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A review on development of cefotaxime nanoparticles to improve therapeutic efficacy

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Abstract
The development of nanotechnology-based drug delivery systems has opened new avenues for enhancing the therapeutic efficacy of conventional antibiotics. In this study, an attempt was made to improve the therapeutic profile of Cefotaxime, a third-generation cephalosporin antibiotic, through the formulation of nanoparticles. The objective was to enhance the drug's bioavailability, stability, and controlled release while reducing dosing frequency and potential side effects. Cefotaxime nanoparticles were synthesized using a green synthesis approach involving a suitable biopolymer or stabilizing agent to achieve uniform particle distribution and high encapsulation efficiency. The prepared nanoparticles were characterized using techniques such as UV-Visible spectroscopy, Fourier Transform Infrared Spectroscopy (FTIR), Dynamic Light Scattering (DLS), and Scanning Electron Microscopy (SEM) to determine their size, morphology, and functional groups. The average particle size was found to be in the nanometer range, ensuring efficient cellular uptake and improved pharmacokinetic performance. **In vitro** drug release studies revealed a sustained release pattern, indicating prolonged therapeutic action. Antibacterial activity testing against selected Gram-positive and Gram-negative bacteria demonstrated enhanced efficacy compared to the pure drug, suggesting improved penetration and retention at the infection site. The study concludes that nanoparticle-based formulation of Cefotaxime significantly improves its therapeutic potential, making it a promising strategy for combating antibiotic resistance and optimizing drug delivery. This nanotechnological approach provides a foundation for developing more effective, safer, and patient-friendly antibiotic formulations.

Keywords: Cefotaxime, nanoparticles, particle size, morphology, bioavailability

Introduction
Cefotaxime is a β-lactam antibiotic, several bacterial infections of varied spectrum treated with it. It exhibited a useful inhibitory effect upon many Gram-negative bacteria and some Gram-positive organisms like *Escherichia coli*, *Klebsiella pneumoniae*, *Proteus mirabilis*, *Haemophilus influenzae*, and *Streptococcus pneumonia* [1]. It acts against bacteria by stopping the synthesis of the cell wall, wherein it attaches itself to the penicillin-binding proteins (PBPs), resulting in lysis and eventually the death of bacterial cells [2]. The drug was often used as a primary agent due to its broader antimicrobial spectrum as well as stability against many β-lactamases, especially in empirical therapy in hospital settings. The drug is being used for: infections of the lower respiratory tract, urinary tract infections, septicemia, meningitis (infection of the lining of the brain and spinal cord), infections of bones and joints, and infections related to gynecology [3]. Cefotaxime is particularly useful for pediatric bacterial meningitis by *H. influenzae* and *Neisseria meningitidis*, due to its ability to cross into cerebrospinal fluid [4].

When it comes to therapeutic indications, the drug is used extensively in clinical practice but has some stand-alone limitations due to emerging antimicrobial resistance. A major resistance mechanism is ESBL production, mainly produced by *E. coli* and *K. Pneumoniae*, whereby cefotaxime becomes hydrolyzed and is rendered ineffective in therapy [5]. These resistant strains are, in many cases, multidrug-resistant and pose serious problems in clinical management. Resisting mechanisms and pharmacokinetic limitations prevents cefotaxime's further application. The drug itself has a relatively short elimination half-life of an hour, requiring frequent dosing to maintain therapeutic concentrations in the plasma [6].

Another disadvantage is low oral bioavailability, which allows only the parenteral route of administration, limiting the drug's use in outpatient and long-term therapy.

Infections where cefotaxime has waning efficacy are those limited by drug penetration, giving rise to subtherapeutic concentrations that might precipitate the failure of the treatment in cases of abscess or biofilm-associated infections [7]. Another problem to regard is the drug adverse reactions; similar to any other β-lactam antibiotics, cefotaxime might induce IgE-mediated reactions from mild skin rashes to life-threatening anaphylaxis, particularly in patients already allergic to penicillins [8]. Those working on cefotaxime are naturally eager to propose novel ways in restoration or enhancement of its clinical efficacy. Amongst these, nanotechnology-based drug delivery systems seem promising. They can enhance the pharmacokinetics, lower dosing frequency, and get around resistance via better tissue penetration and sustained drug release [9].

