MINI-REVIEW

RECORDS OF PHARMACEUTICAL AND BIOMEDICAL SCIENCES

Focus on Advancements in Amikacin Sulfate Delivery and Safety

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Abstract

Aminoglycosides are a class of potent antibiotics widely used in the treatment of severe bacterial infections. However, their clinical efficacy is often limited by issues such as poor bioavailability, systemic toxicity, and the emergence of antibiotic resistance. To overcome these challenges, various drug delivery systems have been developed to enhance the therapeutic outcomes of aminoglycosides. This review article provides a comprehensive overview of the different drug delivery systems employed for aminoglycosides, with a specific focus on amikacin. The review discusses the rationale behind the use of drug delivery systems, the various types of delivery systems available, their advantages and limitations, and recent advancements in the field. The aim is to provide a detailed understanding of the current state-of-the-art drug delivery systems for aminoglycosides, particularly amikacin, and their potential in improving the clinical outcomes of aminoglycoside therapy.

Keywords: Aminoglycosides, amikacin, drug delivery systems, encapsulation, nanoparticles, liposomes, hydrogels.

1. Introduction:

A significant weapon in the fight against infectious disease, aminoglycosides were thought to exist in the early days of antimicrobial chemotherapy. *Streptomyces* and *Micromonospora* were the bacterial species from which the first generation of aminoglycosides was isolated. The first antibiotic to effectively cure tuberculosis was streptomycin, which was discovered in 1944 from Streptomyces griseus. Neomycin, gentamicin, and tobramycin soon followed. They were formerly mainstays of antimicrobial therapy for severe bacterial infection, demonstrating excellent effectiveness against a wide variety of Gram-positive and Gram-negative bacteria, including Pseudomonas sp. But as usage increased, resistance started to emerge, which presented a problem. Consequently, a second generation of less resistant semisynthetic aminoglycosides was introduced, including amikacin. Unfortunately, it was found that there was a significant chance of serious side effects, such as nephrotoxicity and ototoxicity, with all aminoglycosides, including amikacin (Deja 2024). Since then, the usage of aminoglycoside antibiotics has generally decreased due to the introduction of new kinds of broad-spectrum antibiotics that are

thought to have less or less severe side effects, such as cephalosporins, carbapenems, and combinations of beta-lactam/beta-lactamase inhibitors. Aminoglycosides made up only 3% of the antibiotic market worldwide in 2022 (Deja 2024). This comes with the fundamental question; is the use of aminoglycosides in modern medicine still warranted when the drug pipeline produces better, safer broad-spectrum antibiotics? Therefore, it is important to focus on more research work regarding enhancing bioavailability and safety of aminoglycoside antibiotics, in order to utilize their superb activity and efficiency.

Aminoacyl-tRNA site (A-site) on 16S ribosomal RNA (rRNA) of the 30S ribosome is the location of bacterial protein synthesis inhibition, and this is the main mechanism of action of aminoglycoside antibiotics. By attaching themselves to the 16S rRNA, they change the structure of the molecule, suppress the production of new proteins, prevent elongation, and encourage the incorrect translation of codons. These erroneous proteins, when released, harm the cytoplasmic membrane and ultimately end in cell death (Krause et al. 2016). Unlike other protein synthesis inhibitors, which are bacteriostatic, aminoglycosides exhibit concentration-dependent bactericidal activity and a sustained post-antibiotic impact that prolongs the antibacterial effect even after the medication has been eliminated from the body (Krause et al. 2016).

The ratio of area under the curve (AUC) to minimum inhibitory concentration (MIC) is the pharmacokinetic/pharmacodynamic measure most strongly connected with efficacy for aminoglycosides, while a precise target ratio is not well defined (Krause et al. 2016; Serio et al. 2018). Because aminoglycosides are poorly absorbed by the gastrointestinal system, they can only be administered intravenously or intramuscularly. A common therapy option for pneumonia in the past was aminoglycosides since they are highly polar compounds with poor protein binding, a broad volume of distribution, and great penetration into most tissues, including the lungs. Since aminoglycosides are virtually totally eliminated by glomerular filtration as unaltered medication, they are excellent for the treatment of urinary tract infections (Serio et al. 2018).

While many Gram-negative pathogens, such as *Enterobacterales*, *Pseudomonas* species, and *Acinetobacter* species, are known to be susceptible to the action of aminoglycosides, *Burkholderia cepacia* and *Stenotrophomonas maltophilia* have negligible susceptibility to these compounds.

Despite their demonstrated efficacy against numerous Gram-positive infections, such as *Staphylococcus* species and certain Mycobacterium species, their combined usage is mostly attributed to their reduced permeability resulting from distinct compositions of cell membranes. Since their absorption across bacterial cell membranes depends on energy from aerobic metabolism, they are naturally inert against anaerobic bacteria. Consequently, aminoglycoside action is restricted in regions with low pH and partial pressure of oxygen, like abscesses. Additionally, they exhibit notable efficacy against a number of uncommon infections, including *Francisella tularensis*, *Listeria monocytogenes*, *Yersinia pestis*, and *Brucella* species (Deja 2024; Hermann 2007).

