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NANOPARTICLES BASED COMBINED ANTIMICROBIAL DRUG DELIVERY SYSTEM AS A SOLUTION FOR BACTERIAL RESISTANCE

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The absence of novel antimicrobials is a main cause of the emergence of antibiotic resistance. Antimicrobial resistance has been evolved because of a variety of methods such as enzyme inactivation, reduced cell permeability, target mutation, changed target site/enzyme, and efflux pump overexpression. Using a combination of two antimicrobials drugs lead to an increase of the spectrum of antibiotics against multi drug resistance bacteria and a decrease in the emergence of resistant mutants. Despite of several advantages of using a combination of antibiotics, resistance can develop during treatment. Encapsulation of antimicrobials within the nanoparticles was proven to reduce the antimicrobial resistance by increasing the intracellular bioavailability of antimicrobial drugs through decreasing the development of resistant mutants and inhibiting the efflux pump. In this review, we will summarize the antimicrobial resistance, use of combined therapy and the use of antimicrobials- loaded nanoparticles and their application in the future to fight multidrug resistant bacteria.

Keywords: *Nanoparticles, antimicrobial resistance, antimicrobial combination, ciprofloxacin, meropenem*

INTRODUCTION

Antimicrobial resistance

Antimicrobial resistance (AMR) is considered one of the major threats to human health as a result of the exposure of bacteria to antimicrobial agents. It reduces the ability of antimicrobial agents to eradicate the bacterial infection[1]. WHO stated that the matter of AMR in Africa is even worse due to the uncontrolled use of antibiotics because most antibiotics are over-the counter medicines and could be taken without a prescription. WHO also, specified that the AMR infections are the major public health threats. Therefore, the professional agency needs to discover a new antibiotic to face this problem[2].

Impact of resistance

Every year, antimicrobial resistance kills at least 50,000 people around the world. As a result, there is a pressing need to protect the efficacy of existing antimicrobials in addition to the discovery of new ones[3].

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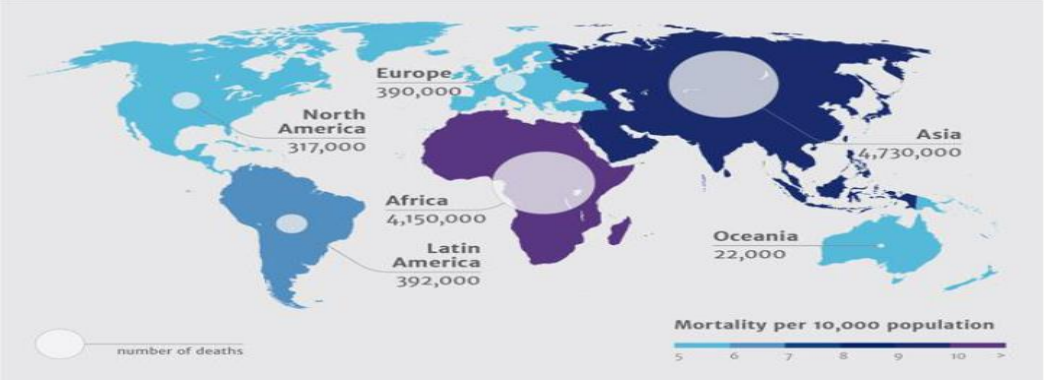


Fig. 1: Deaths progression from antimicrobial resistance every year by 2050 [7].

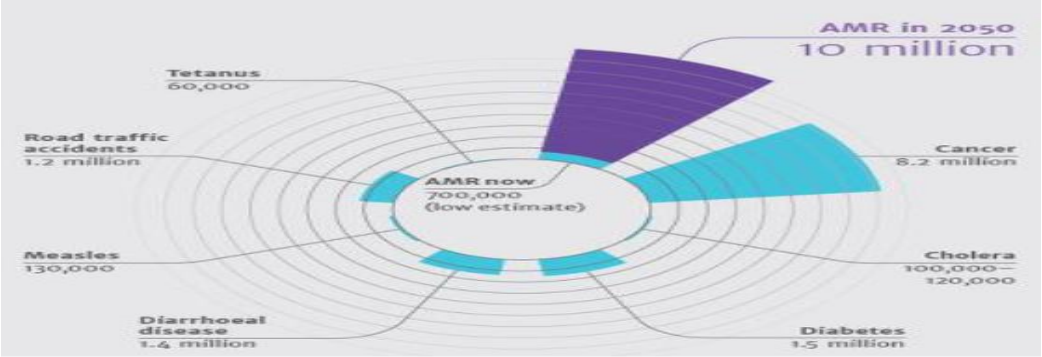


Fig. 2: Deaths progression from antimicrobial resistance every year compared to other causes of death[7].

According to this study, antibiotic resistance will kill 10 millions people per year by 2050, with more than 4 millions of those deaths occurring in Africa (Figure 1 and 2). Several bacteria, such as *Klebsiella pneumoniae*, *Escherichia coli*, and *Staphylococcus aureus*, have already shown alarming levels of resistance[4]. Studies conducted on the FQ (fluoroquinolones) resistance in Egypt presented that FQ resistance increased from 20% to 50% between 2000 and 2007, then hopped to 72% in 2009 and up to 90% in some *Enterobacteriaceae* strains in 2012. The resistance has emerged due to extensive use of FQ therapy in multi-drug resistance pathogens[5].

Antibiotic combination for combating antimicrobial resistance

A great effort has been made to combat bacterial resistance by discovering new antibiotics or using different antibiotics combinations. Adding a second antimicrobial agent can make the pathogen's more sensitive by synergistic effect[7].

Antibiotic combination therapy is a novel strategy for combating bacterial resistance. Antibiotic combinations are the final choice when multiple antibiotic resistances are encountered, and they are the standard of care for critically ill patients[8]. Antibiotic combinations are assumed to be the most effective way to combat multiple resistance caused by antimicrobial monotherapy[9]. Furthermore, antibiotic combinations increase the spectrum coverage supplied by two antimicrobial drugs with different spectra of activity and lowering resistance emergence[8]. When using combination therapy, a number of mechanisms are involved. For example, they block different target sites in the cell via various pathways, obstruct different nodes in the same pathway and block the same cell target using various techniques[10]. The use of fluoroquinolones and carbapenem together has been shown to have a synergistic impact in the treatment of *Pseudomonas aeruginosa* and *Acinetobacter baumanni*[11]. Fluoroquinolones and carbapenem are an appealing combination since each antibiotic has a good safety profile and the combination provides a much higher killing rate than either drug alone. Topoisomerase IV and DNA gyrase are two

enzymes involved in DNA synthesis, and fluoroquinolones function by interfering with them (Figure 3)[12]. Point mutations in target proteins and lower intracellular concentrations as a result of decreased penetration or higher efflux have been identified as two key FQ resistance mechanisms (Figure 4). Carbapenem's route of action begins by binding to penicillin binding protein, as a result, the peptidoglycan weakens, and the bacterial cell explodes due to osmotic pressure[13]. Resistance to carbapenems can develop by mutations in the target site, efflux pumps, porin mutation and enzymatic inactivation. The most current and well-established approach among these strategies is the enzymatic inactivation (plasmid-mediated carbapenemases) (Figure 5)[13]. Unfortunately, despite the numerous benefits of adopting a combination antibiotic medication, resistance may develop during treatment[14].

