

**RECENT TRENDS IN LIPOSOMAL NANOCARRIERS FOR
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ABSTRACT

Microbial infections continue to pose a significant global health challenge due to the increasing prevalence of antimicrobial resistance (AMR), multidrug-resistant (MDR) pathogens, and the limited effectiveness of conventional antimicrobial therapies. Traditional antimicrobial agents often suffer from poor aqueous solubility, low bioavailability, rapid systemic clearance, inadequate tissue penetration, and dose-limiting toxicity, resulting in suboptimal therapeutic outcomes. Liposomal nanocarriers have emerged as a promising nanotechnology-based drug delivery platform capable of addressing many of these limitations through enhanced drug encapsulation, targeted delivery, controlled release, and improved pharmacokinetic behavior. This review comprehensively discusses recent advances in liposomal

nanocarriers for antimicrobial therapy, focusing on their structural characteristics, classification, formulation techniques, physicochemical properties, and mechanisms of microbial targeting and drug release. Furthermore, the review highlights the therapeutic applications of liposomal systems against bacterial, fungal, viral, and biofilm-associated infections, with particular emphasis on their role in overcoming antimicrobial resistance and enhancing intracellular drug delivery. Recent innovations, including PEGylated (stealth), ligand-targeted, cationic, and stimuli-responsive liposomes, are critically examined for their ability to improve therapeutic efficacy while minimizing systemic toxicity. In addition, the review summarizes clinically approved liposomal antimicrobial formulations, recent preclinical and clinical developments, and the challenges associated with large-scale

manufacturing, formulation stability, regulatory approval, and commercialization. Emerging trends such as multifunctional liposomes, combination nanotherapies, artificial intelligence-assisted formulation design, and personalized antimicrobial nanomedicine are also discussed. Overall, liposomal nanocarriers represent a versatile and clinically relevant drug delivery strategy with considerable potential to enhance antimicrobial therapy, improve patient outcomes, and contribute to combating the global burden of infectious diseases and antimicrobial resistance.

1. INTRODUCTION

Microbial infections remain one of the leading causes of morbidity and mortality worldwide, posing a significant burden on global healthcare systems. Bacterial, fungal, viral, and parasitic infections continue to affect millions of individuals annually, particularly in immunocompromised patients, hospitalized individuals, and populations with limited access to healthcare facilities.^[1] Although antimicrobial agents have revolutionized the treatment of infectious diseases, the rapid emergence and spread of antimicrobial resistance (AMR) have become a major public health concern. The indiscriminate and prolonged use of antibiotics has accelerated the development of multidrug-resistant (MDR) microorganisms, thereby reducing the therapeutic efficacy of conventional antimicrobial agents. Pathogens such as methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant enterococci, and drug-resistant *Pseudomonas aeruginosa* have demonstrated increased resistance to existing treatment strategies, making infection management increasingly difficult.^[2]

Conventional antimicrobial therapies are often associated with several limitations, including poor aqueous solubility, low bioavailability, rapid degradation, inadequate tissue penetration, nonspecific distribution, and systemic toxicity.^[3] Furthermore, many antimicrobial drugs fail to achieve therapeutic concentrations at the site of infection due to biological barriers and rapid clearance from the systemic circulation. Frequent dosing and prolonged treatment duration may also contribute to poor patient compliance and increased adverse effects. In addition, conventional formulations may exhibit limited effectiveness against intracellular pathogens and biofilm-associated infections, which are highly resistant to standard antimicrobial treatment.^[4] These challenges necessitate the development of advanced drug delivery systems capable of improving therapeutic outcomes while minimizing toxicity and resistance development.^[5]

In recent years, nanotechnology-based drug delivery systems have gained considerable attention as promising alternatives for antimicrobial therapy. Among various nanocarriers, liposomal nanocarriers have emerged as one of the most extensively investigated and clinically successful delivery platforms.^[6] Liposomes are spherical vesicular systems composed of one or more phospholipid bilayers surrounding an aqueous core, enabling the encapsulation of both hydrophilic and lipophilic antimicrobial agents. Due to their biocompatibility, biodegradability, and ability to protect drugs from degradation, liposomes offer several advantages over conventional dosage forms. Liposomal formulations can enhance drug solubility, prolong systemic circulation, improve targeted delivery, reduce toxicity, and provide controlled or sustained drug release.^[7] Moreover, surface modification of liposomes with ligands, polymers, or antibodies has further improved their targeting efficiency and therapeutic performance against resistant microbial infections.^[4]

Recent advances in liposomal nanotechnology have led to the development of novel approaches such as stealth liposomes, stimuli-responsive liposomes, ligand-targeted liposomes, and multifunctional liposomal systems for enhanced antimicrobial activity. These systems have demonstrated significant potential in overcoming biological barriers, improving intracellular drug delivery, and combating multidrug-resistant pathogens. Several liposomal antimicrobial formulations have also reached clinical application, highlighting their translational and therapeutic relevance.^[6]

