International Journal of Pharmaceutical Drug Design (IJPDD)
Website: https://ijpdd.org/
ISSN: 2584-2897
Vol. 3, Issue 2, July-December, 2026
Page No.: 67-72

Research

Nanocarrier-Mediated Antimicrobial Delivery Against Resistant Eskape Pathogens: Experimental Evidence and Translational Challenges

Shaikh Fmm[1], Arya V[2]*
[1]Independent Researcher, Vadodara, Gujarat, India
[2]Bhupal Noble's University, Udaipur

Corresponding Author:
Dr Vishwajeet Arya

Email:
Vishwajeetarya23@gmail.com

DOI: *10.62896/ijpdd.3.2.07*

Conflict of interest: *NIL*

Article History
Received: 12/08/2025
Accepted: 28/08/2025
Published: 14/09/2026

Abstract:
Antimicrobial resistance among ESKAPE pathogens has reduced the reliability of several established treatments and intensified interest in nanotechnology-based antimicrobial delivery. This narrative review critically examines experimental nanocarriers used to deliver antimicrobial payloads against resistant ESKAPE organisms. A focused literature search of PubMed/MEDLINE, Scopus, Web of Science and Embase was undertaken using terms related to nanocarriers, ESKAPE organisms and antimicrobial resistance. Eight illustrative experimental studies were synthesized, covering mesoporous silica nanoparticles, liposomes, polymeric micelles, polymeric nanoparticles, albumin nanoparticles and nanoemulsions. Reported benefits included lower inhibitory concentrations, sustained release, improved local delivery, suppression of virulence and increased inhibition of biofilm formation. The magnitude of benefit was formulation-dependent. Some liposomal meropenem preparations showed no improvement or performed worse than free drug, demonstrating that encapsulation is not inherently advantageous. Most evidence was generated in vitro, animal validation was uncommon and no clinical trial evidence was identified among the selected studies. Resistance status, dose equivalence and biofilm endpoints were also inconsistently reported. Current evidence supports cautious, formulation-specific development rather than a general conclusion that nanocarriers reverse antimicrobial resistance. Standardized comparisons, mature-biofilm models, pharmacokinetic evaluation, organ-specific safety testing and reproducible manufacturing are required before clinical translation.

Keywords: antimicrobial resistance; ESKAPE pathogens; nanocarriers; drug delivery; nanoparticles; biofilms

1. INTRODUCTION

Antimicrobial resistance (AMR) has become a major threat to global health because it reduces the effectiveness of established treatments and complicates the management of serious bacterial infections. A systematic global analysis estimated that bacterial AMR was associated with approximately 4.95 million deaths in 2019, of which 1.27 million were directly attributable to resistance.[1]

Particular concern surrounds the ESKAPE pathogens: Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa and Enterobacter species. These organisms cause important healthcare-associated infections and can evade multiple antimicrobial agents.[2] Resistant members of this group, including carbapenem-resistant Gram-negative bacteria, vancomycin-resistant E. faecium and methicillin-resistant S. aureus, remain prominent in international priorities for antibacterial research and development.[3]

Resistance among ESKAPE pathogens is supported by enzymatic drug inactivation, modification of antimicrobial targets, reduced membrane permeability, active efflux and biofilm formation. These mechanisms may coexist, limiting treatment options and increasing the probability of therapeutic failure. Alternative approaches include bacteriophages, antimicrobial peptides, combination therapy, immunotherapeutic strategies and nanotechnology-based delivery systems.[4]

Nanocarriers can modify the solubility, stability, release and distribution of antimicrobial agents. Liposomes, polymeric nanoparticles, polymeric micelles, nanoemulsions, albumin nanoparticles and mesoporous silica nanoparticles may protect unstable payloads, support sustained release or improve local exposure. Experimental studies have reported improved activity after incorporation of berberine, imipenem/cilastatin, piperacillin/tazobactam, colistin, meropenem and linezolid.[5–11] Nevertheless, benefit is not universal and depends on carrier composition, drug release, bacterial phenotype and experimental design.