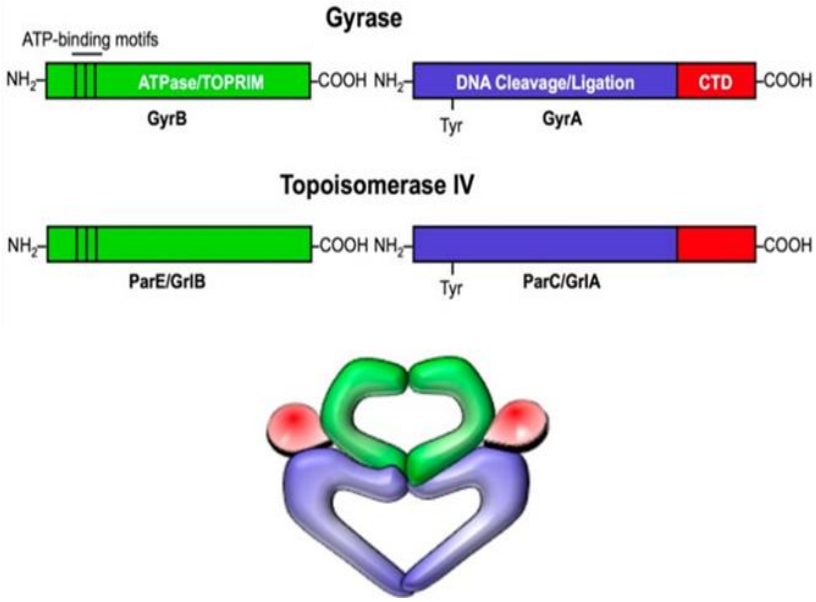


Fig. 3: The structures of DNA gyrase and topoisomerase IV [16].

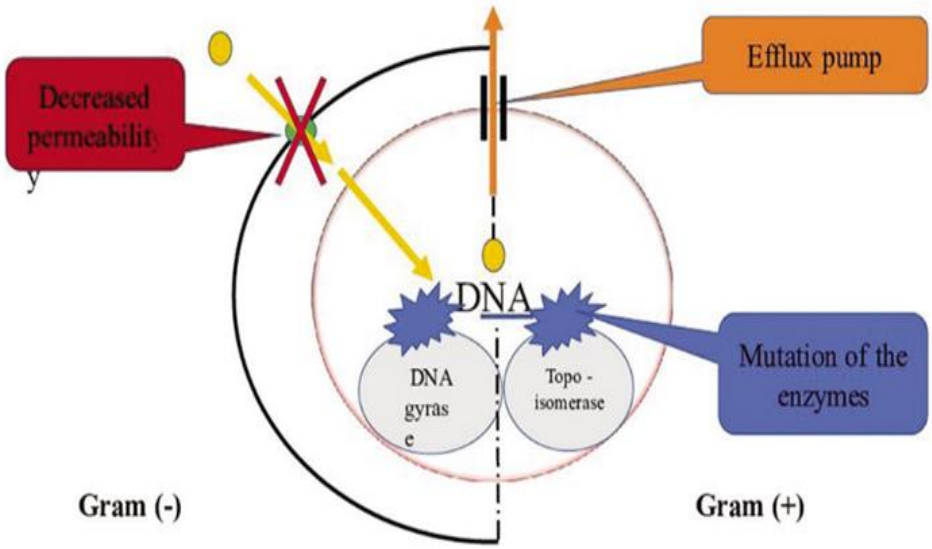


Fig. 4: Fluoroquinolones resistance[17].

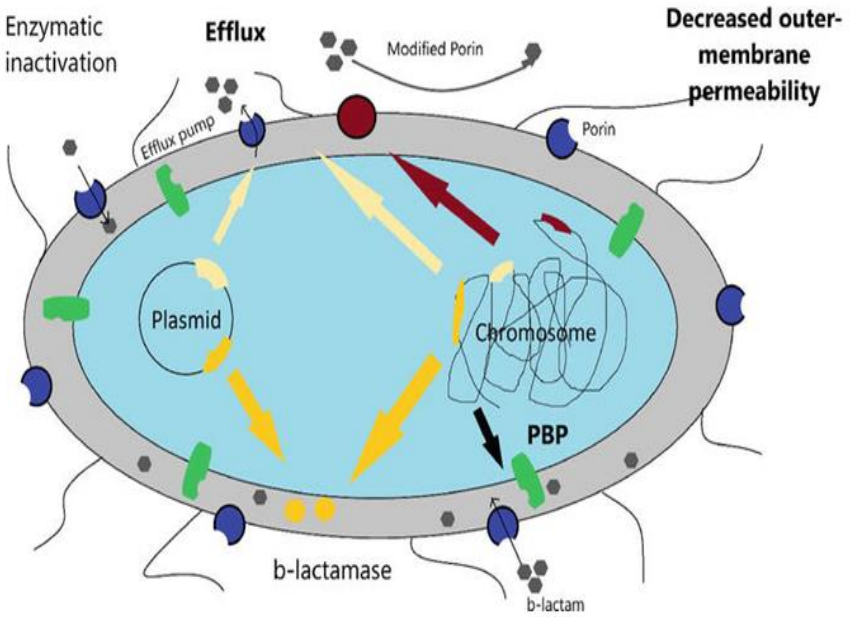


Fig. 5: Mechanism of resistance of Carbapenem in *Enterobacteriaceae*: (a) membrane permeability reduction *via* modified porins and loss of expression in outer-membrane porin proteins; (b) enzymatic inactivation *via* plasmid-mediated or chromosomal enzymes (with hydrolytic activity); and (c) antibiotic efflux *via* efflux pump[22]

Nanoparticles as a solution for antimicrobial resistance:

Despite tremendous advances in antibiotic research, there is still a long way to go. Many infectious diseases, particularly intracellular bacterial infections, are still challenging to be treated. Many antimicrobials have trouble passing through cell membranes and have little effect once inside[18]. The rise of antibiotic-resistant microorganisms is another key issue with antimicrobial medications.

Nanotechnology is the study, development, and application of nanoscale materials (1–1000 nm) (Figure 6). Nanoparticles (NPs) have unique physicochemical features, including small size, a high surface-to-volume ratio, and biological system interactions. As a result, nanoparticles are widely used in medical applications as vehicles for the delivery of a variety of therapeutic or diagnostic agents, including medication delivery, gene therapy, and cell labelling[19].

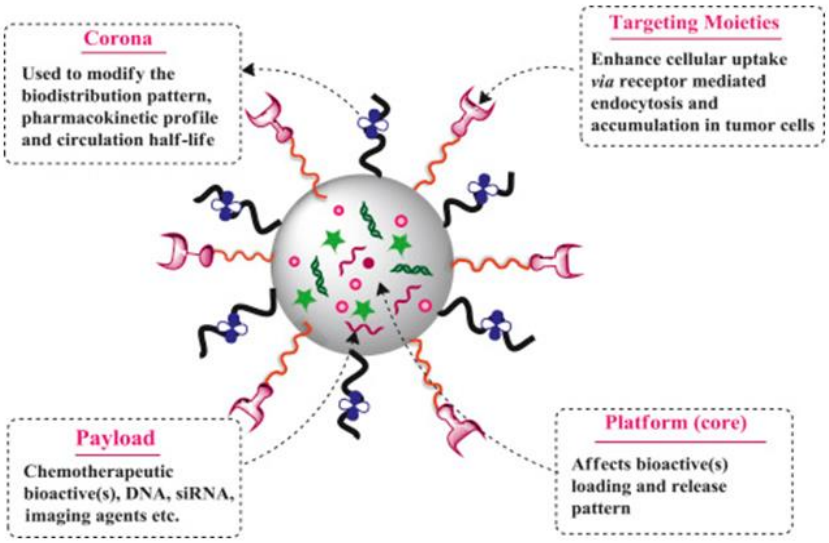
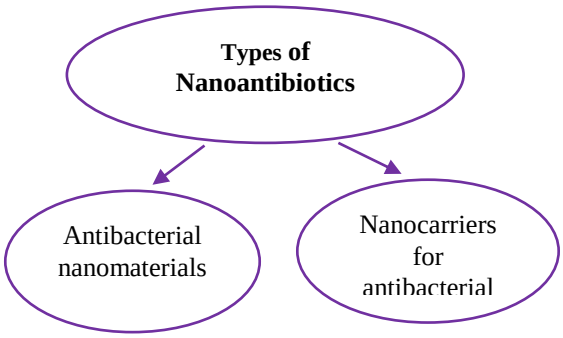


Fig. 6: Multifunctional nanoparticle [28].

