

Targeted Nano-Encapsulated Ceftriaxone: Ligand–Receptor Interactions and Strategies to Overcome Efflux Pump-Mediated Resistance

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Abstract

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Received on 26 Feb, 2026
Accepted on 29 March, 2026
Published on 30 March, 2026

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The issue of antimicrobial resistance is a serious health problem on the international level, which makes traditional antibiotics like ceftriaxone less effective. The mechanisms that limit the accumulation of intracellular drugs and impair the therapeutic outcomes include efflux pumps, enzymatic degradation, and reduced membrane permeability. One of the promising solutions to these challenges involves nanotechnology-based drug delivery system, which entails encasing the antibiotics into nanoscale systems, which not

only stabilizes the drug, but also prevents degradation of the drug, but also allows the controlled and targeted release. Nano-encapsulation enhances conditions of ligand-receptor of ceftriaxone and bacterial targets, elevating local drug concentration, improving binding of penicillin-binding proteins, and improving residence time in the vicinity of bacterial membrane. Nanocarriers also resolve the resistance due to efflux by circumventing the traditional recognition pathways, sustained release of drugs, and co-delivery of ceftriaxone and efflux pump inhibitors. All these measures further compound the intracellular accumulation of the antibiotics, which guarantees constant exposure and overloading of the bacterial defences. Surface plasmon resonance, isothermal titration calorimetry, and fluorescence spectroscopy are experimental biophysical methods that can offer important information regarding the binding dynamics and efficacy of nano-encapsulated antibiotics, whereas molecular docking and molecular dynamics simulations are the two computational methods that present vital information on the binding dynamics and efficacy of nano-encapsulated antibiotics. The quality and performance of formulations and drug release are guaranteed by the dynamic light scattering, transmission electron microscopy and drug release analysis characterization of nanoparticles.

Keywords: Nanoparticles, Antibiotic resistance, Efflux Pump.

Introduction

The emergence of antimicrobial resistance (AMR) is one of the most severe health issues of the twenty-first century that poses a threat to the efficacy of modern medicine and

makes the problem of infectious diseases even heavier on the global level. The high rate of resistance development and spread of bacteria strains has greatly diminished the performance of most traditional antibiotics that used to be very effective in addressing bacterial infections (Alara & Alara, 2024). The World Health Organization states that every year millions of patients are infected and many of them die due to antimicrobial resistance burdened by the health care system, whereas the economic cost of treatment is tremendous. The extensive use and overuse of antibiotics in clinical care, livestock and veterinary care has increased the development of antagonistic pathogens (Dadgostar, 2019; Ashraf et al., 2025; Zahid et al., 2025; Khair et al., 2026). With the changes in the genetic mutation and horizontal gene transfer of bacteria to the antimicrobial agents, bacteria develop more advanced strategies to circumvent the impact of the antibiotics. As a result, diseases that could previously be readily treated are now taking longer to facilitate treatment, increasing doses of drugs or combination therapy, but with limited effectiveness (Khan et al., 2024). To solve the issue of antimicrobial resistance, it is necessary to devise new treatment lines that are able not only to enhance the delivery of antibiotics but also to surmount the biological processes that contribute to resistance (Baker et al., 2018).

The β -lactam antibiotics are some of the most vital categories of antibiotics used in clinical treatment and they include penicillin, cephalosporin, carbapenem, and monobactam antibiotics. Such antibiotics are popular due to their broad-spectrum effects, low toxicity and their efficacy against Gram-positive and Gram-negative bacterial pathogens. Ceftriaxone is a third-generation cephalosporin and one of the most clinically relevant β -lactam antibiotics used in the treatment of severe bacterial infections including pneumonia, meningitis, septicemia as well as urinary tract infections (Vilvanathan, 2021). The mechanism of action of Ceftriaxone is through binding to bacterial penicillin-binding proteins, thus preventing the synthesis of the cell wall and finally resulting in the death of the bacterial cell. It is also especially useful in the treatment of systemic infections due to its high stability and its long half-life. Nevertheless, its clinical application is becoming highly undermined by resistance mechanisms developed by bacteria causing a decline in its therapeutic efficacy despite its wide clinical usage. These resistant mechanisms enable the pathogens to minimize

the concentration of the drug inside the cell, alter the target of the antibiotic, or chemically inactivate the antibiotic molecule, and hence makes the traditional therapeutic methods less successful (Chatterjee & Chatterjee, 2026).