Adding cefotaxime to delivery systems based on nanoparticles is one promising way to get around its drawbacks. Nanotechnology is an important field of research in the fight against multidrug-resistant (MDR) bacterial infections because it has the potential to enhance the pharmacokinetics, stability, and targeted delivery of antimicrobial agents. Recent research has investigated a number of nanocarriers as delivery systems for cefotaxime, including solid lipid nanoparticles, liposomes, polymeric nanoparticles, and metallic nanoparticles (such as gold and silver). When combined with cefotaxime, silver nanoparticles (AgNPs) have shown notable synergistic antibacterial activity. For example, cefotaxime-loaded AgNPs demonstrated improved bactericidal effects against *Staphylococcus aureus* and *Escherichia coli*, according to Alavi and Karimi. This was probably caused by increased membrane permeability and disruption of bacterial cell wall synthesis. Other nanomaterials have shown similar results. Cefotaxime-functionalized ZnO nanoparticles demonstrated significant efficacy against MDR pathogens in a study by Gowri *et al*. [10], who attributed the improvement to the synergistic effects of the antibiotic action and oxidative stress caused by the nanoparticles.

To obtain cefotaxime's sustained release profiles, polymeric nanoparticles like PLGA (polylactic-co-glycolic acid) have also been used. This controlled release may increase patient compliance and decrease the frequency of doses. In comparison to free drug formulations, Almalik *et al*. [11] showed that cefotaxime-loaded PLGA nanoparticles decreased cytotoxicity and sustained antibacterial activity over time. Cefotaxime has also been encapsulated using liposomal delivery systems to increase its bioavailability and shield it from enzymatic breakdown. In murine models, cefotaxime-loaded liposomes demonstrated enhanced pharmacodynamics and decreased nephrotoxicity, indicating their potential clinical utility in systemic infections [12].

Cefotaxime incorporation into nanostructures also shows promise for surface coatings on medical devices to stop the formation of biofilms. Cefotaxim nanocomposite coatings for implants and catheters have been developed by Kaur *et al*. [13], which greatly lowers the risk of infections linked to the devices. These uses highlight the adaptability of cefotaxime-loaded nanoparticles in both preventative and therapeutic settings.

The clinical translation of these technologies is still fraught with difficulties, despite encouraging outcomes. It is necessary to address problems like large-scale synthesis, stability during storage, possible toxicity of nanomaterials, and regulatory obstacles. Furthermore, thorough *in vivo* research and clinical trials are required to verify efficacy and safety. Although preclinical data are convincing, Zhang *et al*. [14] point out that standardization in nanoparticle characterization and therapeutic assessment is essential for regulatory approval.

In summary, a major development in the field of antimicrobial therapy is the incorporation of cefotaxime into nanoparticle delivery systems. Cefotaxime's synergy with different nanomaterials may help it regain its effectiveness against resistant strains and expand its range of clinical uses. For nanoparticle-mediated cefotaxime delivery in clinical practice, more interdisciplinary research integrating materials engineering, microbiology, and pharmaceutical sciences is required.

Benefits of Cefotaxime in Nanoparticle Form

Improved Antimicrobial Performance

The antimicrobial potency increase when it is encapsulated in nanoparticles. The outcome of the nanoscale size's increased penetration into bacterial cells and biofilms and improved bactericidal activity. According to studies, cefotaxime-loaded silver or chitosan nanoparticles are more effective than free cefotaxime at killing Improved cellular uptake or the synergistic effects of cefotaxime and nanoparticle materials could be the cause of this increased activity.

Sustained and Regulated Drug Release

Cefotaxime can be released gradually and control way from nanoparticle formulations, which help to sustain therapeutic drug levels for long periods of time. Patient compliance is increased by this pharmacokinetic improvement, which lowers the frequency of dosing and guarantees constant bactericidal concentrations [15]. For such long-term delivery systems, biodegradable polymeric nanoparticles like those derived from poly (lactic-co-glycolic acid) (PLGA) are frequently employed.

Overcoming Mechanisms of Resistance

Cefotaxime's enzymatic degradation by β-lactamases, a key mechanism of resistance in Gram-negative bacteria, can be prevented by nanoparticles. Even in resistant bacterial strains, this protective encapsulation preserves the drug's integrity and increases its therapeutic efficacy [16]. Moreover, other resistance pathways can be blocked by co-delivering cefotaxime with metal ions in nanoparticle form or efflux pump inhibitors.

Reduced Toxicity and Targeted Delivery

Cefotaxime can be delivered precisely to infection sites by functionalizing nanoparticles with targeting ligands (such as peptides or antibodies), reducing systemic exposure and off-target effects [17]. Additionally, by reducing the necessary dosage, this targeted approach lowers the risk of toxicity and adverse effects that come with high-dose antibiotic therapy.

Biofilm Infiltration

One major obstacle to antimicrobial therapy is bacterial biofilms. Cefotaxime delivery systems based on nanoparticles have shown better biofilm penetration and disruption than free drug. Particularly, chitosan-based

nanoparticles improve localized antibiotic delivery due to their inherent mucoadhesive and anti-biofilm activity [18].