2. Amikacin Sulfate:

One of the most widely used aminoglycoside antibiotics, amikacin was developed from kanamycin in 1972 and has a molecular weight of 585 g/mol and a short half-life of two to three hours. Amikacin's decreased permeability in its natural state makes it difficult to absorb orally (Routledge and Hutchings 2013). Depending on the severity of the illness, amikacin sulphate is administered as gradual intravenous or intramuscular injections once or twice a day. Amikacin sulphate demonstrates bactericidal action that is dependent on concentration (Fujii et al. 2020). Once at the site of action, it actively transports into the cytoplasm where it binds to the 30S subunit to obstruct ribosomal translation, ultimately causing cell death. The initiation complex for peptide creation is blocked, misread m-RNA results in non-functional proteins, or polysomes break down into non-functional monosomes to prevent protein synthesis (Maxwell et al. 2021). Figure 1 shows the amikacin's structural characteristics as well as potential bacterial enzymatic deactivation methods, while Figure 2 illustrates the amikacin's inside bacterial cell mechanism.

In hospitals, where gram-negative bacilli infections are frequent and resistant to gentamicin or tobramycin, amikacin is thought to be the best medication for empirical treatment. Use cases include septicemia, severe burn, urinary tract, respiratory tract, and soft tissue infections; meningitis, peritonitis, osteomyelitis, and severe surgical infections (Serio et al. 2018). To calculate the appropriate dosage, it is necessary to ascertain the patient's body weight prior to treatment. Serum creatinine concentration measurements or endogenous creatinine clearance rate calculations

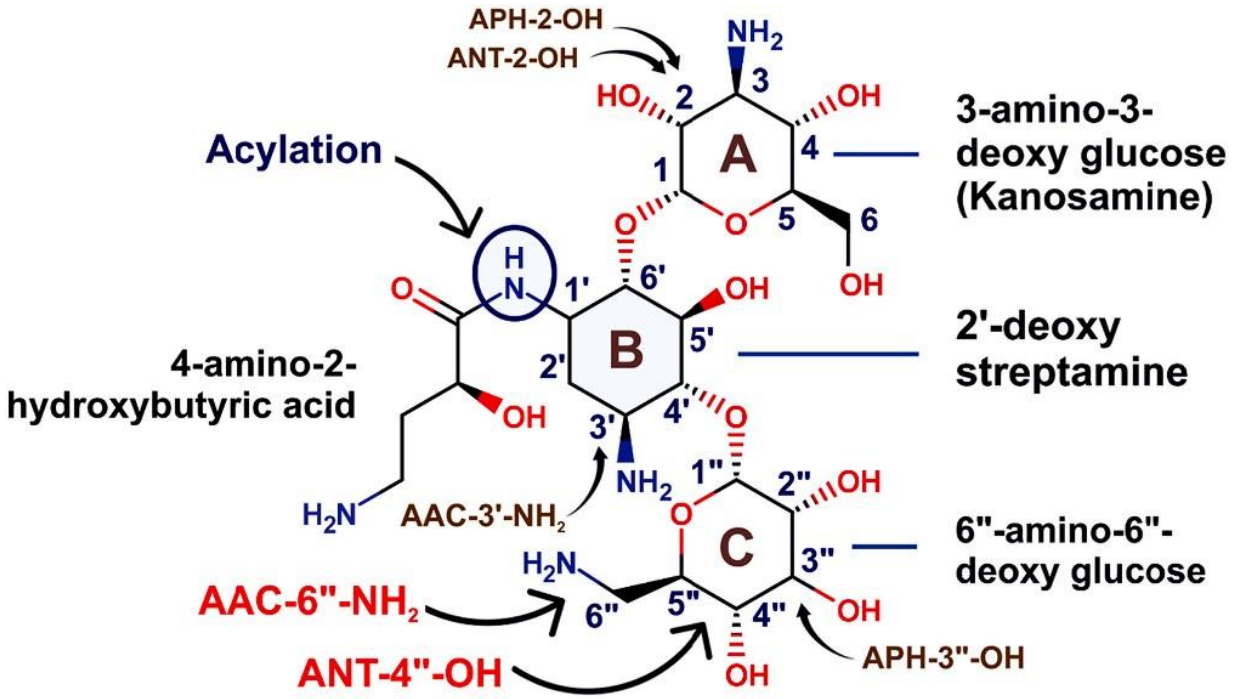

Fig. 1. Amikacin's structural characteristics and potential mechanisms of bacterial enzymatic inactivation. Together, rings A, B, and C stand for the aminoglycoside kanamycin, which is acylated at 1'-NH2 to yield amikacin. Aminoglycoside-N-acetyltransferases (AAC), aminoglycoside-phosphotransferases (APH), and aminoglycoside-O-nucleotidyltransferases (ANT) are important enzymes that deactivate aminoglycosides (Maxwell et al. 2021).

should be used to determine the state of renal function. For this purpose, the blood urea nitrogen (BUN) is far less dependable. Throughout treatment, renal function should be evaluated again on a regular basis (Serio et al. 2018). Amikacin single doses for people with normal renal function have been reported to vary from 5 mg/kg/8h to 7.5 mg/kg/12h, with a total daily dose of amikacin equal to 15 mg/kg body weight. The American Thoracic Society's recommended amikacin dosage range calls for a single dose of 10–15 mg/kg/day. To put it briefly, the single dose of amikacin varied from 5 to 15 mg/kg body weight (El-Say et al. 2024).