There are a number of well-known mechanisms used by bacteria to counteract the effects of antibiotics, and the mechanisms do play a major role in the clinical outcome of antibiotic treatment. The efflux pumps are one of the most notable resistance mechanisms that are responsible membrane protein complexes that transport the antibiotics out of bacterial cells actively (Blanco et al., 2016). The efflux pumps decrease the drug concentration to its target site by lowering the intracellular concentration of the antibiotic to an effective level. RND family of efflux systems thus plays a vital role in the Gram-negative bacteria that are multidrug resistant (Alenazy, 2022). The other, the most common, resistance mechanism is enzymatic degradation of antibiotics, primarily, the production of β -lactamases, which degrade the β -lactam ring structure on which the antibacterial action of these agents depends. This enzyme inactivation makes most β -lactam antibiotics useless. Other than these mechanisms, bacteria can also be subjected to target modification where the structural modifications will happen inside the antibiotic binding site i.e. penicillin-binding proteins altered (Egorov et al., 2018). These changes decrease the affinity of the antibiotics to their targets thus depleting the bactericidal activity. These resistance mechanisms are frequently observed in the same bacterial strain and hence result in multidrug resistance making it very challenging to cure an infection using traditional antibiotics only (Wilson et al., 2020).

The weaknesses of traditional antibiotic delivery methods also increase the issues of antimicrobial resistance. Conventional recipes do not sustain the best drug concentrations in the area of infection leading to subtherapeutic exposure which fosters resistance. The lack of penetration on the biological barriers and high degradation of the drugs and non-selective contravention can greatly diminish the effect of antibiotics. To address such limitations, drug delivery systems based on nanotechnology have been developed as an effective approach to improve the treatment of antibiotics (Ghosh et al., 2019; Maqbool et al., 2026). Antibiotics can be encapsulated in nanocarriers, including liposomes, polymeric nanoparticles, and lipid-based nanostructures that are able to

protect them against degradation and deliver them to the location of infection. It is also reported that these nanoscale systems enhance uptake of cells and enable these systems to release drugs in the form of control, thus sustaining the effective levels of drugs in the bacterial microenvironment (Yeh et al., 2020). Notably, the effectiveness of these systems has a strong association with the biophysical principles of the interaction of these two ligands with the receptors of the antibiotic molecule and bacterial targets. The recognition of the molecule, its binding affinity, and interaction kinetics define the degree to which a drug binds to its receptor and gets its therapeutic effect. It is thus important to maximize nano-encapsulated antibiotic systems by understanding these interactions. In this, the current review will discuss the biophysical processes involved in ligand receptor interactions in nano-encapsulated ceftriaxone and how the processes can be utilized to overcome bacterial efflux pump resistance and enhance the efficacy of antimicrobial therapy (Di Natale et al., 2020).

Table 1: *Major Factors Contributing to Antimicrobial Resistance and Strategies to Improve Ceftriaxone Efficacy*

Category	Key Mechanism/Concept	Description	Impact on Ceftriaxone Therapy	Potential Solution	References
Global Health Challenge	Antimicrobial Resistance (AMR)	The ability of microorganisms to survive and grow despite exposure to antibiotics designed to inhibit or kill them.	Leads to treatment failure, prolonged infections, and increased healthcare costs.	Development of new antibiotics and advanced drug delivery systems.	(Harms et al., 2016)
Antibiotic Class	β -lactam Antibiotics	A class of antibiotics characterized	Ceftriaxone is widely used but	Optimization of drug delivery and	(Etebu & Ariekpar, 2016)

		by a β -lactam ring that inhibits bacterial cell wall synthesis.	increasingly affected by resistance.	combination therapies.	
Antibiotic Example	Ceftriaxone	Third-generation cephalosporin with broad-spectrum antibacterial activity.	Effective against many Gram-positive and Gram-negative bacteria but susceptible to resistance.	Nano-encapsulation to enhance stability and intracellular delivery.	(Kakoullis et al., 2021)
Resistance Mechanism	Efflux Pumps	Membrane transport proteins that actively expel antibiotics from bacterial cells.	Reduces intracellular ceftriaxone concentration, lowering therapeutic efficacy.	Nanocarriers that bypass efflux systems or co-delivery of efflux inhibitors.	(Blair et al., 2022)
Resistance Mechanism	Enzymatic Degradation	Production of β -lactamases that hydrolyze the β -lactam ring of antibiotics.	Inactivates ceftriaxone before it reaches its target.	Use of β -lactamase inhibitors or protective nanocarriers.	(Bonomo, 2017)
Resistance Mechanism	Target Modification	Structural alterations in penicillin-binding proteins (PBPs).	Decreases binding affinity of ceftriaxone to bacterial	Designing targeted drug delivery systems that enhance	(Dabhi et al., 2024)