One of the most novel techniques to decrease the antimicrobial resistance is entrapping the antimicrobial drugs inside nanoparticles. Metallic nanoparticles have recently been identified to have the possibility for blocking bacterial efflux pumps. Nanoparticles are thought to bind directly to the cell membrane's pump, preventing medications from being swept away[20&21].

Nanoantibiotics are nanoparticles that have endogenous antibacterial activities and can help to improve the effectiveness and safety of antibiotic therapy[23]. Nanoantibiotics have many advantageous effects such as extending the antibiotic half-life and maintain higher drug concentration at the site of infection[24]. They might be able to reduce the amount and frequency of administration, as well as to reduce side effects and improve the medicine's pharmacokinetic profile[25]. Antimicrobial-loaded nanoparticles may also aid in the fighting against antimicrobial resistance by increasing intracellular uptake, decreasing drug efflux, and preventing biofilm formation[26].



Antibacterial nanomaterials such as nitric oxide releasing nanoparticles, Metal-based nanoparticles (e.g. Silver, Zinc oxide, Copper, etc.)[27-29], Antimicrobial peptides[30] and Carbon nanotubes (CNTs)[31].They have several mechanisms to combat microorganisms as shown in figure 7 and table 1.

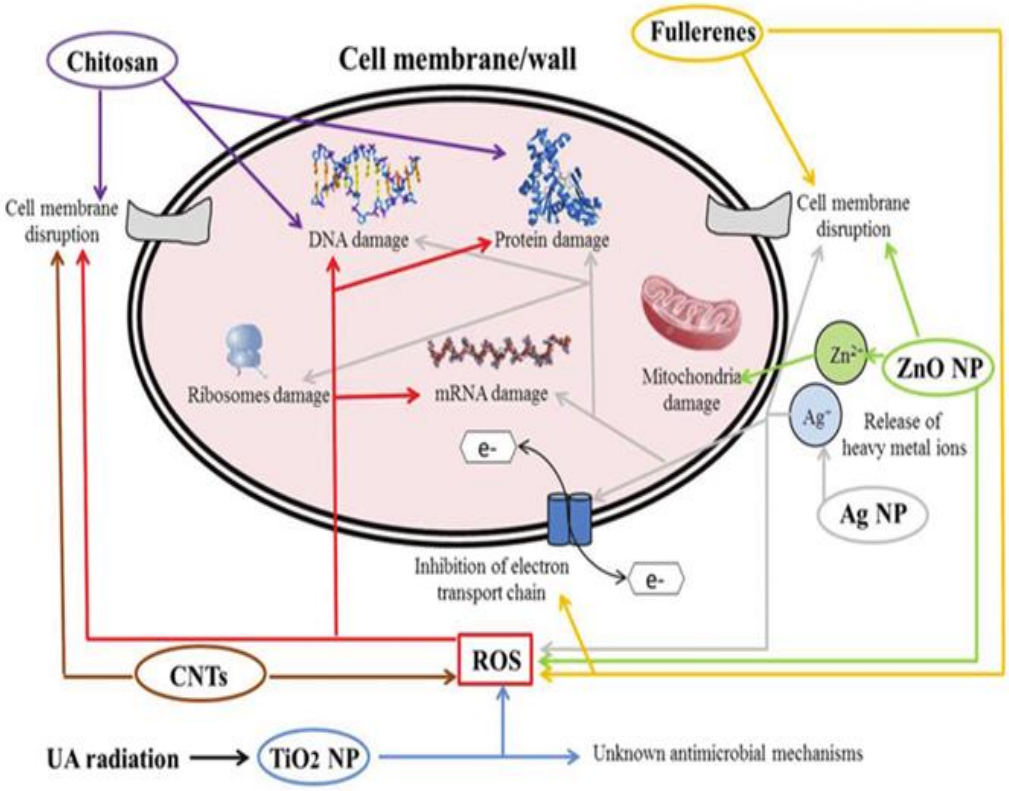


Fig. 7: Antimicrobial mechanisms of Chitosan, silver-containing NPs (Ag NPs), zinc oxide-containing NPs (ZnO NPs), titanium dioxide-containing NPs (TiO2 NPs), and carbon based NPs (CNTs and Fullerenes) [38].

Table 1: Antimicrobial activity of nanomaterials (NM).

Type of NM	Suggested mechanisms of antibacterial action	Target microorganisms	References
Ag	Ag+ ions are released, the cell membrane is disrupted, and electron transport is disrupted, and DNA is damaged.	Methicillin resistance *Staphylococcus aureus* (MRSA), methicillin resistance *Staphyloccus epidermidis* (MRSE) *Escherichia coli*, *Pseudomonas aeruginos*a, *Staphylococcus aureus*, *Streptococcus pyogenes* *Candida albicans*, *Candida glabrata*	34, 39-43
TiO_2	Production of ROS; cell membrane and cell wall damage	*Escherichia coli*, *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, *Staphylococcus aureus* *Bacillus subtilis* *Shigella flexneri*, *Listeria monocytogenes*, *Vibrio parahaemolyticus*, *Staphylococcus aureus*, *Streptococcus* *pyogenes*, *Acinetobacter baumannii*	44-46
ZnO	Formation of ROS; NP interact with bacterial cell, causing bacterial cell damage; nanoparticle release of Zn2+ ions	*Escherichia coli, Pseudomonas aeruginosa* *Staphylococcus aureus* , *Salmonella paratyphi* B, *Klebsiella pneumoniae* MTCC109, *Bacillus subtilis* MTCC441, *Enterobacter aerogenes* MTCC111,*Staphylococcus epidermidis* MTCC3615, Methicillin resistant-MRSA, *Candida albicans* MTCC227, *Campylobacter jejuni*	47-51
CNTs	Damage to cell membrane proteins and lipids caused by ROS.	*Salmonella typhimurium*, *Bacillus subtilis*, *Staphylococcus aureus* *Escherichia coli* K12, *Salmonella enterica*, *Escherichia coli* , *Pseudomonas aeruginosa*,	52-54

Nanocarriers for antibiotics

Antibiotic nanocarriers are a type of nanocarriers that is used to transport antibiotics. Physical encapsulation, adsorption, or chemical conjugation can be used to integrate antimicrobial medicines into nanoparticles, resulting in improved pharmacokinetics and therapeutic index over free drugs.

Several different types of nanoparticles have been used as antimicrobial medication nanocarriers, including: dendemirs, liposomes, solid lipid nanoparticles (SLN) and polymeric nanoparticles (nanoparticles made of polymers) (Figure 8)[49].