3. Toxicity and Resistance:

Because the drug is retained in the cortical proximal tubule cells of the kidney and the cochlear cells of the ear, significantly exceeding contemporaneous serum concentrations, aminoglycoside usage is known to cause nephrotoxicity and ototoxicity (Serio et al. 2018). Because research objectives and patient populations differ, the reported incidence of aminoglycoside-induced nephrotoxicity varies greatly, but it is generally thought to be between 10% and 20% (Humes 1988). Nephrotoxicity usually appears 5-7 days into therapy and can show up even after stopping the medication because of drug sequestration that lasts a long time in the tubule cells. Usually, non-oliguric acute kidney injury with a lack of renal concentrating ability—which results in hypomagnesemia and polyuria—presents clinically (Humes 1988; Serio et al. 2018). Individuals with advanced age, pre-existing renal impairment, long-term therapy, intravascular volume depletion (e.g., sepsis, heart failure, liver illness), or high peak plasma drug levels are among those most at risk for nephrotoxicity (Deja 2024; Humes 1988). Gentamicin has been linked to the highest nephrotoxic potential in prospective comparative trials, with tobramycin and amikacin following closely behind (Humes 1988). Compared to traditional intermittent dosing, risk may be reduced by utilizing extended-interval dosing tactics because proximal tubule cells can saturate aminoglycoside uptake. Reversible nephrotoxicity caused by aminoglycosides often returns renal function to baseline within two to three weeks of stopping the offending medication (Serio et al. 2018). Aminoglycoside-induced ototoxicity can manifest as vestibular toxicity, which causes disequilibrium, vertigo, and/or ataxia, or cochlear toxicity, which causes tinnitus and/or hearing loss.

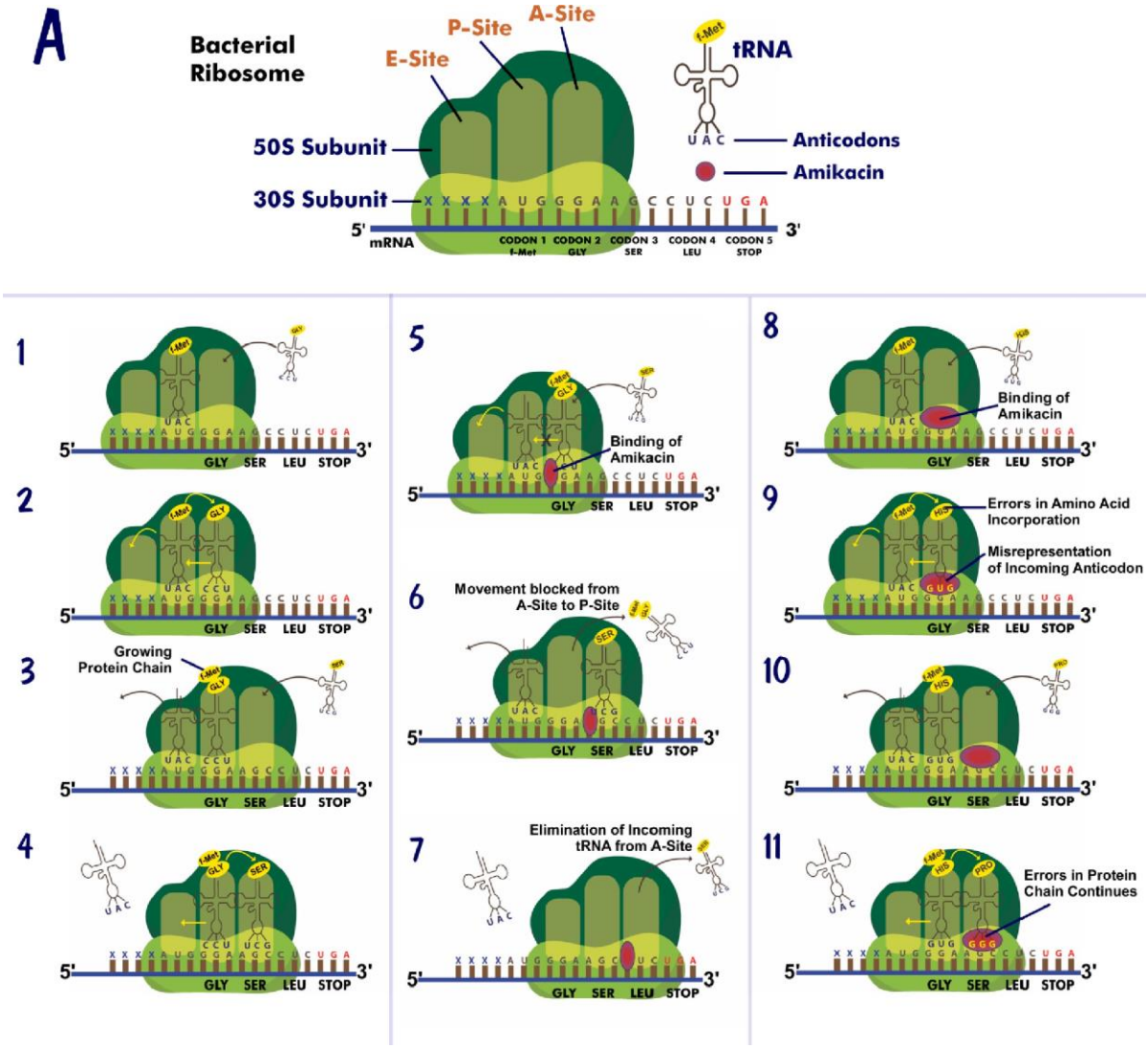

Fig. 2. Amikacin's mechanism of action and binding to the 30S component of the bacterial ribosome. (A) shows the entering anticodon-tRNA, the graphical depiction of amikacin, and the structure of a bacterial ribosome, which includes the 30S and 50S subunits and three active sites (A-Site, P-Site, and E-Site) (Maxwell et al. 2021).

Gentamicin and tobramycin are mostly thought to be vestibuli-toxic, whereas amikacin is thought to be more cochlea-toxic (Serio et al. 2018). It has been reported that 2–25% of patients having cochlear toxicity and 1–10% having vestibular toxicity. Although the exact mechanism underlying aminoglycoside-induced toxicity is unknown, it seems to be connected to harm to the inner ear's hair cells and is frequently permanent. Prolonged medication duration and elevated aminoglycoside plasma levels are risk factors for ototoxicity (Deja 2024; Serio et al. 2018).

