ISSN: 2573-9514

Review Article

Journal of Addiction Research

A Systematic Review on the Novel Drug Delivery System in the Development of Antimicrobial Drug

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Submitted: 2024, Dec 27; **Accepted:** 2025, Apr 15; **Published:** 2025, Apr 23

Citation: Parthasarathy, S., Keservani, R. K., Kesharwani, R. K., Bhise, M. R., Arya, R. K. K., et al. (2025). A Systematic Review on the Novel Drug Delivery System in the Development of Antimicrobial Drug. *J Addict Res, 9*(1), 01-10.

Abstract

Background: *The growing global concern over antimicrobial resistance necessitates the development of new and efficient antimicrobial drugs. Traditional methods of drug delivery often face challenges such as poor bioavailability, rapid clearance, and side effects. Novel drug delivery systems have emerged as promising solutions, improving the effectiveness of antimicrobial agents by enhancing their stability, targeted delivery, and controlled release.*

Aim: *To systematically review and analyze the role of novel drug delivery systems in the development of antimicrobial drugs, focusing on their mechanisms, efficacy, and potential applications in combating microbial infections.*

Method: *A comprehensive systematic review was conducted, sourcing studies from databases such as PubMed, Scopus, and Google Scholar. Research articles published between 2000 and 2024 were included, focusing on innovative drug delivery systems for antimicrobial agents. The date of search for this study was 10/10/2024 to 13/11/2024.*

Results: *The review identified several promising NDDS, including liposomes, polymeric nanoparticles, and micelles, which demonstrated enhanced antimicrobial activity and reduced side effects. These systems facilitated sustained and controlled drug release, improving the pharmacokinetics of antimicrobials. Notably, nanoparticles showed significant promise in overcoming bacterial biofilms and multi-drug resistance. Liposomal formulations were found to improve the stability of certain antimicrobial drugs, while hydrogels provided localized treatment.*

Conclusion: *Novel drug delivery systems are transforming the field of antimicrobial drug development by enhancing drug bioavailability, targeting specific infection sites, and addressing antimicrobial resistance. However, further clinical trials and long-term studies are necessary to fully realize the potential of these systems.*

Impact Statements

- NDDS have the potential to significantly improve the therapeutic outcomes of antimicrobial drugs by increasing their bioavailability and ensuring more targeted and sustained release at infection sites.
- By improving the pharmacokinetics and overcoming barriers like bacterial biofilms and multidrug resistance, NDDS can play a crucial role in addressing the growing global challenge of antimicrobial resistance.
- The use of NDDS, such as liposomes and nanoparticles, can reduce systemic side effects of antimicrobial drugs, offering safer treatment options for patients.
- NDDS allow for the customization of treatment strategies based on the specific microbial strain or infection site, paving the way for more personalized and effective antimicrobial therapies.
- The integration of NDDS into clinical settings holds promise for revolutionizing infection management, offering new avenues for the development of novel, more effective antimicrobial agents.

1. Introduction

Bacterial diseases can be deadly. Every year, at least 700,000 people die around the world from superbug infections. Antibacterial drugs are very important for treating illnesses caused by germs. Despite this, bacteria have become more resistant to antibiotics because they are used too much in hospitals, farms, and animal farms [1-3]. This is very dangerous to people's health and lives because it could cause many bacterial illnesses. Microbes can get around the way an antimicrobial drug works, which helps them stay alive. This is called antimicrobial resistance [2-4]. Some common ways that bacteria can become resistant are by changing and protecting drug targets, turning off antibiotic agents, or making it harder for antibiotics to get to their target site by either increasing efflux or making entry more difficult [3-5].

Because some antibiotics work on targets inside bacteria, they have to get through the pore protein in the cell's outer membrane and the active transport channel in the cell's inner membrane. When the antibiotic gets into the bacterial cell, it binds to its target and stops the bacteria from doing its molecular work [5-7]. The target's structure and function, or develop or enhance complex efflux pumps to swiftly remove the antibiotic from the bacterial cell. The World Health Organization has identified antibiotic resistance as a major public health concern [6-8]. Figure 1 consists of antimicrobial therapy strategies.

