Chapter 12
Nanoformulations Against Multidrug-Resistant Members of ESKAPE Pathogens

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Abstract The rise and spread of antimicrobial resistance (AMR) and drug-resistant nosocomial infections have become a significant global threat for human health and well-being. Injudicious and persistent antibiotic usages have resulted in the creation of drug-resistant microorganisms. Multidrug-resistant (MDR) ESKAPE pathogens consisting of *Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and *Enterobacter* spp. have been reported to raise the mortality and the expense of long-term therapy, significantly. With the drying pipeline of novel-efficient drugs declining, urgent need for novel therapies is required. Nanotechnology is a rapidly growing field of research with tremendous applications in medicine owing to their tiny size and extensive surface area. Recent reports on nanoformulations against MDR ESKAPE pathogens have revealed their enhanced therapeutic efficiency, bioavailability, target specificity, and antimicrobial activity confirming their potential role in nanoformulation strategies to combat ESKAPE pathogens. In this chapter, we discuss about the evolution of the resistance mechanisms in ESKAPE pathogens and how these pathogens are posing a serious threat for human health and environment. The chapter further discusses on the potential exploration of nanoformulations as emerging combating tool against ESKAPE with their drug delivery applications to these drug

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resistance determinants. Finally, we discuss about the various challenges faced for implementing ESKAPE nanoformulations in clinical settings.

Keywords Antimicrobial resistance · Drug resistance determinants · Biofilm · ESKAPE · Multidrug resistance · Nanoformulations

12.1 Introduction

In 1928, the miraculous medication penicillin ushered in the age of infections and had a huge impact on contemporary medicine since then. Injudicious antibiotic usage and continuous infection exposures have resulted in the overall rise of multidrug resistance (MDR) bacteria in nosocomial-related areas/regions. Recent reports on hospital-acquired infections (HAI) have identified ESKAPE pathogens as one of the major microorganisms resisting in these areas (Avershina et al. 2021). The ESKAPE microorganisms comprise of six major drug-resistant pathogens, i.e., ***E****nterococcus faecium*, ***S****taphylococcus aureus*, ***K****lebsiella pneumoniae*, ***A****cinetobacter baumannii*, ***P****seudomonas aeruginosa*, and ***E****nterobacter* spp. making them a major group of microorganisms involved in life-threatening nosocomial infections (Santajit and Indrawattana 2016). In 2017, the World Health Organization (WHO) produced a list of pathogens causing MDR infections for which new antimicrobials/antibiotics are urgently required to concentrate and steer research and developments (De Oliveira et al. 2020) enlisting ESKAPE pathogens as a critical priority 1 pathogens revealing their looming threat to humanity in upcoming years (Asokan et al. 2019). Similar reports were reviewed by the Department of Biotechnology (DBT) in India with *K. pneumoniae*, *A. baumannii*, and *P. aeruginosa* as critical priority pathogens, *Staphylococcus aureus* and *Enterobacter* spp. as high-priority pathogens, while others in medium-priority pathogens list (DBT 2021).

Antimicrobial resistance (AMR) or antibiotic resistance (ABR) has become a global health threat where these microorganisms acquire new resistance mechanisms becoming "superbugs" and causing non-treatable MDR infections (Morrison and Zembower 2020). The rise of MDR bacteria has coincided with the drying up of the antibiotic research pipeline. To overcome these AMR situations, several attempts to find effective and innovative antibacterial drugs have been made in recent years. However, delivering powerful antimicrobial drugs in a safe and efficacious manner has proven to be a huge challenge. The use of nanotechnology has emerged as a proven and efficient tool for eradicating MDR and AMR. Recent advancements in the nanoformulations of drugs and other antimicrobials for targeting MDR ESKAPE pathogens have been proven to be advantageous concerning bioavailability, cost-effectiveness, efficiency, target specificity, and antimicrobial activity (Mba and Nweze 2021) that target antimicrobial resistance determinants such as biofilms, efflux pumps, cell membrane, and other enzyme production

mechanisms (Peterson and Kaur 2018). In this chapter, we highlight the evolution of ESKAPE pathogens and their resistance mechanisms in the environment. Nanoformulation is the newer technology to combat ESKAPE; further, we discuss various nanoformulation-based drug delivery to drug resistance determinants. At last, we discuss the challenges in implementing these nanoformulations in clinical trials and clinical settings.

12.2 ESKAPE Pathogens and Evolution of Their Resistance Mechanisms

The abbreviation "ESKAPE" refers to a collection of life-threatening nosocomial pathogens, viz., ***E****nterococcus faecium*, ***S****taphylococcus aureus*, ***K****lebsiella pneumoniae*, ***A****cinetobacter baumannii*, ***P****seudomonas aeruginosa*, and ***E****nterobacter* spp. (Pandey et al. 2021). The development of various antibiotics against these pathogens has led to the development of different resistance mechanisms for them to escape the antibiotics and survive in the environment. The development and marketing of new antibiotics and antimicrobials have slowed down since the 1990s (Conly and Johnston 2005). In the twentieth century, discoveries of antibiotic combinations such as imipenem/cilastatin/relebactam (Mansour et al. 2021), niclosamide-tobramycin (Berry et al. 2021), meropenem-vaborbactam (Patel et al. 2018), imipenem-relebactam (Zhanel et al. 2018), eravacycline-colistin (Ozger et al. 2019), and other combinations enhanced the targeting of pathogens.

