically spheroid in shape with Liposomes made up of either a single or multilayer of phospholipids that are used to form the outside of the liposome and contain an "aqueous" of solution or liquid in the center.

Antibiotics when encapsulated in liposomes will where hydrophilic and lipophilic antibiotics preserve their characteristics and remain protected from enzymatic degradation, thereby increasing the accumulation of the drug in areas of infection. There have been considerable documented evidence of antibiotic delivery using liposomal formulation, such as in delivering Vancomycin, Colistin, Ciprofloxacin, and Amikacin by way of liposomal formulations with resulting improved antibacterial capabilities against Multi-resistant bacteria and also lessened systemic toxicity in their final liposomal formulation(s) [6].

Solid lipid Nanoparticles carriers are created from solid lipid material and are physiologically categorized as solid lipid matrices containing a drug that will provide for a continuous release of the drug, increasing the stability of the drug and protecting the drug against degradation.

Nanostructured lipid carriers (NLCs) represent the second-generation of lipid nanoparticles. NLCs are composed of both solid and liquid lipids to yield a more intricate crystalline structure than solid lipid nanoparticles (SLNs). Due to the more complicated crystalline lattice structure of the NLC, more drug may be entrapped in the three-dimensional crystalline structure than in the SLN and also reduces drug leakage when compared to SLNs. Compared to SLNs, NLCs will demonstrate increased antibacterial activity against poorly water soluble antibiotics.Polymeric Nanoparticles [7].

Polymeric nanoparticles consist of polymers that can be biocompatible such as: Poly(lactic-co-glycolic acid) (PLGA), chitosans, alginates, polycaprolactones (PCL), and gelatins.

Polymeric nanoparticles can sustain release prolonged periods when delivering drugs, are able to encapsulate large quantities of drugs and enhance the pharmacokinetics of the delivered drug.

Chitosan nanoparticle possess inherent anti-bacterial properties due to the presence of their cationic amino groups which will electrostatically bind to the anionic surface of the bacteria

disrupting the cell membrane and allowing the cell contents to leak out. Chitosan nanoparticles will also enhance the adhesion of the nanoparticles to the mucosa and enhance the nanoparticles ability to penetrate into biofilms making chitosan nanoparticles an attractive choice for treating chronic bacterial infections.

Metallic Nanoparticles

Metallic nanoparticles also possess excellent antibacterial properties and do not need to be used with traditional antibiotics. Metallic nanoparticles that also possess good antibacterial properties include: Silver NPs (AgNP), gold NPs (AuNP), zinc oxide NPs (ZnO NPs), copper oxide NPs (CuO NPs), and iron oxide NPs.

AgNPs are the most widely studied metallic NPs and are used throughout as antimicrobials against both gram positive and gram negative bacteria. The AgNPs will act as antibacterial through several mechanisms including disruption of the structural organisation of the bacterial membrane, generation of reactive oxygen species (ROS), inhibition of proteins and DNA of the bacteria, and inhibition of enzymes responsible for cellular respiration.Antimicrobial Activity of Silver Nanoparticles (AgNPs)

The antimicrobial properties of AgNPs can also have a synergistic effect on the overall activity of antibiotics; thus allowing for decreased dosages of both AgNPs and antibiotics needed to effectively treat an infection; as well as providing a return to the antibiotic susceptibility of bacteria [8].

2.4 Mesoporous Silica Nanoparticle (MSN)

Mesoporous silica nanoparticles (MSNs) consist of highly ordered porous structures with substantial surface areas and the ability to control their pore sizes. Some characteristics of MSNs include:

- High drug-loading capabilities
- Controlled drug release
- Surface functionalization (allowing for targeted delivery)

MSNs have been extensively studied and demonstrate great potential as effective carriers for antibiotics, antimicrobial peptides, enzymes and nucleic acids, especially for the treatment of biofilms and/or for intracellular delivery [9, 10].

2.5 Dendrimers

Dendrimers represent a class of highly branched, synthetic macromolecules with many functional groups on the surface of these molecules.

Some characteristics of dendrimers include:

- Uniform size
- Very high degree of water-solubility
- Ability to have a high drug loading capacity
- Surface functionalization provides for targeted delivery of drugs.