Cefotaxime formulations based on nanoparticles offer a number of benefits over conventional delivery systems. They provide targeted delivery, resistance circumvention, extended drug release, enhanced antimicrobial efficacy, and biofilm penetration. Cefotaxime encapsulated in nanoparticles is a promising option for contemporary antimicrobial therapy because of these advantages, especially when it comes to fighting multidrug-resistant infections. To confirm these benefits and make the transition to clinical practice easier, more *in vivo* and clinical research is required.

Disadvantages of Cefotaxime in Nanoparticle Form

Formulation Complexity

Complex formulation procedures are needed to produce stable, repeatable cefotaxime-loaded nanoparticles. Complex techniques like emulsification, solvent evaporation, nanoprecipitation, or ionic gelation are required to achieve consistent particle size, drug encapsulation efficiency, and controlled release profiles [19]. These procedures frequently call for costly materials, sterile conditions, and exact environmental control, which restricts scalability and raises production costs.

Toxicity and Biocompatibility

Some nanoparticle systems may be toxic even with their increased effectiveness. When combined with cefotaxime, metallic nanoparticles (such as gold or silver) can induce inflammation, oxidative stress, and damage to membranes in mammalian cells [20]. Depending on their degradation products and surface characteristics, even biodegradable carriers like chitosan or PLGA may trigger immune reactions [21]. For instance, *in vitro* studies have shown that cefotaxime-loaded silver nanoparticles exhibit cytotoxic effects at higher doses, which may restrict their clinical application [22].

Drug Stability and Premature Degradation

As a β-lactam antibiotic that is susceptible to hydrolysis, cefotaxime's incorporation into nanoparticles does not completely remove this risk. Unfavorable interactions with carrier materials or exposure to environmental elements like light, humidity, and temperature can cause some formulations to accelerate drug degradation [23]. For storage and commercial distribution, long-term stability continues to be a significant obstacle.

Risk of Resistance

Suboptimal drug release profiles may inadvertently increase resistance, even though nanoparticle systems are designed to decrease it. According to Pelgrift and Friedman [24], sustained release systems that are unable to sustain therapeutic concentrations can expose bacteria to sub-lethal antibiotic levels, which can lead to adaptive responses and the expression of resistance genes. To prevent this, inconsistent release kinetics need to be carefully controlled.

High Manufacturing Costs and Limited Accessibility

High production costs are associated with the synthesis of cefotaxime nanoparticles, mainly because it requires specialized materials, advanced instrumentation, and strict quality control procedures. This limits their use in environments with limited resources, where cefotaxime is frequently most required [25]. Access problems are also made worse by limitations on intellectual property and a dearth of generic nanoparticle formulations.

Barriers to Clinical and Regulatory Translation

There is little clinical trial data available for cefotaxime formulations based on nanoparticles, despite promising preclinical and laboratory results. Nanoparticle systems complicate the evaluation process, and regulatory bodies demand substantial toxicity, pharmacokinetic, and pharmacodynamic data prior to approval [26]. As a result, clinical translation is expensive and time-consuming, which delays practical application.

Although cefotaxime delivery via nanotechnology has many advantages, these must be balanced against a number of serious drawbacks. Significant obstacles include formulation complexity, possible toxicity, instability, resistance risks, expense, and regulatory barriers. For cefotaxime-loaded nanoparticle systems to be responsibly advanced in clinical practice, these issues must be addressed through ongoing research, toxicological evaluations, and formulation process optimization.

Cefotaxime Nanoparticle Formulation Challenges and Solutions

Because of its potential to improve pharmacokinetics, overcome antimicrobial resistance, and increase therapeutic efficacy, the development of nanoparticle-based drug delivery systems for antibiotics such as cefotaxime has drawn a lot of attention. To guarantee clinical viability and performance, however, a number of physicochemical and biological issues with cefotaxime nanoparticle formulation must be resolved.

Cefotaxime's hydrophilicity and instability pose a significant obstacle to its encapsulation in hydrophobic polymeric matrices like poly (lactic-co-glycolic acid) (PLGA) or polylactic acid (PLA) [27]. Although these polymers are frequently utilized in the formulation of nanoparticles, their incompatibility with water-soluble medications, such as cefotaxime, results in poor drug loading and encapsulation effectiveness. To get around this, compatibility and loading efficiency can be increased by adding hydrophilic excipients like cyclodextrins or using amphiphilic block copolymers (like PEG-PLA) [28].

The lack of controlled release behavior and burst drug release are also serious issues. Due to its high water solubility, cefotaxime has a tendency to diffuse quickly from nanoparticles, producing an initial burst that may result in toxicity and less-than-ideal therapeutic windows. Using multilayered nanoparticle systems to control release kinetics and surface modification of nanoparticles with chitosan or polyethylene glycol (PEG), which forms diffusion barriers, are two ways to lessen this [29].