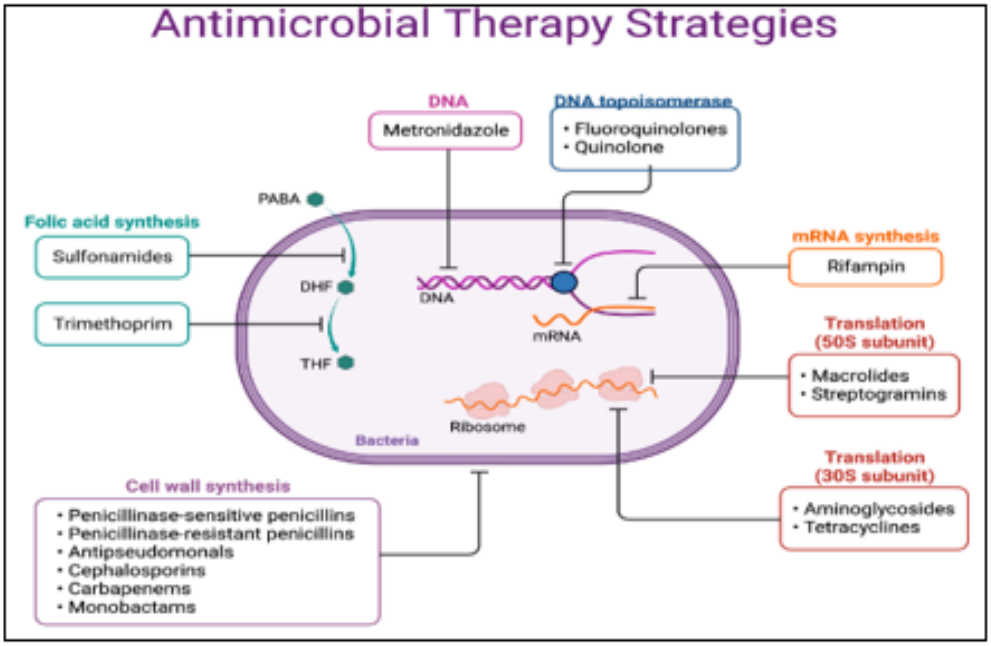

Figure 1: Antimicrobial Therapy Strategies

At this point, it has spread around the world and put at risk the efficiency of important infection prevention and treatment. The main advice from the WHO and national health organizations has always been to limit the use of antibiotics and make cleaning and throwing away medicines better. We need more international cooperation and study that combines different fields in order to protect and improve public health measures against the global threat of antibiotic resistance [7-9]. Because of this, pharmaceutical experts are becoming more and more interested in how medicines and nanotechnology can work together. As an example of how important nanodrugs are, this study will look at recent progress in new drug delivery methods for treating microbial infections [8-10].

1.1. Aim

To thoroughly examine and evaluate the function of innovative drug delivery methods in the creation of antimicrobial medications, paying particular attention to their workings, effectiveness, and possible uses in the fight against microbial infections.

2. Method

2.1. Literature Selection

Studies were sourced from sources including PubMed, Scopus, and Google Scholar in order to conduct a thorough systematic review. Novel antimicrobial drug delivery methods were the subject of the included research articles, which spanned the years 2000–2024. From October 10, 2024, to November 13, 2024, this study's search period was in effect.

3. Results

3.1. Antimicrobial Drug Delivery Systems in Nanomedicine

Nano-drug delivery technologies are getting better, which opens up new ways to treat and avoid diseases. These systems can make drugs better by making their effects last longer, improving their targeting and effectiveness, getting around drug resistance, and lowering their toxicity and immunogenicity. Nanodrug delivery systems are being used a lot in both the experimental and clinical stages right now [9-11].