Cationic dendrimers can disrupt cellular membranes as a result of their inherent antibacterial properties and can also be utilized to carry antibiotics [11].

2.6 Hybrid Nanoparticles

Hybrid nanoparticles are defined as nanoparticles that are made from a combination of two or more nanoparticles, taking advantage of their unique characteristics.

Examples of hybrid nanoparticle combinations include: 1) lipid-polymer hybrid nanoparticles, 2) silver-polymer hybrid nanoparticles, 3) liposome-coated metallic nanoparticles and 4) magnetic-polymer coated nanoparticles.

Using hybrid nanoparticles for drug delivery will provide the following benefits: improved drug stability, improved targeting efficacy, controlled release of the drug from the hybrid nanoparticle, improved antimicrobial effect, and decreased toxicity for the patient [12].

Benefits of Using Nanoparticles for Drug Delivery Systems

When compared to traditional drug delivery systems, nanoparticles used as drug delivery systems offer several advantages, including: [13-15].

- Greater ability to penetrate bacterial biofilms
- Enhanced ability to deliver drugs intracellularly
- Protection of the antibiotic from degradation
- Controlled sustained release of drugs
- Increased availability of drug; circulation time in the body
- Less potential for systemic toxicity to humans
- Targeted delivery of drug to infected tissues
- Multiple types of antimicrobials can be delivered concurrently
- Less antibiotic required for effective treatment, thus increasing the effectiveness of the delivered antibiotic
- Decreased risk of developing antibiotic resistant bacteria

Table 1. Major Nanoparticle-Based Drug Delivery Systems for MDR Bacterial Infections

Nanoparticle Type	Common Materials	Major Advantages	Representative Antibiotics
Liposomes	Phospholipids, Cholesterol	Biocompatible, targeted delivery	Vancomycin, Ciprofloxacin, Colistin
Solid Lipid Nanoparticles (SLNs)	Stearic acid, Glyceryl monostearate	Controlled release, improved stability	Rifampicin, Amikacin
Nanostructured Lipid Carriers (NLCs)	Solid + liquid lipids	Higher drug loading, sustained release	Ciprofloxacin, Levofloxacin

Polymeric Nanoparticles	PLGA, Chitosan, Alginate	Biodegradable, prolonged release	Gentamicin, Doxycycline
Metallic Nanoparticles	Silver, Gold, Zinc oxide	Intrinsic antibacterial activity	Silver–antibiotic combinations
Mesoporous Silica Nanoparticles	Silica	High drug loading, biofilm penetration	Vancomycin, Tobramycin
Dendrimers	PAMAM, PPI	Surface functionalization, membrane disruption	Antimicrobial peptides
Hybrid Nanoparticles	Lipid–polymer composites	Multifunctional delivery, synergistic action	Multiple antibiotics

3. MECHANISMS OF NANOPARTICLES AGAINST MULTIDRUG-RESISTANT BACTERIA

Nanoparticles can combat multidrug-resistant bacteria through multiple mechanisms, making them more effective than traditional antibacterials. They disrupt the bacterial cell membrane, thereby increasing permeability and causing leakage of intracellular constituents. Metallic nanoparticles produce a large amount of reactive oxygen species that lead to oxidative damage of the protein, lipid, and DNA of bacteria. Nanoparticles can additionally enhance the penetration of antibiotics into bacterial biofilms, inhibit multidrug efflux pumps, and enhance the intracellular delivery of drugs. In addition, by controlling and sustaining the release of drugs from nanoparticles, effective drug concentrations can be maintained at the site of infection, thus enhancing the antibacterial activity while minimizing the toxicity of the drug to the organism. These synergistic activities will reduce the potential for the development of resistance to antibiotics and restore susceptibility to antibiotics [16].