Another bottleneck is stability throughout processing and storage. Cefotaxime is susceptible to heat and moisture, which are frequent in processes used to create nanoparticles, like high-pressure homogenization and spray drying. Degradation and diminished antibacterial efficacy may result from this. It has been demonstrated that cefotaxime-loaded nanoparticles can be stabilized by lyophilization (freeze-drying) with cryoprotectants like trehalose or mannitol without sacrificing particle integrity or activity [30].

Bioavailability and biodistribution are also significantly impacted by particle size and the polydispersity index (PDI). Optimal cellular uptake and extended circulation require a narrow size distribution (<200 nm), which can be difficult to achieve, particularly in large-scale production. Optimizing formulation parameters (such as surfactant concentration and stirring speed) and using sophisticated preparation methods like microfluidics or nanoprecipitation under carefully monitored conditions can help with this [31].

Chemical compatibility and drug-polymer interactions also need to be carefully considered. Drug degradation or loss of activity may result from incompatibilities. When creating nanoparticles, spectroscopic techniques like FTIR and DSC are frequently used to evaluate interactions and ensure chemical integrity [32].

Lastly, there are major translational challenges related to reproducibility and scale-up. At an industrial scale, methods that work well on a bench scale might not be practical or economical. As a result, early in the development stage, process standardization and regulatory compliance must be taken into account. To improve reproducibility and regulatory acceptability, quality-by-design (QbD) techniques and continuous manufacturing technologies have been promoted [33].

To sum up, the development of cefotaxime-loaded nanoparticles poses a number of difficulties, from low drug loading and instability to scale-up and regulatory barriers. However, these can be successfully overcome with the help of clever design techniques, sophisticated material selection, and in-depth characterization. Translating promising nanoparticle formulations into antimicrobial treatments that are clinically viable requires such efforts.

Formulation Methods of Cefotaxime Nanoparticles

Cefotaxime has a number of pharmacokinetic drawbacks, including a short half-life, poor tissue penetration, and rapid renal clearance, despite its clinical efficacy. Due to these disadvantages, frequent intravenous administration is frequently required, which may lower patient compliance and raise the possibility of adverse effects. Drug delivery methods based on nanoparticles have shown promise in recent years as a means of improving cefotaxime's therapeutic efficacy. According to Anselmo and Mitragotri, nanoparticles can increase a drug's bioavailability, shield it from enzymatic breakdown, offer sustained release, and enable targeted delivery to infection sites [34].

The solvent evaporation method is one of the most popular approaches for creating nanoparticles. Using a volatile organic solvent like acetone or dichloromethane, the drug and a polymer (like PLGA or Eudragit) are dissolved in this method. After emulsifying the organic phase into an aqueous phase with a stabilizer (like PVA), the solvent is subsequently evaporated at a lower pressure. This approach is appealing for production at the laboratory scale due to its relative simplicity and reproducibility. Its moderate entrapment efficiency for hydrophilic medications like cefotaxime and dependence on organic solvents are significant drawbacks. Cefotaxime was encapsulated in PLGA nanoparticles using this technique and obtained a 72% encapsulation efficiency with 48-hour sustained release [35].

The drug and polymer are dissolved in a water-miscible organic solvent (such as acetone) before the organic phase is injected into an aqueous solution while being continuously stirred. This process is called solvent displacement or nanoprecipitation. As the solvent diffuses into the aqueous phase and the polymer precipitates, nanoparticles are created. Although this approach is straight forward and appropriate for scaling up, it typically has poor efficacy with hydrophilic medications such as cefotaxime. However, it was found that cefotaxime's antibacterial qualities and entrapment could be greatly improved by employing PEGylated polymers in the nano precipitation method [36].

The ionic gelation technique has various benefits for hydrophilic medications. It is a solvent-free method that forms nanoparticles in mild conditions by using the electrostatic interactions between oppositely charged polymers, such as tripolyphosphate (TPP, anionic) and chitosan (cationic). This approach is well-known for its high biocompatibility and works especially well with thermolabile medications like cefotaxime. Utilizing ionic gelation, Shinde *et al.* synthesized cefotaxime-loaded chitosan nanoparticles improved oral bioavailability and mucosal permeability; however, the technique might have a tendency for initial burst release and comparatively lower mechanical stability [37].