The present review aims to provide a comprehensive overview of recent trends in liposomal nanocarriers for antimicrobial therapy. The review discusses the structure and classification of liposomes, methods of preparation, mechanisms of antimicrobial action, and recent advancements in liposomal formulations for bacterial, fungal, viral, and parasitic infections.^[6] Furthermore, the review highlights current challenges, clinical applications, regulatory considerations, and future perspectives associated with liposomal antimicrobial delivery systems. This review is intended to emphasize the growing importance of liposomal nanocarriers as an effective strategy for improving antimicrobial therapy and addressing the global challenge of antimicrobial resistance.^[8]

2. Liposomal Nanocarriers: Structure and Functional Properties

Liposomal nanocarriers are among the most widely explored nanoscale drug delivery systems due to their unique structural characteristics, excellent biocompatibility, and versatility in therapeutic applications.^[9] Liposomes are microscopic or nanoscopic vesicular structures

composed primarily of phospholipid bilayers enclosing an aqueous core. Their structural similarity to biological membranes enables efficient interaction with cells and tissues, making them highly suitable for antimicrobial drug delivery. Depending on their composition, size, surface charge, and lamellarity, liposomes can be engineered to improve the pharmacokinetic and pharmacodynamic properties of antimicrobial agents.^[10]

Composition and Structure of Liposomes

Liposomes are mainly composed of natural or synthetic phospholipids, cholesterol, and occasionally surface-modifying agents such as polymers or targeting ligands. Phospholipids are amphiphilic molecules containing hydrophilic head groups and hydrophobic fatty acid tails. When dispersed in aqueous media, these molecules spontaneously arrange themselves into bilayer vesicles, with the hydrophilic heads facing the aqueous environment and the hydrophobic tails oriented inward.^[11] This self-assembled bilayer structure forms a stable vesicle capable of encapsulating both hydrophilic and hydrophobic drugs.^[11]

Hydrophilic antimicrobial agents are generally entrapped within the aqueous core of the liposome, whereas hydrophobic drugs are incorporated into the phospholipid bilayer. Cholesterol is frequently added to improve membrane rigidity, stability, and permeability control. The physicochemical properties of liposomes, including particle size, zeta potential, lipid composition, and bilayer fluidity, significantly influence drug loading, release behavior, circulation time, and therapeutic efficacy.^[12]

The size of liposomes may range from a few nanometers to several micrometers. Nanoliposomes, typically ranging between 50–300 nm, are particularly advantageous for antimicrobial applications due to their enhanced penetration into infected tissues and improved cellular uptake. Surface modification using polyethylene glycol (PEG), antibodies, peptides, or other ligands can further enhance liposomal stability and targeting efficiency.^[4]

Types of Liposomal Systems

Liposomal systems can be classified based on lamellarity, size, composition, and functional modifications. According to lamellarity, liposomes are categorized into unilamellar vesicles and multilamellar vesicles. Unilamellar vesicles contain a single phospholipid bilayer and are further divided into small unilamellar vesicles (SUVs) and large unilamellar vesicles (LUVs), whereas multilamellar vesicles (MLVs) possess multiple concentric lipid bilayers.^[13]

Based on functional properties and surface engineering, several advanced liposomal systems have been developed for antimicrobial therapy:

- **Conventional liposomes:** Basic phospholipid vesicles used for encapsulation of antimicrobial agents.^[14]
- **Stealth liposomes:** PEGylated liposomes designed to evade rapid clearance by the reticuloendothelial system, thereby prolonging systemic circulation.^[15]
- **Cationic liposomes:** Positively charged liposomes that interact strongly with negatively charged microbial membranes, enhancing antimicrobial activity.^[16]
- **pH-sensitive liposomes:** Stimuli-responsive systems that release drugs in acidic environments commonly found at infection sites.^[17]
- **Ligand-targeted liposomes:** Liposomes conjugated with antibodies, peptides, sugars, or other targeting moieties for site-specific drug delivery.^[18]
- **Fusogenic liposomes:** Specialized liposomes capable of fusing directly with microbial or cellular membranes to facilitate intracellular drug delivery.^[14]
- **Thermosensitive liposomes:** Liposomes engineered to release drugs in response to temperature changes.^[18]

These advanced liposomal formulations have demonstrated improved therapeutic performance against resistant and intracellular pathogens.

Advantages of Liposomal Antimicrobial Delivery

Liposomal nanocarriers offer numerous advantages over conventional antimicrobial formulations. One of the primary benefits is their ability to enhance the solubility and stability of poorly water-soluble antimicrobial agents. Encapsulation within liposomes protects drugs from enzymatic degradation and premature inactivation, thereby improving bioavailability and therapeutic efficiency.^[19]

Another important advantage is targeted drug delivery. Liposomes can preferentially accumulate at infection sites through enhanced permeability and retention effects or ligand-mediated targeting mechanisms. This targeted delivery minimizes drug exposure to healthy tissues and reduces systemic toxicity. Liposomal formulations also allow sustained and controlled drug release, maintaining therapeutic drug concentrations for prolonged periods and reducing dosing frequency.^[20]

Furthermore, liposomes can improve intracellular delivery of antimicrobial agents, particularly against pathogens residing within macrophages or biofilms. Their biocompatible

and biodegradable nature reduces the risk of severe adverse reactions compared to conventional formulations. Liposomal encapsulation has also been shown to decrease nephrotoxicity and hepatotoxicity associated with several potent antimicrobial drugs such as amphotericin B.^[21]