Drug Delivery Limitation	Conventional Antibiotic Delivery	targets.		ligand–receptor binding.	
		Traditional formulations often lead to poor drug distribution and rapid degradation.	Insufficient drug concentration at infection sites.	Advanced nano-based delivery platforms.	(Kalepu & Nekkanti, 2015)
		Use of nanoparticles to encapsulate antibiotics and improve targeted delivery.	Enhances drug stability, penetration, and sustained release.	Liposomes, polymeric nanoparticles, and solid lipid nanoparticles.	(Nasr et al., 2025)
Biophysical Principle	Ligand–Receptor Interaction	Molecular interactions between antibiotic molecules and bacterial target proteins.	Determines binding affinity and therapeutic effectiveness.	Surface-engineered nanoparticles to optimize binding dynamics.	(Cossar et al., 2020)

2. Ceftriaxone: Structures, Mechanism of Action and Limitations

2.1 Chemical and Structural Properties

Ceftriaxone is a third-generation cephalosporin antimicrobial agent which is a β -lactam group of antibiotics and is highly applicable in clinical practice as it has good antibacterial properties and pharmacokinetic properties. Ceftriaxone is a derivative of the cephalosporin nucleus with the four member 4-membered ring of 2-lactam combined with the six member 1,5-diol ring (Arumugham et al., 2023). The crucial

structural element that leads to the antibacterial effect of the drug is the β -lactam ring because the drug is able to interact with bacterial enzymes that make up the cell wall. The presence of structural changes in the side chains of the cephalosporin nucleus that differentiate ceftriaxone of other older generations of cephalosporins and promotes its increased resistance to various β -lactamases in addition to broader spectrum of antimicrobial activity. Certain functional group characteristics such as a methoxyimino side chain and a thiotriazinedione moiety contribute to the resistance of the drug towards enzymatic hydrolysis and enhances pharmacological characteristics (Gambo et al., 2023).

Besides its structural properties, ceftriaxone also has distinct pharmacokinetic properties which make it a very useful drug in the treatment of severe infections. The most significant of the properties is its long elimination half-life ranging between about six to nine hours in adults. The long half-life makes it possible to administer the drug once a day in most therapeutic cases, enhancing patient compliance and reducing therapy adherence. Ceftriaxone is very protein-bound in plasma and is usually bound by albumin with a rate of approximately 85-95 which has led to its long time circulation in the blood (Schleibinger et al., 2015). The drug spreads extensively all over body tissues and in body fluids such as the lungs, liver, kidneys, skin, bone, and cerebral blood. This penetration profile of different tissues allows ceftriaxone to treat a large number of systemic infections. Besides, ceftriaxone is excreted by renal and biliary routes, and the process does not necessitate any dose alteration in patients with moderate impaired renal conditions as compared to certain other cephalosporins (Haripriya & Suthindhiran, 2023).

Ceftriaxone is regarded as a broad-spectrum antibiotic since it is active against a broad spectrum of Gram-positive and Gram-negative bacteria. It works best with organisms, including *Streptococcus pneumoniae*, *Neisseria gonorrhoeae*, *Haemophilus influenzae*, as well as some of the *Enterobacteriaceae* family. Ceftriaxone is typically used to treat infections such as pneumonia, meningitis, sepsis, urinary tract infections, intra-abdominal infections and some sexually transmitted diseases due to this broad activity (Khan et al., 2017). It has been prescribed to patients all currently all over the globe since it is very effective in treating community as well as hospital acquired pathogens.

Nevertheless, even with its broad spectrum of antimicrobial activity and usefulness in clinical settings, the rising rates of antibiotic-resistant strains of bacteria have considerably restricted the effectiveness of ceftriaxone treatment in the long run (Metlay et al., 2019).

2.2. Complex Mechanism of Antibacterial Action

The action of ceftriaxone is mainly antibacterial as it suppresses the cell wall production of bacteria. The cell walls of bacteria contain a compound referred to as peptidoglycan, whose main element is a complex polymer, which gives the cell structural integrity and safeguards it against osmotic pressure. Peptidoglycan is composed of long chains of glycan cross-linked to short peptide bridges creating a rigid three dimensional network (Fisher & Mobashery, 2020). The construction and repair of this network is catalyzed by a number of enzymes called penicillin-binding proteins (PBPs). These proteins serve as transpeptidases and carboxypeptidases which attack the cross-linking reactions required to help in strengthening the bacterial cell wall. The antibacterial effect of ceftriaxone is mediated by binding them to these PBPs and preventing their enzymatic action (Dabhi et al., 2024).