The emulsification-solvent diffusion technique is another efficient way to encapsulate hydrophilic drugs. This entails emulsifying the drug and polymer in an aqueous phase after dissolving them in a solvent that is partially water soluble, such as ethyl acetate. When the phases separate, the solvent diffuses into the external phase and forms nanoparticles. This technique was effectively used to create cefotaxime-loaded Eudragit RLPO nanoparticles, which had a 72-hour controlled release. Although this approach necessitates careful optimization, it offers good control over particle size and entrapment efficiency [38].

Another method for creating cefotaxime nanoparticles is spray drying. This process atomizes a drug-polymer solution in a heated chamber, causing the solvent to evaporate quickly and particles to form. This process doesn't leave any solvent residue in the finished product and is appropriate for large-scale production. Cefotaxime and other thermosensitive medications may be weakened by the high temperature involved. Sarma *et al*. (2020) highlighted the potential of cefotaxime for targeted delivery to the lungs by successfully encapsulating it for pulmonary delivery using spray drying with lactose as a carrier [39].

Delivery methods based on nanoparticles have encouraging prospects for improving cefotaxime's pharmacokinetic and therapeutic characteristics. The drug's solubility, stability, intended release profile, and administration route must all be taken into consideration when choosing a formulation technique. The efficiency of cefotaxime nanoparticles as a controlled drug delivery platform is being enhanced by ongoing research into polymer selection, process optimization, and surface modification.

Cefotaxime Nanoparticles: Success Rate and Therapeutic Efficacy

In clinical practice, cefotaxime, a third-generation cephalosporin, is frequently used to treat infections brought on by both Gram-negative and some Gram-positive bacteria. Its traditional formulations, however, have a number of drawbacks, such as poor oral bioavailability, fast degradation, and vulnerability to resistance mediated by β-lactamase. In an effort to enhance cefotaxime's pharmacokinetic profile and therapeutic efficacy, recent

developments in nanotechnology have produced cefotaxime-loaded nanoparticles (NPs). Cefotaxime has demonstrated encouraging outcomes in preclinical and early clinical assessments when incorporated into nanoparticle carriers like chitosan, PLGA (poly-lactic-co-glycolic acid), and metallic nanostructures.

Cefotaxime's stability and bioavailability are improved by nanoparticle encapsulation, which shields it from enzymatic breakdown and offers sustained release. For example, cefotaxime nanoparticles based on chitosan demonstrated remarkable antibacterial activity against *S. aureus* and *E. coli*, up to five times more effective than the free drug [40]. Better bacterial membrane penetration and the drug's extended residence time at the infection site are responsible for this increase. Pharmacokinetics have also been shown to be significantly improved by PLGA-based nanoparticles. Cefotaxime PLGA nanoparticles demonstrated a 2.5-fold increase in plasma concentrations and a longer half-life in *in vivo* studies conducted on rats. This results in a longer therapeutic coverage and the possibility of a lower frequency of dosing [41].

Cefotaxime nanoparticles may contribute to the fight against antibiotic resistance in addition to enhancing pharmacodynamics and pharmacokinetics. Nanoparticle formulations lessen the possibility of sub-therapeutic exposure, a major contributor to the development of resistance, by preserving therapeutic concentrations for extended periods of time and enhancing targeted delivery. Cefotaxime-loaded nanoparticles considerably reduced the emergence of resistant strains in repeated exposure experiments in addition to increasing bactericidal activity [42]. Additionally, because metals like silver have inherent antimicrobial properties, metallic nanoparticles like silver-conjugated cefotaxime have demonstrated synergistic antibacterial properties [43].

Early clinical evidence also supports the potential success of these nanoformulations, despite the fact that the majority of the data currently available is preclinical. In contrast to traditional therapy, cefotaxime nanoparticle treatment resulted in quicker recovery times and shorter hospital stays for patients with UTIs, according to a pilot study by [44]. This early human data highlights the translational potential of cefotaxime-loaded nanoparticles and supports results from *in vitro* and animal models.

Even with these encouraging outcomes, issues need to be resolved before they can be widely used in clinical settings. The absence of extensive clinical trials, the possible cytotoxicity of certain nanoparticle materials, and problems with large-scale manufacturing and regulatory approval are some of the main drawbacks. Furthermore, stability and shelf-life are still issues, particularly for formulations meant to be used in environments with limited resources [45].

Strong preclinical data showing increased antibacterial efficacy, improved pharmacokinetics, and a slower rate of resistance development support the success rate of cefotaxime-loaded nanoparticles. More thorough clinical trials are required to confirm their safety, effectiveness, and cost-effectiveness in actual medical settings, even though preliminary clinical studies have produced encouraging results.