Table 2. Antibacterial Mechanisms of Nanoparticles

Mechanism	Biological Effect
Membrane disruption	Cell lysis and increased permeability
ROS generation	Oxidative damage to proteins, lipids, and DNA
Biofilm penetration	Enhanced antibiotic diffusion
Efflux pump inhibition	Increased intracellular antibiotic concentration
Controlled drug release	Sustained therapeutic levels
Intracellular targeting	Improved bacterial killing

4. RECENT ADVANCES AND CLINICAL PERSPECTIVES

Recent advances in nanotechnology have enabled the development of multifunctional nanoparticles capable of co-delivering antibiotics, antimicrobial peptides, phytochemicals, and nucleic acids. Liposomal amikacin, silver nanoparticles, polymeric nanoparticles, and nanostructured lipid carriers have shown promising activity against MRSA, *Pseudomonas aeruginosa*, and carbapenem-resistant *Acinetobacter baumannii*. Smart nanoparticles responsive to pH, enzymes, or bacterial toxins have further improved targeted drug delivery. Several nanoformulations are currently under preclinical and clinical investigation for the treatment of resistant bacterial infections [17,18].

5. CHALLENGES AND FUTURE PROSPECTS

Despite encouraging results, challenges remain regarding large-scale manufacturing, formulation stability, toxicity, pharmacokinetics, regulatory approval, and production costs. Standardized characterization methods and long-term safety studies are required before widespread clinical use. Future research should focus on AI-assisted nanoparticle design, targeted nanocarriers, biodegradable materials, combination therapies, and personalized antimicrobial treatment strategies to overcome multidrug resistance [19,20].

6. CONCLUSION

Nanoparticle-based drug delivery systems represent a promising strategy for combating multidrug-resistant bacterial infections. Their ability to improve drug delivery, enhance biofilm penetration, provide controlled drug release, and overcome bacterial resistance mechanisms offers significant therapeutic advantages over conventional antibiotics. Continued advances in nanotechnology, precision medicine, and smart drug delivery platforms are expected to accelerate the clinical translation of nanoparticle-based antimicrobial therapies and contribute to addressing the global challenge of antimicrobial resistance.

Declarations

Ethics Approval and Consent to Participate

Not applicable. This review article is based entirely on previously published scientific literature and does not involve human participants, animals, or clinical samples.

Consent for Publication

Not applicable.

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Authors' Contributions
All authors contributed substantially to the conception, literature review, manuscript writing, critical revision, and final approval of the manuscript. All authors have read and approved the final version of the manuscript.

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Code Availability
Not applicable.

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This article is a review based on published scientific literature and does not involve any studies with human participants or animals performed by the authors.

Declaration on the Use of Artificial Intelligence
The authors used artificial intelligence (AI)-assisted tools only to support language refinement and manuscript drafting. All scientific content was critically reviewed, verified, and approved by the authors, who accept full responsibility for the accuracy, originality, and integrity of the manuscript.

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Abbreviations

Abbreviation	Full Form
AI	Artificial Intelligence
AMR	Antimicrobial Resistance
ATP	Adenosine Triphosphate
AuNPs	Gold Nanoparticles
CuO NPs	Copper Oxide Nanoparticles
DNA	Deoxyribonucleic Acid
DDS	Drug Delivery System
MDR	Multidrug-Resistant
MIC	Minimum Inhibitory Concentration
MRSA	Methicillin-Resistant *Staphylococcus aureus*
MSNs	Mesoporous Silica Nanoparticles
NLCs	Nanostructured Lipid Carriers
NDDSs	Nanoparticle-Based Drug Delivery Systems
NPs	Nanoparticles
PCL	Polycaprolactone
PDR	Pan-Drug-Resistant
PEG	Polyethylene Glycol
PLGA	Poly(lactic-co-glycolic acid)
PPI	Polypropylene Imine
ROS	Reactive Oxygen Species
SLNs	Solid Lipid Nanoparticles
TEM	Transmission Electron Microscopy
XDR	Extensively Drug-Resistant
ZnO NPs	Zinc Oxide Nanoparticles

Bacterial Species

Abbreviation	Scientific Name
A. baumannii	*Acinetobacter baumannii*
E. coli	*Escherichia coli*
K. pneumoniae	*Klebsiella pneumoniae*

P. aeruginosa	*Pseudomonas aeruginosa*
S. aureus	*Staphylococcus aureus*
E. faecium	*Enterococcus faecium*

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