Three ways exist for bacteria to develop resistance to aminoglycosides. The first is lowering the drug's intracellular concentration through changes to the cell membrane transport pathways. MexXY-Op-M in *P. aeruginosa* is involved in the resistance to aminoglycosides and other antibiotics. Pan-aminoglycoside resistance may arise from mutations in the mexZ repressor, which controls the expression of mexXY. Therefore, aminoglycoside resistance brought on by enhanced efflux is significant in *P. aeruginosa* isolates, especially when it comes to people with cystic fibrosis who have persistent lung infections. Aminoglycoside resistance is also influenced by mutations in the AdeRS regulator in Acinetobacter species. Nonetheless, resistance through efflux is

incredibly uncommon in *Enterobacterales*. The second resistance mechanism involves nucleotide methylation or mutations that alter the 16S rRNA. Since the majority of organisms have several copies of the genes encoding rRNA, mutations at the target region itself are extremely rare. Because they each only have one copy of the 16S rRNA or the ribosomal operon, *Mycobacterium* spp. and *Borrelia* spp. are the only organisms that have shown aminoglycoside resistance via this mechanism. Resistance can be conferred by methyltransferases that methylate the nucleotide residues on the 16S rRNA in order to prevent aminoglycoside binding. Numerous Gram-negative species, such as *Enterobacterales* (most frequently *K. pnuemoniae*), *P. aeruginosa*, and *A. baumanii*, have these enzymes (Deja 2024; Serio et al. 2018). The final and most prevalent route of resistance to aminoglycosides is the enzymatic alteration of the medication by enzymes that modify aminoglycosides (AMEs). Because aminoglycosides exert selective pressure on enzymes involved in normal cell metabolism, it is believed that AMEs developed from those enzymes (Becker and Cooper 2013). Hundreds of AMEs have been found, and depending on their chemical structure, they exhibit varying degrees of activity against different aminoglycosides. They can be encoded on transposons, integrons, and plasmids, which encourages organism mobility and the propagation of resistance. Additionally, they frequently contribute to multi-drug resistant (MDR) phenotypes because they are frequently encoded alongside other antimicrobial resistance genes, such as carbapenemases or extended spectrum beta-lactamases (ESBLs). Acetyltransferases (AACs), nucleotidyltransferases (ANTs), and phosphotransferases (APHs) are the three different types of AMEs. The most prevalent AMEs are acetylate amino groups (-NH2), which are present in both Gram-positive and Gram-negative species. The phosphorylation of hydroxyl groups (-OH) is catalysed by APHs. Amikacin resistance is caused by a number of subclasses of APHs seen in Enterobacterales and P. aeruginosa, even though many of them do not give clinically significant resistance to aminoglycosides. *Enterococcal* and *Staphylococcal* species frequently contain these AMEs. Lastly, ANTs are primarily found in Gram-positive organisms like *Staphylococcus* species, *Enterococcus* species, and *Bacillus* species. They transfer an adenosine monophosphate (AMP) group from ATP to a hydroxyl (-OH) group on the aminoglycoside (Serio et al. 2018). None of the AME inhibitors that have been successfully developed to date are clinically beneficial (Hermann 2007). Targeted structural alterations can be made to try to avoid AME modification and stop aminoglycoside resistance, though, as each AME is unique to different functional groups within the aminoglycoside molecule. The pathways of bacterial resistance to amikacin are depicted in Figure 3.

4. Why Do We Need Drug Delivery Systems for Amikacin?

Biofilms are the most common form of bacteria found in nature, and most traditional antimicrobials have not been able to effectively combat the major challenge posed by these intractable bacteria. A strong physicochemical barrier called the biofilm matrix helps to shield the bacterial cells from some of the effects of antibiotic therapy. An appealing way to prevent the development of bacterial biofilms is through the use of nano-drug delivery systems. While there are a few instances of silver nanoparticle-containing antimicrobial dressings, implants, and catheters that can be used in medicine, research on advanced anti-biofilm methods is still in its infancy and primarily focuses on in vitro environments (Fulaz et al. 2019). As of right now, two antibiotic formulations based on nanotechnology have been approved for clinical use: Arikace™ (a Phase III clinical trial) and Fluidosomes™ (a Phase II clinical trial) (Fulaz et al. 2019; Maxwell et al. 2021). Combining antimicrobials with nanoparticles may stop bacterial resistance or bring drug-resistant bacteria back to sensitivity; nevertheless, a full understanding of the "pharmacokinetics/pharmacodynamics" of nanoparticles is necessary for practical translation.

Bacteria are rarely able to acquire resistance because of the multifunctional processes that enable nanoparticles to demonstrate antimicrobial action against them. The Nextar Pharmaceuticals-developed amikacin liposomes, often known as Mikasomes®, are well-known for having a longer drug residency and a lower renal clearance than regular amikacin. Because they merge with the outer bacterial membrane to deliver a large dose of aminoglycosides into bacterial cells, they are efficient against intracellular infections. According to previous studies, amikacin delivered as liposomes resulted in a 64-fold reduction in dosage (512 mg/L for free medication vs. 8 mg/L for liposomal amikacin). This investigation verified that the molecular mechanism responsible for