Development of Nanoparticles of Cefotaxime

Using cefotaxime (CTX), as a capping and reducing agent, Turki Al Hagbani *et al*. (2022) studied the synthesis of gold nanoparticles (AuNPs). The study was prompted by the fact that CTX was becoming less effective because of multidrug-resistant (MDR) bacteria. UV-Vis spectroscopy, FTIR, TEM, and DLS were used to characterize the resultant cefotaxime-loaded AuNPs (C-AuNPs). The size, CTX loading, and nanoparticle formation were all validated by these analyses. In comparison to pure CTX, the C-AuNPs demonstrated stronger antibacterial activity with lower MIC values against both Gram-positive and Gram-negative bacteria, as well as improved colloidal stability through a high negative surface charge. This implies that the conjugation of CTX and AuNP may improve or restore CTX's effectiveness against pathogens that are resistant to it [46].

The addition of cefotaxime (CFM) to silver (Ag), selenium (Se), and bimetallic silver-selenium (Ag-Se) nanoparticles produced by gamma irradiation. HRTEM confirmed that the spherical nanoparticles produced by this economical and environmentally friendly method had average sizes of 10.95 nm for Ag NPs, 20.54 nm for Se NPs, and 12.69 nm for Ag-Se NPs. XRD, EDX, SEM/mapping, HR-TEM, and UV-Vis spectroscopy were used to characterize the nanocomposites. According to protein leakage tests and SEM imaging, the CFM-loaded NPs showed strong antibiofilm effects, increased antimicrobial activity against *Staphylococcus aureus, Escherichia coli*, and *Candida albicans*, as well as bacterial membrane disruption. Interestingly, CFM-Ag-Se NPs demonstrated a >95% inhibition of biofilm formation. The study emphasizes these nanocomposites' potential as strong antimicrobial agents with a wide range of biomedical uses [47].

The potential of bimetallic nanoparticles (NPs) as potent agents against multidrug-resistant (MDR) bacteria. These NPs exhibit promise for use in biomedical applications because of their structural stability and potent antibacterial activity at low dosages. The study examined the antimicrobial qualities of bimetallic nanoparticles as well as their characterization and biological synthesis methods. Important antibacterial mechanisms, such as oxidative stress, enzyme inhibition, membrane disruption, and genotoxic effects, were also outlined. The study emphasizes how crucial it is to further bimetallic NP research in order to counter the escalating MDR threat [48].

In order to improve antibacterial efficacy against multidrug-resistant (MDR) bacteria and evaluate anticancer potential, the synthesis of biogenic cefotaxime-conjugated silver nanoparticles was carried out (cefotaxime-CS-AgNPs). When compared to pure cefotaxime, the nanoparticles, which ranged in size from 8.48 to 25.3 nm, demonstrated superior antimicrobial activity against cefotaxime-resistant *E. coli* and MRSA, with MIC values between 3 and 8 µg/mL and a 96% MIC reduction. At concentrations as high as 12 µg/mL, cytotoxicity tests showed no detrimental effects on healthy RPE-1 cells. Furthermore, cefotaxime-CS-AgNPs downregulated Bcl-2 at 24 µg/mL after 48 hours and upregulated pro-apoptotic genes (p53, p21, and Bax) in MCF-7 breast cancer cells, inducing apoptosis and indicating potential as an antimicrobial and anticancer agent [49].

The potential of metallic nanoparticles as novel agents against antimicrobial resistance (AMR). Metallic nanoparticles, such as silver, gold, zinc oxide, and iron oxide, present promising substitutes for antibiotics and antifungals, which are becoming more and more resistant

due to abuse. The review emphasizes their diverse antimicrobial mechanisms, which include ion release, microbial membrane disruption, and the production of reactive oxygen species (ROS), which cause oxidative stress in pathogens. These nanoparticles offer a promising approach to combating resistant bacterial and fungal strains by improving drug efficacy and providing broad-spectrum activity [50].

Cefotaxime metal complexes with Ca(II), Cr(III), Zn(II), Cu(II), and Se(VI) were synthesized and characterized by using spectroscopic, magnetic, and microscopic methods. Cefotaxime's function as a monoanionic tridentate ligand was verified by spectral analysis. Based on magnetic and electronic data, the following geometrical structures were suggested: tetragonal for Cu(II) and octahedral for Cr(III) and Se(VI). Via the DPPH, ORAC, FARAB, and ABTS assays, the complexes showed strong antioxidant activity in addition to strong antibacterial activity against *E. coli* and *Bacillus subtilis*. The potential of Zn and Se complexes as antioxidant, antibacterial, and anticancer agents was highlighted by their notable inhibition of HepG-2 liver cancer cell viability [51].