12.2.1 Vancomycin-Resistant Enterococcus faecium *(VRE*fm*)*

In the 1980s, *E. faecium* and *E. faecalis*, well-known for gut commensal bacteria, became a prominent source of MDR hospital-acquired illness (Lebreton et al. 2013). *E. faecium* therapeutic importance stems from its inherent poor sensitivity to a wide range of antimicrobial drugs, including third-generation cephalosporins, vancomycin, ampicillin, and other antibiotics (Table 12.1) (Kolář 2018). Antibiotic exposure usually precedes VRE*fm* entry into the bloodstream of hospitalized patients, allowing VRE*fm* to become the dominant species in the gastrointestinal tract (De Oliveira et al. 2020; Carvalhaes et al. 2021). Other strains such as glycopeptide-resistant *Enterococcus faecium* ST80 and ST117 are also found to be residing in a healthcare facility (Rodríguez-Lucas et al. 2021). Apart from various antibiotics, small RNAs present in VRE*fm* are recently been found to be involved in daptomycin resistance (Sinel et al. 2017). Exposure to multiple drugs, VRE*fm* has developed various resistance mechanisms to survive the drug exposures in nosocomial areas. Virulence factors such as *asa1*, *gel E*, *cylA*, *esp*, *hyl*, and *Van*; resistance genetic determinants such as *vanA*, *vanB*, *vanM*, *vanN*, and *vanD*; and *D1*, *D2*, *D3*, *D4*, and *D5* resistant

Table 12.1 Clinical manifestation and drug resistance determinants of ESKAPE pathogens

ESKAPE pathogens	Antibiotic resistance	Clinical manifestations	Drug resistance determinants					References
			Cell membrane	Efflux pumps	Biofilm formation	Quorum sensing	Other mechanisms	
Enterococcus faecium	Vancomycin, ampicillin, linezolid, teicoplanin, piperacillin, cephalosporins	Bacteraemia, infective endocarditis, intra-abdominal and pelvic infections, urinary tract infections, central nervous system infections, skin and skin structure infections	Phosphatidylglycerol (PG), cardiolipin, lysyl-phosphatidylglycerol (LPG), and glycerolphospho-diglycodiacylglycerol (GP-DGDAG) rearrangement	EfrAB, EfmA	Hemolytic exotoxin (encoded by *cyl*), gelatinase (encoded by *gelE*), serine protease (encoded by *sprE*), hyaluronidase (encoded by *hyl*), endocarditis- and biofilm-associated pili genetic locus (*ebp*ABC), sortase-encoding gene (*srt*), pili (*pil*), aggregation substance (*agg* and *asa1*), collagen-binding protein (*ace*), enterococcal surface protein (*esp*), enterococcal endocarditis antigen (efaAfm for *E. faecium*)	Fecal streptococci regulator (*fsrA, fsrB, fsrC*)	Transposon genes (*inf*Tn916, tndX), plasmid rep genes, mutations in GyrA, ParC	Nishioka et al. (2009), Mishra et al. (2012), Lavilla Lerma et al. (2014), Miller et al. (2014), Sadowy and Luczkiewicz (2014), O'Driscoll and Crank 2015, Stępień-Pyśniak et al. (2019)

Staphylococcus aureus	Penicillin, methicillin, oxacillin, vancomycin, daptomycin, tetracyclines, linezolid	Vascular catheter-related infections, skin and soft tissue infections (SSTIs), pleuropulmonary infections, osteoarticular infections, infective endocarditis, impetigo, osteomyelitis, septic arthritis	Lower cell permeability led to defect in energy metabolism resulting in reduced drug intake	QacA, NorA, Nor B, NorC, MepA, MdeA, QacA/B, QacG, QacH, QacJ, LmrS, and Smr	crtN, hemolysin genes (*hld, hlb, hla*), *cap*8H, *tst, sea, eta, etb*, *cap*5H, *seb, see, sec*, and *sed*	Accessory gene regulator (Agr) system, *LuxS*	Transposon Tn552 or Tn552-like elements, e SCC mec elements, mecA gene, mutation in e multiple peptide resistance factor (mrpF) gene	Costa et al. (2013), Le and Otto (2015), Tong et al. (2015), Foster (2017), Derakhshan et al. (2021)
Klebsiella pneumoniae	Carbapenem, cephalosporin, piperacillin-tazobactam, ciprofloxacin, levofloxacin, and amikacin	Pneumonia, pyogenic liver Abscess, urinary tract, respiratory tract, lung, wound sites and bloodstream infections	Outer membrane protein A (ompA), lipid A modification	AcrAB, tolC, mdtK, OmpK35, OmpK36	Capsular polysaccharides, type 1 and type 3 fimbriae, virulence-associated genes (*mrkD, fimH-1, entB, iutA, ybtS*)	*LuxS*, autoinducers of signal system I (AI-1)	Extended-spectrum β-lactamase (ESBLs) and carbapenemase enzyme	Balestrino et al. (2005), Chung (2016), Ferreira et al. (2019), Nirwati et al. (2019)
Acinetobacter baumannii	Piperacillin, ceftazidime, amikacin, tetracycline, ampicillin-sulbactam, meropenem, ciprofloxacin, imipenem, and gentamicin	Ventilator-associated pneumonia, central line-associated bloodstream infection, catheter-associated urinary tract infection, surgical site infection	OmpA, K1 capsule, CarO, modification of LPS	AdeABC, AdeFGH, AdeIJK, AbeM, MacAB-TolC, EmrAB-TolC, A1S_1535, A1S_2795, and ABAYE_0913	Fimbriae, *plc*N and *las*B genes, *bap* gene	Auto inducers (AHLs),	β-Lactamase (TEM, SHV, GES, CTX-M, SCO, PER, VEB, KPC, OXAs, IMP, VIM, CARB, and AmpC), insertion sequence element (ISAba1-like sequence)	Kanafani and Kanj (2016), Lee et al. (2017), Aliramezani et al. (2019), Basatian-Tashkan et al. (2020)

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Table 12.1 (continued)