The evidence also presents interpretive difficulties. Many reports remain limited to in-vitro experiments, resistance is not always established at the isolate level, and assays measuring prevention of biofilm formation are sometimes described as biofilm eradication. This narrative review critically compares selected drug–carrier systems, evaluates the strength of their experimental evidence and identifies requirements for clinical translation.

2. METHOD

Study design

A focused narrative review was undertaken to provide a critical, formulation-centred synthesis. It was not conducted or reported as a systematic review or scoping review, and no claim of exhaustive study identification is made.

Literature search strategy

PubMed/MEDLINE, Scopus, Web of Science and Embase were searched during August–September 2026. Search concepts combined terms for nanotechnology-based delivery (including nanoparticle, nanocarrier, liposome, micelle, nanoemulsion, mesoporous silica and polymeric nanoparticle), ESKAPE organisms and antimicrobial resistance phenotypes. Reference lists and related-article records were used to identify additional illustrative studies. The final narrative synthesis prioritized studies that allowed comparison between a loaded nanocarrier and a free antimicrobial, or that supplied particularly informative translational evidence.

Inclusion criteria

- Original experimental research evaluating a nanoscale carrier or delivery platform with a separately identifiable antimicrobial payload.
- Evaluation against at least one ESKAPE organism, preferably with an explicitly reported resistance phenotype.
- In-vitro, animal or clinical evidence reporting antibacterial, antibiofilm, delivery, safety or related translational outcomes.
- Sufficient information to identify the carrier, payload, organism and principal result.

Exclusion criteria

- Narrative or systematic reviews, editorials, protocols and non-original reports.
- Bare or intrinsically antimicrobial nanoparticles without a separately identifiable delivered payload.
- Diagnostic, environmental, textile or coating applications without therapeutic antimicrobial delivery.
- Studies without an eligible organism or without enough information for meaningful interpretation.

Data extraction and synthesis

For each selected study, the carrier, payload, organism, resistance context, experimental model, comparator, principal findings and major limitations were recorded. Findings were synthesized narratively because the formulations, microbial models, dosing conventions and outcomes were too heterogeneous for quantitative pooling. Particular attention was paid to free-drug and empty-carrier controls, isolate-level resistance, dose equivalence, mature-biofilm testing, animal validation and safety assessment.

3. RESULTS

3.1 Characteristics of the evidence

Eight illustrative studies were included in the critical synthesis (Table 1). The platforms comprised mesoporous silica nanoparticles, liposomes, PLGA–PEG micelles, PLA–PEG nanoparticles, chitosan-coated albumin nanoparticles, BSA–chitosan nanoparticles and a pulmonary nanoemulsion. Most studies were conducted exclusively in vitro. Only two incorporated animal infection models, and no human clinical trial evidence was identified among the selected studies.

Table 1. Experimental evidence for nanocarrier-mediated antimicrobial delivery

Study	Carrier / payload	Organism and model	Principal finding	Major limitation
Abd El-Hamid et al.[5]	Mesoporous silica / berberine	VRSA; in vitro and mouse skin infection	Improved antibacterial, antibiofilm and antivirulence effects	No pharmacokinetic or comprehensive toxicity evaluation
Milani et al.[6]	Nanoliposomes / imipenem–cilastatin	Resistant P. aeruginosa; in vitro	Generally lower MIC/MBC and greater inhibition of biofilm formation	Small isolate panel; not a mature-biofilm eradication assay
Milani et al.[7]	PLGA–PEG micelles / piperacillin–tazobactam	MDR P. aeruginosa; in vitro	Modest MIC and biofilm-formation improvement	Single-centre in-vitro study
Scutera et al.[8]	Chitosan-coated albumin / colistin	Colistin-resistant A. baumannii and K. pneumoniae; in vitro	Pronounced MIC reductions in resistant isolates	No animal efficacy or nephrotoxicity assessment
Martínez-Guitián et al.[9]	Nanoemulsion / colistin	A. baumannii; in vitro and mouse pneumonia	Greater pulmonary bacterial reduction than free colistin	Animal strain not shown to be colistin resistant
Drulis-Kawa et al.[10]	Twelve liposomes / meropenem	Susceptible and low-permeability-resistant P. aeruginosa; in vitro	Benefit varied; some formulations were worse than free drug	Eight strains; formulation-dependent results
Oliva et al.[11]	PLA–PEG nanoparticles / linezolid	Primarily MRSA; VREfm in broader panel; in vitro	Sustained release and activity against MRSA biofilm	No superiority demonstrated specifically for VREfm
Roy et al.[12]	BSA–chitosan / C. militaris extract or cordycepin	Panel including E. cloacae; in vitro	Antibacterial activity reported	Isolate-level MDR status and controls insufficiently reported