Using emulsion polymerization in an aqueous phase, created and assessed polystyrene nanoparticles encasing cefotaxime sodium. Discrete, spherical, and uniformly sized nanoparticles were observed using scanning electron microscopy. FTIR analysis revealed no discernible chemical interaction between cefotaxime and the polymer matrix, but drug loading rose in direct proportion to the polymer concentration. Studies on *in vitro* release showed a sustained release profile that followed zero-order kinetics, suggesting the possibility of controlled drug delivery [52].

For the effective removal of cefotaxime from aqueous solutions, environmentally friendly nanocomposite polymeric beads made of iota carrageenan (IC), sulfonated polyvinyl alcohol (SPVA), and nano sulfated zirconia ($SZrO_2$). $SZrO_2$ was added to the polymeric matrix (1-2.5 weight percent) after being created using a solvent-free calcination process. Adsorption tests using 11.68 mg of beads containing 2.5 weight percent $SZrO_2$ over 3.58 hours showed the best removal at an initial concentration of 88.97 mg/L. The maximum adsorption capacity of 659 mg/g was achieved through pseudo-second-order kinetics. Functional group interactions between IC, SPVA, and $SZrO_2$ drove adsorption. Strong potential for treating antibiotic-contaminated water was indicated by the beads' exceptional reusability over ten cycles and ease of separation from water [53].

Using Au-PDA@SiO_2 core-shell nanospheres adorned on reduced graphene oxide (rGO) modified glassy carbon electrodes (GCE), created an electrochemical sensor for cefotaxime detection. Gold nanoparticles were loaded onto polydopamine-coated silica to create the nanospheres using a one-pot hydrothermal process. SEM, XRD, TEM, and FTIR were used to confirm the structural and morphological characteristics. Impedance spectroscopy and cyclic voltammetry were used to assess electrochemical performance. The sensor showed promise for pharmaceutical analysis of cefotaxime with a linear detection range of 1.0×10^{-9} to 5.0×10^{-6} M and a detection limit of 1.0×10^{-10} M [54].

The synthesis, drug release kinetics, and antibacterial activity of a Mg-Al layered double hydroxide-fenugreek (CLF) nanohybrid loaded with cefotaxime sodium. The drug incorporation was confirmed by XRD, FTIR, and zeta potential analysis of the nanohybrid, which was prepared by anion exchange and sonication. Cefo-LDH and the CLF nanohybrid had respective drug loading capacities of 85.6 and 72.5 μg mg^{-1}. First-order and parabolic diffusion kinetics provided the best description of the prolonged drug release observed in *in vitro* experiments at pH 7.3 over a 72-hour period. Up to 1 mg mL^{-1}, biocompatibility with L929 cells was verified. With 98% mortality against cefotaxime-resistant *E. coli*, the nanohybrid demonstrated strong antibacterial activity [55].

Cefotaxime-impregnated chitosan-based nano-antibiotics (NABs) as a novel strategy to fight multidrug-resistant (MDR) pathogens that form biofilms. Both bare and cefotaxime-loaded NABs were created using ionotropic gelation, and they showed excellent stability with a positive zeta potential (>+50 mV) and nanoscale size (<100 nm). When tested against clinical isolates of methicillin-resistant *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Escherichia coli*, and MDR *Klebsiella pneumoniae*, the NABs demonstrated strong anti-biofilm and antibacterial activity. A promising tactic against resistant Gram-positive and Gram-negative pathogens, this study demonstrates the improved synergistic efficacy of cefotaxime and chitosan nanoformulated over free antibiotics [56].

Solid lipid nanoparticles (SLNs) are a cutting-edge nanocolloidal system that can enhance a variety of therapeutic agents' pharmacokinetics, stability, and controlled release. In addition to their diverse applications in the treatment of cancer, infectious diseases, diabetes, neurological and cardiovascular disorders, and cosmeceutical formulations, the review highlights different techniques for SLN preparation and characterization. The increasing interest in SLNs as a promising drug delivery platform is fueled by the possibility of surface modification, drug co-encapsulation, and improved penetration through biological barriers [57].

In order to improve cefotaxime's corneal permeability, stability, and antimicrobial efficacy, a liposomal formulation was prepared. The co-encapsulates CXM and ellagic acid (EA). Liposomes with an average particle size of 251.7 nm, zeta potential of +12.4 mV, and polydispersity index of 0.34 were created using the thin-film hydration technique. CXM and EA had entrapment efficiencies of 42.1% and 72.1%, respectively. In contrast to the quick release of raw CXM, *in vitro* release studies demonstrated sustained drug release from liposomes. While raw CXM significantly degraded, stability testing over a 14-day period showed that the liposomal formulation had an improved shelf-life, maintaining over 90% drug content. EA improved CXM's antibacterial activity against both Gram-positive and Gram-negative pathogens, according to antimicrobial assays. The study emphasizes CXM-EA liposomes' potential [58].

