Role of Nanotechnology in Antibiotic Drug Delivery: Review study on the Advancement of Transforming Infection Management in Critical Care, Challenges and Future Directions

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Abstract
Nanotechnology has changed the face of antibiotic delivery with new and innovative approaches to address major infections, particularly in the intensive care units where multidrug resistance is emerging as an important problem. This review outlines the utility of nanocarriers like liposomes, polymeric nanoparticles, dendrimers, and hybrid systems as precision drug delivery devices. These drug delivery devices enhance the solubility and stability of the drugs while simultaneously ensuring minimum systemic toxicity and delivering them in controlled and targeted manners. Essentially, stimuli responses of nanocarriers and AI-informed design represent major paradigm shifts towards potentially overcoming some MDR mechanisms and possibly maximally attaining therapeutic advantage. Their incorporation into everyday clinic practice poses significant challenges; issues include potential nanotoxicities, lack of scalability at the pilot plant scale for production purposes, and possible regulatory burdens. Bio-inspired nanocarriers have great promise for future advancement together with personalized medicines and a combination of nanotechnology and machine learning. This comprehensive analysis brings forward the transformative power of nanotechnology in redefining the management of infection in critical care and makes way for a future of precision medicine.

Keywords: Nanotechnology, Antibiotic Delivery, Multidrug Resistance, Critical Care, Nanocarriers, Targeted Therapy, Nanotoxicology

1. Introduction

Generally, nanotechnology can be defined as the research, manipulation, and application of materials, devices, and systems at a nanoscale. By general definition, it occurs in the range between 1 and 100 nanometers (nm) (Ferreira et al., 2021). Among the possible applications of nanotechnology in medicine, nanoparticles have been studied for their use as drug delivery systems (Mi et al., 2018). There has been significant research on nanoparticle-based delivery systems that include liposomes, polymerases, and solid lipid nanoparticles, acting as carriers for conventional antibiotics (Motamedi et al., 2015). Such nanoparticle-based delivery systems provide several advantages compared to traditional antibiotic administration: targeting improvement, controlled

release, improved bioavailability, and decreased toxicity (Zare-Zardini et al., 2022). The physicochemical properties and incorporation properties make liposomes a efficient delivery vehicle for antibiotics (Ferreira et al. 2021). These have led to clinical-stage developments of antibiotic liposomal formulations called Arikace, or more simply amikacin liposome inhalation suspension, to the use in the treatment of NTM lung disease (Mi et al. 2018).

Other than liposomes, there are also other nanoparticle-based delivery systems that have been reported to deliver antibiotics. As one example, the effectiveness of antimicrobial action will improve and toxicity reduced from antibiotic gentamicin in its conjugation with gold nanoparticles (Motamedi et al., 2015). Also, protein-based nanosphere like soy protein nanosphere with filled drugs such as vancomycin was assessed for their antipseudomonal functions besides drug delivery systems and activities (Zare-Zardini et al., 2022). Nanoparticle-based delivery systems can significantly enhance the effectiveness of antibiotic therapy as these overcome most drawbacks of conventional antibiotic drugs (Gao et al., 2014). The disadvantages of conventional antibiotic drugs include poor solubility and poor ability to cross the cell membrane, with increasing strains of bacteria that are antibiotic-resistant (Dai, 2024). In this regard, nanoparticles increase the concentration of antibiotics delivered to the site of infection, further elevating their intracellular concentrations with the possibility of overcoming antibiotic resistance mechanisms (Dai, 2024). The possibilities opened by nanotechnology in antibacterial approaches also include further development of new antibacterial approaches, such as vaccination against bacteria, anti-virulence treatment, and bacterial detection (Gao et al., 2014). Firstly, the critical care units have a higher rate of nosocomial infections compared to general wards. This is due to the high-risk nature of the department since the patients are immunocompromised with their natural barriers disrupted (Cheng et al., 2020; Voort, 2014). The risk of cross-infection increases because patients are closely located to one another, have invasive devices inserted in them, and frequently interact with health care providers (Bhattacharya & Mondal, 2010). Critical care units face the challenges of quickly identifying and managing newly emergent resistant pathogens, including multidrug-resistant Gram-negative bacteria. It is a serious threat that antimicrobial resistance has risen to such an extent that mortality is as high as 16% for some multidrug-resistant Gram-positive infections in the ICU (Kunz & Brook, 2010; Rampal et al., 2019). This means that effective infection control practice and antimicrobial stewardship should be implemented to reduce the spread of these resistant organisms (Kunz & Brook, 2010).

In addition, the sudden influx of critical care cases related to events such as the COVID-19 pandemic can put critical pressure on healthcare systems, forcing quick rapprochements of resources and facing new challenges among healthcare personnel (Contreras et al., 2020). The amplified need for infection control during such crises demands the redefinition of almost each of the existing work practices with testing and implementation (Contreras et al., 2020). Moreover, the specific infections with nonspecific clinical presentations, such as nosocomial meningitis, make differential diagnosis complex and delay proper management in critical care situations (Valdoleiros et al., 2022). Changes in the implementation of surveillance differently in various facilities will also impede comparisons and the development of effective prevention approaches in health facilities (Wise et al., 2013). Finally, the cost of managing such infections as those witnessed during the COVID-19 pandemic, like severe and critically ill patients, exerts huge fiscal burdens on healthcare systems when managed, particularly in resource-limited setups (Thant et al., 2021).

2. Overview of Nanotechnology in Antibiotic Delivery

Nanocarriers have been found to be a promising delivery method for antibiotics against bacterial infections. Among the different nanocarriers that have been studied, liposomes, polymeric nanoparticles, micelles, and dendrimers have shown high promise (Li, 2023). Liposomes have been one of the most widely investigated types of nanocarriers prepared specifically for the delivery of antibiotics (Li, 2023; Canaparo et al., 2019). According to Li, (2023) Liposomes are built from phospholipid bilayers which may capture both hydrophilic as well as hydrophobic antibiotics. Once PEG is included in the liposomal formulation, circulation time of the drugs will be increased and would also be more potent with a lesser amount of these drugs as well as lesser concentration thereof. In addition, liposomes can be designed to be responsive to many stimuli, ranging from pH, light and ultrasound to specific proteins and enzymes, which would allow for a site-specific as well as controlled release of the antibiotics entrapped within them (Li, 2023).
More recently reported nanocarriers for delivering antibiotics include polymeric nanoparticles by Le et al. 2021. Such nanoscale particles may prolong their systemic circulation times and could provide sustained release of drugs they encapsulate since they could be engineered to enhance the aqueous solubility of poorly water-soluble antibiotics. Polymeric nanocarriers can perhaps aid overcome some of the disadvantages connected with free-form antibiotic delivery that relates to poor bioavailability, short biological half-lives, fast clearance, and the possible development of antimicrobial resistance. Recently, studies on amphiphilic polymer-based nanocarriers for antibiotic delivery have taken the form of self-assembled micelles (Dai et al., 2018). The drug release within the micelles is controlled, and hydrophobic antibiotics can be dissolved by these micelles (Dai et al., 2018). Click-crosslinked micelles have been applied to enhance the solubility and efficacy of antibiotic delivery.
Dendrimers are highly branched macromolecules with tree-like structures, which were explored lately as nanocarriers for antibiotic delivery. In fact, through the multivalent nature, dendrimers that could be able to encapsulate wide hydrophilic and hydrophobic drugs, it could be decorated with targeting ligands to enhance the specificity of drug targeting (Canaparo et al., 2019). Other than those types of nanocarriers, hybrid systems like exosome-liposome hybrids have been explored in terms of the delivery of antibiotics (Sato et al., 2016). Hybrid nanocarriers can take on properties from more than one type of nanocarrier. This may, in turn, improve delivery and efficacy of the antibiotic (Sato et al., 2016).