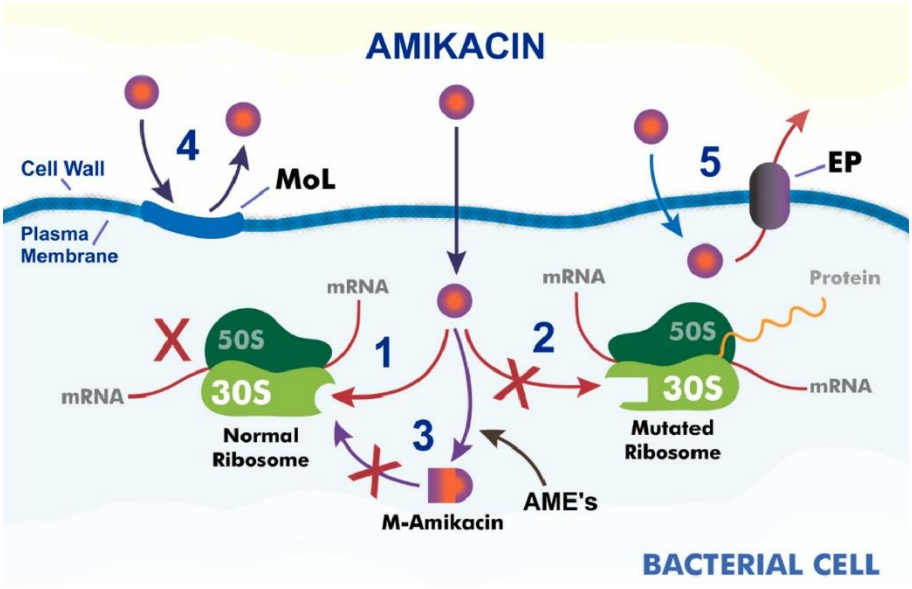

Fig. 3. Mechanisms of amikacin resistance in bacteria. Amikacin binds to a particular location in the 30S subunit of the bacterial ribosome, demonstrating its typical activity in (1), while (2–5) display different strategies for resistance (Maxwell et al. 2021).

enhanced bactericidal activity is the fusion of liposomes with the bacterial membrane. Additionally, liposomes prevent and lessen the toxicity of entrapped bioactive compounds by providing antimicrobial agents with protection from bacterial enzymes and the efflux pathways, which suppresses the drug resistance of pathogenic organisms (Maxwell et al. 2021).

5. Drug Delivery Systems for Amikacin

5.1. Polymeric nanocarriers

By encasing the medication inside the polymer matrix, polymeric nanocarriers shield it from destruction brought on by metabolism (Brewer et al. 2011; Sánchez et al. 2020). This lowers dosage, frequency of dosing, and dose-related adverse effects by increasing drug residence duration and bioavailability. These added benefits eventually turn polymer nanoparticles into an ideal option for delivering powerful medications. Amikacin-loaded polymeric nanoparticles showed a biphasic release pattern, with a burst release at first and a steady, protracted release afterward, in contrast to the free drug (Fatima et al. 2018). Amikacin that was present on the surface or near the surface of the nanoparticles was shown to be expelled from the hydrophobic polymer matrix into the aqueous medium during the nanoparticle synthesis, resulting in the initial burst release. Meanwhile, amikacin that was trapped in the polymer matrix underwent slow diffusion because of the longer path length and reduced penetrability of the aqueous medium (Figure 4). This biphasic release profile plays a special role in antimicrobial activity because the sustained release may lessen the likelihood of drug resistance by supporting therapeutic action for an extended length of time, while the initial burst release aids in achieving high therapeutic concentrations (Fatima et al. 2018).

The capacity of polycyanoacrylate nanoparticles to enhance amikacin's, a hydrophilic medication, to penetrate the cornea was studied. The stabilizers used in the study—Synperonic F 68, sodium lauryl sulphate, and dextran 70,000—were changed. It was established that drug loading, electrophoretic mobility, and particle size were all significantly impacted by the type of stabilizer. When compared to the control, there was a statistically significant rise in amikacin concentration in the aqueous humor and cornea for the nanoparticle formulation (Maxwell et al. 2021). Amikacin is classified as a Class III medication under the Biopharmaceutical Classification System (BCS). Its short half-life and decreased permeability limit its use to parenteral administration (Fatima et al. 2018). An oral amikacin delivery formulation is necessary since parenteral therapy necessitates hospitalization, which results in low patient compliance. Amikacin was synthesized and its potential for oral delivery via thiol linked chitosan nanoparticle formulation was examined (Figure 5). The sodium sulphate gelation technique and sodium tripolyphosphate