3.2. Nanogels

Nanogels, or nanoscale hydrogels, are characterized by a network of amphiphilic or water-soluble polymers interconnected through physical or chemical interactions. Nanogels are advantageous nanocarrier drug delivery systems due to their numerous features, such as facile dispersion in water, hydrophilic and pliable appearance, elevated water content, ability to encapsulate a substantial quantity of physiologically active chemicals, and excellent biocompatibility. Standard nanogel forms often possess a diameter ranging from 5 to 500 nm [11-13]. The effective size range is essential for averting fast renal separation, hence inhibiting absorption via the reticuloendothelial system. Nanogels demonstrate significant permeability and can easily traverse the blood-brain barrier due to their nanoscale characteristics. Drugs may also be encapsulated in nanogels through hydrophobic interactions, hydrogen bonding, and salt formation, in addition to physical encapsulation. The hydrophilic surface of the nanogel impedes blood opsonization and inhibits macrophage phagocytosis [12-14].

In addition to being biodegradable and very compatible with the body, nanogels can increase the effectiveness of chemotherapeutic agents loaded with drugs against cancer cells that are sensitive to the drugs as well as those that are resistant to them. Consequently, nanogels represent a highly promising nanocarrier drug delivery system in the biotechnology and pharmaceutical sectors at present [13-15]. At a dosage below the minimum inhibitory concentration, azithromycin may decrease the motility of Pseudomonas aeruginosa and the production of several virulence factors. Nonetheless, concentrations near the infection site, especially within bacterial biofilms, affect the in vivo efficacy of azithromycin. At lower dosages, both systems can inhibit and eradicate bacterial biofilms while augmenting the antibacterial efficacy of azithromycin [14-16]. No detectable toxicity is observed in lung epithelial and liver cells, and this nanogel demonstrates excellent cell selectivity. Both formulations demonstrated effective azithromycin mucosal administration for treating P. aeruginosa-induced lung infections, notwithstanding their variances. Nevertheless, researchers must establish the definitive dosage form and in vivo efficacy evidence before the complete potential of this formulation can be evaluated [15-17].

3.3. Liposomes

Liposomes are one of the most promising ways to deliver nanodrugs used in antibiotic studies. In the 1970s, lipid-based nanosystems were first created as ways to deliver drugs. Since then, a lot of work has been done in liposome technology, making them a very good way to deliver antibacterial drugs. Liposomes are round bubble-like structures with a liquid center and one or more lipid bilayers surrounding it. These two layers are usually made up of amphiphilic lipids, like phospholipids [16-18].

In general, liposomes are between 20 nm and several microns across, and each membrane is about 4 nm thick. Compared to other drug delivery systems, liposomes have a number of benefits, including the ability to contain both hydrophilic and hydrophobic small molecules in a single structure, being biocompatible and biodegradable, having low toxicity, and interacting less with the immune system [19-21]. The results show that the pegylated liposome method may enhance the concentration of vancomycin in the body when the drug is loaded into liposomes [22-24]. Pegylation solves the problem of conventional liposomes being quickly absorbed by the reticuloendothelial system, which greatly increases the delivery system's circulation duration in the body [23-25]. Figure 2 consists of different types of liposome-based drug delivery.