ESKAPE pathogens	Antibiotic resistance	Clinical manifestations	Drug resistance determinants					References
			Cell membrane	Efflux pumps	Biofilm formation	Quorum sensing	Other mechanisms	
Pseudomonas aeruginosa	Aminoglycosides, quinolones and β-lactams	Central venous catheter infections, pneumonia, soft tissue infections, urinary tract infections, and sinusitis	Bacterial cell wall biosynthesis blockage, OprF, OprB, OprD, OprE, OprO, OprP, OprC, OprH, OprM, OprN, and OprJ	MexAB-OprM, MexCD-OprJ, MexEF-OprN, MexXY-OprM,	GacS/GacA system, extracellular DNA (eDNA)	LasI-LasR, RhlI-RhlR, and PQS-MvfR QS system	Extended-spectrum-β-lactamases (ESBLs); gene mutations of transcriptional regulators, *mexR, nalB, nalC,* or *nalD*, DNA gyrase (gyrA and gyrB); topoisomerase IV (parC and parE)	Dropulic et al. (1995), Pang et al. (2019)
Enterobacter spp.	Carbapenem, chloramphenicol, tetracycline, tigecycline, fluoroquinolones, trimethoprim	Endophthalmitis, brain abscess, meningitis, spondylodiscitis, endocarditis, urinary tract infections (UTIs)	Alteration of outer membrane (OM) permeability, lipopolysaccharide (LPS) modifications, porins (Omp35, Omp36, Omp37, LamB and PhoE)	AcrAB-tolC, AcrZ-AcrAB-TolC	Curli fimbriae, virulence-encoding (ter and sea) and resistance-encoding (blaCTX-M-9, qnrA1, aadB, aadA2, sukK, and sat) genes	Type 6 secretion system (T6SS2), C4 and C6-HSLs quorum sensing molecules, AHL signaling molecules	Mutations in phoQ, ampR, and pmrB, deletion of mcr-1 and mcr-2	Davin-Regli et al. (2019), Lazar et al. (2021)

to vancomycin and teicoplanin have been discovered in VRE*fm*-associated infections (Kiruthiga et al. 2020) (Ahmed and Baptiste 2018). Recent reports on the spread of VRE*fm* strain ST133 into the aquatic environment have been reported with vancomycin resistance-conferring *van*A gene cluster on transposon Tn*1546* (Biggel et al. 2021).

12.2.2 Methicillin-Resistant Staphylococcus aureus *(MRSA)*

The introduction and overuse of penicillin in the nineteenth century accelerated the emergence and spread of penicillinase-producing methicillin-resistant *Staphylococcus aureus* (MRSA). However, the first report of MRSA with reduced susceptibility to drug vancomycin came from Thailand (Trakulsomboon et al. 2001). Reports have confirmed the resistance of MRSA organisms to trimethoprim, ß-lactamase, chloramphenicol, tetracycline, and aminoglycosides (De Oliveira et al. 2020). Current economic considerations have steered biopharmaceutical firms away from new antibiotic research and approvals, leaving drug-resistant *S. aureus*-infected patients with little choice (Fukunaga et al. 2016). With a tendency to colonize and form biofilms, certain strains of MRSA have contributed to the spread of hospital-acquired MRSA (HA-MRSA) (Turner et al. 2019). However, the growing prevalence of community-acquired MRSA (CA-MRSA) has significantly become the major risk factor for their colonization in India (Mehta et al. 2020). MRSA has developed numerous resistant mechanisms to thrive in the environment. They express virulence factors such as hemolysin and leukocidin toxins and capsule and protein A immune-evasive surface factors as the line of defense (Turner et al. 2019). Apart from virulence factors, mobile genetic elements (MGEs) such as *blaZ*, *dfrA*, *dfrK*, *ermC*, *tetK*, and *tetL* have been identified to play a major role in providing resistance to penicillin, trimethoprim, erythromycin, clindamycin, and tetracycline antibiotics, respectively (Turner et al. 2019). The continuous exposure of bacteria to antibiotics has led to genetic changes and the production of other resistant strains such as vancomycin-resistant *S. aureus* (McGuinness et al. 2017).

12.2.3 Klebsiella pneumoniae

Klebsiella pneumoniae, gram-negative and clinically significant microorganisms, has sparked widespread public concern becoming a major albatross around the infection control professionals with majorly causing urinary tract infections (UTIs), pneumonia, surgical wound infections, cystitis, endocarditis, and septicemia (Effah et al. 2020). Third generation Cephalosporins (beta-lactam antimicrobials) and carbapenems are used for treating severe infections caused by Klebsiella pneumonia (Karaiskos et al. 2019). For the past few years, drug resistance rates of *K. pneumoniae* strains obtained from hospitals and other healthcare systems have increased dramatically leading to the emergence of extensively drug-resistant (XDR) *K.*

Table 12.2 Nanoformulations against major drug resistance determinants with their antimicrobial agents

Nanoformulation	Antimicrobial agent included in nanoformulation	Bacterial pathogens	Nanoformulation concentration	Targeted drug resistance determinant	Advantages provided by nanoformulation	References
Lipid-polymer hybrid nanoparticle loading the antibiotic linezolid (LIN-LPN)	Linezolid antibiotics	Methicillin-resistant *Staphylococcus aureus* (MRSA)	2–8 μg/ml	Bacterial biofilm	High linezolid payload (12% by weight of nanoparticles) and controlled released characteristic of antibiotics with MRSA biofilm growth Suppressed by 35–60% of the values achieved with free linezolid	Guo et al. (2020)
PEG-PLGA NPs that synergistically carried benzamide and rutin (RB-PEG-PLGA NPs)	Rutin and benzamide	MDR bacterial strains (*S. aureus* (MTCC 96) and *P. aeruginosa* (MTCC 2488))	180 μg/ml (for *S. aureus*) and 160 μg/ml (for *P. aeruginosa*)	Disruption of bacterial membrane and biofilm surface	Controlled release of antibacterial agents and 2 times lowered MIC as compared to free drugs with no toxicity against tested using human erythrocytes and human cell lines	Deepika et al. (2020)
Solid lipid nanoparticles of silver sulfadiazine (SSD-SLNs) laden chitosan gel supplemented with DNase-I	Silver sulfadiazine	*Pseudomonas aeruginosa* PA01 (ATCC 15692)	18.75 μg/mL	Bacterial biofilm	Improved cell viability of SSD-SLNs (90.3 ± 3.8%) as compared to SSD alone (76.9 ± 4.2%) and controlled release (83%) for up to 24 h further, the combination of SSD SLNs with DNase-I, inhibited around 96.8% of biofilm of *P. aeruginosa* as compared to SSD with DNase-I (82.9%), complete wound healing by SSD-SLN with DNase-I as compared to SSD and SSD-SLNs after 21 days	Patel et al. (2019)