3. Applications of Nanotechnology in Critical Care

3.1. Enhanced Drug Delivery

Nanocarriers play a significant role in ensuring the targeted delivery of antibiotics to infection sites. Among the various benefits of nanocarriers is that they enhance the bioavailability and efficacy of currently available antibiotic treatments (Le et al., 2021). Nanoparticle-based drug delivery systems may help enhance solubility and stability, control drug release profiles, and co-deliver multiple drugs (Le et al., 2021). Stimuli-responsive nanocarriers are very good options for targeted antibiotic delivery. They can recognize the unique microenvironment of bacteria and infection

sites and offer a response to specific stimuli in a dynamic way. This is how there will be prevention of prelease or "leakage" of the antibiotics before they have reached the site of infection, hence ensuring that nanocarriers accumulate for increased delivery of antibiotics specifically at the site of bacterial infection (Devnarain et al., 2020). The drug concentration at the site of infection becomes optimized, and the bacteria itself becomes better targeted while reducing toxicity and adverse side effects (Devnarain et al., 2020).

Apart from stimuli-responsiveness, surface modification of nanocarriers may increase antibiotic delivery and activity. Surface modifications improve targeting along with the internalization of nanocarriers by bacteria, their penetration into bacterial biofilms (Osman et al., 2021). However, the issue of toxicity of antibiotic nanocarriers and their nanomaterials is still there, for which further nanotoxicological assessments are needed (Osman et al., 2021). Nanocarriers are also engineered to possess targeted intracellular bacterial infections. Liposomes, inorganic nanoparticles, and degradable polymeric nanoparticles have been applied in antibiotic delivery into phagocytes, including macrophages to treat infections (Wang et al., 2023; Yang et al., 2018). This technique also resolves the issue of delivering antibiotics to the site of intracellular bacterial infections, which is inaccessible for the conventional formulations of antibiotics (Wang et al., 2023; Yang et al., 2018).

The route of administration can also determine the targeted delivery of antibiotics via nanocarriers. In this regard, pulmonary delivery of antibiotic-eluting nanocarriers can lower systemic exposure of the formulation, avoiding liver first-pass metabolism and enhancing the delivery of the antibiotic cargo to the infected lung tissue (Le et al., 2021; Juntke et al., 2021). This is extremely helpful for the therapeutic intervention of respiratory infection, including cystic fibrosis (Juntke et al., 2021). Other important considerations involve the loading capacity and kinetics of nanocarriers, whereby there should be good control in the design of delivery systems of antibiotics by their rate of loading or accumulation. Preferably, at the optimum dose and interval, there is supposed to be effective delivery and subsequent release at the target location of the infection (Osman et al., 2021). Techniques, like host-guest loading where the antibiotic has strong binding interactions to attach it within the nanocarrier, can be advantageous in increasing the loading capacity with drug-responsive release characteristics in the nanocarrier itself (He, 2023).

3.2. Overcoming Multidrug Resistance

One of the key mechanisms is the interference of nanoparticles with bacterial efflux pumps, which are one of the main contributors to antibiotic resistance (Arya et al., 2019; Mishra et al., 2018; Christena et al., 2015). It is established that nanoparticles produced from silver, copper, and carbon disrupt the proton motive force required for efflux pump activity and thus prevent them from functioning. For instance, copper nanoparticles inhibited the efflux pump activity of AcrAB-TolC in multi-antibiotic-resistant Staphylococcus aureus and Pseudomonas aeruginosa, according to studies by Mishra et al. (2018) and Christena et al. (2015). Besides the above direct role, nanoparticles can play additional roles as carriers or adjuvants to increase or decrease the effectiveness of the traditional antibiotics. Nanoparticles in combination with antibiotics were demonstrated to generate drastically increased efficacy against both Gram-negative and Gram-positive, including resistant, bacteria (Tischer et al., 2019; Banoee et al., 2010). This synergistic effect is due to the ability of nanoparticles to penetrate bacterial biofilms and deliver antibiotics to the target site (Tischer et al., 2019; Gurunathan et al., 2014).

In addition, the size and morphology of nanoparticles can act as a crucial physicochemical property in their antibacterial as well as anti-biofilm activities (Gurunathan et al. 2014; Rheima et al. 2019). Nanoparticles less than 10 nm have been reported for inhibiting bacterial growth by breaking biofilms (Gurunathan et al. 2014; Rheima et al. 2019). However, bigger nanoparticles around 20 nm have also presented promising antibacterial activity and indicates that inhibition may rely on the global morphology of nanoparticles rather than size itself (Rheima et al., 2019). NPs can directly interact with and modulate cellular functions by penetrating through bacterial cell membranes, hence causing cell death (Gurunathan et al., 2014). The multi-approach mechanism of nanoparticles makes it promising as an alternative or even complement to classical antibiotics.

3.3. Sepsis Management

Nanotechnology plays an important role in the administration of antibiotics for sepsis treatment at critical care, and there are extensive research and development on this one (Fu, 2024; Gao et al., 2014). Among the applications of nanotechnology in sepsis treatment, nanoparticle-based drug delivery system is significant (Fu, 2024; Pant et al., 2021; Zare-Zardini et al., 2022). Such nanoparticles may be engineered to deliver and encapsulate antibiotics much better, enhancing their bioavailability and targeting specific infection sites (Pant et al., 2021; Zare-Zardini et al., 2022). This reduces the limitations associated with antibiotic use, such as poor solubility, drug resistance, and poor penetration through tissues (Gao et al., 2014; Zare-Zardini et al., 2022).

Nearer uses of gold nanoparticles, magnetic nanoparticles, and lipid-based nanoparticles have been significantly studied against this background, particularly in application into diagnostics and therapeutic management of sepsis (Pant et al., 2021; Luo et al., 2021; Lim et al., 2021). These nanoparticles can be functionalized with specific ligands or antibodies to capture and detect sepsis-associated biomarkers such as procalcitonin and C-reactive protein that could eventually enable rapid and accurate diagnosis (Pant et al., 2021; Luo et al., 2021). Nanoparticles can also be applied for the delivery of antimicrobial agents, immunomodulatory agents, or detoxifying agents to neutralize the different features of the pathogenesis of sepsis (Fu, 2024; Luo et al., 2021).

Nanotechnology-based approaches hold the potential for individualized and targeted care in sepsis management. The use of nanochips, genomic and proteomic analysis, etc. may assist clinicians to adjust treatment according to the different patients' requirements and optimize their care system for managing sepsis (Fu, 2024; Luo et al., 2021). Furthermore, nanomaterials are distinguished from the conventional counterparts by a high surface-to-volume ratio, the possibility of tuning physicochemical properties, and ability to cross biological barriers; these properties have made them candidates for innovative antimicrobial strategies (Motamedi et al., 2015). For example, the conjugation of nanoparticles with antibiotics enhances the activity of antibiotics and reduces drug toxicity (Motamedi et al., 2015; Zare-Zardini et al., 2022).