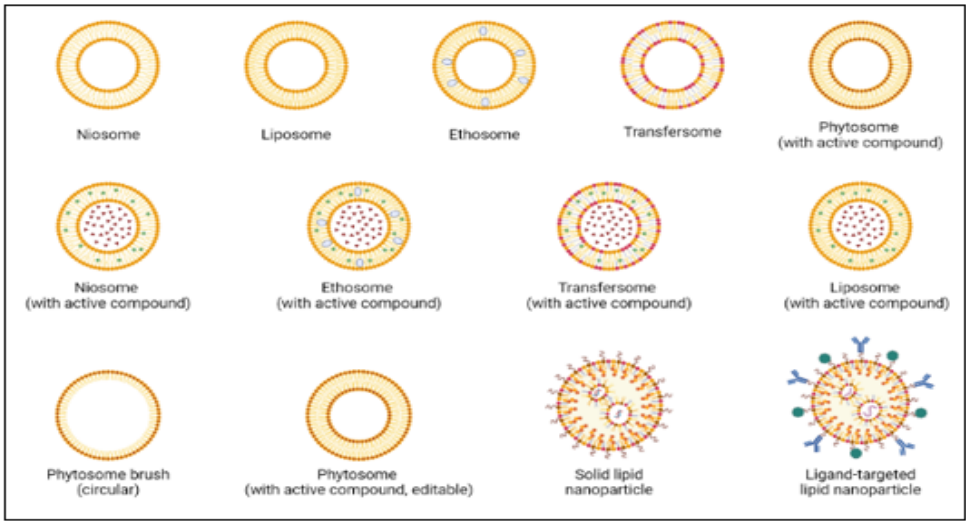

Figure 2: Different Types of Liposome-Based Drug Delivery

Thin film hydration is the process used to make liposomal moxifloxacin [26-28]. It was found that neutral moxifloxacin, cationic moxifloxacin liposomes, and the free drug all had minimum inhibitory concentrations of 1, 1, and 0.5 against S. aureus. Based on these findings, moxifloxacin's antibacterial properties are amplified when enclosed in liposomes, more especially cationic vesicles [27-29]. To get rid of Pseudomonas aeruginosa infections, pharmaceuticals and PSLG were also used. However, PSLG can be broken down by proteolysis. Help keep PSLG stable and protect it from proteolytic breakdown. LCNPs are used to give PSLG and tobramycin [28-30]. Because of this, liposomes are supposed to make the medicine much more effective at healing. Liposomes have many benefits, but they also have some problems. For example, they can't fully encapsulate hydrophilic components, they are very small they leave behind liquids, and it's hard to change the particle size distribution [29-31]. Additionally, the liposomes produced were consistently of high quality. Additionally, the method has shown up to 99% encapsulation effectiveness when tested for antibiotic encapsulation [30-32].

3.4. Nanoemulsion

The smaller particles and larger surface area of nanoemulsions, which are composed of stabilized droplets the size of nanometers, make them more stable and permeable than conventional emulsions. Because the NE was stable and could dissolve in water, it was a good way to deliver drugs [31-33]. Antimicrobial resistance could be something they can conquer as well. There is more than one way to give NE. The majority of these are water and oil nanoemulsions. There is an oil phase on the outside and a water phase on the inside, with a combination of the two phases [32-34]. Because the water and oil are always moving back and forth at the contact, the continuous nanoemulsion is isotropic. Pharmaceuticals can be added to nanoemulsions in both the inside and outside parts [33-35]. Figure 3 consist of structure of nanoemulsion.