Dendrimers

A dendrimer is a highly organized hyperbranched polymer made up of a core unit and layers of branching repeat units with conjugated terminal functional groups that emerge from the core (Figure 9)[50]. There are different types of dendrimers conjugated with antibiotics (Figure 10). PAMAM (polyamidoamine) is the first and most widely investigated dendrimer for antimicrobial drug delivery[51].This is due to the fact that dendrimers have certain characteristics, such as: their highly branched nature offers high surface area-to-volume ratio, leading to great reactivity against microorganisms *in vivo*[52]. Both hydrophobic and hydrophilic drugs can

encapsulate inside the cavities of the hydrophobic core and on the multivalent surfaces of dendrimers, respectively[51]. Dendrimers with a large concentration of positively charged surfaces had higher antibacterial activity than free antibiotics. This is due to quaternary ammonium compounds' polycationic composition, which enables attachment to the negatively charged bacterial cell wall. This increases membrane permeability, allowing additional dendrimers to enter the bacteria, causing potassium ion leakage, and eventually causing the bacterial cell membrane to be destroyed[53].

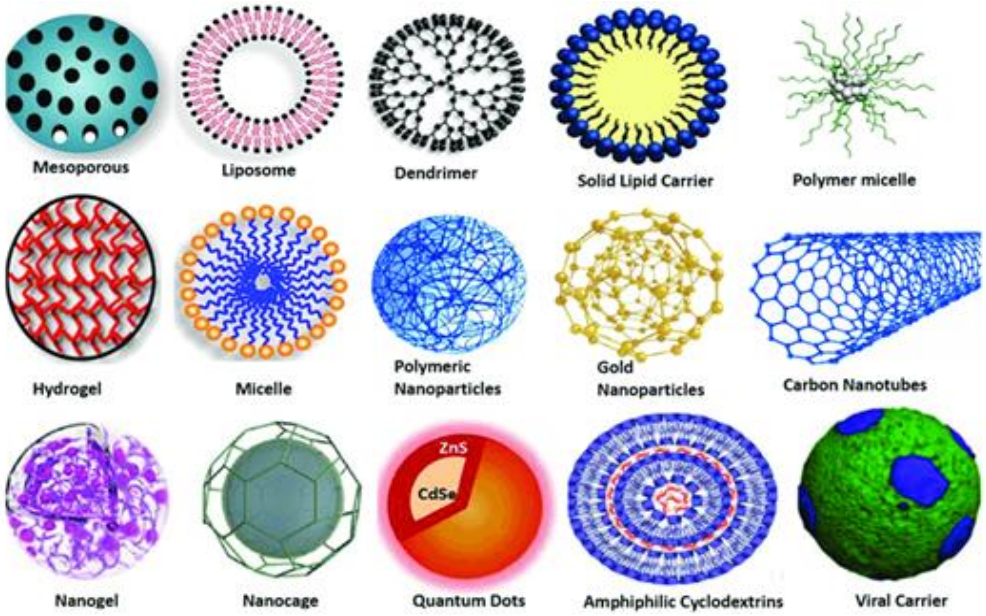


Fig. 8. Different type of nanoparticles[55].

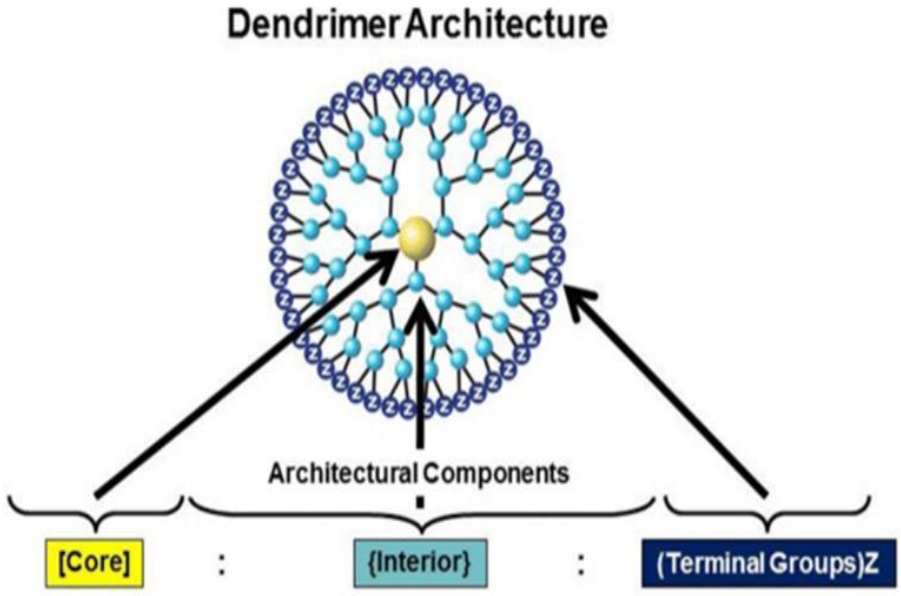


Fig. 9: Structure of dendrimer[60].

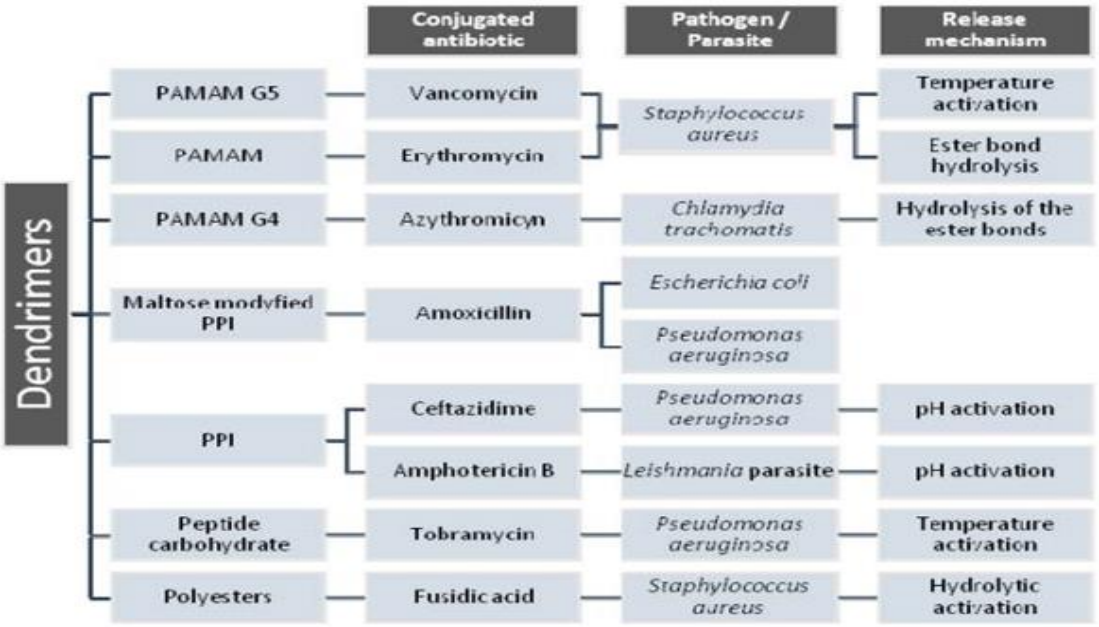


Fig. 10: Dendrimers conjugated with antibiotics[58].