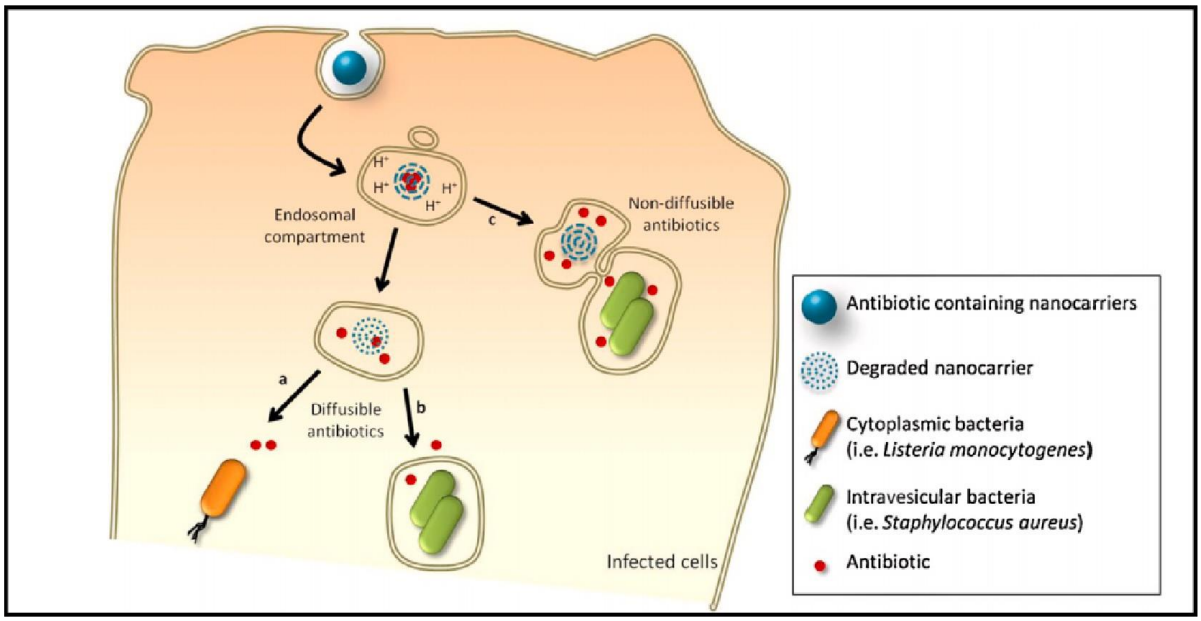

Fig. 4. The pattern of release for intracellular transport of nanocarriers containing antibiotics (Maxwell et al. 2021).

(TPP) were used to create the thiomer and chitosan nanoparticles. The resulting nanoparticles were spherical and had a smaller size dispersion (150–300 nm). It was discovered that the conjugated polymer improved the muco-adhesion capabilities 20 times more than the polymer alone. It was observed that the mucoadhesive qualities of amikacin loaded into thiolated nanoparticles enhanced the absorption rate and allowed the nanoparticles to pass through the intracellular space. Amikacin could be administered within these nanoparticles to cellular cavities containing obligate aerobes such as *Mycobacterium TB* (Maxwell et al. 2021).

In order to ensure effective penetration and eventually better bioavailability, poly d,L-lactide-co-glycolide (PLGA) microparticles loaded with amikacin were produced. These microparticles had an ideal particle size of 260.3 nm, a low polydispersibility index, and a greater loading capacity of 3.645%. The Higuchi model of diffusion was followed by amikacin-loaded PLGA microparticles, which showed drug diffusion together with erosion from the polymer matrix of the nanoparticles. Amikacin-loaded PLGA microparticles made it easier to administer drugs orally by avoiding the gastrointestinal tract's membrane barriers. It was proposed that increased bioavailability resulted from improved microparticle absorption through Peyer's patches covering the small intestine (Fatima et al. 2018; Maxwell et al. 2021).

5.2. Solid lipid nanoparticles

A controlled drug delivery method with numerous important advantages, including biocompatibility, high tolerability, and simplicity of scale-up, is solid lipid nanoparticles, or SLNs (Ghasemiyeh and Mohammadi-Samani 2018; Schwarz 1999). By formulation, surfactants and one or more solid lipids make up the whole composition of SLNs (Figure 6).

SLNs of amikacin for pulmonary delivery were developed with the goal of lowering toxicity, especially for long-term care, by reducing the dose and the intervals between administrations. Amikacin-SLNs produced with cholesterol were reported to have a two-fold lower minimum bacteriostatic concentration (MBC) and minimum MIC of the medication compared to the free form. The increased cellular entry of amikacin through the bacterial membrane was related to the lipophilicity and particle size of SLNs, which resulted in a stronger antibacterial activity (Ghaffari et al. 2010). As a result, it was demonstrated that SLNs could effectively treat the illness at lower doses of amikacin while experiencing less side effects and greater safety. Additionally, the data demonstrated that the freeze-dried SLNs exhibited a biphasic release pattern, releasing up to 95% of the loaded drug over the course of 144 hours in an early burst release

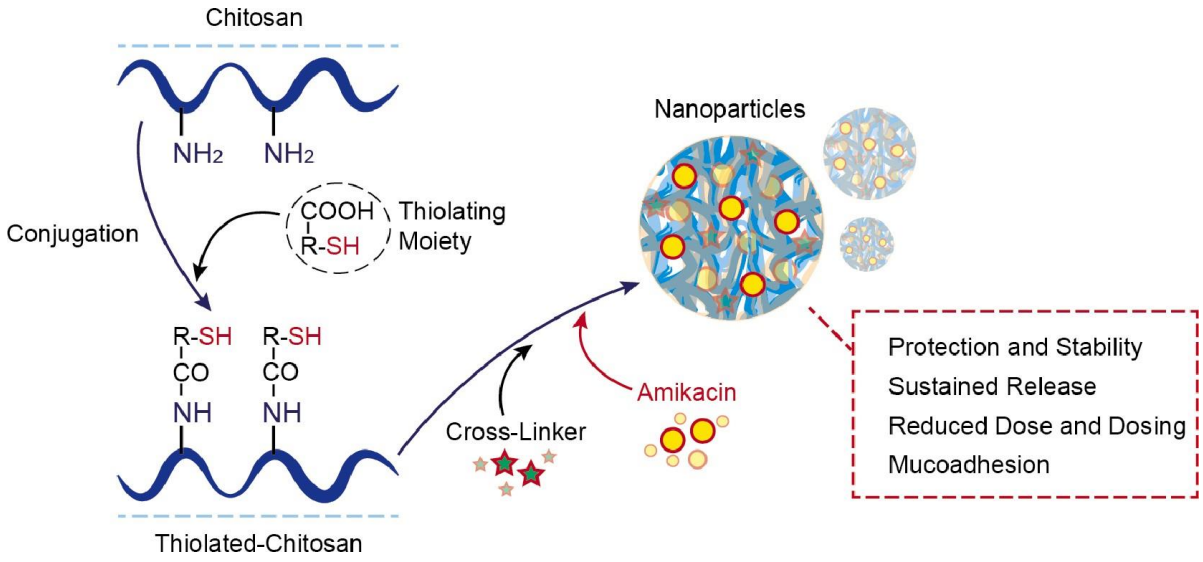

Fig. 5. Muco-adhesive thiolated-chitosan nanocarriers for amikacin retarded release pattern (Maxwell et al. 2021).