3.2 Carrier-specific findings

Berberine-loaded mesoporous silica nanoparticles demonstrated lower inhibitory concentrations and stronger inhibition of biofilm and virulence-related gene expression than free berberine against VRSA isolates. Improvement was also reported in a mouse skin-infection model, but pharmacokinetic, biodistribution and formal toxicity evidence was absent.[5]

Imipenem/cilastatin nanoliposomes generally improved activity against resistant clinical P. aeruginosa isolates. However, the treatment was present while biofilms developed; the experiment therefore supported inhibition of biofilm formation rather than eradication of established biofilm.[6]

PLGA–PEG micelles carrying piperacillin/tazobactam produced comparatively modest improvements in inhibitory concentrations, biofilm development and bacterial motility.[7]

Chitosan-coated albumin nanoparticles carrying colistin markedly improved in-vitro activity against colistin-resistant A. baumannii and K. pneumoniae. Empty carriers were essentially inactive, supporting a payload-delivery effect. Nevertheless, resistance-reversal mechanisms and nephrotoxicity were not evaluated.[8] A pulmonary colistin nanoemulsion achieved a greater reduction of lung bacterial burden than free colistin in mice, but the animal strain was not demonstrated to be colistin resistant.[9]

Meropenem liposomes produced the clearest counterexample to an assumption of universal benefit. Certain cationic formulations improved activity against susceptible isolates, while none showed bactericidal activity against low-permeability resistant strains and Fluidosomes performed worse

than free meropenem.[10] Linezolid-loaded PLA–PEG nanoparticles provided sustained release and activity against MRSA biofilm; VREfm was included in the broader bacterial panel, but superiority against VREfm was not established.[11]

BSA–chitosan nanoparticles containing C. militaris-derived material showed antibacterial activity against a panel including E. cloacae. However, isolate-level resistance, organism-specific outcomes and relevant free-payload and empty-carrier comparisons were not sufficiently clear for this study to provide strong resistant-ESKAPE evidence.[12]

Overall, most studies reported at least one improvement following nanocarrier incorporation, although the magnitude and consistency of benefit varied substantially among drug–carrier combinations.[5–12]

3.3 Recurrent evidence gaps

Table 2. Recurrent methodological and translational gaps

Evidence domain	Common limitation	Recommended minimum improvement
Comparators	Missing empty-carrier or dose-equivalent free-drug control	Include both controls and state the concentration basis
Resistance	Broad MDR label without isolate-level evidence	Report susceptibility standard, breakpoints and mechanisms
Biofilms	Formation inhibition described as eradication	Treat a mature biofilm before viable-count assessment
Safety	Cell viability or haemolysis only	Add organ-specific toxicity, histopathology and repeated exposure
Translation	In-vitro efficacy without exposure data	Add pharmacokinetics, biodistribution and infection-site concentration
Manufacturing	Limited batch and stability evidence	Report reproducibility, sterilization and storage stability

4. DISCUSSION

The selected evidence indicates that nanocarrier-mediated delivery can improve the experimental performance of certain antimicrobial agents against resistant ESKAPE pathogens. Benefits included sustained release, enhanced local exposure, lower inhibitory concentrations and improved inhibition of biofilm formation. These outcomes were nevertheless formulation-specific and should not be generalized to nanocarriers as a uniform therapeutic class.