Liposomes

Liposomes are spherical vesicles with one or more phospholipid bilayers encasing aqueous compartments or units (Figure 11)[55]. As antibiotic delivery nanosystems, liposomes offer a number of advantages, addressing issues of free antibiotics such as increase the drug efficacy and decrease the resistance strain selection. Several studies have found that liposomal encapsulation improves antibiotic stability and safety, resulting in more appropriate pharmacokinetic and pharmacodynamic profiles by extending the time that antibiotics spend in the bloodstream, allowing for more precise targeting of infection sites via various routes of administration (Figure 12)[26]. Antibiotics incorporated within liposomes may assist to overcome bacterial resistance mechanisms (Table 2). Gram-negative bacteria's outer membrane, for example, is a complex barrier that can impede internalization or alter antibiotic interactions with the bacterial wall, making it a primary source of emerging resistances[56]. Nonetheless, as previously stated, liposomes may promote bacterial membrane fusion, causing structural disturbance and perhaps reversing low permeability (Figure 13)[56&57].

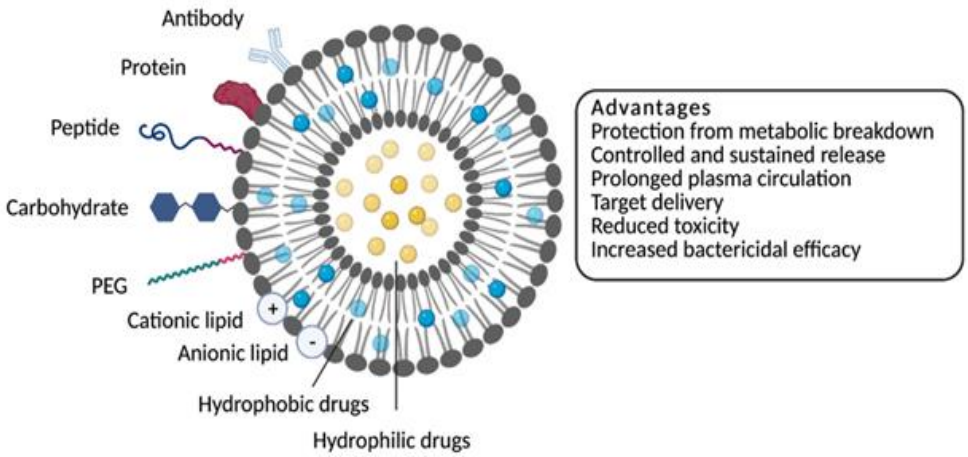


Fig. 11: Different types of liposomes and their main advantages[61].

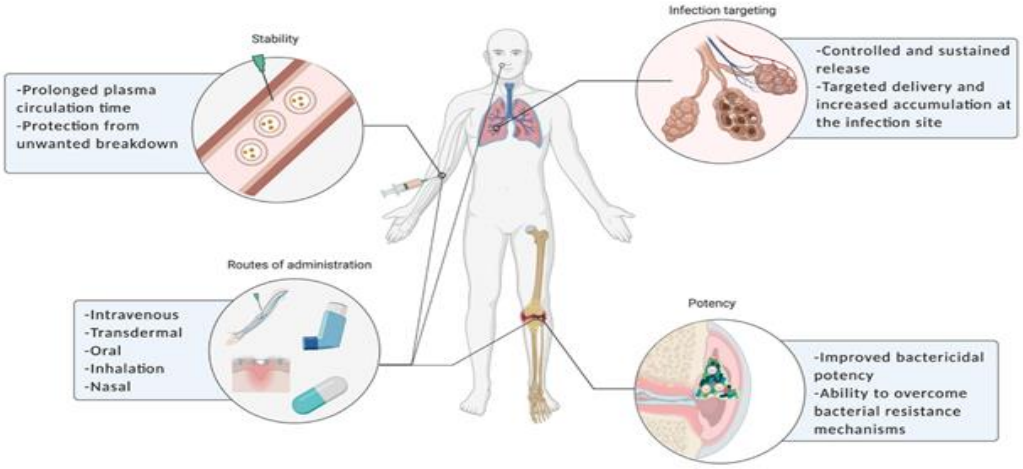


Fig. 12: The fundamental advantage of liposomes as antibiotic carriers[61].

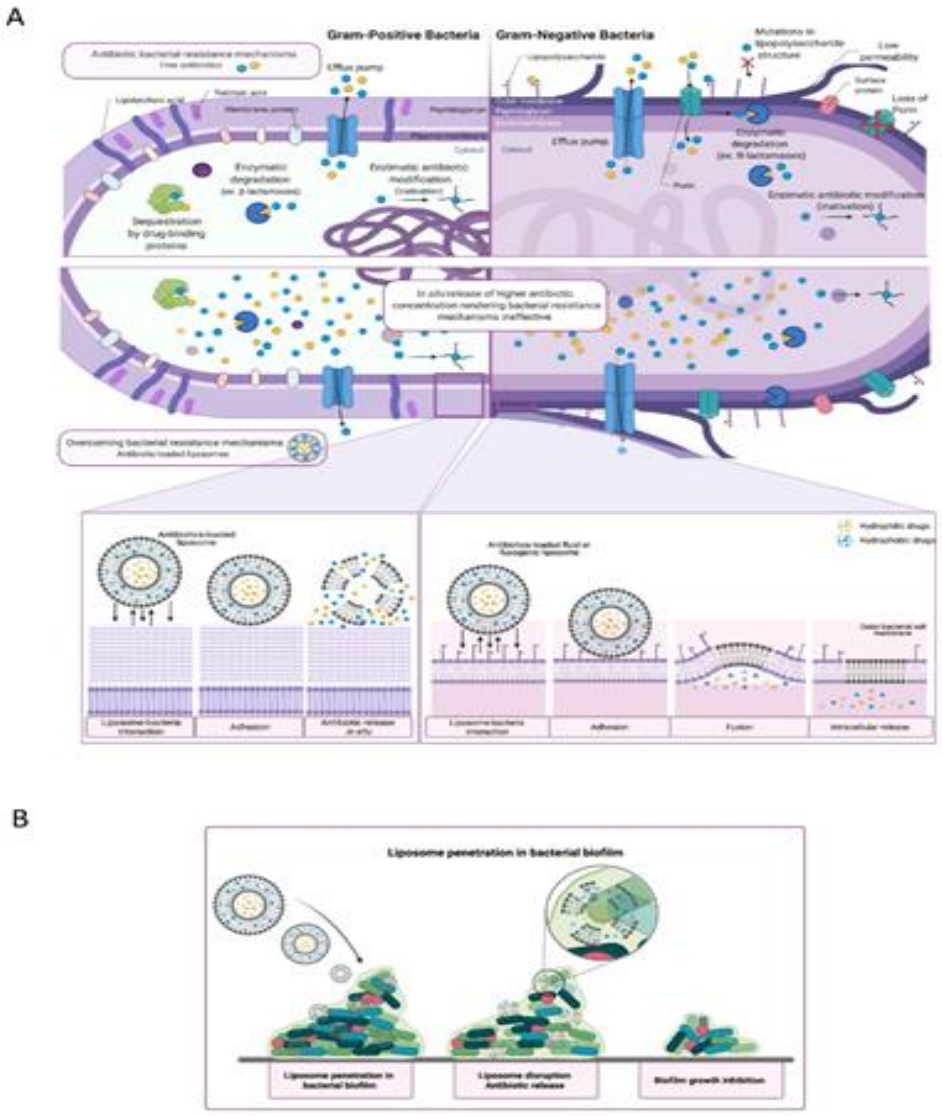


Fig.13: Several mechanisms of antibiotics-loaded liposomes nanoparticles to overcome the bacterial resistance[61]

Table 2: Antibiotics- loaded liposome nanoparticles for multidrug resistance pathogen.