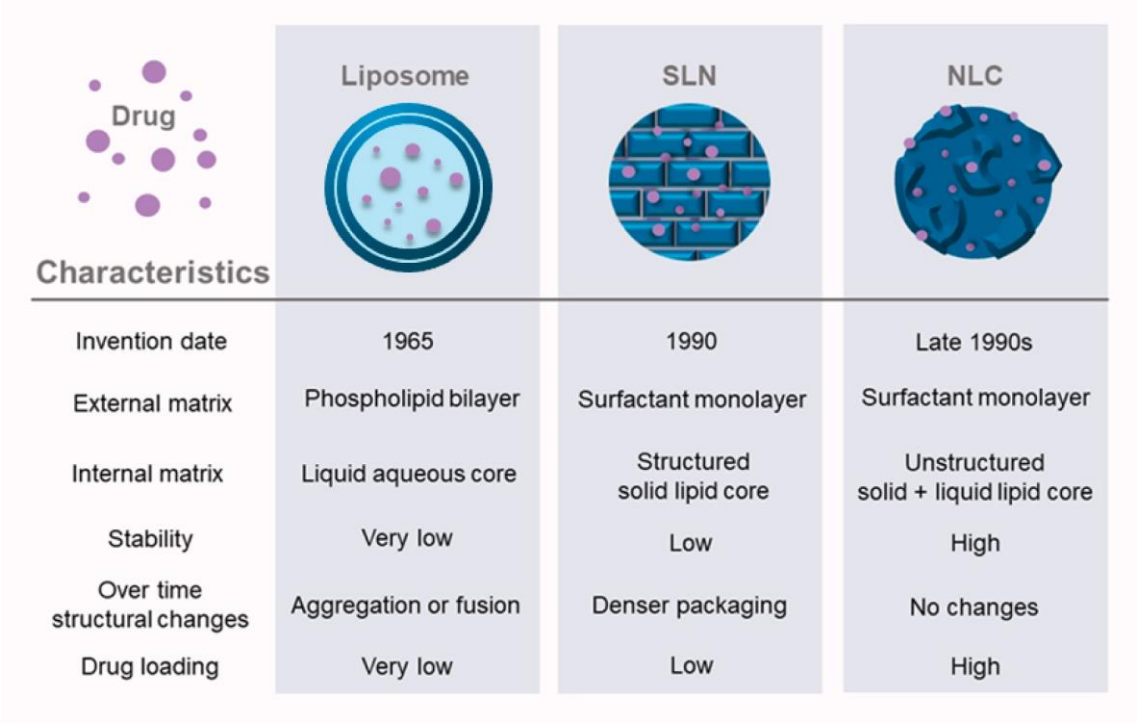

Fig. 6. The most important characteristics of SLNs and lipid-based nanocarriers (Vairo et al. 2023).

followed by a long-sustained release. Because of its prolonged release, amikacin-SLN offers great potential for pulmonary delivery and hence has a great deal of room for further investigation (Ghaffari et al. 2010). After pulmonary delivery, the biodistribution pattern of amikacin-loaded SLN was investigated to improve the drug's activity in the lungs for the treatment of lung infections in cystic fibrosis patients. This was accomplished by giving male rats SLN and 99mTc-labeled amikacin intravenously and through the lungs. According to the bio-distribution experiments, pulmonary delivery resulted in a much larger concentration of SLN in the lungs as opposed to intravenous delivery. Furthermore, pulmonary delivery of SLN resulted in a lower drug concentration in the kidney

than intravenous treatment, suggesting a reduction in nephrotoxicity. Amikacin SLN for pulmonary usage decreased the frequency of doses and offered increased efficacy in minimizing amikacin adverse effects, improving the drug's pharmacological index in the process (Varshosaz et al. 2013).

5.3. Lipid-based Nanocarriers

Lipid-based nanocarriers, which range in size from nanometers to micrometers, are biocompatible and reasonably safe drug delivery devices made of phospholipid bilayers encasing the aqueous core (Figure 6). The ability of liposome-based medications to increase therapeutic index while lowering side effects is their most important feature. The exceptional potential of liposomal antibiotics in microbial infections is demonstrated by recent developments in liposomal formulations and their targeted administration of bioactive chemicals and chemotherapeutics (Maxwell et al. 2021). Aminoglycosides were encapsulated in liposomes, which improved the nephrotoxicity, C_{max}, AUC-time curve, and plasma half-life (Shulha et al. 2019). Amikacin-liposomes prevented an enzyme, immunological, and chemical inactivation, which increased the sensitivity of bacteria and decreased the dose required. In comparison to pure amikacin, a previous work revealed that once-weekly or once-monthly therapy with amikacin-liposomes greatly decreased bacterial load and increased the survival rate, producing a sustained release effect.