Importantly, liposomal systems may help overcome antimicrobial resistance by enhancing drug accumulation within microbial cells, disrupting microbial membranes, and improving penetration into biofilms. Combination drug loading within a single liposomal carrier can also facilitate synergistic antimicrobial therapy.^[22]

Mechanisms of Microbial Targeting and Drug Release

The antimicrobial efficacy of liposomal nanocarriers largely depends on their ability to target infected tissues and release encapsulated drugs effectively. Liposomal targeting can occur through passive or active mechanisms. Passive targeting primarily relies on enhanced permeability at inflamed or infected tissues, where increased vascular permeability allows accumulation of nanosized liposomes. Phagocytic cells such as macrophages can also internalize liposomes, making them highly effective for treating intracellular infections.^[23]

Active targeting involves surface modification of liposomes with ligands such as antibodies, peptides, aptamers, or carbohydrates that specifically recognize microbial cells or infected tissues. These targeted liposomes exhibit enhanced binding and uptake by pathogens or infected host cells, resulting in improved therapeutic outcomes.^[24]

Drug release from liposomes may occur through several mechanisms, including diffusion, membrane destabilization, fusion with microbial membranes, enzymatic degradation, or stimuli-responsive release. Environmental triggers such as acidic pH, elevated temperature, enzymes, or reactive oxygen species present at infection sites can destabilize the liposomal membrane and facilitate controlled drug release. In mucogenic liposomes, direct fusion with microbial or cellular membranes enables rapid intracellular delivery of antimicrobial agents.^[14]

Additionally, cationic liposomes can interact electrostatically with negatively charged microbial membranes, causing membrane disruption and enhanced drug penetration. This interaction may increase antimicrobial effectiveness against resistant microorganisms and biofilm-associated infections. Through these multiple mechanisms, liposomal nanocarriers

significantly improve the therapeutic performance of antimicrobial agents while minimizing systemic side effects.^[24]

Mechanisms of Microbial Targeting and Drug Release

The therapeutic effectiveness of liposomal antimicrobial systems is largely dependent on their ability to selectively target microbial cells or infected tissues and subsequently release the encapsulated drug in a controlled manner. Liposomal nanocarriers employ both passive and active targeting mechanisms to improve antimicrobial delivery and minimize systemic toxicity.^[24]

Passive targeting primarily occurs through the enhanced permeability of infected and inflamed tissues. During microbial infection, inflammatory mediators increase vascular permeability, allowing nanosized liposomes to accumulate preferentially at the site of infection. In addition, cells of the mononuclear phagocyte system, particularly macrophages and neutrophils, readily internalize liposomes through phagocytosis. This property is highly beneficial in the treatment of intracellular infections caused by pathogens such as *Mycobacterium tuberculosis*, *Salmonella*, and *Leishmania* species, which survive within host macrophages.^[25]

Active targeting involves the modification of liposomal surfaces with specific ligands such as antibodies, peptides, aptamers, carbohydrates, or receptor-specific molecules. These ligands recognize and bind selectively to microbial surface components or receptors expressed on infected cells, thereby enhancing site-specific drug delivery. Targeted liposomes improve drug accumulation at infection sites and increase therapeutic efficacy while reducing exposure to healthy tissues.^[26]

Drug release from liposomes may occur through diffusion, membrane destabilization, lipid bilayer fusion, enzymatic degradation, or stimuli-responsive mechanisms. Environmental factors such as acidic pH, elevated temperature, enzymes, and oxidative stress at infected tissues can trigger liposomal membrane disruption and controlled drug release. pH-sensitive liposomes are particularly useful for releasing antimicrobial agents in acidic intracellular compartments such as endosomes and lysosomes.^[27]

Fusion of liposomal bilayers with microbial or cellular membranes also facilitates direct intracellular delivery of antimicrobial agents. Cationic liposomes exhibit strong electrostatic

interactions with negatively charged microbial membranes, leading to enhanced membrane permeability and improved drug penetration. Furthermore, liposomal systems can effectively penetrate microbial biofilms, which are otherwise resistant to conventional antimicrobial therapy. These combined mechanisms contribute significantly to enhanced antimicrobial activity and reduced resistance development.^[22]

3. Formulation and Characterization of Liposomal Systems

The successful development of liposomal nanocarriers for antimicrobial therapy depends on appropriate formulation strategies and comprehensive physicochemical characterization. Various formulation parameters, including lipid composition, preparation technique, vesicle size, surface charge, and encapsulation efficiency, greatly influence the therapeutic performance, stability, and targeting ability of liposomal systems. Careful optimization of these parameters is essential for achieving efficient drug delivery and improved antimicrobial efficacy.^[24]

Preparation Methods of Liposomes

Several techniques have been developed for the preparation of liposomal systems, each offering distinct advantages depending on the desired physicochemical characteristics and therapeutic application. The selection of an appropriate preparation method depends on factors such as drug solubility, lipid composition, vesicle size requirements, and scalability.^[28]