Imipenem-loaded poly Ɛ-c aprolactone (PCL) nanoformulation (IMP/PCL)	Imipenem antibiotics	Imipenem-resistant *P. aeruginosa* and *Klebsiella pneumonia* clinical isolates	0.6–20 µg/mL	Bacterial biofilm	Faster microbial killing with 2–3 hours by (IMP/PCL), compared to the imipenem-loaded polylactide-co-glycoside (PLGA) and free drug, protection of imipenem from enzymatic degradation by resistant isolates, lowered the mutation prevention concentration of free imipenem by twofold, thereby preventing the emergence of resistance colonies, and eliminated bacterial attachment and biofilm assembly by 74 and 78.4%	Shaaban et al. (2017)
Quorum sensing inhibitor (ajoene) loaded nanoparticles (QSINPs) using the biopolymers, chitosan (CS), and dextran sulfate (DS) polymer	Ajoene	*Pseudomonas aeruginosa* PAO1	600 mg/kg body weight of infected mice	Quorum sensing regulated virulence and bacterial biofilm	Developed nanoformulation QSINPs exhibited double-fold anti-virulence activity than solo QSI agent against *P. aeruginosa*, further exhibited around 73–97% reductions ($p < 0.5$) in virulence factors when nanoformulation combines with ciprofloxacin. In addition, QSINP nanoformulation also showed around 1.75 log reductions in biofilm alone and 4.3 log reduction when combined with CIP	Vadekeetil et al. (2019)

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Table 12.2 (continued)

Nanoformulation	Antimicrobial agent included in nanoformulation	Bacterial pathogens	Nanoformulation concentration	Targeted drug resistance determinant	Advantages provided by nanoformulation	References
Antimicrobial silver nanoparticles (AgNPs) decorated in a layer-by-layer fashion with the oppositely charged aminocellulose (AM) and acylase (LbL ag@ AM_AC NP)	Aminocellulose (AM) and acylase (AC)	*P. aeruginosa* (ATCC 10145)	(6.25×10^7 NPs mL^{-1})	Bacterial biofilm and QS-related virulence factor	Eightfold lower MBIC (6.25×10^7 NPs mL^{-1}) and MBEC (1.25×108 NPs $mL - 1$) of the NPs decorated with AM and the anti-QS enzyme was observed compared to stand-alone AgNPs template demonstrating the effectiveness of nanoformulation in inhibiting QS-regulated pathological processes and at the same time eliminating the biofilm-forming bacteria at a lower dosage of the bactericidal agent, thus exerting less evolutionary pressure on bacteria for resistance development	Ivanova et al. (2020)

pneumoniae (resistant to carbapenem and cephalosporin) (CRPK) (Bi et al. 2017). A rise in CRPK bacteria-producing severe diseases was documented between 2005 and 2010 (Paczosa and Mecsas 2016). Several mechanisms such as extended-spectrum beta-lactamase (ESBLs), serine carbapenems, acquisition of MGEs, 16 s rRNA methyltransferase, cephalosporinases, topoisomerase, gyrase, LPS and PmrA-PmrB two-component genetic modification, plasmid-mediated quinolone resistance (PMQR), aminoglycoside-modifying enzyme (AME), and Mcr1 gene mutations are the prevalent resistance mechanisms among the XDR *K. pneumoniae* (Karaiskos et al. 2019). $bla_{CTX\text{-}M}$ and bla_{SHV} genes are the major ESBL virulence genes isolated from the clinical and healthcare systems (Carvalho et al. 2021). Recent investigations have revealed the involvement of efflux pumps (AcrAB-TolC), insertion elements (IS1, IS3), and integrons (Intl1) in the clinically isolated pan-resistant *K. pneumoniae* strains with overexpression of *acrB*, *ramA*, *phoQ*, and *phoP* virulence genes (Lv et al. 2021).

12.2.4 Acinetobacter baumannii

These microorganisms are typically found in hospital-acquired infections with high incidences in immunocompromised individuals referring to them as "red alert" microorganisms (Howard et al. 2012). *Acinetobacter* is commonly implicated in infections that are hospital-acquired or community-acquired and infect bloodstream, meningitis, wounds, and pneumonia (Morris et al. 2019). Various antimicrobials and therapies such as bacteriophage, gene transfer, radioimmunotherapy, photodynamic therapy, nanoparticles, and cathelicidins have been used to eradicate drug-resistant *Acinetobacter* (Howard et al. 2012). Reports have described the outbreak of *A. baumannii* in the neonatal intensive care units (NICUs) in Latvia with increased risk to newborns as HAIs (Gramatniece et al. 2019). Such infection outbreaks are certainly linked to the multidrug resistance acquired by the bacteria via injudicious or continuous exposure to antibiotics. In 2000, endemic carbapenem-resistant *A. baumannii* (resistant to carbapenems and other antibiotics) was reported in Brooklyn, New York, involving the strategies and practices to control the spread of MDR (Manikal et al. 2000). Further outbreak of *A. baumannii* in 2012–2013, accumulation of carbapenem resistance genes (*oxa23* and *oxa24*), tetracycline resistance genes (*tet39*), *sul2* gene (encoding sulfamethoxazole resistance), and *aadB* gene cassette (encoding gentamicin, kanamycin, and tobramycin resistance) in bacterial isolates from Tehran burns hospital were reported (Douraghi et al. 2020). Other virulence factors such as porins (OmpA), trimeric autotransporters, FhaBC secretion system, RecA, PmrAbB, and biofilm-associated proteins (BAPs) are also found to be produced by bacteria in biofilms and other environmental conditions (Mea et al. 2021).