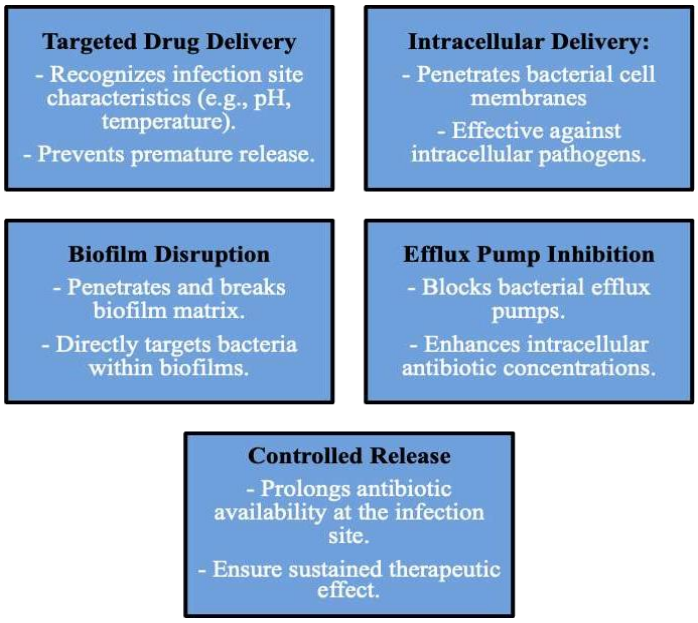

Figure 1. Mechanisms of action of nanotechnology in antibiotic delivery.

4. Advantages of Nanotechnology in Antibiotic Delivery

Nanotechnology has been emerging as a promising approach toward pharmacokinetics and minimizing the systemic toxicity of antibiotics (Ferreira et al., 2021; Jamil et al., 2017; Zhang et al., 2010). These particles can be ultra-small in size, with controlled sizes, high surface area-to-mass ratio, and even have functionalize structure to help improve delivery and the therapeutic activity of the drugs of antimicrobial resistance (Zhang et al., 2010). One of the significant benefits of drug delivery systems based on nanoparticles is that they could potentially enhance the pharmacokinetics of antibiotics (Jamil et al., 2017; Zhang et al., 2021). Nanocarriers are reported to improve the solubility of drugs that are hydrophilic or lipophilic and enhance the absorption of the drugs in the body, also ensuring controlled and sustained release of the active principles (Zhang et al., 2021). This results in enhanced bioavailability and decreases systemic exposure, while enhancing the effective delivery of the antibiotics to the target site (Jamil et al., 2017; Zhang et al., 2021).

In addition, nanoparticles might be engineered to selectively deposit specifically to targeted pathogens or infected tissue with the hope of that localized delivery of antibiotics should rise while systemically disseminated into healthy tissue could lower (Ferreira et al., 2021; Gao et al., 2014). Lower systemic toxicity shall be expected compared to routine intramuscular injection of antibiotics also (Ferreira et al., 2021; Gao et al., 2014). Various types of nanoparticles have been evaluated for the delivery of antibiotics. Some of them include liposomes, polymeric nanoparticles, dendrimers, and inorganic nanoparticles (Zhang et al., 2010; Gao et al., 2014). For example,

liposomes have been able to encapsulate and deliver antibiotics into Staphylococcus aureus biofilms, thereby improving the penetration of the antimicrobial agents (Ferreira et al., 2021). Another relevant paper was also published by Zhang et al. in 2019, where gold nanocages loaded with tetracycline combined with photothermal therapy improved antibiotic activity as well as the toxicity profile in the treatment of periodontitis.

Table 1: Comparison of nanocarrier systems for antibiotic delivery.

Parameter	**Liposomes**	**Polymeric Nanoparticles**	**Dendrimers**	**References**
Biocompatibility	High, widely accepted for drug delivery	Moderate, dependent on polymer type	High, tunable for targeting	Ferreira et al., 2021; Li, 2023
Loading Capacity	Moderate, suitable for both hydrophilic and hydrophobic drugs	High, especially for hydrophobic antibiotics	Very High, encapsulates diverse drug types	Canaparo et al., 2019
Targeting Capability	Stimuli-responsive to pH, enzymes, and temperature	Limited but can be improved with surface modifications	Multivalent interactions enable precise targeting	Le et al., 2021; Dai et al., 2018
Release Profile	Controlled, stimuli-dependent	Sustained, dependent on polymer degradation	Precise control over release kinetics	Zare-Zardini et al., 2022
Toxicity	Low toxicity, well-established profiles	Moderate, requires thorough toxicological assessments	Low toxicity if appropriately functionalized	Osman et al., 2021

Even in nanoparticle-based drug delivery systems, formulation to withstand harsh environments like high temperatures and sterilization that degrade free antibiotics could be possible. This will further enhance pharmacokinetics, stabilize, and sustain a more stable release formulation that further decreases repeated dosing requirements (Thaher et al., 2017). These CD inclusion complexes with antibiotics and other antimicrobial agents have been assessed as agents to improve drug solubility, stability, and targeted delivery. The surface-modified nanoparticles could be conjugated with the CD-based nanocarriers to develop advanced drug delivery systems (Boczar & Michalska, 2022).

Nanotechnology is emerging as a promising strategy to improve the therapeutic potency and reduce off-target effects of various treatments, especially in cancer therapy (Senapati et al., 2018; –Arranja et al., 2017). These properties-small size, high surface-to-volume ratio, and ability to be functionalized-have allowed nanomaterials to be applied in the design of sophisticated drug delivery systems that are capable of selectively targeting tumor sites while minimizing the

exposure of healthy tissues to therapeutic agents (Senapati et al., 2018; Arranja et al., 2017). Being one of the major merits nanotechnologies enjoys as off-target effect minimizers, it indeed possesses a specific application, such as achieving targeted drug delivery. Nanoparticles with some ligands equipped onto them to be specifically targeting like antibodies and peptides would target overexpressed receptors or antigens on the surfaces of cancerous cells (Eira, 2023). A targeted approach generally enhances the concentration of the therapeutic agent at the site of the tumor and, as a result, decreases diffusion to normal tissues. This therefore decreases off-target effects (Eira, 2023).

In addition, because of the EPR effect-feature of solid tumors, the nanoparticle-based drug delivery systems can take advantage of this for selective accumulation within the tumor microenvironment (Senapati et al., 2018). In that regard, nanoparticles preferentially extravasate through leaky vasculature and poor lymphatic drainage in the tumors and hence accumulate in the tumor thus boosting targeted delivery of the therapeutic agent (Senapati et al., 2018). This might even further advance towards the creation of stimulus responsive nanocarriers with an ability to provide possibility of triggering and controlling a release of therapeutic payload from the system, hence significantly enhancing overall therapeutic efficacy whilst reducing undesirable side effects which occur by off-target exposures (Zhao et al., 2021). These nanocarriers might be designed to respond specifically to the environmental cues found in the tumor microenvironment, including pH, temperature, or enzymatic activity, to ensure selective drug release at the target site (Zhao et al., 2021).