Thin-Film Hydration Method

The thin-film hydration method, also known as the Bangham method, is one of the most commonly used techniques for liposome preparation. In this method, phospholipids and cholesterol are dissolved in an organic solvent, which is subsequently evaporated under reduced pressure to form a thin lipid film on the wall of a round-bottom flask. Hydration of the lipid film with an aqueous drug solution leads to the formation of multilamellar vesicles. Further size reduction can be achieved by sonication or extrusion. This method is simple and widely applicable; however, it may produce heterogeneous vesicle populations.^[29]

Reverse-Phase Evaporation Method

In the reverse-phase evaporation technique, lipids are dissolved in an organic solvent and emulsified with an aqueous phase containing the drug. Removal of the organic solvent under reduced pressure results in the formation of large unilamellar vesicles with high

encapsulation efficiency, especially for hydrophilic drugs.^[30]

Ethanol Injection Method

The ethanol injection method involves rapid injection of a lipid solution dissolved in ethanol into an aqueous phase under continuous stirring. Spontaneous vesicle formation occurs as ethanol diffuses into the aqueous medium. This technique is relatively simple, reproducible, and suitable for producing small unilamellar vesicles.^[31]

Sonication and Extrusion Techniques

Sonication uses ultrasonic energy to reduce the size of multilamellar vesicles into smaller unilamellar vesicles. Similarly, extrusion involves forcing liposomal suspensions through polycarbonate membranes of defined pore sizes to obtain uniform vesicles with narrow size distribution.^[32]

Microfluidization and Advanced Techniques

Modern approaches such as microfluidization, supercritical fluid technology, freeze-thaw cycling, and microfluidic methods have gained increasing attention for the large-scale production of liposomes with controlled size and enhanced reproducibility. These advanced techniques improve scalability, formulation consistency, and industrial applicability.^[33]

Selection of Lipids and Excipients

The choice of lipids and excipients plays a crucial role in determining the stability, drug loading capacity, release profile, and biological performance of liposomal formulations. Phospholipids are the primary structural components of liposomes and may be derived from natural or synthetic sources.^[34]

Commonly used phospholipids include phosphatidylcholine, phosphatidylserine, phosphatidylethanolamine, and sphingomyelin. Natural phospholipids exhibit excellent biocompatibility, whereas synthetic phospholipids provide better purity and controlled physicochemical properties. Cholesterol is frequently incorporated into liposomal formulations to improve membrane rigidity, reduce permeability, and enhance vesicle stability.^[28]

Surface modifiers such as polyethylene glycol (PEG) are often used to prepare stealth liposomes with prolonged circulation time by reducing opsonization and uptake by the reticuloendothelial system. Charged lipids may also be incorporated to alter surface charge

and improve interaction with microbial membranes. Positively charged lipids enhance binding to negatively charged bacterial cell walls, whereas negatively charged lipids may improve formulation stability.^[24]

Additional excipients such as cryoprotectants, stabilizers, antioxidants, and buffering agents are employed to improve shelf life, prevent aggregation, and maintain formulation integrity during storage and lyophilization.^[35]

Physicochemical Characterization

Comprehensive physicochemical characterization is essential for evaluating the quality, stability, and performance of liposomal formulations. Several analytical techniques are employed to assess critical parameters influencing antimicrobial efficacy and formulation behavior.^[36]

Particle Size and Zeta Potential

Particle size is one of the most important parameters affecting circulation time, tissue penetration, cellular uptake, and drug release behavior. Liposomal size is commonly measured using dynamic light scattering (DLS), nanoparticle tracking analysis, or electron microscopy. Nanoliposomes with sizes ranging from 50–300 nm is generally preferred for antimicrobial applications due to enhanced penetration into infected tissues and improved bioavailability.^[37]

Zeta potential indicates the surface charge of liposomes and plays a significant role in colloidal stability and microbial interaction. High positive or negative zeta potential values help prevent vesicle aggregation through electrostatic repulsion. Cationic liposomes with positive surface charge often demonstrate enhanced interaction with negatively charged microbial membranes.^[38]

Encapsulation Efficiency

Encapsulation efficiency refers to the percentage of drug successfully entrapped within the liposomal vesicles relative to the total amount of drug used during formulation. High encapsulation efficiency is desirable for improving therapeutic effectiveness and minimizing drug wastage. Encapsulation efficiency is influenced by lipid composition, preparation method, drug solubility, and vesicle structure. Techniques such as ultracentrifugation, dialysis, and gel filtration are commonly used to separate free drug from encapsulated drug

prior to analysis.^[39]