12.2.5 Pseudomonas aeruginosa

Pseudomonas aeruginosa is a gram-negative bacterium that belongs to the family *Pseudomonadaceae.* It is the most opportunistic bacterium and is mostly associated with nosocomial infections and ventilator-associated pneumonia (Barbier et al. 2013). *P. aeruginosa* infections have become a great challenge because of its resistance to currently available antibiotics. (Lister et al. 2009). The World Health Organization (WHO) listed this carbapenem-resistant *P. aeruginosa* in the critical priority list to which there is an urgent need of developing new antibiotics. Studies have found *P. aeruginosa* mainly resistant to the aminoglycosides, beta-lactams, and quinolones. Antibiotic resistance in *P. aeruginosa* can be classified as intrinsic and acquired/adaptive resistance where production of antibiotic resistance enzymes, expression of efflux pumps, and low outer membrane permeability are seen with the acquired resistance of *P. aeruginosa* achieved by the horizontal gene transfer (HGT) or mutational changes. It also involves biofilm formation in the lungs of infected patients. In *P. aeruginosa* outer membrane acts as a selective barrier to prevent antibiotic penetrations, with the porins classified as specific (OprB, OprD, OprE, OprO, and OprP), non-specific (OprF), gated (OprC and OprH), and efflux (MexAB-OprM, MexCD-OprJ, MexEF-OprN, and MexXY-OprM) porins (Hancock and Brinkman 2002) contributing to antibiotic resistance (Dreier and Ruggerone 2015). MexAB-OprM is responsible for efflux of β-lactams and quinolones (Masuda et al. 2000; Dupont et al. 2005). MexCD-OprJ is able to pump out β-lactams (Okamoto et al. 2002). MexEF-OprN is capable of extruding quinolones (Llanes et al. 2011), while MexXY-OprM expels aminoglycosides (Masuda et al. 2000; Hocquet et al. 2003). *P. aeruginosa* possesses an inducible *ampC* gene, encoding the hydrolytic enzyme β-lactamase responsible for breaking the amide bond of β-lactam ring, leading to the inactivation of β- lactam antibiotics (Wright 2005). Further, mutational changes can also cause modification of antibiotic targets, reduced antibiotic uptakes, and antibiotic-inactivating enzymes.

12.2.6 Enterobacter spp.

Enterobacter, another gram-negative bacillus, is the microorganisms mostly involved in the nosocomial infections belonging to the family *Enterobacteriaceae*. To date, almost 22 species of *Enterobacter* have been identified that confer many drugs resistance genes such as cephalosporins in *Enterobacter cancerogenus*, carbenicillin to *Enterobacter asburiae*, and β-lactams to *Enterobacter cloacae* (Davin-Regli et al. 2019). *Enterobacter* is found to be highly resistant to carbapenems polymyxins, tigecycline, fosfomycin, and carbapenems (used in a double carbapenem regimen) leading to UTI infections (Ramirez and Giron 2020). In the early 1990s, the most common cause of *Enterobacter* nosocomial infections was *E. aerogenes* that led to the spread of pandemic clones in Western Europe (De Oliveira

et al. 2020). However, the spread and persistence of these microorganisms in the twenty-first century led to the production of carbapenem-resistant *Enterobacter* (Codjoe and Donkor 2017). Various virulence factors/genes involved are enlisted in Table 12.1.

12.3 Nanoformulations as an Emerging Combating Tool Against ESKAPE Pathogens

The incredible potential of nanoformulations in the pharmaceutical area to enhance healthcare has piqued scientists' interest, promoting substantial study throughout the world to gain a competitive advantage. Several nanoformulated products are studied in human research with approval by US Food and Drug Administration (FDA) for treating drug-resistant infections and other diseases. The rapid advancement of nanotechnology has dominated the drug delivery sector resulting in the development of drug-formulated deliveries with several clinical testing (Khiev et al.

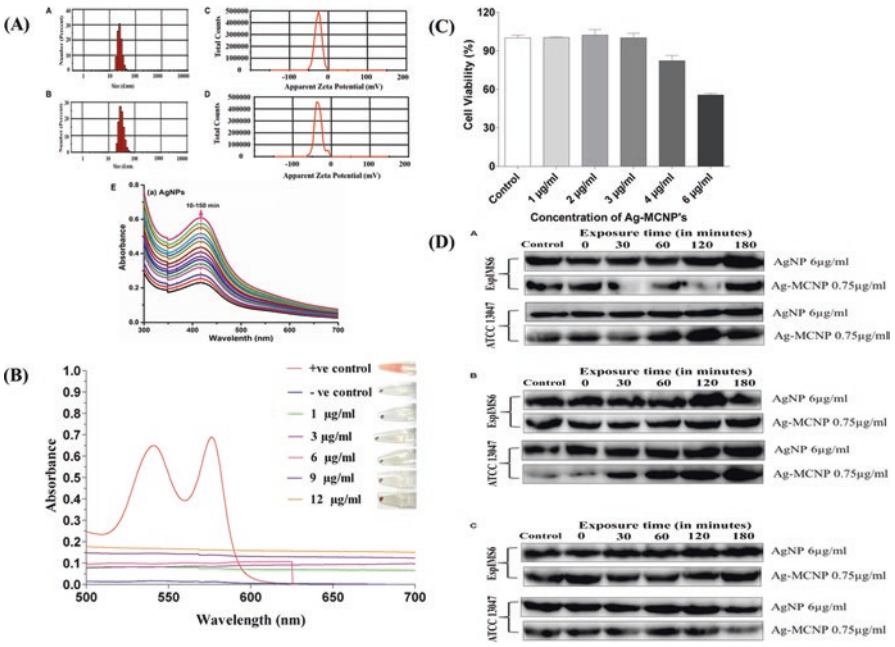

Fig. 12.1 Antibacterial efficacy of polysaccharide-capped silver nanoparticles against MDR *Enterobacter cloacae* clinical isolate (EspIMS6) harboring multidrug efflux system AcrAB-TolC; (**a**) characterization of Ag-NPs; (**b**) hemolysis activity of Ag-NPs; (**c**) cytotoxicity assay of Ag-MCNPs on macrophage RAW 264.7 cell line; (**d**) effect of silver and silver-metal composite nanoparticles on AcrAB-TolC expression. (Reproduced from Mishra et al. (2018) https://doi.org/10.3389/fmicb.2018.00823 under Creative Commons; Copyright Frontiers Media, Switzerland)

2021). ESKAPE pathogens being on the priority list of several countries, various nanoformulations have been developed and are under development for treating infection caused by MDR organisms (Lee et al. 2019). Nanoformulations involve formulation in surface chemistry, reactivity, and other properties of nanosized materials making them useful in other applications of environmental science, engineering science, cosmetology, etc. (Siddiqui et al. 2020). Nanocrystals, nanoemulsions, micellar encapsulation, nanodendrimers, and nanoliposomes are some examples of nanoformulations that enhance drug solubility, bioavailability, drug efficiency, and targeting (Patra et al. 2018).