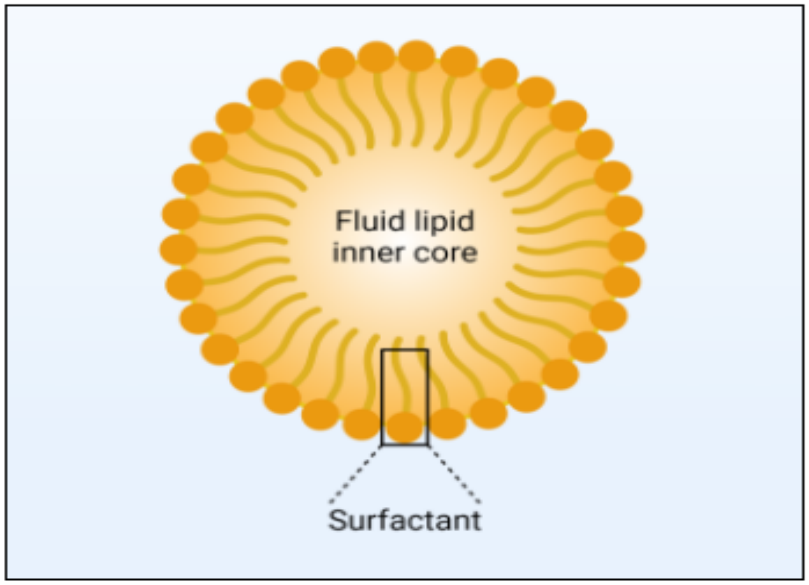

Figure 3: Structure of Nanoemulsion

Research has demonstrated that a PDI is efficient against several human infections, such as viruses, fungi, protozoa, parasites, and bacteria [35-37]. Even though it works well as a PS, it can't be used very often because it has a high lipophilicity, a high molecular weight, and doesn't dissolve well in water. These properties keep it inside Gram-negative bacterial bilayer membranes and stop it from getting to the target cytoplasmic membrane [36-38].

3.5. Polymeric Micelles

Micelles are formed when the concentration of the hydrophobic portions of the polymer rises over a certain point, known as the critical micelle concentration. This happens because of electrostatic forces, hydrogen bonding, hydrophobic interactions, and other molecular factors. Because of their chemical and biophysical qualities, they have shown a lot of promise in DDS [39-41]. Figure 4 consist of structure of Polymer micelles.

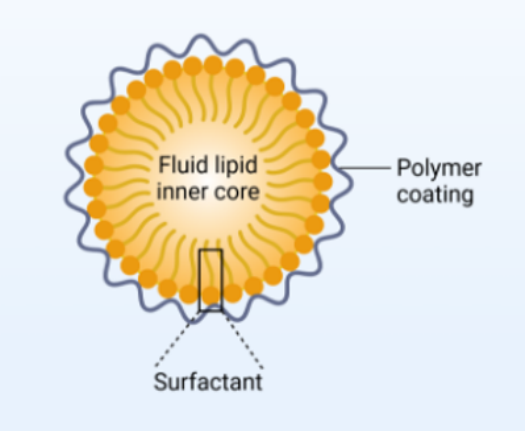

Figure 4: Polymer Micelles

At a 1:4 ratio, the particle size can be smaller, the particle size distribution can be more even, the zeta potential can be stronger, and the PMAC can better encapsulate things. Not only that, but the water solubility is a thousand times better than before it was attached. The spherical shape of PMAC is revealed by the transmission electron microscope photograph [42-44]. The MTT assay demonstrated that normal cells are unaffected by the PMAC concentration. These findings provide more evidence that PMAC is an effective and safe antibacterial agent that has the potential to eradicate pathogenic microorganisms found in dental biofilms [43-45]. Rifampicin is one of the best medicines for infections inside cells, but it shouldn't be used by itself because there is a big chance that bacteria will become resistant to it [44-46]. This points to an alternative mechanism of bactericidal action to liberate colistin. This study demonstrates that micelles cross-linked with drugs have the potential to be a valuable biomaterial derived from legally available antibiotics [45-47].

3.6. Nanoparticles

Metal nanoparticles can kill bacteria in different ways depending on their size and form. They do this in a number of ways, such as by binding to polymers, changing their function, and making free radicals through reactive oxygen species. Because they can target different parts of cells, like the cell wall, DNA, membrane, and proteins, metal nanoparticles are seen as good choices for antibacterial treatments [48-50]. To combat germs that have developed resistance to numerous medications, another option is to employ biogenic metallic and metal oxide nanoparticles. Magnetic nanoparticles are used a lot in biomedicine and nanomedicine [49-51]. The agar-diffusion method was employed to demonstrate that the concentration-dependent inhibition of S. aureus and E. coli growth can be achieved by magnetic nanoparticles. In addition, certain magnetic nanoparticles were much more effective against all pathogens than standard treatments [52-54]. Figure 5 consist of Different types of nanoparticles.