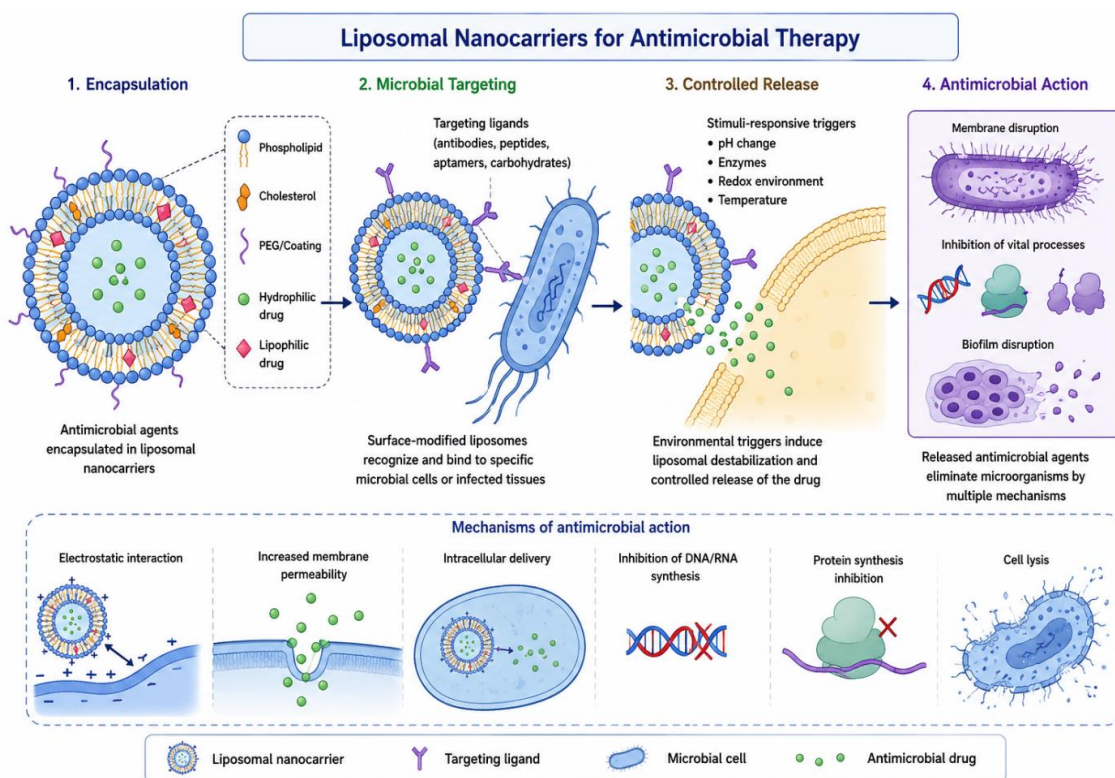
Stability and Release Behavior

Stability studies are essential for evaluating the physical and chemical integrity of liposomal formulations during storage. Parameters such as particle size, drug leakage, aggregation, phospholipid oxidation, and vesicle fusion are monitored under different environmental conditions. The incorporation of cholesterol and surface stabilizers significantly improves liposomal stability.^[40]

Drug release behavior is another critical factor influencing therapeutic efficacy. Controlled and sustained drug release from liposomes helps maintain therapeutic concentrations for extended durations while reducing dosing frequency and systemic toxicity. In vitro release studies are commonly performed using dialysis methods or diffusion techniques to evaluate release kinetics under simulated physiological conditions. Stimuli-responsive liposomes capable of releasing drugs in response to pH, temperature, enzymes, or oxidative stress have shown considerable promise for targeted antimicrobial therapy.^[41]

4. Therapeutic Applications of Liposomal Nanocarriers in Antimicrobial Therapy

Liposomal nanocarriers have emerged as highly promising platforms for the treatment of various microbial infections due to their ability to improve drug solubility, enhance therapeutic efficacy, reduce systemic toxicity, and overcome antimicrobial resistance. Their versatile structural properties allow encapsulation of a wide range of antimicrobial agents, including antibiotics, antifungal drugs, antiviral agents, peptides, and nucleic acids.^[6] Recent advancements in liposomal technology have significantly expanded their applications in combating bacterial, fungal, viral, and biofilm-associated infections. Furthermore, both in vitro and in vivo studies have demonstrated the superior therapeutic performance of liposomal antimicrobial formulations compared with conventional drug delivery systems.^[6]



Liposomal Systems Against Bacterial Infections

Bacterial infections remain a major global healthcare challenge, particularly due to the rapid emergence of multidrug-resistant (MDR) pathogens. Liposomal nanocarriers have shown remarkable potential in enhancing the efficacy of antibacterial agents while minimizing toxicity and resistance development. Liposomal encapsulation improves the pharmacokinetic profile of antibiotics by protecting them from enzymatic degradation, prolonging systemic circulation, and increasing drug accumulation at infection sites.^[42]

Several antibiotics, including vancomycin, ciprofloxacin, gentamicin, amikacin, and colistin, have been successfully incorporated into liposomal formulations for improved antibacterial therapy. Liposomal antibiotics exhibit enhanced penetration into infected tissues and intracellular compartments, making them particularly effective against intracellular pathogens such as *Mycobacterium tuberculosis* and *Salmonella* species.^[43]

Cationic liposomes have demonstrated strong antibacterial activity due to their electrostatic interaction with negatively charged bacterial membranes. This interaction increases membrane permeability, facilitates drug uptake, and may directly disrupt bacterial cell walls. Liposomal formulations have also been explored for pulmonary delivery of antibiotics in respiratory infections, including cystic fibrosis-associated bacterial infections caused by