Nanoemulsions, also known as mini-emulsions, are the dispersing systems with kinetic stability that have emerged as the potential tool for addressing the bioavailability difficulties lined with weakly water-soluble medicinal compounds (Pandey and Kohli 2020). Besides bioavailability, nanoemulsions exhibit multifunctionalities for carrying numerous antimicrobials with dual targeting capabilities (Chime et al. 2014). Khan and Ramalingam (2019) investigated ten nanoemulsions against eight ESKAPE pathogen strains showing their antimicrobial efficiencies as antibiofilm agents. Besides nanoemulsions, erythromycin-conjugated nanodendrimers against *S. aureus*, *S. epidermidis*, *S. saprophyticus*, and P. aeruginosa have shown great antimicrobial, bacteriostatic, and bactericidal activities with sustainable delivery of drug to the target site (Fallah et al. 2018). Recent technology of combining nanoformulations with antimicrobial peptides (AMP) has attracted researchers as natural host defense peptides against AMR (Mukhopadhyay et al. 2020). AMP dendrimers against MDR ESKAPE pathogens have improved the drug/antimicrobials targeting, pharmacokinetics, and efficiency (Kawano et al. 2020; Song et al. 2021). Patrulea et al. (2021) studied the synergistic effects of antimicrobial peptide dendrimer-chitosan polymer conjugates against *P. aeruginosa* via damaging cell membrane with the absence of toxicity to mammalian cells. Recently, nanoformulation of colistin-loaded human albumin nanoparticles (Col/haNPs) against MDR *Acinetobacter* and *Klebsiella* resulted in the decline of bacterial growth over time and inhibition of biofilm formation representing Col/haNPs as a promising tool with greater antimicrobial activity (Scutera et al. 2021).

12.4 Nanoformulation-Based Drug Delivery to Drug Resistance Determinant in ESKAPE

Ineffectiveness of existing drugs and the emergence of multidrug resistance in ESKAPE led to the development of novel strategies that can efficiently reverse multidrug resistance. Recent leads showed that nanoformulation-based drug delivery of antimicrobial agents against drug resistance determinants is an effective strategy to tackle multidrug resistance in ESKAPE as they effectively restore the efficacy of old unresponsive antibiotics and reduce toxic side effects associated with higher drug doses by reducing minimum inhibitory concentration without contributing to

resistance emergence; for example, ampicillin silver nanoformulation showed MIC in range of 3–28 μg/ml (lower than the MIC of ampicillin alone (12–720 μg/ml)) against ampicillin-resistant *E. coli* and *S. aureus* and multidrug-resistant *Pseudomonas aeruginosa* and *Klebsiella pneumoniae* (Khatoon et al. 2019). Further studies on bacterial strain did not show any resistance development even after exposure to ampicillin silver nanoformulation up to 15 successive cycles demonstrating the emergence of resistance against ampicillin silver nanoformulation (Khatoon et al. 2019). Another study reported enhanced antibacterial effect nanoformulation of biogenic cefotaxime conjugated-silver nanoparticles with the highest reduction in MIC [26–96%] against cefotaxime-resistant MDR *E. coli* and *MRSA* and no cytotoxic effect on normal cell lines (human RPE-1), restoring the efficacy of otherwise unresponsive cefotaxime (Halawani et al. 2020) highlighting the need to incorporate nanoformulation strategies into the development of next-generation antimicrobial therapeutics (Table 12.2).

12.4.1 Cell Wall, Cell Membrane, and Membrane Permeabilization

Bacterial cell wall/membrane makes up the first and most powerful line of bacterial defense preventing interaction of an antimicrobial agent with its target molecule. Membrane permeability plays an important role in providing a protective layer for regulating the inflow and intracellular concentration of antimicrobial agents; hence, the nanoformulation damaging bacterial cell becomes the prime focus of research for combating ESKAPE; for example, graphene (Gr)-based nanoformulation containing curcumin (C.C.M.) and zinc oxide nanoparticles (ZnO-NPs) displayed a wide range of anti-microbial activity against MRSA biofilm and also showed >five-fold improved inhibitory effect when GrZnO nanocomposites combined with curcumin (31.25 μg/ml M.I.C. of nanoformulation contrasting with GrZnO-NCs or C.C.M. alone having M.I.C. value of 125 μg/ml) with bacterial cell wall damage and cytoplasmic spillage as a major mechanism of inhibitory action, thereby diminishing their metabolism (Oves et al. 2020). In another study novel chitosan-mastoparan nanoconstruct (Mast-Cs NC) was designed and assessed for its therapeutic potential against clinical multidrug-resistant (MDR) *A. baumannii* and reported significantly lowered MIC nanoformulation compared to chitosan alone, with loss of cell membrane integrity (Hassan et al. 2021). Further, Thorat et al. (2021) synthesized gold nanorods (GNRs) coated pegylated thiol, mPEG-SH, further modified by adding curcumin, and a cell-targeting deoxyribonucleic acid (DNA) aptamer, displaying bacterial cell wall disruption and block in biofilm formation through photothermal action mechanism, and killing of MRSA due to the combination of photothermal effect, ROS generation, and transmembrane potential loss.