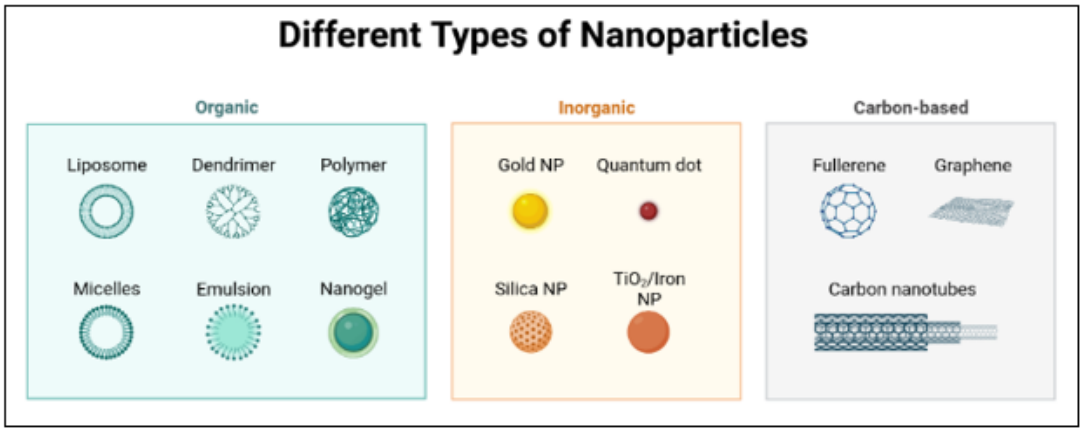

Figure 5: Different Types of Nanoparticles

3.7. Solid Lipid Nanoparticles

Ability of these vesicular structures made of lipids to release medications at a controlled and targeted rate is what piques people's interest in them. Emulsification makes use of surfactants to stabilize SLN. They can be man-made or natural biopolymers that work well for enclosing meds that are fat-loving [55-57]. This could help avoid vancomycin's side effects, such as neutropenia and renal failure [56-58]. MLNs combine the benefits of solid lipid nanoparticles and double emulsions to make it easier to encapsulate both lipophilic and hydrophilic compounds at the same time. This supports combination treatment for a wide range of illnesses [57-59]. The ultrasonication method was used to load VAN and CAR onto MLNs, which were then tested for their antibacterial and physical and chemical qualities. Antimicrobial study shows that co-encapsulation made the VAN antibiotic work better against Staphylococcus aureus, which could be more helpful in systemic treatments [58-60].

3.8. Other Emerging Approaches and Carriers

However, depending on how often they've been exposed to antibiotics, they can also become resistant to many of them. One of the most hopeful ways to fight resistance is to use modified bacteriophages. Using a phage to carry a nucleic acid drug makes it easier to attack a specific type of bacteria. New developments in CRISPR gene editing have made it possible to create a phage that can remove a gene that makes bacteria resistant, killing the pathogens for good. If you only use random bacteriophage infection methods, bacteria may be able to fight them off [61-63].

3.9. Conventional and Novel Methods for Antimicrobial Therapy

Many diseases have found relief with controlled extended-release formulations. However, when it comes to infectious diseases, prolonged antibiotic release may unintentionally make germs more resistant [62-64]. This result has been seen when vancomycin leaks from a bone graft void filler to a certain area [63-65]. So, in order to treat internal bugs, you need to use formulations that are made just for this complicated situation [64-66]. This meant that the antibiotic was effective against S. aureus through two channels: its own action and the better phagocytic function. By going after intracellular growth, both the initial infections can be controlled and the recurrence of secondary infections may be lowered [65-67].

3.10. Infection Responsive Drug Delivery Systems

Drug delivery systems that respond to tissue-or disease-specific molecular cues have recently attracted a lot of attention. Multiple disorders have been associated with elevated levels of specific proteases. These proteases have multiple potential applications, including as disease biomarkers and therapeutic targets. At the same time, macrophages make cholesterol esterase in reaction to infection, and neutrophils and monocytes have been found to make higher levels of myeloperoxidase. These biological signs can be used to make new, infection-responsive, localized drug delivery systems that improve therapeutic effectiveness while lowering harmful systemic side effects. It is important to note that attacking these drug delivery methods would not be necessary [66-68].