Ceftriaxone simulates the natural substrate of PBPs when it gets into the bacterial cell because of the structural similarity of its 8-lactam ring with the D-alanine-D-alanine dipeptide used to compose peptidoglycans. This molecular mimicry enables ceftriaxone to covalently occupy the active site of PBPs forming a stable acyl-enzyme complex (Shlosman et al., 2023). The antibiotic is attached after which the transpeptidation process necessary to cross-link the peptidoglycan chains is blocked. Consequently, the bacterial cell wall gets feeble and structurally unstable. Owing to the fact that the cell wall is crucial in ensuring shape and integrity of the bacterial cells, loss of its production leads to the ultimate cell lysis and eventual death (Walter & Mayer, 2019).

The other factor that is significant in the antibacterial mode of action of ceftriaxone is its bactericidal property. Bactericidal antibiotics cause permanent cell damage and kill bacteria in contrast to bacteriostatic agents that only prevent bacterial growth. Ceftriaxone causes an inhibition of cell wall synthesis which leads to the activation of bacterial autolytic enzymes in addition to the degradation of the cell wall, which is already weakened (Khan et al., 2017). The result of this process is osmotic

imbalance and tearing up of the bacterial membrane which causes eventual death of bacterial cells. Ceftriaxone has a specific significance in severe infections like meningitis and septicemia, when there is a strong need to eliminate the pathogenic bacteria in the shortest possible time to avoid the complications which can endanger the life of the person (Jothi et al., 2022).

2.3 Mechanisms of Resistance to Ceftriaxone

Although ceftriaxone is effective, several bacteria species have developed resistance against the antibiotic, which determines the low activity of the drug. The activity of bacterial efflux pump systems is considered to be one of the most important resistance mechanisms (Lorusso et al., 2022; Richards et al., 1984). The efflux pumps are proteins that are transmembraneous and actively transport antibiotics and other toxic substances out of the bacterial cell. These pumps do this by decreasing the intracellular levels of the antibiotics, which does not allow the drug to reach the target site in the effective levels. Efflux systems E. coli AcrABToIC and P. aeruginosa MexABOprM E. coli AcrABToIC ET OprM Efflux systems play a key role in multidrug resistance in Gram-negative bacteria (Alenazy, 2022). These transporters can identify and expel a broad range of structurally unrelated antimicrobial agents, such as β -lactam antibiotics. The efflux pumps may be overexpressed, thus leading to a significant reduction in the susceptibility of bacteria to ceftriaxone and other antibiotics (Gaurav et al., 2023).

Production of β -lactamase enzymes is another great mechanism of resistance. These enzymes cleave the β -lactam ring in antibiotics, without which they cannot be active as antibiotics. When the β -lactam ring is broken the antibiotic molecule is structurally inactive and it is unable to bind to PBPs effectively anymore. Different types of β -lactamases such as extended-spectrum β -lactamases (ESBLs) and AmpC enzymes can be produced by bacteria and these enzymes can inactivate many cephalosporins including ceftriaxone. These enzymes are frequently encoded by genes on plasmids, and when they become part of the bacteria they may be passed on to other bacteria quickly by means of horizontal gene transfer. This has led to more and more resistance of infection by β -lactamase-producing bacteria to traditional cephalosporin antibiotics (Lin & Kück, 2022; Nayeem et al., 2024).

3. Efflux Pump Systems in Bacterial Resistance

Efflux pump systems are considered to be one of the most significant ways in which bacteria develop resistance to antimicrobial agents (figure 1). Such membrane-related transport proteins actively extricate toxic substances, such as antibiotics, out of the bacterial cell, and reduce the concentration of the drug in the cell to subtherapeutic levels. The efflux pumps are common to both Gram-positive and Gram-negative bacteria and are a cause of intrinsic and acquired antibiotic resistance (Jiang et al., 2022). Through its operational and acquired antibiotic resistance. These systems make the bacteria survive in the environment characterized by the presence of antimicrobial substances, as well as other destructive chemicals as they work as protective molecular machines. Efflux pumps may be expressed naturally in the bacterial defence system, but the activity of the efflux pump is, in most instances, increased by genetic mutations or regulation alterations resulting in overexpression (Huang et al., 2022; Afzal et al., 2025). This leads to bacteria developing the ability to withstand several groups of antibiotics at the same time, a process better known as multidrug resistance. The growing efflux pump-mediated resistance has become a major problem in contemporary medicine, especially in the handling of the infections with opportunistic pathogens and nosocomial strains of bacteria (Zhang et al., 2024).