Pseudomonas aeruginosa.^[44]

In addition, ligand-targeted liposomes functionalized with antibodies, peptides, or carbohydrates have shown improved specificity toward bacterial cells and infected tissues. Combination liposomal therapy involving multiple antibiotics or antibiotics with antimicrobial peptides has further enhanced antibacterial efficacy and reduced resistance development.^[45]

Liposomal Approaches for Fungal and Viral Infections

Liposomal nanocarriers have also gained substantial importance in the treatment of fungal and viral infections, where conventional therapies are often associated with severe toxicity and poor therapeutic outcomes.^[6]

Among antifungal applications, liposomal amphotericin B is one of the most successful clinically approved liposomal formulations. Conventional amphotericin B is highly effective against systemic fungal infections but is associated with severe nephrotoxicity. Encapsulation within liposomes significantly reduces toxicity while maintaining potent antifungal activity. Liposomal formulations improve drug distribution to infected tissues and reduce damage to healthy organs. Other antifungal agents such as fluconazole, itraconazole, and voriconazole have also been incorporated into liposomal systems to improve solubility, bioavailability, and therapeutic efficacy.^[46]

In viral infections, liposomal carriers have demonstrated considerable potential for delivering antiviral drugs, vaccines, and genetic materials. Liposomal systems enhance cellular uptake of antiviral agents and protect them from premature degradation. Antiviral drugs such as acyclovir, zidovudine, and interferons have been successfully formulated into liposomal systems for improved therapeutic outcomes.^[43]

Furthermore, liposomes serve as effective vaccine delivery vehicles due to their adjuvant properties and ability to stimulate immune responses. During recent viral outbreaks, including coronavirus infections, liposomal nanocarriers gained significant attention for nucleic acid and vaccine delivery applications. Lipid-based nanoparticle systems used in mRNA vaccines have highlighted the growing clinical importance of nanocarrier-mediated antiviral therapy.^[47]

Biofilm Targeting and Controlled Release Strategies

Microbial biofilms represent one of the most challenging forms of infection because biofilm-associated microorganisms exhibit significantly higher resistance to conventional antimicrobial agents. Biofilms are complex microbial communities embedded within an extracellular polymeric matrix that acts as a protective barrier against antibiotics and host immune responses.^[48]

Liposomal nanocarriers have shown promising potential in overcoming biofilm-associated resistance through enhanced penetration and localized drug delivery. Due to their nanoscale size and surface-modifiable properties, liposomes can diffuse through the biofilm matrix more effectively than free drugs. Cationic liposomes are particularly advantageous because they interact strongly with negatively charged biofilm components, promoting deeper penetration and increased antimicrobial action.^[22]

Stimuli-responsive liposomes capable of releasing antimicrobial agents in response to environmental triggers such as pH, enzymes, temperature, or oxidative stress have been widely investigated for biofilm treatment. Since biofilm microenvironments often exhibit acidic pH and elevated enzyme activity, these triggers can induce site-specific drug release directly within the biofilm structure.^[49]

Controlled release liposomal systems maintain sustained antimicrobial concentrations at infection sites, thereby reducing dosing frequency and improving therapeutic outcomes. Co-delivery of enzymes, quorum sensing inhibitors, or biofilm-disrupting agents along with antibiotics within liposomal carriers has also demonstrated enhanced biofilm eradication. These multifunctional strategies offer significant potential for treating chronic and device-associated infections.^[4]

In Vitro and In Vivo Antimicrobial Studies

Numerous in vitro and in vivo investigations have demonstrated the superior antimicrobial performance of liposomal formulations compared with conventional drug delivery systems. In vitro studies commonly evaluate antimicrobial activity using parameters such as minimum inhibitory concentration (MIC), bacterial killing assays, cellular uptake studies, biofilm disruption analysis, and cytotoxicity evaluation.^[50]

Liposomal antimicrobial systems have consistently shown enhanced microbial killing

efficiency, improved intracellular penetration, and prolonged drug retention. Several studies have reported increased antibacterial and antifungal activity against resistant strains following liposomal encapsulation. In vitro biofilm studies further indicate improved penetration and eradication of mature biofilms by liposomal formulations.^[22]

In vivo studies using animal infection models have provided strong evidence supporting the therapeutic advantages of liposomal nanocarriers. Liposomal formulations demonstrate improved pharmacokinetic behavior, prolonged circulation time, targeted tissue distribution, reduced systemic toxicity, and enhanced survival rates in infected animals. Reduced nephrotoxicity and hepatotoxicity have been particularly evident with liposomal antifungal formulations.^[51]

Pulmonary, topical, intravenous, ocular, and oral liposomal antimicrobial formulations have all demonstrated promising results in preclinical and clinical studies. Moreover, targeted and stimuli-responsive liposomal systems continue to show encouraging outcomes in experimental infection models, indicating their potential for future clinical translation.^[52]

Overall, therapeutic applications of liposomal nanocarriers have significantly advanced antimicrobial therapy by improving drug delivery efficiency, overcoming resistance mechanisms, enhancing biofilm penetration, and reducing adverse effects. Continued research in this field is expected to further expand the clinical utility of liposomal systems in combating complex microbial infections.^[4]