3.11. Development and Discovery of Antibiotic Drugs

In one method, the goal is to stop gram-negative bacteria from making lipopolysaccharide, especially the lipid a component. A more focused way to deal with the core oligosaccharide is to stop enzymes that are only found in certain strains of bacteria from making O-antigens. Aminoglycosides are the main source of small drugs used to find new ways to target RNA. They mostly stop bacteria from making proteins. But with each new medicine, a new targeted delivery system or one that is triggered by the microenvironment should be created at the same time [67-69].

3.12. Targeted Drug Delivery Systems

A recent study found that some lytic enzymes that come from bacteria and bacteriophages can be very good at killing certain types of microbes. Sexually transmitted diseases are mostly caused by Chlamydia trachomatis, which grows in large numbers in the cells that line the genital area. CT is an intracellular pathogen that only interacts with the exocytic pathways while living in a protective inclusion body inside the target cell. Being able to attach antibiotics to transferrin makes it possible for this protein to carry drugs inside cells. Using the iron scavengers and transporters that are naturally found in bacteria is an interesting way to fight CT's resistance to a number of drugs [68-70].

4. Discussion

4.1. Key Findings

Novel drug delivery systems (NDDS), including liposomes, nanoparticles, micelles, and hydrogels, have shown significant promise in enhancing the bioavailability, stability, and targeted delivery of antimicrobial drugs. NDDS have been effective in overcoming barriers such as bacterial biofilms, multi-drug resistance, and poor solubility of antimicrobial agents. Systems like polymeric nanoparticles and liposomes have demonstrated controlled release properties, improving pharmacokinetics and reducing the side effects typically associated with traditional drug delivery methods. Despite their potential, the efficacy of NDDS varies depending on the antimicrobial agent, the infection type, and the delivery system used [69-71].

4.2. Strengths and Weaknesses

- Strengths: NDDS can improve the stability and solubility of antimicrobial drugs, which is critical for drugs with low water solubility or those susceptible to degradation. They offer the potential for targeted therapy, which is particularly useful for localized infections and reducing systemic exposure, minimizing side effects. The ability to combat drug resistance through strategies like overcoming bacterial biofilms and enabling sustained drug release is a significant advantage [71-73].
- Weaknesses: The complexity and cost of developing NDDS can be a limitation, particularly when scaling up for clinical application. Inconsistent results across different microbial strains and infection types highlight the need for more tailored approaches. There is limited clinical data on the long-term safety and efficacy of these systems, making it difficult to assess their full potential in real-

world applications [72-74].

4.3. Interpretation

NDDS represent a promising advancement in antimicrobial therapy by addressing critical challenges like drug resistance and poor drug delivery efficiency. However, their success depends on careful optimization of formulation parameters, including drug type, carrier material, and method of administration. While early-stage research shows promise, further exploration into the mechanism of action, safety, and long-term effectiveness of NDDS is essential [73-75].

4.4. Further Research

There is a need for more clinical trials to assess the safety, efficacy, and potential side effects of NDDS in diverse patient populations. Future research should focus on optimizing the formulation of NDDS for specific antimicrobial agents and infection types to enhance treatment personalization. Investigating the interaction of NDDS with the immune system and their role in reducing microbial resistance over time would provide deeper insights into their long-term benefits. Exploration of scalable and cost-effective production methods is needed to make NDDS more accessible for widespread clinical use [76-79].

5. Conclusion

Antibacterial drugs were developed in the 20th century to treat infectious diseases and reduce death rates. However, antimicrobial resistance has made many antibiotics ineffective, posing a health risk. Nanodrug delivery methods, like polymeric micelles and liposomes, can enhance drug properties, making them less toxic, immunogenic, and effective. Research on nanomedicine delivery systems aims to target germs and increase permeability, potentially lowering public health risks associated with biofilm-related illnesses and resistant infectious diseases.

Declarations

Acknowledgements: We are all authors are acknowledging our host institutes for their all type of support to complete this work.

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