Drugs	Type of NP	Out come	Target microorganisms	References
Vancomycin	1- DOPE:DPPC:CHEMS 2- DPPC:Chol	Free vancomycin and non-fusogenic formulation (DPPC:Chol) had no bactericidal action, however fusogenic liposomes (DOPE:DPPC:CHEMS) had MICs of 6–12.5 µg/mL against clinical isolates.	*Acinetobacter baumannii*	64
Polymyxin B	1- DPPC:Chol 2- POPC:Chol	Liposomal formulations have a 16-fold lower MIC than free antibiotic formulations.	*Acinetobacter baumannii*	65
Amikacin Gentamicin Tobramycin	DPPC:Chol	In compared to free antibiotics, liposomal formulations maintained or reduced MICs against all clinical isolates tested, for all medicines incorporated inside the nanoparticles (MIC reductions were antibiotic and strain dependent: amikacin, 2–64-fold; gentamicin, 2–64-fold; tobramycin, 1–128-fold).	*Pseudomonas aeruginosa*	66
Polymyxin B	1- DPPC:Chol 2- POPC:Chol	Liposomal formulation had 4–32-fold lower MICs against clinical isolates than free antibiotic.	*Pseudomonas aeruginosa*	65
Cefepime	1- EPC:Chol 2- EPC:Chol:12NBr	Cefepime-loaded liposomes had antibacterial activity comparable to cefepime in its free form against *E. coli* strain.	*Enterobacteriacea*	67
Azithromycin	EPC:EPG:HSPC-3	Antibiotic-loaded EPC:EPG:HSPC-3 had a lower $MBIC_{50}$ than free antibiotic against the E. coli k-12 strain (8-fold lower).	*Enterobacteriacea*	68
Norfloxacin	1- PCT1–EPC:Chol:α tocopherol 2- PCT2–EPC:Chol:α tocopherol	The PCT1–EPC: Chol: α tocopherol formulation has an enhanced antibacterial activity against an *E. coli* strain, resulting in a MIC 9-fold lower than free antibiotic. PCT2–EPC: Chol: α tocopherol had the best antibacterial efficacy against *Salmonella* strains, with MICs of 2–17 and 16–42 times lower than the other formulation and free antibiotic, respectively.	*Enterobacteriacea*	69
Azithromycin	DPPC:DODAB	Among all clinical isolates studied, the DPPC:DODAB formulation had the best antibacterial efficacy against both planktonic and biofilm forms. MICs and MBICs were decreased from 8–32 and 16–32 times than free azithromycin, respectively.	*Staphylococcus.aureus*	70
Methicillin	1- DOPE:DPPC:CHEMS:DSPE-PEG-MAL 2- DOPE:DPPC:CHEMS:DSPE-PEG-Tat	Antibacterial activity was shown to be reduced in both formulations, particularly in DOPE: DPPC:CHEMS:DSPE-PEG-Tat formulation.	*Staphylococcus.aureus*	71
Vancomycin	1- DOPE:DPPC:CHEMS:DSPE-PEG-MAL 2- DOPE:DPPC:CHEMS:DSPE-PEG-Tat	Both formulations had MICs that were about 2-fold lower than the free antibiotic. DOPE:DPPC:CHEMS:DSPE-PEG-Tat showed better outcomes, with a 1- and 2-fold reduction in viable bacteria when compared to the other formulation and free vancomycin, respectively.	Streptococcus pneumoniae	70

1DPPC, dipalmitoyl phosphatidyl choline; DSPE, distearoyl phosphatidyl choline; Chol, cholesterol; DOPE, dioleoyl phosphatidyl ethanolamine; CHEMS, cholesteryl hemisuccinate; PEG, propylene glycol; POPC, palmitoyloleoyl phosphatidyl choline; EPC, egg phosphatidyl choline; PCT1, pectin from apple, found in the aqueous phase that surrounds the liposomes; PCT2, pectin from apple, distributed in the water phase inside and outside the liposomes; EPG, egg phosphatidyl glycerol; HSPC-3, hydrogenated soybean phosphatidyl; DODAB, dioctadecyldimethyl ammonium bromide; ; 12NBr, N,N,N-triethyl-N-(12-naphthoxydodecyl)ammonium surfactant; DSPE-PEG-MAL, distearoyl phosphatidyl ethanolamine covalently linked to poly(ethylene glycol) 2000 linked to maleimide; DSPE-PEG, distearoyl phosphatidyl ethanolamine covalently linked to poly(ethylene glycol) 2000; Tat, cell penetrating peptide (Cys-Tyr-Gly-Arg-Lys-Lys-Arg-Arg-Gln-Arg- Arg-Arg-NH2)

Solid lipid nanoparticles (nanoparticles made of solid lipids)

Since the 1990s, colloidal carriers known as solid lipid nanoparticles (SLNPs) have received attention as vehicles for the delivery of antimicrobial drugs. They are made up of lipids that are solid at room temperature and surfactants for emulsification (Figure 14). SLNPs shared the advantages of traditional solid nanoparticles and liposomes, while avoiding disadvantages of these carriers[66]. SLNPs can incorporate several antibiotics, and reduce antimicrobial resistance by several mechanisms (Table 3). SLNPs can improve the efficacy of conventional antimicrobial therapies by enhancing drug absorption, not only through multiple barriers in the organism but also through the bacterial cell wall[66]. SLNPs have also been shown to minimize efflux pump-mediated drug ejection, prevent the action of antibiotic-modifying enzymes, improve cell uptake to treat intracellular infections, and diminish the biofilm formation or survivability of biofilm-forming bacteria[67].

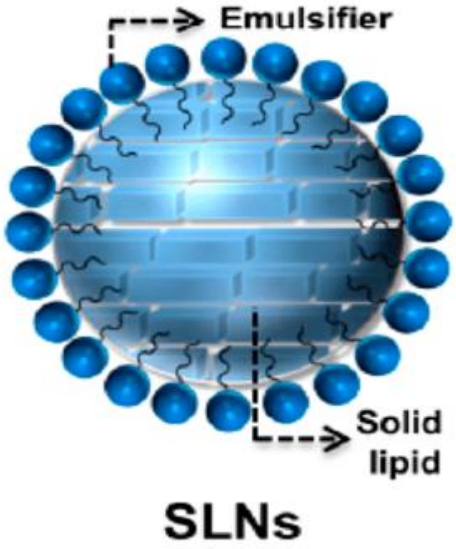


Fig. 14: A diagrammatic representation of solid lipid nanoparticles[74].

Table 3: SLNPs encapsulated different antimicrobial drugs and its ability to decreaseantimicrobial resistance.

Drugs	Out come	Target microorganisms	References
Rifampicin	Drug ejections are reduced	*Mycobacterium fortuitum (ATCC 2701P)*	75
Fluconazole	Drug identification by efflux pump proteins is avoided.	*Candida glabrata*	76
Doxycycline	The amount of microorganisms inside J444A.1 macrophages has decreased.	*Intracellular Brucella melitensis*	77
Enrofloxacin	Improved cellular absorption; Delayed clearance of enrofloxacin after extracellular drug elimination; Better inhibitory action against intracellular Salmonella CVCC541.	*Intracellular Salmonella CVCC541*	78
Cefuroxime axetil	Drug minimum biofilm inhibitory concentration is 50% lower when cefuroxime axetil encapsulated within SLNs	*Staphylococcus aureus (ATCC-25923*	79
Clarithromycin	In-vitro antibacterial activity improved; In comparison to free medicines, it has a greater potential for biofilm elimination; Relative oral bioavailability has increased by about fivefold.	*Staphylococcus aureus; (MTCC86)Wistar rats*	80
Colistin sulfate	Effective eradication of biofilms	*Pseudomonas aeruginosa*	81
Tobramycin	Eradication of biofilms has risen.	*Pseudomonas aeruginosa*	82