Table 1: Summary of recent liposomal nanocarrier formulations developed for antimicrobial therapy and their physicochemical and therapeutic characteristics.^[66]

Antimicrobial Agent	Liposomal Composition	Particle Size (nm)	Encapsulation Efficiency (%)	Target Microorganism	Key Findings
Amphotericin B	Hydrogenated soy phosphatidylcholine (HSPC), cholesterol, DSPG	80–120	85–95	<i>Candida albicans</i> , <i>Aspergillus fumigatus</i>	Reduced nephrotoxicity and enhanced antifungal efficacy compared to conventional amphotericin B
Vancomycin	Phosphatidylcholine, cholesterol, PEGylated lipids	120–180	70–88	MRSA	Improved penetration into infected tissues and prolonged circulation time
Ciprofloxacin	DPPC, cholesterol	90–150	65–80	<i>Pseudomonas</i>	Enhanced pulmonary

				<i>aeruginosa</i>	delivery and sustained antibacterial activity
Gentamicin	Phosphatidylcholine, stearyl amine, cholesterol	100–200	60–75	<i>Escherichia coli</i>	Increased intracellular uptake and reduced systemic toxicity
Colistin	DSPC, cholesterol, PEG-DSPE	100–140	75–90	Multidrug-resistant Gram-negative bacteria	Improved antibacterial efficacy against resistant strains
Fluconazole	Soy lecithin, cholesterol	110–170	68–84	<i>Candida</i> species	Enhanced solubility and prolonged antifungal release
Acyclovir	Phosphatidylcholine, cholesterol, PEGylated lipids	90–130	60–78	Herpes simplex virus (HSV)	Improved cellular uptake and antiviral effectiveness
Rifampicin	Phosphatidylcholine, cholesterol, diacetyl phosphate	150–220	72–89	<i>Mycobacterium tuberculosis</i>	Enhanced macrophage targeting and intracellular delivery
Clarithromycin	Egg phosphatidylcholine, cholesterol	100–160	70–85	<i>Helicobacter pylori</i>	Improved gastric retention and antibacterial efficacy
Tobramycin	DPPC, cholesterol, PEG-lipid conjugates	120–190	67–82	<i>Pseudomonas aeruginosa</i> biofilms	Enhanced biofilm penetration and sustained drug release
Voriconazole	HSPC, cholesterol, DSPE-PEG2000	95–145	80–92	<i>Candida albicans</i>	Reduced toxicity and improved antifungal activity
Azithromycin	Phosphatidylcholine, cholesterol, DOTAP	130–210	66–83	Intracellular bacterial pathogens	Improved intracellular accumulation and therapeutic efficacy

Abbreviations

DPPC = Dipalmitoyl phosphatidylcholine; DSPC = Distearoylphosphatidylcholine; DSPG = Dipalmitoyl phosphatidylcholine; DSPE-PEG2000 = Polyethylene glycol-conjugated Dipalmitoyl phosphatidylcholine; DOTAP = Dioleoyl trimethylammonium propane; HSPC = Hydrogenated soy phosphatidylcholine; MRSA = Methicillin-resistant *Staphylococcus aureus*.

5. Challenges, Future Perspectives, and Conclusion

Despite the significant advancements and therapeutic potential of liposomal nanocarriers in antimicrobial therapy, several scientific, technological, regulatory, and clinical challenges continue to limit their widespread commercial and clinical application. Although liposomal formulations have demonstrated improved antimicrobial efficacy, reduced toxicity, and enhanced targeting capabilities, the successful translation of these systems from laboratory

research to large-scale industrial production remains complex.^[53] Continuous innovation and interdisciplinary research are therefore essential to overcome existing barriers and fully exploit the clinical potential of liposomal antimicrobial delivery systems.^[6]

Limitations in Formulation and Scale-Up

One of the major challenges associated with liposomal nanocarriers is formulation complexity. The physicochemical properties of liposomes, including particle size, surface charge, lipid composition, encapsulation efficiency, and membrane stability, are highly sensitive to preparation conditions. Minor variations during formulation may significantly influence therapeutic performance, reproducibility, and stability of the final product.^[54]

Large-scale manufacturing of liposomal formulations remains technically demanding and economically expensive. Conventional laboratory-scale preparation methods such as thin-film hydration and sonication often face limitations in industrial scalability, batch-to-batch reproducibility, and process control. Achieving uniform vesicle size distribution and high encapsulation efficiency during mass production continues to be challenging. Furthermore, liposomal systems are susceptible to aggregation, phospholipid oxidation, hydrolysis, and drug leakage during storage, which may reduce shelf life and therapeutic effectiveness.^[55]

Another limitation involves the relatively low physical and chemical stability of certain liposomal formulations under varying environmental conditions such as temperature, pH, and ionic strength. Sterilization and long-term storage of liposomal products may also affect vesicle integrity and drug retention. Additionally, the high cost of pharmaceutical-grade phospholipids, specialized equipment, and sophisticated manufacturing technologies can restrict commercial feasibility.^[54]