12.4.2 Biofilm Formation

Bacterial biofilm emerges as a severe health concern due to its multidrug resistance ability. Biofilm is defined as an intricate three-dimensional aggregation of bacteria attached to a surface and buried inflexibly in an extracellular polymeric substance matrix (Srinivasan et al. 2021) further helping bacteria to withstand the harsh environmental/physiological conditions or factors such as dehydration, antibiotic, biocides stress (Kaur et al. 2021) and played a major role emergence of multidrug resistance (MDR)/ pan-drug resistance (PDR)/ extensive drug resistance (XDR) by preventing the penetration of antibiotic inside the biofilm via EPS; increasing the chance for the genetic exchange among the bacterial species due to high population density and proximity of cells in biofilm; accumulation of antibiotic degrading enzymes; the presence of either non-growing cell (dormant or persister cells) /cells which triggered stress response under unfavorable chemical condition within the biofilm (Jolivet-Gougeon and Bonnaure-Mallet 2014; Balcázar et al. 2015; Srinivasan et al. 2021). Therefore, discovering novel strategies that can treat and prevent biofilm becomes the prime focus in combating AMR.

Nanoformulations such as chitosan oligosaccharide-capped gold nanoparticles (COSAuNPs) are shown to inhibit biofilm formation as well as eradication of preexisting mature biofilm, in addition to reduced virulence factor in *P. aeruginosa* (Khan et al. 2019). Similarly, curcumin-loaded poly(lactic-co-glycolic) acid nanoformulation with a drug loading of ~98 μg of curcumin/mg and release of ~45% of cargo displayed biofilm disruption and strong antibacterial activity compared to pure curcumin against *E. coli* and *S. aureus* (Kumari et al. 2020). Hydrophilic antibiotics such as gentamicin commonly used for treating *Pseudomonas* infection face problems such as relative short half-life limiting their application in clinical settings; therefore Abdelghany et al. (2012) developed a controlled-release gentamicin formulation using poly(lactide-co-glycolide) (PLGA) nanoparticles that enhance in vitro and in vivo antimicrobial effects off gentamicin on both planktonic and biofilm-based infection through controlled drug release from PLGA nanoparticles and optimized encapsulation. Further, this optimized formulation, when incorporated in murine peritoneal-infected mice model, resulted in both free and nanoparticle-encapsulated gentamicin effectively clearing the infection (both serum and peritoneal lavage) by the 96 hours suggesting nanoformulation could act as a potential agent exhibiting inhibitory properties against the ESKAPE pathogenesis arisen from biofilm formation (Abdelghany et al. 2012).

12.4.3 Quorum Sensing

The chemical communication process involved in the regulation of cooperative and communal activities in bacteria such as biofilm formation, virulence production, and bioluminescence is defined as quorum sensing (QS) (Qin et al. 2018). Hence

inhibition of quorum sensing has been emerged as a promising alternative to deal with MDR/XDR/PDR bacterial pathogens. Sharma et al. (2020) developed zingerone-loaded chitosan nanoparticles (Z-NPs) nanoformulation with 67% drug entrapment efficiency and pH-dependent controlled release of zingerone, when evaluated against *P. aeruginosa*, depicting significant downregulation of quorum sensing-related genes (*rhlR*, *rhlI*, *lasR*, and *lasI*), the complete absence of quorum sensing signaling molecules with the eradication of biofilm, and reduction of motility phenotypes (swimming, swarming, and twitching motilities). Similarly, nanostructured lipid carriers (NLCs) containing α-terpineol (αT) when evaluated against *P. aeruginosa* resulted in a significant reduction of gene expression of key QS-related genes (*lasI*, *lasR*, *rhlI*, and *rhlR*) and QS-associated genes (*rhlAB*, *toxA*, *lasB*, and *plcH*) with suppression of QS-related virulence factor production and biofilm formation compared to conventional antibiotics (Bose et al. 2020).

12.4.4 Efflux Pump Inhibition

In recent years, multidrug efflux pumps (EPs) are established as major determinants of AMR in both gram-negative and gram-positive bacteria, extruding multiple antibiotics, toxic substances, and metabolite out of cell mostly in a non-specific manner, playing a vital role in the process such as virulence, biofilm formation, stress adaptation, pathogenicity, and transportation of essential nutrient, hence emerging as a potential drug target for combating AMR (Shriram et al. 2018). Khan et al. (2020) synthesized dextran-capped gold nanoparticles (GNPDEX) with attached concanavalin-A (ConA) and methylene blue (MB) photosensitizer (MB@GNPDEX-ConA formulation) that showed the multitargeted killing of MDR *Klebsiella pneumoniae*, targeting major determinants of pathogenicity such as efflux pump, cell wall, and bacterial biofilm by the combined effect of both photodynamic therapy (PDT) and efflux pump inhibitor (carbonyl cyanide m-chlorophenylhydrazone). Further, they also reported 96.2, 92.9, 80.8, and 70% biofilm reduction in the presence of MB@GNPDEX-ConA nanoconjugate with varied concentrations of MB such as 20, 10, 5, and 2.5 μg/ml in the presence of EPI as compared to 80.8, 71.5, 53.9, and 38% reduction in control biofilm (absence of CCCP), further reporting bacterial killing by more than 3 log10 via PDT and EPI combinations, confirming EPI-based enhanced killing of MDR pathogens. In another study nanoliposome formulation co-loaded with piperine and gentamicin was investigated with remarkable inhibition and killing of MRSA pathogen via piperine-mediated inhibition of efflux pump and increased intracellular concentration of gentamicin (Khameneh et al. 2015), hence highlighting the importance of efflux pump inhibition in tackling multidrug resistance in ESKAPE. Figure 12.1 depicts the antibacterial efficacy of polysaccharide-capped silver nanoparticles against MDR *Enterobacter* species.

12.5 Challenges in Clinical Applications of ESKAPE-Combating Nanoformulations

Apart from the several advantages of nanoformulation such as protection of biomolecules from degradation, improved pharmacokinetics, enhanced solubility and bioavailability, reduced toxicity, and enhanced therapeutic efficacy (Agrahari and Hiremath 2017), implementation of nanoformulation in clinical setting still faces challenges that include biological understanding, large-scale manufacturing, biocompatibility and safety, government regulation, and cost-effectiveness as compared to conventional formulations (Hua et al. 2018).