4.1 Improvement is not equivalent to resistance reversal

A reduction in MIC after loading does not by itself demonstrate reversal of resistance. Improvement may result from prolonged exposure, altered carrier–cell interaction or differences between nominal and freely available drug concentrations. The marked in-vitro activity of colistin-loaded albumin nanoparticles against resistant isolates is promising, but its mechanism remains uncertain.[8] The pulmonary nanoemulsion study demonstrated improved local treatment, not efficacy against a confirmed colistin-resistant animal infection.[9] Similarly, VREfm in the linezolid study was resistant to vancomycin rather than linezolid.[11]

4.2 Formulation characteristics determine performance

The liposomal meropenem findings directly challenge the claim that encapsulation always improves antibacterial activity.[10] Particle size, surface charge, carrier composition, loading, stability and release kinetics can alter the effective exposure of bacteria to a payload. Strong retention may prevent an active concentration from being released, while rapid leakage may eliminate the intended benefit. Reports should therefore state whether comparisons use nominal, encapsulated, released or freely available drug concentrations.

4.3 Biofilm claims require careful interpretation

Biofilm formation contributes to persistence and antimicrobial tolerance. Several formulations improved antibiofilm outcomes, but simultaneous exposure of bacteria and treatment measures prevention of biofilm development rather than eradication.[6,7] True eradication experiments should allow biofilms to mature before treatment and should

measure viable surviving organisms, not biomass alone.

4.4 Limitations of the evidence base

The evidence was dominated by heterogeneous in-vitro studies, frequently involving small isolate collections. Animal evidence was uncommon, and no selected study established clinical effectiveness. Resistance characterization, nanoparticle controls and dose-equivalence reporting were inconsistent. Safety evaluation was also limited; basic cytocompatibility cannot substitute for systemic and organ-specific toxicity assessment. These limitations prevent strong conclusions about clinical superiority.

4.5 Translational implications

Nanocarriers should be developed as individual carrier–payload products. Their most plausible benefits include localized delivery, protection of unstable agents, sustained exposure and reduced systemic toxicity. Translation requires comparisons with optimized standard treatment, reproducible manufacturing, sterilization compatibility, storage stability, pharmacokinetic evidence and appropriate regulatory characterization. Figure 1 summarizes this progression.

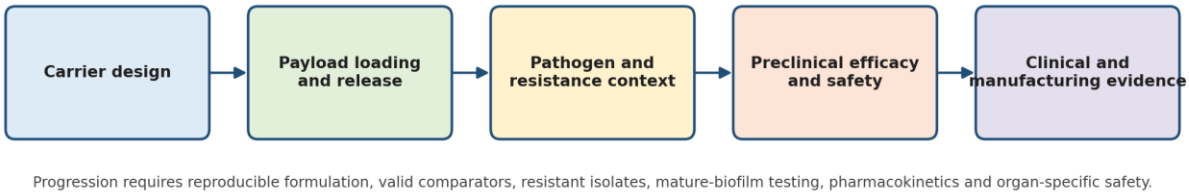

Figure 1. Evidence pathway for translation of nanocarrier antimicrobial formulations.

5. FUTURE DIRECTIONS

Future studies should compare each nanoformulation with dose-equivalent free antimicrobial and empty-carrier controls. Particle size, surface charge, loading, encapsulation efficiency, stability and release kinetics should be reported using reproducible methods. Resistance should be confirmed using recognized susceptibility standards, and claims of resistance reversal should require restoration of susceptibility according to accepted breakpoints together with mechanistic evidence.

Biofilm experiments should distinguish attachment prevention, maturation inhibition, biomass disruption and killing within established biofilms. Promising formulations should advance to appropriate animal infection models incorporating pharmacokinetics, biodistribution, repeated-dose toxicity and relevant organ-specific outcomes. Colistin systems particularly require renal biomarkers and kidney histopathology. Clinical translation will additionally require scalable production, batch consistency, sterilization validation and comparison with current standards of care.

6. CONCLUSION

Nanocarrier-mediated antimicrobial delivery is a promising experimental strategy against resistant ESKAPE pathogens. Selected formulations improved antibacterial activity, inhibited biofilm development, supported sustained release or enhanced local delivery. These advantages were not universal: outcomes depended on the carrier, payload, pathogen and experimental design, and some formulations performed no better or worse than free treatment. Current evidence therefore supports cautious, formulation-specific development rather than a general conclusion that encapsulation overcomes antimicrobial resistance. Standardized testing, mature-biofilm models, comprehensive safety assessment and clinically relevant comparative studies are required before routine therapeutic application.