Drug loading limitations represent another important concern, particularly for hydrophilic antimicrobial agents with poor encapsulation efficiency. Moreover, rapid clearance by the reticuloendothelial system may reduce circulation time and targeting efficiency in some formulations. Although PEGylation and surface engineering strategies have improved stability and circulation, these modifications may occasionally alter biodistribution or induce immunological responses.^[56]

Regulatory and Clinical Challenges

The clinical translation of liposomal antimicrobial systems faces numerous regulatory and

safety-related challenges. Regulatory approval of nanomedicine products requires comprehensive evaluation of physicochemical characteristics, pharmacokinetics, biodistribution, toxicity, immunogenicity, and long-term safety. However, standardized regulatory guidelines specific to nanocarrier-based antimicrobial systems remain limited in many regions.^[57]

The complexity of liposomal formulations often makes characterization and quality control difficult. Parameters such as vesicle morphology, lipid composition, drug release behavior, sterility, and storage stability must be carefully monitored to ensure product consistency and safety. Lack of harmonized analytical methods and regulatory standards can delay product approval and commercialization.^[58]

Clinical evaluation of liposomal antimicrobial formulations is also associated with challenges related to patient variability, dose optimization, biodistribution, and long-term safety assessment. Although several liposomal formulations such as liposomal amphotericin B have achieved clinical success, many experimental systems remain in preclinical or early clinical stages. Potential concerns regarding hypersensitivity reactions, complement activation, and unexpected immune responses require further investigation.^[59]

Additionally, the high production cost of nanocarrier-based therapeutics may limit accessibility and affordability, especially in low- and middle-income countries where infectious diseases are highly prevalent. The need for advanced manufacturing facilities and specialized storage conditions further complicates global distribution and clinical implementation.^[60]

Emerging Trends in Targeted Antimicrobial Nano therapy

Recent advances in nanotechnology and biomedical sciences have led to the development of highly sophisticated liposomal systems with improved targeting efficiency, controlled drug release, and multifunctional therapeutic capabilities. Emerging trends in targeted antimicrobial nano therapy are focused on overcoming antimicrobial resistance, improving intracellular delivery, and enhancing precision medicine approaches.^[61]

Stimuli-responsive liposomes capable of releasing antimicrobial agents in response to specific environmental triggers such as pH, temperature, enzymes, redox conditions, or light are gaining considerable attention. These smart delivery systems enable site-specific drug

release while minimizing systemic toxicity and off-target effects.^[62]

Surface-functionalized liposomes incorporating antibodies, peptides, aptamers, carbohydrates, or receptor-specific ligands have shown enhanced microbial targeting and cellular uptake. Such targeted systems improve accumulation of antimicrobial agents at infected tissues and enhance therapeutic selectivity. Multifunctional liposomes co-loaded with antibiotics, antimicrobial peptides, biofilm-disrupting agents, or gene-silencing molecules are also being extensively investigated to combat multidrug-resistant pathogens.^[63]

Nanotechnology-based combination therapies represent another promising approach for improving antimicrobial efficacy and reducing resistance development. Co-delivery of multiple drugs within a single liposomal carrier enables synergistic therapeutic action and optimized pharmacokinetics. Furthermore, theranostic liposomes integrating diagnostic and therapeutic functions are emerging as innovative platforms for simultaneous infection imaging and treatment monitoring.^[64]

The integration of artificial intelligence, computational modeling, and advanced microfluidic technologies is expected to further optimize liposomal formulation design and manufacturing processes. Personalized nanomedicine approaches tailored to specific infections and patient characteristics may also play an important role in the future of antimicrobial therapy.^[65]

Conclusion and Future Outlook

Liposomal nanocarriers have emerged as highly versatile and effective drug delivery systems for antimicrobial therapy, offering substantial advantages over conventional formulations. Their unique structural properties enable improved drug solubility, enhanced bioavailability, targeted delivery, controlled release, and reduced systemic toxicity. Liposomal systems have demonstrated promising therapeutic outcomes against bacterial, fungal, viral, and biofilm-associated infections, including infections caused by multidrug-resistant microorganisms.^[66] Recent advancements in liposomal engineering, surface modification, stimuli-responsive systems, and targeted delivery strategies have significantly expanded the scope of antimicrobial nano therapy. In vitro and in vivo studies have consistently highlighted the superior antimicrobial efficacy and safety profile of liposomal formulations. Furthermore, clinically approved liposomal products have validated the translational potential of nanocarrier-mediated antimicrobial therapy.^[67] However, several challenges related to large-scale manufacturing, formulation stability, regulatory approval, and clinical translation still

need to be addressed. Future research should focus on developing cost-effective, scalable, and clinically translatable liposomal systems with enhanced targeting capabilities and long-term safety. Standardized regulatory frameworks and advanced characterization techniques will also be essential for accelerating commercialization and clinical adoption.^[67] Overall, liposomal nanocarriers represent a promising and rapidly evolving platform for next-generation antimicrobial therapy. Continued advancements in nanotechnology, materials science, and pharmaceutical engineering are expected to further improve the effectiveness of liposomal systems and contribute significantly to the global fight against antimicrobial resistance and infectious diseases.^[6]

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