12.5.1 Large-Scale Manufacturing/Scale-Up and Reproducibility

One of the most important factors slowing the pace of nanoformulations in clinical settings is the physiological complexity of nanoformulation. A formulation that required laborious or complex procedures and costly materials for synthesis generally is not compatible with large-scale production and, therefore, has a limited clinical translation potential. It is easier to maintain the size, composition, and complexity of nanomaterials at a smaller laboratory scale than at a large scale. Challenges arise when nanoformulation becomes more complex by the addition of multiple components in single nanocarriers/coating of formulation with multiple ligands, targeting molecules, or encapsulation of more than one antibacterial agent; therefore, the effective clinical translation, nanoformulation, must be prepared by a method that allows large-scale production with same high level of quality and reproducibility during scale-up (Muthu and Wilson 2012; Paliwal et al. 2014; Tinkle et al. 2014; Hua et al. 2018).

12.5.2 Biological Understanding

Considerable fewer research efforts in understanding the relationship between nanomedicine behavior (intracellular uptake, trafficking nanomaterial distribution, and retention in complex biological network), patient's biology and disease heterogeneity in patients are likely the major reasons for failure seen in the implementation of nanoformulation in clinical settings. Employing patient pre-selection strategies (preselecting patients likely to respond to nanomedicine-based therapy) and adopting a disease-driven approach to develop new nanoformulations and understanding between disease pathophysiology and nanomedicine behavior are the factors needed to be improved to access nanoformulation translatability and applicability (Hare et al. 2017). Lack of specific regulatory guidelines for

characterization and preclinical development of the nanoformulation-based product at the biophysiological level has hampered their potential in clinical practice (Agrahari and Hiremath 2017). The approval process for nanodrugs is essentially the same as that for any medicines and, therefore, is no longer appropriate to confirm clinical safety, efficacy, and quality of nanomedicines (Ventola 2017) due to nanomedicine properties such as the complex structure, unclear interactions with cell, tissue within the human body, and multifunctional nature of some formulation; hence, regulatory standard protocol specifically validated for nanomedicines which should take into account nanoformulation complexity, pharmacokinetics, safety, and toxicity profile and also provide information on patient selection and clinical trials is a must.

12.5.3 The Economic and Financial Barrier

Despite several patents of nanodrug delivery technologies, commercialization is still in its early stage, because of the high developmental costs of nanodrugs and medical devices (Zhang et al. 2016); in addition, the success of nanodrugs is also hampered by the fact that expenses involved in development and regulatory approval may not be compensated by limited sales for drugs especially in cases of increasingly complex nanodrugs that are associated with higher cost (Ventola 2017). Hence economical and financial barriers are also regarded as the biggest limitations in the successful implementation of nanoformulation-based drugs in clinical settings.

12.5.4 Nanoformulated Drug Characterization and Quality Control Challenges

Nanoformulated drug characterizations include analysis of stability, toxicity, size, morphology, surface functionality, charge, distribution, drug loading, solubility, entrapment efficiency, drug release, and retention that required advanced approaches and instruments such as small-angle X-ray scattering (SAXS), wide-angle X-ray scattering (WAXS), transmission electron microscopy (TEM), liquid chromatography-mass spectrometry (LC/MS), high-performance liquid chromatography (HPLC), atomic force microscope (AFM), the micropositron emission tomography (PET)/CT imaging system, and FRET imaging together with spectroscopy methods that are not only expensive but also require a team of expert to perform data analysis and interpretation increasing the cost of nanoformulation drug manufacturing and testing (Landesman-Milo and Peer 2016). Further low therapeutic efficiency of nanoformulation by self-aggregation at low drug concentration and the swelling mechanism that leads to increase in the size of nanoformulated drug further add to limited translation of nanoformulation in clinical settings (Jeevanandam et al. 2016).

12.5.5 Biocompatibility and Safety

Despite several pharmacokinetic advantages of nanodrugs, there is increasing concern over their safety and biocompatibility. Several in vitro and in vivo studies have shown that some nanoparticles used in nanoformulation demonstrated toxicity in the biological system causing cytotoxicity, inflammation, allergic response oxidative stress (generating ROS and free radicle), and DNA damage (genotoxicity). Nanoparticle toxicity is very complex and multifactorial depending on various physiological factors such as size, shape, composition, charge, and reactivity with biological system; hence a better understanding of pharmacodynamics, safety, and toxicity profile of nanodrugs and limitation of each nanoformulation-based drug delivery system is very crucial for the development of efficacious nanodrugs (Onoue et al. 2014).

12.6 Conclusion

Several approaches for nanoformulations have been developed so far. Among all these nanoformulations, nanoemulsions, nanoliposomes, nanodendrimers, etc. are the most promising models to combat and deliver drugs/antimicrobials. Nanopharmaceuticals and nanomedicines such as Emend, Ostim, Rapamune, Vitoss, Ritalin, TriCor, Doxil, DaunoXome, Onivyde, DepoCyt, Marqibo, AmBisome, Adagen, Oncaspar, Copaxone, Eligard, etc. are currently available in the market (Farjadian et al. 2019). Controlling the particle size, shape, controlled manufacturing, production, modifications, nucleation, pharmacokinetics, growth kinetics, and functionalization can lead to various nanoformulations that can target various drug-resistant determinants. The controlled release of drugs/antimicrobials/combinations to the target site will increase the antimicrobial efficiency and effectiveness via deep penetrations (Kumar et al. 2020). Biofilm formations and quorum sensing being interlined can be inhibited by the exposure of the nanoformulations (Jegel et al. 2022). However, to fully comprehend the biological effectiveness of nanoformulations, toxicity and biological activities must be properly investigated prior to clinical trials with the challenges of implementing these ESKAPE nanoformulations in clinical settings. Henceforth, these nanoformulated medications can be a promising tool in the future for combating and delivering drugs to the MDR ESKAPE pathogens.

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