DECLARATIONS

Author contributions: Vishwajeet Arya: literature evaluation, critical review and manuscript revision. Faiza Mohammad Mubin Shaikh: conceptualization, literature searching, evidence extraction and initial manuscript preparation. Both authors contributed to interpretation of the literature, reviewed the manuscript and approved the final version

Acknowledgements: None.

Funding: The authors received no specific funding for this work.

Conflict of interest: The authors declare no conflict of interest.

Ethics approval: Not applicable; this article reviews previously published literature and involved no new human or animal participants.

Data availability: No new datasets were generated. The information synthesized is available in the cited publications.

7. REFERENCES

1. Antimicrobial Resistance Collaborators. Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis. Lancet. 2022;399(10325):629-655. DOI: 10.1016/S0140-6736(21)02724-0.
2. Rice LB. Federal funding for the study of antimicrobial resistance in nosocomial pathogens: no ESKAPE. J Infect Dis. 2008;197(8):1079-1081. DOI: 10.1086/533452.
3. World Health Organization. WHO bacterial priority pathogens list, 2024. Geneva: World Health Organization; 2024.
4. Mulani MS, Kamble EE, Kumkar SN, Tawre MS, Pardesi KR. Emerging strategies to combat ESKAPE pathogens in the era of antimicrobial resistance: a review. Front Microbiol. 2019;10:539. DOI: 10.3389/fmicb.2019.00539.
5. Abd El-Hamid MI, Ibrahim D, Elazab ST, Gad WM, Shalaby M, El-Neshwy WM, et al. Tackling strong biofilm and multi-virulent vancomycin-resistant Staphylococcus aureus via natural alkaloid-based porous nanoparticles: perspective towards near future eradication. Front Cell Infect Microbiol. 2024;13:1287426. DOI: 10.3389/fcimb.2023.1287426.
6. Milani F, Adibkia K, Hamishehkar H, Gholikhani T, Bani F, Milani M. Increased antibiofilm and growth inhibitory effect of imipenem/cilastatin nanoliposomes against clinical Pseudomonas aeruginosa isolates. J Mater Sci Mater Med. 2023;34:47. DOI: 10.1007/s10856-023-06752-0.
7. Milani M, Shokri R, Hamishehkar H, Zakeri-Milani P, Aghazadeh M. Synthesis and evaluation of polymeric micelle containing piperacillin/tazobactam for enhanced antibacterial activity. Drug Deliv. 2019;26(1):1292-1299. DOI: 10.1080/10717544.2019.1693708.
8. Scutera S, Argenziano M, Sparti R, Bessone F, Bianco G, Bastiancich C, et al. Enhanced antimicrobial and antibiofilm effect of new colistin-loaded human albumin nanoparticles. Antibiotics (Basel). 2021;10(1):57. DOI: 10.3390/antibiotics10010057.
9. Martínez-Guitián M, Sanjurjo L, Vázquez-Ucha JC, Muras A, Beceiro A, Crecente-Campo J, et al. Nanoemulsion-based colistin for pulmonary delivery: enhanced antibacterial efficacy against Acinetobacter baumannii. Drug Deliv Transl Res. 2026;16(7):2474-2487. DOI: 10.1007/s13346-026-02083-z.
10. Drulis-Kawa Z, Gubernator J, Dorotkiewicz-Jach A, Doroszkiewicz W, Kozubek A. In vitro antimicrobial activity of liposomal meropenem against Pseudomonas aeruginosa strains. Int J Pharm. 2006;315(1-2):59-66. DOI: 10.1016/j.ijpharm.2006.02.017.
11. Oliva R, Ginestra G, Piperno A, Mazzaglia A, Nostro A, Scala A. Harnessing the power of PLA-PEG nanoparticles for linezolid delivery against methicillin-resistant Staphylococcus aureus. Int J Pharm. 2023;642:123067. DOI: 10.1016/j.ijpharm.2023.123067.
12. Roy A, Mate CC, Kumari K, Khatak D, Patel AK, Jeza Almotairi RM, et al. Bovine serum albumin-chitosan nanoparticles loaded with Cordyceps militaris extract: a novel approach to combat MDR bacteria. Microb Pathog. 2025;205:107662. DOI: 10.1016/j.micpath.2025.107662.

*****