Besides, nanotechnology has been implemented in cancer immunotherapy where nanoparticles may be designed to deliver immune-modulating agents selectively, including checkpoint inhibitors or cytokines, directly to the immune cells infiltrating the tumor site (Glass et al., 2016). Such site-selective delivery enhances the activation and effectiveness of the patient's endogenous immune system to ensure better therapeutic outcomes and limits systemic exposure and related toxicities of these agents (Glass et al., 2016).

5. Types of Nanomaterials in Antibiotic Delivery

5.1. Lipid-Based Nanocarriers

The development and study of liposomes for application as a delivery vehicle enhances the efficacy of both hydrophobic and hydrophilic antibiotics (Ferreira et al., 2021). Their unique properties for the encapsulation of a broad spectrum of drug molecules, improvement in solubility of drugs, and targeting offer a good platform for delivering antibiotics (Selvadoss et al., 2017; Hwang et al., 2023). Hydrophobic antibiotics are encapsulated in liposomes to increase their bioavailability and thus their therapeutic efficacy, since they can be solubilized and prevented from degradation (Gómez et al., 2019; Huck et al., 2022). Moreover, the lipid bilayer of liposomes may offer free space for the encapsulation of hydrophobic antibiotics, such as vancomycin and teicoplanin, to prevent their inactivation during the encapsulation process (Yang et al., 2011; Ommen et al., 2022). More than that, liposomal drug delivery can enhance hydrophobic antibiotics to the site of infections where most biofilms lie; these are usually resistant to most treatments (Ferreira et al., 2021; Yang et al., 2011).

Liposomes are highly significant delivery vehicles for hydrophilic antibiotics to the site of action. For example, water-soluble antibiotics such as ciprofloxacin and colistin encapsulated in the core

of liposomes are protected from the degradation process before reaching their site of action (Wallace et al., 2012; Ghosh et al., 2019). These liposomes can further be functionalized with targeting moieties such as wheat germ agglutinin or antimicrobial peptides, enhancing the interaction and uptake by the bacterial cells and hence increasing the delivery of the encapsulated hydrophilic antibiotics (Yang et al., 2011; Yang et al., 2011). The improved delivery of liposomes containing hydrophobic and hydrophilic antibiotics can lead to better therapeutic results, especially in antibiotic-resistant bacterial infections (Ferreira et al., 2021; Selvadoss et al., 2017; Ommen et al., 2022). Liposomes can increase the local concentration of antibiotics at the site of infection while reducing systemic toxicity and side effects (Hwang et al., 2023; Wallace et al., 2012). Moreover, the pulsatile release of antibiotics from liposomes could prolong the duration of antibacterial effects and may even overcome drug resistance mechanisms (Ferreira et al., 2021; Yang et al., 2011).

5.2. Polymeric Nanoparticles

There is vast literature related to the benefits of biodegradable polymers for controlled drug delivery. In drug delivery applications, many advantages are provided by biodegradable polymers compared to non-degradable materials (Raval & Parikh, 2011; Kim et al., 2010; Noorsal et al., 2010). First, degradable polymers can be synthesized that will have a degradation profile with the same time frame to ensure delivery of the drug; the carrier device can remain in situ without needing to surgically remove the carrier (Raval & Parikh, 2011; Kim et al., 2010; Noorsal et al., 2010). This is very desirable since the problems that relate to the removal of nondegradable implants can be evaded (Raval & Parikh, 2011; Kim et al., 2010). The degradation rate of the polymer can be tailored in relation to its molecular structure and intermolecular bonding such that the drug release kinetics is precisely controlled (Hong et al., 2010; Hsu et al., 2012).
Biodegradable polymers are generally non-toxic and biocompatible, which means there is no adverse immune response triggered by the implantation of them in the body (Kim et al., 2010; Nagarjuna et al., 2016). This must be ensured for the biocompatibility of the delivery system. Among the many biodegradable polymers frequently used, PLGA, PCL, and PG have established known biocompatibility profiles (Kim et al., 2010; Noorsal et al., 2010). More than this, biodegradable polymers can be engineered for releasing therapeutic agents, either in the form of small molecules, peptides, or proteins in a controlled manner (Binauld & Stenzel, 2013; Mucha et al., 2014). With these options, one develops a rather high customized drug delivery system that will be helpful for a huge scope of medical purposes (Binauld & Stenzel, 2013; Mucha et al., 2014). Moreover, biodegradable polymers can also be formulated in different configurations, including matrices, reservoirs, and hydrogels that can be tailored to different needs of the drug delivery (Noorsal et al., 2010; Mucha et al., 2014). This flexibility allows for preparation of drug delivery systems that will be administered through various routes or means, such as through the oral, parenteral, and topical routes (Noorsal et al., 2010; Mucha et al., 2014). Biodegradable polymers have further been engineered for degradation in response to the environmental cues like pH or the enzyme activity that triggers stimuli responsive drug delivery (Binauld & Stenzel, 2013). Such may present better drug delivery systems, having increased drug efficacy and targeting.

Table 2: Types of nanocarriers and their applications in antibiotic delivery.

Type of Nanocarrier	Key Features	Applications	References
Liposomes	Biocompatible, can encapsulate hydrophilic and hydrophobic drugs, stimuli-responsive to pH, temperature, and enzymes	Used for delivering antibiotics like ciprofloxacin and colistin to treat respiratory and biofilm-associated infections	Ferreira et al., 2021; Li, 2023
Polymeric Nanoparticles	Biodegradable, controlled drug release, high systemic circulation times	Effective in treating systemic bacterial infections and increasing the solubility of poorly water-soluble antibiotics	Le et al., 2021
Dendrimers	High drug loading capacity, multivalent interaction, ability to encapsulate diverse drugs	Targeted delivery to intracellular pathogens and specific infection sites	Canaparo et al., 2019
Metallic Nanoparticles	Antimicrobial activity through ROS generation, DNA damage, and disruption of bacterial membranes	Effective against multidrug-resistant strains and biofilm penetration	Gurunathan et al., 2014; Mathews & K, 2020
Hybrid Nanocarriers	Combines properties of multiple nanocarriers, dynamic response to environmental stimuli	Enhanced targeting for nosocomial infections and dual-drug delivery systems	Sato et al., 2016; Zhu & Wang, 2006