Polymeric nanoparticles

Polymeric nanoparticles are solid particles with a size of 10 nm to 1000 nm that can contain drugs either inside them (nanocapsules) or scattered in the polymeric matrix (nanospheres) (Figure 15). Polymeric nanoparticles can encapsulate different categories of antimicrobial drugs (Table 4). There are various advantages of using polymeric nanoparticles as carriers to deliver antimicrobial agents: (i) decreased dose and drug resistance; (ii) better in vivo circulation stability; (iii) improved penetration ability; (iv) sustained antibacterial effectiveness; and (v) improved bioavailability[77]. Polymeric nanoparticles can combat the antimicrobial resistance by several ways as, penetrate and disrupt the microbial cell membrane through membrane-damaging abrasiveness, induce intracellular antimicrobial effects such as the production of reactive oxygen species, interact with DNA/RNA and proteins, inactivate enzymes, increase efflux by overexpressing efflux pumps, decrease cell permeability, release metal ions, and hinder biofiltration. Variables including chemistry, particle size and shape, surface-to-volume ratio, and zeta potential have a direct impact on nanoparticle antibacterial efficacy[25&78].

Polymeric nanosystems can be synthesized from a variety of natural or synthetic precursors, such as collagen, chitosan, gelatin, or albumin, and polyethylene glycol, polylactic acid, poly(lactic-co-glycolic acid) (PLGA), polylactic acid (PLA) or polycaprolactone (PCL), respectively[77]. Chitosan (CS), for example, is a natural, polycationic aminopolysaccharide copolymer of glucosamine and N-acetylglucosamine generated by the alkaline, partial deacetylation of chitin, which is the second most abundant natural polysaccharide and is found in crab shells. Chitosan displays favorable characteristics, which include, biocompatibility, biodegradability, low toxicity, mucoadhesiveness and antimicrobial activity against a broad spectrum of microorganisms including, Gram-positive and Gram-negative bacteria, filamentous fungi and yeast. Because of these properties, chitosan is a good choice for encapsulating antimicrobial medicines and developing innovative nano-therapeutics to treat microbial infections[79].

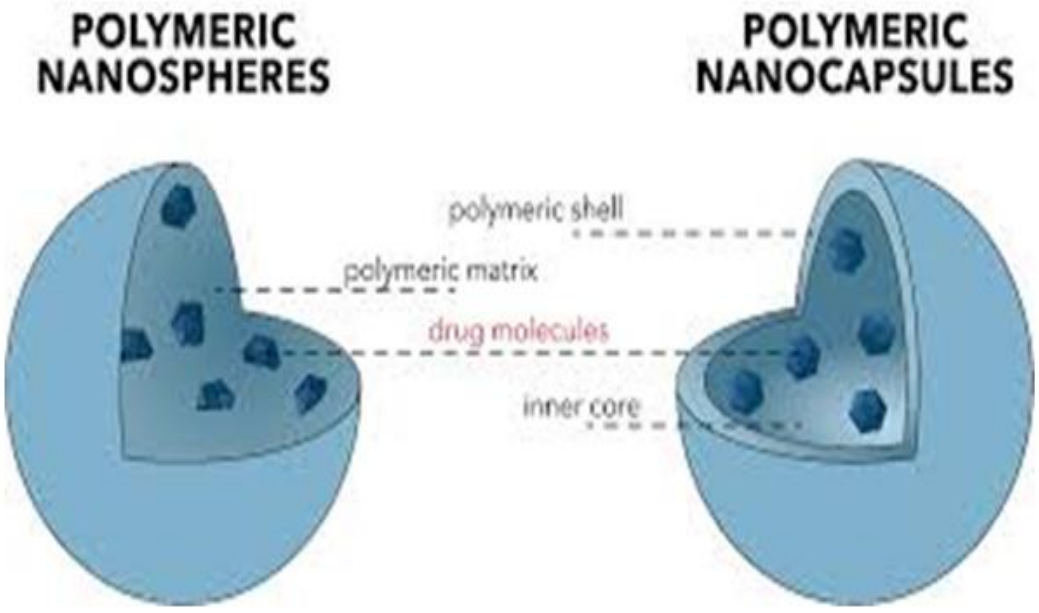


Fig.15: The two main types of polymeric nanoparticles [85].

Table 4: The antibacterial properties of different antibiotics-loaded natural and synthetic polymers.

Drugs	Type of NPs	Target microorganisms	Out come	References
Gentamycin	Phosphatidylcholine Chitosan nanoparticles (CS NPs)	*S. aureus P.aeruginosa, E.coli*	The minimum inhibitory concentration (MIC) results showed that the nanosized gentamicin and gentamycin alone had equal antibacterial activities; however, the biofilm mass results showed that the nanosized gentamicin had a higher inhibitory capability than gentamycin alone.	[86]
Gentamycin	CS NPs and CS NPs dispersed into carbopol sol–gel systems	*S. aureus, E. coli*	Zone of inhibition (ZOI) was greater for gentamicin- loaded nanoparticles than gentamicin eye drop that found in the market.	[87]
Ampicillin	CS–Polyanion NPs	*S. aureus* (ATCC2592, ATCC29213, and ATCC43300)	When the antibiotic was encapsulated into the NPs, the MIC increased by 50%, regardless of the degree of ampicillin resistance.	[88]
Vancomycin	Hyaluronic acid–oleylamine polymersomes	*S. aureus and MRSA*	Polymersomes were not as powerful as free vancomycin, but due to their delayed and regulated release over time, they wer)((e able to improve antibacterial effects.	[89]
polymyxin B sulphate .	Sodium alginate NPs layer and a chitosan and hyaluronic acid layer make up this double-layered membrane.	*S. aureus* (ATCC2592) *P. aeruginosa* (ATCC2785)	Because of the synergistic antibacterial actions of the free antibiotics with nanoparticles, MIC values for the NPs were lower than for the antibiotic alone.	[90]
Teicoplanin	poly(lactic co-glycolic acid) nanoparticles (PLGA NPs)	*S. aureus* (ATCC29213, ATCC25923, ATCC43300), *B.cereus* (ATCC1222), *MRSA* (EGE-KK13, EGE-KK-95)	For all bacterial strains, MIC values were significantly reduced following encapsulation of teicoplanin into NPs; MIC values were even lower after aptamer attachment for *S. aureus* strains, but significantly elevated for *B. cereus* strains.	[91]
Rifampicin	Poly (lactic acid) NPs (PLA NPs);	*S. aureus* (SH1000)	MICs and anti-biofilm properties are the same with the free antibiotic.	[92]
Ampicillin .	Polyelectrolyte complex nanoparticles (PEC NPs) (PEC NPs)	*S. aureus* (ATCC2592, ATCC29213, ATCC43300)	Depending on the type of strain, antibacterial activities change.	[93]

Nanoantibiotics to Combat Antibiotic Resistance

Nanoantibiotics (nAbts) is one of the most of favorable applications of nanotechnology. NAbts use physicochemical conjugation of nanoparticles with antibiotics or intentionally generated pure antibiotic molecules in at least one dimension with a size range of 100 nm to decrease the bacterial resistance[89].