The phenomena of higher antibiotic-liposome uptake into bacterial cells in comparison to free antibiotics was investigated, which revealed that at a minimum inhibitory concentration (MIC) of 16 μg/mL, amikacin-liposomes stopped bacterial growth in 6 hours, while free amikacin at 512 μg/mL had the same lethal effect. It is thought that the essential process for the adequate transport of medicines into the impermeable bacterial membrane is liposome-bacterial fusion. The effectiveness of antibiotic-loaded oleic acid-based liposomes was tested against 32 multidrug-resistant strains of Pseudomonas aeruginosa that were obtained from burn sites and urine samples (Maxwell et al. 2021). According to the study, liposome-bacterial fusion is responsible for the 15-fold reduction in resistance observed in oleic acid-loaded liposomes when compared to pure oleic acid. Moreover, the susceptibility to Pseudomonas aeruginosa was increased by the encapsulating of antibiotics in liposomes based on oleic acid.

5.4. Hydrogel dressing

A hydrogel patch with nano-formulations was created to prevent diabetic foot ulcers and associated problems that are frequently brought on by Pseudomonas aeruginosa and methicillin-resistant Staphylococcus aureus (MRSA). The MIC for bacterial isolates was found to be 95% lower when amikacin-loaded chitosan-silver nanoparticles were combined into a nano-formulation. However, the hydrogel's amikacin-loaded nanoparticle dose (4 μg/mL) was significantly less than the topical amount (125 mg/mL) that was recommended.

Furthermore, it was observed that the dressing formulation exhibited no harmful effects on the liver or kidneys, confirming its safety and biocompatibility. Because the chitosan metal nanoparticle disrupted various drug resistance pathways, such as decreased drug uptake and enhanced efflux from the bacterial cell and suppression of biofilm formation, it demonstrated 3.9-fold stronger antibacterial efficacy than amikacin alone. Additionally, the three-dimensional hydrogel polymeric network was semipermeable to gases and water vapor, creating an environment that was hydrated and moist for the healing of wounds (Maxwell et al. 2021).

5.5. Depo-Foam encapsulating amikacin sulfate (DEAS)

A basic systemic antibiotic regimen is often effective in treating simple illnesses. However, a locally injected antibiotic is favored in some circumstances, such as the presence of a foreign body, necrotic tissue, an extensive bacterial inoculum, or insufficient vascular supply to the tissues. The injectable, tiny Depo-Foam particles are made up of many bilayer lipid membranes encasing several non-concentric aqueous vesicles. Large internal aqueous cores are enclosed by these lipid-based drug delivery systems, which facilitate the effective encapsulation of hydrophilic medicines and their prolonged release, as well as improved storage stability. It has been discovered that altering the length of the triglyceride (TG) chain utilized to generate the multi lamellar vesicles changed the release rate of physiologically active chemicals. When compared to short chain TGs, long chain TGs generally had slower release rates. Furthermore, the osmolarity of the drug's aqueous solution combined with the immiscible lipid-solvent phase affected the in vivo release rate (Mantripragada 2002). Depo-Foam encapsulating amikacin (DEAS), a lipid-based, biodegradable, sustained-release formulation of AS releases the encapsulated medication over a period of 7 to 10 days. It was reported that the DEAS treatment considerably decreased the amount of infected

foreign bodies (from 86% to 25%) when compared to local injection with free amikacin (Maxwell et al. 2021).

5.6. Nanofibers

Polymeric fibers with widths in the nanoscale range are known as nanofibers, and they are often created by the thermally induced-phase separation or electrospinning processes. Because of its special qualities, which include considerable porosity, mechanical characteristics, flexibility, and the capacity to release medications locally under regulated conditions, nanofibers have attracted a lot of interest in biomedical applications (Maxwell et al. 2021). Additionally, no sophisticated machinery or wet chemical techniques are needed for the preparation of electrospun nanofibers, which are used to encapsulate medicinal compounds. Additionally, they are frequently utilized in the creation of wound dressings due to their large surface area and efficient absorption of moisture and wound exudates (Maxwell et al. 2021).

Utilizing the electrospinning method, Mira et al. recently synthesized amikacin nanofibers utilizing poly (methyl-vinyl ether-maleic acid) (PMVE/MA/ac) (Mira et al. 2020). Amikacin nanofibers' antibacterial activity was evaluated and contrasted with the drug's unbound form. When it came to Staphylococcus aureus and Escherichia coli, the minimum inhibitory concentration (MIC) values of the free drug and the amikacin-encapsulated nanofibers did not differ significantly. However, while the nanofibers demonstrated comparable antibacterial activity to the pure medication, additional studies evaluating the nanofibers' potential benefits for controlled release, targeted administration, and therapeutic benefits were not conducted.

6. Conclusion and future scope

Both Gram-positive and Gram-negative bacteria can cause life-threatening infections that can be treated with amikacin alone or in conjunction with other antimicrobials. While amikacin has demonstrated its efficiency as an antibiotic in managing infections resistant to many drugs, the emergence of antibacterial resistance has prompted more investigation into enhancing medication efficacy through the utilization of nanocarriers and the synthesis of novel aminoglycoside derivatives. A significant outcome of combined industry and academic efforts has been the development of innovative clinical candidates that may have fewer adverse effects and exhibit efficacy against resistant strains. The research presented here underlines how important it is to take a strong interest in amikacin as it will help us better understand how resistance develops and how to formulate antibiotics that will help fight infections caused by bacteria that are resistant to multiple drugs. Pharmacokinetic and pharmacodynamic research are needed to further amikacin-encapsulated nanocarrier antibacterial therapy and ensure the formulation's safety and effectiveness before commercialization. Furthermore, additional research and exploration are required to conduct a long-term safety and tolerability profile study of the excipients used.

Declaration of interest

The authors declare that they have no conflicts of interest.

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