5.3. Metallic Nanoparticles

Silver and gold nanoparticles have antimicrobial action, but they do this by many mechanisms: Silver and gold nanoparticles range normally from 10-100 nm (Hovhannisyan, 2023; Gahlawat et al., 2016; Shinde et al., 2012). This ensures easy passing through the microbial cells membranes to obtain close contact with microbial cells (Hovhannisyan, 2023; Gahlawat et al., 2016). They may also liberate silver ions, Ag^+, and gold ions, Au^+ and Au^{3+}, interfering with the microbial cellular process that can damage DNA, RNA, and proteins (Mathews & K, 2020). It can also create ROS that can bring about oxidative stress in microbes. As a result, the cell would be damaged and even dead (Hovhannisyan, 2023; Gahlawat et al., 2016). The nanoparticles interact with diverse cell processes including respiration, division, and signal transduction leading to the killing of microbes (Hovhannisyan, 2023; Mathews & K, 2020). The nanoparticles bind to the constituents of microbes, such as cell walls, membranes, and biomolecules, causing structural and functional changes, leading to cell death (Hovhannisyan, 2023; Gahlawat et al., 2016; Daima et al., 2013). Generally, the antimicrobial activity of silver nanoparticles is much more than gold nanoparticles (Biterge-Süt & Canpolat, 2019). The antimicrobial activity of silver ions is highly potent. In

addition, it can easily penetrate microbial cells and kill them (Mathews & K, 2020; Gouyau et al., 2021). Besides the antimicrobial activities mentioned above, size, shape and other surface-related characteristics of nanoparticles may impact the antimicrobial activity of these materials. Generally, it has been reported that with the smaller sizes and a larger surface area, greater antimicrobial activity is achievable from these particles (Gahlawat et al., 2016; Shinde et al., 2012). A means by which modulate the antimicrobial characteristics of the nanoparticle has involved the functionalization or capping of these nanoparticles through some varied biomolecules (VanOosten et al., 2016). Well-known antimicrobial action on various types of microorganisms such as Gram-positive and Gram-negative bacteria and fungi are the significant advantages of silver and gold nanoparticles (Mathews & K, 2020; Gouyau et al., 2021). They offer a lot of potential in numerous antimicrobial applications that could be used in the field of wound dressing, medical devices, or water purification (Tuzyuk & Pokryshko, 2022; Sorescu et al., 2019).

5.4. Hybrid Nanoparticles

Hybrid systems are a class of dynamical systems that combine several functionalities and have both continuous and discrete dynamics (Zhu & Wang, 2006; Dib et al., 2016; Khademian, 2024). Such systems are characterized by the interaction between continuous-time and discrete-time components, allowing for the combination of different types of subsystems within a single framework (Khademian, 2024; Kong et al., 2020). That is, hybrid systems can absorb advantages of separate elements and then, for certain applications, possess better properties or functions (Kong et al., 2020). For instance, hybrid systems can integrate in one framework continuous-time physical processes together with discrete-time control logic thereby integrating mechanical, electrical, and computational technologies (Zhu & Wang, 2006; Khademian, 2024;, Chamberlain et al., 2007).

The interaction between continuous and discrete dynamics makes theoretical development complicated, so developing hybrid systems is not an easy task (Zhu & Wang, 2006; Lou & Gao, 2012). To address this, researchers have proposed a variety of analytical tools and techniques that are regarded as the primary tools for studying switched systems; among these are the CLF method and MLF methods Zhu & Wang, 2006;, Lou & Gao, 2012;, Li & Teel, 2016. The hybrids have been extremely utilized and practiced in the following applications: control systems, robotics, power systems, and communication networks (Zhu & Wang, 2006; Khademian, 2024; Chamberlain et al., 2007; Soh & Joy, 2004). In this respect, control systems utilize hybrid models for appropriate and precise description of the mechanical, biological, electrical, and economic systems' behavior (Khademian, 2024). Besides this, hybrid systems are implemented in the smart grids developed where PLC and wireless communication technology has been integrated for data transfer and control in efficient manners (Dib et al., 2016).

In addition, hybrid nanostructures, such as host-guest systems, organometallic systems, and metal-organic coordination systems, have recently attracted significant attention (Kong et al., 2020). Hybrid nanostructures may take advantage of the best features of the individual components and, for certain applications, can have improved properties or functions. Despite the intricacies in the theoretical progress of hybrid systems, a lot has been achieved concerning their stability and convergence properties. Application of Lyapunov functions-the common and multiple type has proved very useful in proving the hybrid systems to be stable and convergent (Zhu & Wang, 2006;

Lou & Gao, 2012; Li & Teel, 2016). They have investigated hybrid systems with memory that exhibit both delayed and hybrid dynamics, and applied principles of invariance to prove stability and convergence for such systems (Li & Teel, 2016; Li & Teel, 2018).

6. Challenges in Critical Care Infection Management

The management of infections in critically ill patients presents several unique challenges. Among them, based on biofilm-associated infections and the emergence of multi resistant pathogens, as summed up by Vincent et al. (2020). Biofilm-associated infections present special challenges in the intensive care unit environment. Biofilms are aggregates of microorganism's adherent to surfaces that form an extracellular matrix which endows them with remarkable resistance to antimicrobial agents and host immune response (Stortz et al., 2018). Biofilm-related infections are often identified in patients with implanted medical devices, such as central venous catheters, endotracheal tubes, and urinary catheters (Stortz et al., 2018). These infections are quite difficult to eradicated and could, in some instances, require antimicrobial therapy combined with the removal of the device and other focused interventions that will break down the biofilm (Stortz et al., 2018).

Multidrug-resistant pathogens are also another significant problem in infection management in critically ill patients (Vincent et al., 2020). Due to relatively long hospital stay, frequent application of invasive devices, and broad-spectrum antibiotics usage, the critically ill patients are more prone to develop MDR infections. The problems related to MDR infections were mortality rates, prolongations in hospital stays, and increase in healthcare costs related to infections such as carbapenem-resistant Acinetobacter baumannii, carbapenem-resistant Klebsiella pneumoniae, and vancomycin-resistant Enterococcus (Vincent et al., 2020). This MDR pathogen development is further coupled with the selective pressure of antibiotic use resulting in the emergence and transmission of resistance (Grasselli et al., 2021; Pasero et al., 2021). It is essential that infection control strategies such as hand hygiene, contact precautions, and stewardship of antimicrobials should curb the spread of MDR infections in the ICU.

In addition to this, critically ill patients may experience a prolonged immunosuppression that may be induced post-septic insult, making them more prone to developing secondary infections (Stortz et al., 2018). The condition of immunosuppression is thought to be due to chronic antigenic stimulation and T-cell exhaustion, and so further research is needed in developing specific interventions for these conditions. Studies have shown that sicker patients have the potential to gain hospital-acquired infections, which further comprises MDR pathogens in the context of the COVID-19 pandemic (Grasselli et al., 2021). This is due to several reasons: health care may be overwhelmed; appropriate adherence to infection control policies, and selective antibiotic pressure therapies (Grasselli et al., 2021). This requires source control at an early phase, appropriate antimicrobial therapy, interventions targeted at biofilm, and proper infection control measures (Vincent et al., 2020; Grasselli et al., 2021). Clinicians, microbiologists, and infection control practitioners should be integrated to design and implement customised "infection service bundles" that maximize diagnostic, therapeutic, and infection control resources in the ICU environment (Bhattacharya & Mondal, 2010).