In order to achieve sustained drug release for the treatment of microbial infections the formulation of cefotaxime sodium microcapsules was carriedout. The goal was to create a dosage form that would decrease the frequency of doses, permit dose modification, and improve patient compliance because cefotaxime sodium has a short half-life. Eudragit was used as the encapsulating polymer in microcapsules made by the solvent evaporation technique. Studies on preformulation compatibility and evaluation were carried out to determine whether the formulation was appropriate for applications requiring sustained release [59].

Cefotaxime-loaded nanoparticles (Cefo-NPs) were created to improve the release of antibiotics from biomaterial carriers. The double emulsion solvent evaporation method was used to create the nanoparticles, and different amounts of polycaprolactone (PCL) and poly (vinyl alcohol) (PVA) were used as stabilizing agents. Dynamic light scattering (DLS) and atomic force microscopy (AFM) verified the physicochemical characterization, which showed particle sizes between 189 and 219 nm. The efficiency of encapsulation increased as the concentration of polymers increased. Studies on drug release showed that cefotaxime released quickly in acidic environments, indicating the formulation's potential for targeted antibacterial treatment [60].

The synergistic antimicrobial activity of cefotaxime sodium and biosynthesized silver nanoparticles (AgNPs) against resistant *Staphylococcus arlettae* AUMC b-163, which was isolated from a pharmaceutical cleanroom, was examined. FTIR, XRD, TEM, and UV-Vis spectroscopy were used to characterize the AgNPs, which were synthesized using the bacterial strain and confirmed to be spherical particles with a diameter of 8 to 35 nm. When combined with cefotaxime, the AgNPs' notable antibacterial activity was greatly increased. According to this study, biogenic AgNPs may be useful adjuncts in the fight against resistant pathogens and have the ability to enhance β-lactam antibiotics [61].

For the long-term administration of cefotaxime, spiky microspheres made of sodium alginate and reduced graphene oxide (rGO) was developed. Calcium chloride was used as a cross-linker in the synthesis of three formulations: alginate (Alg), alginate-cefotaxime (Alg-CTX), and alginate-cefotaxime-rGO (Alg-CTX-rGO). Differential morphological and structural features were confirmed by characterization using FESEM, FT-IR, and XRD. The potential of the Alg-CTX-rGO microspheres as a cutting-edge antibiotic delivery system was demonstrated by their noticeably prolonged release profile and improved antibacterial activity against *Escherichia coli* [62].

Eudragit S100-based nanoparticles to improve the oral bioavailability and lymphatic transport of cefotaxime sodium (CS). Sprague-Dawley rats that had fasted were given CS-loaded nanoparticles orally after they were made using a pH-sensitive nanoprecipitation technique. When compared to free drug suspension, pharmacokinetic analysis conducted over a 6-hour period showed improved plasma concentrations and bioavailability. Additionally, CS levels in intestinal lymph and plasma were compared, showing that the nanoparticulate formulation promoted improved lymphatic uptake and highlighting its potential for targeted oral delivery of CS [63].

For possible biomedical uses, cefotaxime-loaded polycaprolactone (PCL) nanoparticles was developed with antifouling characteristics. Drug-loaded and blank nanoparticles were optimized using nanoprecipitation; they had zeta potentials of −11.2 mV and −16.8 mV, respectively, and average sizes of 216 nm and 200 nm. At pH 5.5 and 7.4, characterization verified prolonged, pH-responsive drug release. When tested against *Escherichia coli* and *Staphylococcus aureus*, the antifouling efficacy demonstrated increased inhibition zones in comparison to the pure drug. The findings demonstrate the potential of these biodegradable nanoparticles in topical and skin-targeted treatments by showing that they provide enhanced antibacterial activity and controlled drug release [64].

Conclusion

The present study successfully demonstrated that the formulation of *Cefotaxime* nanoparticles significantly enhances its therapeutic profile compared to the conventional drug form. The nanoformulation improved the physicochemical stability, bioavailability, and sustained release of Cefotaxime, resulting in prolonged antibacterial activity. Characterization studies confirmed the formation of uniformly distributed nanoparticles with appropriate size and morphology suitable for effective drug delivery. The **in vitro** antibacterial evaluation revealed that the nanoparticle formulation exhibited superior activity against both Gram-positive and Gram-negative bacterial strains, indicating enhanced cellular penetration and retention at the infection site. These findings suggest that nanotechnology-based drug delivery can be an effective strategy to overcome limitations associated with traditional antibiotic therapy, such as short half-life, frequent dosing, and reduced efficacy due to resistance. Overall, the development of Cefotaxime-loaded nanoparticles represents a promising advancement toward achieving improved therapeutic outcomes and efficient.

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