Because of the intrinsic properties of NPs, these NP-based antibiotics can cross bacterial cell membrane barriers and reach particular spots with greater specificity and stability than

"free" antibiotic molecules. NAbts have a great potentials to decrease the bacterial resistance, NPs' distinctive size, shape, and composition-related features can pose many simultaneous obstacles[90]. NAbts have a two different mechanisms to decrease bacterial resistance. One of them is oxidative mechanisms and anther non-oxidative mechanisms. Oxidative mechanisms include: stress induction via reactive oxygen species (ROS) and free radical generation, inhibition of the electron transport chain, plasmid damage, disruption of the cell wall, DNA damage, disruption of enzyme activity, interruption of the electron transport chain, disruption of enzyme activity. While, non-oxidative mechanisms include: surface energy, size shape, surface roughness, types and materials of nanoconjugates, cytoplasm release, atomically thin structures, zeta potential (surface charge), stability, increased specific surface area/volume ratio, high surface reactivity, poly- or multi-valency, magnetism, conductivity, bioavailability of NPs, drug delivery systems at target sites. These characteristics allow for optimal interaction with bacterial cells as target sites. These characteristics allow for optimal interaction with bacterial cells as well as increased penetration beyond the cell membrane, all while actively interfering with cellular components and metabolic machinery [91&92]. Figure 16 shows how nanoscale particles work as drug carriers over bacterial membrane barriers in a simple graphic.

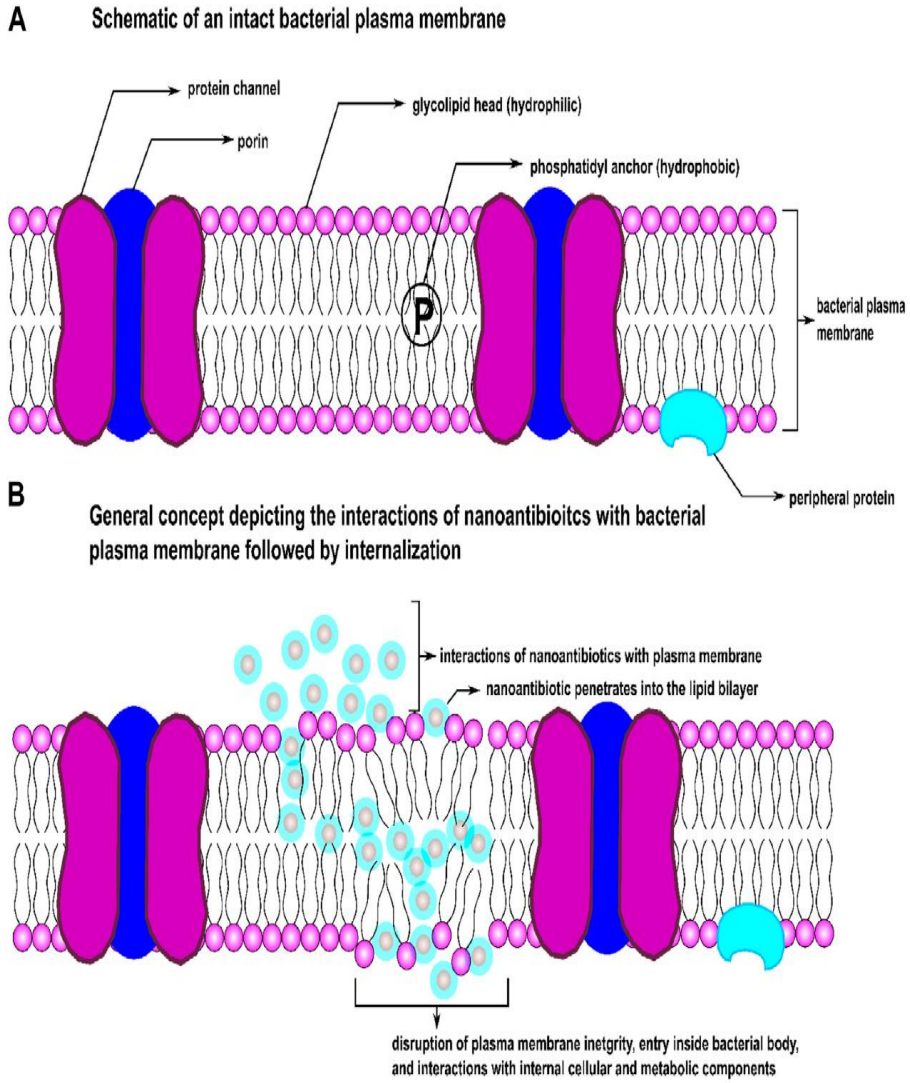


Fig. 16: (A) Schematic of an intact bacterial cell membrane and (B) the effect of nAbts on bacterial cell membrane integrity[90]

Mechanisms of nanoparticle-based antimicrobial drug delivery to microorganisms

Nanoparticles connect to the cell wall and serve as a drug depot, slowly releasing drug molecules and allowing them to permeate into the microbe's interior. Then, nanoparticles disrupt the membrane integrity. As a result, there is a transport imbalance, inadequate respiration, energy transduction halting and/or cell lysis, and eventually cell death [93]. Another antibacterial function of nanoparticles is reactive oxygen species (ROS). A surge of reactive oxygen species (ROS) causes severe oxidative stress in all of the cell's macromolecules, leading to lipid peroxidation, protein modification, enzyme inhibition, RNA and DNA damage. At high quantities, ROS causes cell death, whereas at low concentrations, it produces considerable DNA damage and mutations. [94]. Metallic nanoparticles have also recently been identified as a potential means of inhibiting bacterial efflux pumps. Nanoparticles are hypothesized to adhere directly to the pump in the cell membrane, preventing drugs from being washed away [20&95].

Recommendation

From the previous findings, we can conclude that the antimicrobial encapsulated within nanosized material is superior to other formulations in decreasing microorganisms' ability to form resistant mutants. It is recommended to apply antimicrobial-loaded nanoparticles in pharmaceutical industries to decrease the antimicrobial resistance.

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نشرة العلوم الصيدلية
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نظام توصيل مزيج المضادات الحيوية المعتمد على جسيمات النانو و ذلك للحد من مقاومة البكتيريا

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يعد عدم توافر المضادات الحيوية الجديدة سببًا رئيسيًا لظهور مقاومة المضادات الحيوية. تم تطور مقاومة المضادات الحيوية بسبب مجموعة متنوعة من الطرق مثل تعطيل الإنزيم ، وأنخفاض نفاذية الخلية للمضادات الحيوية ، وزيادة تكوين طفرات جديدة بالخلية، وتغيير الموقع / الإنزيم المستهدف لعمل المضاد الحيوى ، وزيادة المضخات الطاردة للمضادات الحيوية. و يعد أستخدام مزيج من أثنين مختلقين من المضادات الحيوية يؤدي إلى توسيع نطاق عمل المضادات الحيوية ضد البكتيريا المقاومة لهذه للمضادات و تقليل قدرتها على إنتاج طفرات مقاومة. وعلى الرغم من أن هناك عدة مزايا لأستخدام مزيج من أثنين مختلقين من مضادات الميكروبات ، لكنها يمكن أن تؤدى الى زيادة مقاومة البكتريا أثناء فترة العلاج. و قد ثبت أن تغليف المضادات الحيوية داخل الجسيمات النانوية يقلل من ظهور المقاومة لهذه المضادات الحيوية عن طريق زيادة التوافر البيولوجي داخل الخلايا للأدوية المضادة للميكروبات من خلال تقليل تطوير طفرات مقاومة وتثبيط مضخات التدفق. و في هذا العمل ، سنلخص الأستراتجيات المختلفة لمقاومة مضادات الحيوية، واستخدام العلاج المركب الذى يتكون من مزيج من المضادات الحيوية واستخدام الجسيمات النانوية المحملة بمضادات الميكروبات وتطبيقها في المستقبل لمحاربة البكتيريا المقاومة للأدوية المتعددة.