7. Advances in Nanotechnology for Antibiotic Delivery

7.1. Stimuli-Responsive Nanocarriers

The pH- and temperature-sensitive nanoparticles, by harnessing the pH and temperature fluctuations between the tumor microenvironment and normal healthy tissues, can improve drug targeting (Gujrati et al., 2016; Ling et al., 2014; Wang et al., 2014). In comparison, the TME usually contains a more acidic pH in terms of 6.5-6.0, when contrasted with normal healthy tissues containing a pH of 7.4 (Wang et al., 2014). This pH gradient could be taken advantage of through the fabrication of nanoparticles that have pH-sensitive elements inside them, which can, according to the acidic TME surroundings, selectively release their drug payload (Gujrati et al., 2016; Ling et al., 2014; Wang et al., 2014). In this direction, for example, nanoparticles functionalized with ligands harboring acid-labile linkages are hydrolysed at the low pH found inside the TME, leading the drug to be released (Cao, 2024). Or even nanoparticles can be designed that possess protonatable groups, carboxyl groups for instance that become charged and disturb the nanoparticle structure at low TME pH to elicit drug release (Cao, 2024).

Besides pH sensitivity, temperature-sensitive nanoparticles also act as enhancers in targeting drugs. Temperatures in tumors are always slightly higher than in the normal tissues due to the augmented metabolic activities of tumors (Wang et al., 2020). These nanoparticles can be designed in such a way that in the higher temperatures of TME, they change structure by the collapse of the thermosensitive polymer coating that coats them, releasing drugs (Wang et al., 2020). The dual sensitivity to both pH and temperature of the targeting agent within one nanoparticle system might provide a new dimension of specificity. Already, a hybrid pH/temperature-sensitive coating for copolymer, the liposome system is a pH-sensitive and temperature-sensitive system; therefore, upon arrival at that location, the TME might alter the pH and temperature conditions, which could then shield the targeting ligand (folic acid, for instance) up to the time of release and delivery (Wang et al., 2020).

Table 3: Challenges and future directions in nanotechnology for antibiotic delivery.

Challenge	Description	Proposed Solutions	References
Nanotoxicity	Potential adverse effects on human cells, bioaccumulation risks	Use of biocompatible materials, rigorous toxicological evaluation	Naskar & Kim, 2019; Carver et al., 2020
Regulatory Compliance	Lack of standardized protocols for nanoparticle approval	Development of universal guidelines, integration of AI to predict safety profiles	Alshawwa et al., 2022
Drug Resistance	Risk of bacteria developing resistance to nanoparticle-conjugated antibiotics	Combined therapy using nanoparticles with adjuvants to disrupt resistance mechanisms	Mishra et al., 2018; Arya et al., 2019
Cost and Scalability	High production costs and challenges in scaling nanoparticle synthesis for widespread clinical use	Optimization of production methods, public-private collaborations	Thaher et al., 2017
Inconsistent Outcomes	Variability in nanoparticle efficacy due to differences in pathogen strains, infection sites, or host immune responses	Personalized medicine approaches leveraging AI to tailor nanoparticle designs for specific patient and pathogen profiles	Kalhapure et al., 2015

7.2. Nanotechnology-Enabled Combination Therapies:

Nanocarriers have been explored as an emerging avenue toward enhanced antibiotic delivery and efficacy, mainly in addressing the problem of bacterial infections and biofilms (Teirlinck et al., 2019; Perni et al., 2018; Juntke et al., 2021). This will engineer nanocarriers that will encapsulate the antibiotic and adjuvant or immunomodulators to provide numerous advantages in comparison to traditional means of antibiotic delivery. Some of the main advantages of nanocarriers include their ability to enhance the pharmacokinetics and biodistribution of antibiotics (Teirlinck et al., 2018; Le et al., 2021). It has been conceivable to preserve antibiotics from getting degraded early by encapsulating the nanoparticles around them, to be targeted more accurately at the area of infection (Blom et al., 2016; Subramaniam et al., 2019). Thus, it might lead to a higher concentration of antibiotics where the action needs to occur, thereby improving their efficacies against biofilms in bacteria and intracellular infections (Dai et al., 2018; Subramaniam et al., 2019). Also, nanocarriers may be used to deliver adjuvants or immune modulators combined with the antibiotics. This delivery, administered simultaneously, would improve the host immunity effects; supplementation of their impacts would make the enhancement of infection clearance more favorable (Blom et al., 2016; Le et al., 2021). For instance, influenza virosomes have been explored as nanoparticle antigen delivery systems which, besides being capable of antigen transfer, exhibit immune potentiating activity because of their inherent composition (Blom et al., 2016). One promising tactic is stimuli-responsive nanocarriers. Their delivery mechanisms could be engineered in response to an environment where some antibiotics get discharged depending on, for instance pH and temperature sensitivity, or response to enzymes in specific triggers (Devnarain et al., 2020). This minimizes the risk of antibiotics being released prematurely and delivers them precisely to the intended target site, enhancing their efficacy further (Devnarain et al., 2020). Moreover, nanocarriers can be functionalized with targeting moieties, such as antibodies, to enhance specificity towards the infecting bacteria or the host immune cells (Le et al., 2021). Targeted delivery may enhance the accumulation of antibiotics at the site of infection and therefore may potentially overcome antimicrobial resistance as well as off-target effects (Le et al., 2021).

7.3. Personalized Medicine

Nanotechnology has emerged as one of the promising approaches through which the effectiveness of antibiotic treatment will be enhanced and deficiencies in conventional antibiotic delivery will be overcome. Nanoengineered drug delivery systems have many advantages, such as targeted delivery, nearly uniform distribution in the targeted tissue, improved cellular uptake with solubility, sustained drug release, and hence less side effects. These nanomaterial properties can be used to enhance the pharmacokinetics and biodistribution profiles of loaded antibiotics and hence the efficacy of antimicrobial treatment (Kalhapure et al., 2015; Canaparo et al., 2019). Improving the intracellular delivery of antibiotics: This is one of the major aspects of the nanoparticle-based delivery systems, which in turn enhances the treatment efficacy of intracellular pathogens. Nanocarriers can be applied to transport antibiotics to the host cells, like macrophages, where bacteria are located and enhance the efficacy of antibiotics against bacteria. This is because most antibiotics cannot pass through cell membranes and thus find it difficult to reach the site of infection (Canaparo et al., 2019; Dai, 2024).

These systems may be engineered to respond to the various stimuli within the infected host; this can be made using components of the bacteria themselves or of the host defense mechanism. For instance, these nanoparticles can be designed to release antibiotics, considering the pH of the

infected host's phagosome, as well as by the ROS produced by immune cells in the host. The drug delivery is of assistance in targeting and responding very well to provide a meaningful antibiotic therapy that has the potential of overcoming systemic side effects of the disease condition (Canaparo et al., 2019; Dai, 2024). Nanoparticle-based antibiotic delivery also has another important advantage of overcoming some of the issues regarding antibiotic resistance and biofilm formation. Nanoparticles can be made in such a way that the antibiotics will be released in a controlled and sustained way, ensuring that the effective concentrations of antibiotics will remain at the site of infection to avoid resistance buildup. Furthermore, nanoparticles can be formulated to disrupt the structure of biofilms and improve the penetration of loaded antibiotics (Ferreira et al., 2021; Thaher et al., 2017).

The delivery systems of antibiotics can also be designed to cater to individual patient needs through the modification of physicochemical properties of nanoparticles for optimized drug release kinetics or targeting specific pathogens or other patient-specific factors. For example, the diameter, charge of the surface and composition of nanoparticles could be modified for the improved interactions of nanoparticles with targeted cells or tissues, stability, circulation time, and the profile of release of loaded antibiotics (Kalhapure et al., 2015; Thaher et al., 2017). Furthermore, nanoparticles of antibiotics can increase the solubility and stability of the drugs in the loaded nanoparticle, which is a property necessary for many hydrophobic or labile antibiotics. Nanoparticles can preserve the degradation of antibiotics while increasing the bioavailability and hence result in better therapeutic effects (Thaher et al., 2017; Haddada et al., 2018). Beyond these benefits of enhanced delivery and action of classical antibiotics, nanotechnology-based strategies may also be applied in designing new antimicrobial agents through conjugating nanoparticles with antibiotics or through nanoparticles that exhibit inherent antimicrobial activity. Such "nanobiotics" are more potent and have less propensity for the development of resistance and more favorable pharmacokinetic properties compared to their traditional counterparts, antibiotics (Ferreira et al., 2021).

8. Case Studies and Clinical Applications

Among the most promising is using nanocarriers that are antibody conjugated for the targeted delivery of antibiotics to treat bacterial biofilms. The nanocarriers can penetrate the matrix of the biofilm and bring the antimicrobial agent straight to the bacteria within the biofilm, therefore creating a much-enhanced antibiotic effect compared to free antibiotics. This method has been reported in many nano-antibiotic formulations, including lipid or polymer-based nanocarriers (Le et al., 2021). For example, in antibacterial therapy, there is the application of stimuli-responsive drug-delivery systems and therapeutic nanoparticles (Canaparo et al., 2019). The application of nanoparticle drug delivery systems may enhance the solubility of hydrophobic antibiotics, extend the systemic circulation time and half-life of antibiotics, and allow a controlled release of antibiotics, that may reduce the systemic side effects and enable drug reduction to a minimum dosage of drugs (Canaparo et al., 2019). Developed for treatment of intracellular pathogens are various nanocarriers consisting in liposomes, silica nanoparticles, polymeric carriers and dendrimers, encapsulated with antibiotics (Canaparo et al., 2019).

Nanocarriers have also been used in the improvement of intracellular delivery of antibiotics towards intra-cellular bacterial infections. Several nanocarriers were designed specifically for drugs aimed at the treatment of tumors, genes or CRISPR gene editing system; however, some

were specifically prepared only for antibiotic drugs and targeted to improve their intracellular antibacterial efficiency (Wang et al., 2023). Cell membrane-coated nanoparticles have been explored for the treatment of bacterial infections. The nanoparticles have been found to be spectacular in their physical and chemical properties, such as improved solubility of antibiotics, controlled release of antimicrobial effects, and targeted delivery of infection to enhance the efficacy of antibacterial therapy (Ma et al., 2022).

Polymeric nanoparticles are antibiotic delivery systems of interest because they can avoid problems associated with free-form antibiotics, such as low bioavailability, fast clearance rates, and the development of antimicrobial resistance (Le et al., 2021). Such nanocarriers allow for the improvement of the pharmacokinetic characteristics of antibiotics and better targeting towards the site of interest. In addition, vancomycin-mediated targeting and pH/lipase-triggered release of antibiotics through antibacterial micelles have been designed to enhance the effectiveness and duration of action of antibiotics while minimizing off-target toxicity and antibiotic resistance (Chen et al., 2018). Nanotechnology has been highly promising in the treatment of bacterial infections, and the development of these antibiotic delivery systems is a very pragmatic approach to the problems of antimicrobial resistance (Chen et al., 2018).

Advanced antibacterial nanocarriers based on nucleic acid hybrids have also been of major interest, as they have solved inherent toxicity, high dose-dependent needs, rapid degradation, and short half-life cases for antimicrobials (Obuobi & Škalko-Basnet, 2020). These nanocarriers have been well determined to improve pathogen targeting as well as improve delivery for the antibiotics at the target place (Obuobi & Škalko-Basnet, 2020). It was further demonstrated that nanoparticles also aided in shielding the antibiotics from masking mechanisms of the bacteria in which targeted delivery was supported by surface functionalization via aptamers or even antibodies (Modi, 2023). Those nanocarriers enhance the release kinetics for antibiotics also enabling their controlled release by the developments such as those of the nanotechnology based antibiotic bone cements, as for instance, noted by Thaher et al. (2017). In the veterinary sector, nanoformulations of antibiotics have also been promising, showing higher efficacy, less toxicity, and reduced dosage requirements compared to conventional pharmaceuticals, thus providing a solution to the issue of antibiotic resistance in animal health (Danchuk, 2023).

9. Safety and Regulatory Considerations

The potential toxicity concerns of nanomaterials in antibiotic delivery are multi-dimensional and must be addressed with due caution. Some of the critical factors identified to influence the toxicity level of nanomaterials in this application are mentioned below. First, the size and shape of the nanomaterial significantly determines its toxicity (Carver et al., 2020). For example, pristine SWNTs have been shown to be harmful to human as well as bacterial cells (Carver et al., 2020). Again, while the non-functionalized nanomaterials confer toxicity, functionalization extent is also a critical factor, where functionalized SWNTs and nanographene oxide showed a higher ability to combat antibiotic resistance with lower toxicity.

Another critical consideration is the type of cell involved. Nanomaterials may be differentially toxic to various cell types, including human fibroblasts and endothelial cells (Wierzbicki et al., 2019). The extent of agglomeration of the nanomaterial also matters, since agglomeration affects the interaction of the nanomaterial with cells and its overall toxicity (Carver et al., 2020). Besides the physical and chemical properties of the nanomaterials, the specific mode of action for antimicrobial activity can cause potential toxicity issues. Nanomaterials can be toxic to pathogenic

cells by either cellular toxicity or immunity induction (Han et al., 2018). This can be useful, however, in terms of antimicrobial activity, but that also raises concerns about side effects and toxicity to non-target cells.

Moreover, retention capability of nanomaterials in the body is greater than that of antibiotics; this could be beneficial for prolonged therapeutic applications, yet the issue of accumulation and chronic toxicity cannot be avoided (Naskar & Kim, 2019). Careful functionalization and targeting of nanomaterials can also help in minimizing these problems because nanomaterials could be designed to be effective against bacterial cells without being toxic to mammalian cells (Naskar & Kim, 2019). Such metal nanomaterials that should be considered are their cytotoxicity in case applications as antibacterial, as metal nanomaterials of such as silver, zinc, copper, and iron; their potential has proven very strong as antimicrobial agents but at the same time highly toxic to human cells that must be extensively probed (Chidre, 2023; Zhan, 2024).

10. Future Directions in Nanotechnology for Infection Management

Emerging trends in nanotechnology for antibiotic delivery are bioinspired nanoparticles, nanobots. For instance, there is the development of gastric epithelial cell membrane-coated nanoparticles designed to target antibiotics at sites where Helicobacter pylori-infected individuals have localized infections. Those "cell membrane-coated nanoparticles" (AGS-NPs) are designed with a diameter of about 100 nm and a negative surface charge to efficiently penetrate the mucus layer and allow direct delivery of antibiotics to the site of infection (Angsantikul et al., 2018). Another emerging trend is the use of bacteria-responsive nanoliposomes to facilitate targeted antibiotic delivery and sonodynamic therapy of multidrug-resistant bacterial infections. Such nanoliposomes could selectively deliver sonosensitizers to the site of infection, thereby maximally enhancing the efficacy of sonodynamic therapy (Pang et al., 2019). Nevertheless, there is still an enormous challenge of the emerging "superbugs" multidrug resistance that necessitates alternative targeting strategy (Pang et al., 2019).

Another research area through which the delivery of antibiotics can occur is through inorganic, non-liposomal porous silicon nanoparticles. These particles are biocompatible, degrade into silicic acid, and are naturally found in tissues; moreover, they carry a high capacity for therapeutic payload. The release of antibiotics from the pSiNPs may be controlled, and the surface of the nanoparticles can be engineered with targeting peptides to make them more specific (Hussain et al., 2018). Biodegradable polymeric nanoparticles, liposomes, and inorganic nanoparticles are also used to deliver antibiotics inside the phagocytes to treat intracellular bacterial infections. These delivery systems from nanoparticles improve the intracellular delivery of antimicrobial agents, an effort to answer the challenge of infection treatment caused by intracellular pathogens (Yang et al., 2018).

Polymeric nanoparticles, self-healing hydrogels especially, have been investigated as potential dual drug delivery systems that targeted fluoroquinolone-resistant Staphylococcus aureus. Nano-scale-based systems, despite improving the solubility and stability of antibiotics, obviate the issues of resistance that comes with antibiotics, expressivity of multidrug efflux pumps, and development of biofilm (Thamilselvan et al., 2023). It was shown that liposomes and nanostructured lipid carriers - as part of lipid nanoparticles - can increase delivery and bioresponse to precision medicine therapies. Several types of LNPs, such as ionizable cationic nanoparticles, opened the

prospects for their application in medicine, such as the delivery of antibiotics (Tenchov et al., 2021).

Multi-drug-resistant nosocomial pathogens including Acinetobacter baumannii, have sparked ventures in the use of nanotechnology for the prevention and treatment of nosocomial infections. Nanoparticles made from different elements can enhance the physico-chemical properties and stability of antibiotics. They can also inhibit biofilm formation or reduce it and, more importantly, target and deliver antimicrobials to the site of the infection, reducing side effects (Ananda et al., 2022). Nanotechnology in combination with targeted delivery strategies has emerged as one of the promising approaches to combat bacterial infections. The technology explores the concentration of antibiotics at the site of infection and reduces its side effects in normal tissues. Nanocarriers that respond to the infection microenvironment, target specific bacterial structures, or target infected cells may be recommended (Zhang et al., 2021).

Local antimicrobial treatment using therapeutic nanoparticles, such as liposomes, polymeric nanoparticles, dendrimers, and inorganic nanoparticles, is being considered as a developing strategy to increase drug concentration at the site of infection, avoiding systemic exposure, hence potentially reducing the development of antibiotic resistance (Gao et al., 2018). Besides these new technologies such as CRISPR-Cas9, nanotechnology is also used to counter antimicrobial resistance in ESKAPE pathogens, which include Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa, and Enterobacter species. Antimicrobial nanoparticles and conjugates of antibiotics with antibodies are promising nanotechnology-based solutions (Sachithanandan, 2024).

AI and ML, significantly add to the development of nanocarriers across various biomedical applications, mainly to cancer treatment. The interlink of these technologies with nanotechnology has been termed by many scientists as "nanoinformatics," that seems extremely promising in terms of increasing the development and optimization of nanocarriers' process (Soltani et al., 2021). One of the primary modes through which AI and ML can impact nanocarrier design is through the prediction of interactions between targeted cancer cells and nanocarriers, as well as the kinetics of drug release (Goswami et al., 2021). Utilize large volumes of data and complex algorithms that have the capability to recognize patterns to aid in the search for optimal physicochemical properties of nanocarriers with respect to size, shape, surface charge, and composition to enhance therapeutic efficiency (Adir et al., 2019).

Thus, for instance, by applying machine learning-driven data analysis, structural parameters of spherical nucleic acid nanoparticles can be aligned and optimized to build correlation between nanostructure and immune activation to be built (Zhou, 2023). Similarly, computer vision and machine learning methods by AI can be used to measure and predict the intracellular delivery of anticancer drugs by nanocarriers (Goswami et al., 2021). Additionally, AI and ML will aid nano-bio interface challenges such as interacting nanoparticle with biological media and cell membranes drug encapsulation efficiency. Physics-based modeling coupled with data-driven approaches should allow for an even more insightful understanding of nanocarrier behavior and the complexity of mechanisms in its designs. Gao, 2024.

Further, AI and ML can be also used in the development of nanocarriers to address the challenge given by the heterogeneity of tissue and cells-a significant hurdle that may significantly contribute to nanoparticle traffic, uptake, and deposition (Boehnke & Hammond, 2021). With imaging and screening tools, in addition with bioinformatics approaches, there is more room to add a better

understanding of how nanomaterials interact within cells and tissues leading into better designs for nanocarrier design (Boehnke & Hammond, 2021). Also, with the integration of AI in nanotechnology, optimized characterization of nanocarriers shall be achieved and advancements towards overcoming the deficits found due to the classical characterizations applied, therefore shifting lab-bound nanocarriers into clinicals (Alshawwa et al., 2022). AI-based models could become helpful in predicting in vitro as well as in vivo performances of nanocarriers besides being useful in safety and regulation aspects (Alshawwa et al., 2022).

AI and ML in nanocarrier design have shown promising use in enhancing the delivery of chemotherapeutic agents, siRNA, and miRNA in the therapy of cancer treatment for the multiple myeloma and other solid tumors (Yang, 2024). Scientists recognize a sophisticated tumor microenvironment and then apply nanoscale imaging and design very specific nanocarrier-based therapies to address these tumors more effectively (Yang, 2024). In the design of nanocarriers, it is an important control area because exposure to blood plasma could dramatically alter the properties and behaviors of the nanocarriers (Simon et al., 2018). AI and ML can be used to predict and optimize protein corona formation so that the stealth properties of nanocarriers are ensured alongside their therapeutic efficacy (Simon et al., 2018).

Conclusion

Nanotechnology is one paradigm shift in antibiotic delivery because it is going beyond the limits of conventional therapies in developing new approaches to MDR pathogens in critical care. The sophisticated designs of nanocarriers include stimuli-responsive and hybrid systems that promote the exactitude, efficacy, and safety of antibiotic treatment. Overcoming poor solubility and bioavailability also enables a better target on the site of infection and possibly fewer side effects systemically. This is further enhanced by combining artificial intelligence and machine learning to the potential of nanotechnology, which helps in offering customized and adaptive treatment strategies. Despite the challenges imposed by nanotechnology research through issues involving safety and regulatory agency restrictions, continued innovation has translated scientific discoveries into the clinic. To date, such translation suggests a transformative effect on infections' management, allowing critical care environments to be improved upon. This future work would aim towards optimization of nanocarrier design, regulatory compliance, and transdisciplinary collaboration.

Author contributions

The first author drafted the original manuscript with the help of the corresponding author. All co-authors were involved and participated in the manuscript editing and literature collection including table and figure creation. All authors are given the final approval for the manuscript submission to journal for publication.

Conflict of Interest

The authors declare they don’t have any conflict of interest.

Ethical Approval

Not Applicable

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