A number of families of efflux pumps have been recognized in bacteria and each of them is characterized by specific structural and functional peculiarities. Some of the most famous ones are named ATP-binding cassette (ABC) transporters, which utilize the energy produced by the ATP hydrolysis to move substrates across the cell membranes. These transporters have transmembrane domains which define the substrate transport pathway and nucleotide binding domains which bind and hydrolyze ATP (AL-Lami et al., 2022). The ABC transporters are also very essential in the exportation of various molecules, such as antibiotics, toxins and other metabolic products. Other significant families of efflux pumps include the Major Facilitator Superfamily (MFS) which is one of the largest families of membrane transport proteins present in bacteria. In contrast to the ABC transporters, MFS pumps do not typically use the ATP hydrolysis, but rather the proton motive force to provide the transport of the substrates. These transporters operate by proton drug antiport where flow of protons across the membrane offer

energy needed to drive out antibiotics out of the cell. The structurally diverse compounds transported by MFS transporters help to create multidrug resistance in Gram-positive and Gram-negative bacteria (Huang et al., 2022).

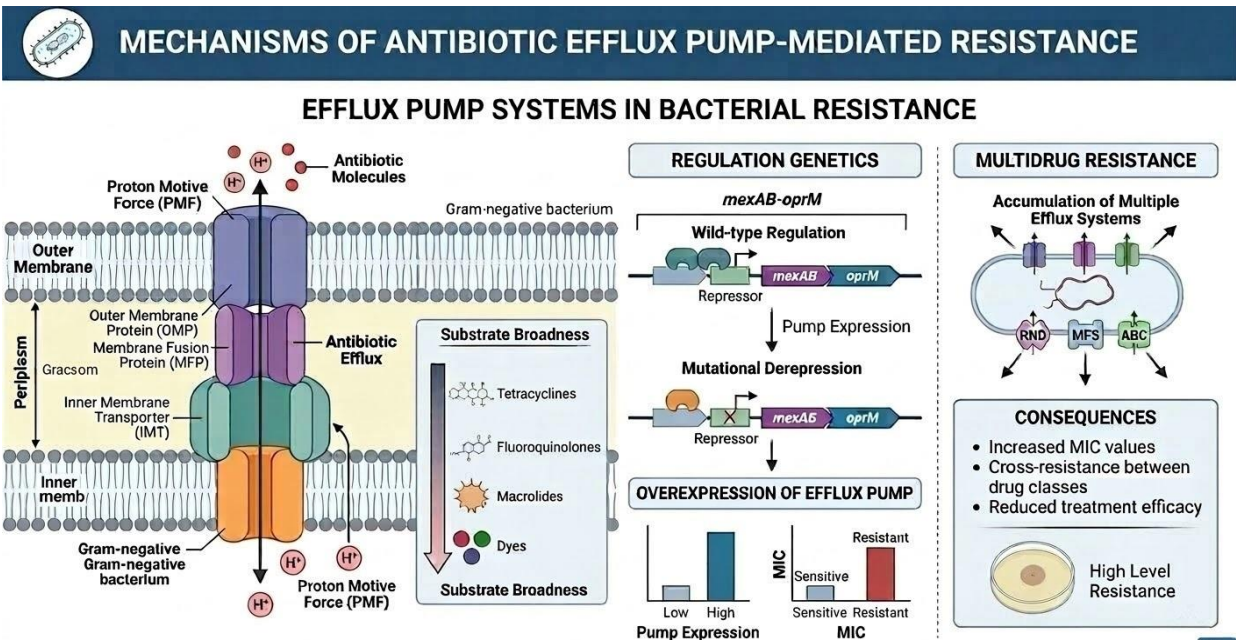


Figure 1: Efflux Pump Systems in Bacterial Resistance

Antibiotic resistance is particularly significant in Gram-negative bacteria where the Resistance Nodulation Division (RND) family of efflux pumps have been shown to be relevant. RND transporters are normally structured into tripartite complexes that traverse the inner membrane, periplasmic space and outer membrane of the bacterial cell envelope (Agreles et al., 2025; Kavanaugh et al., 2024). Such a complicated arrangement enables them to effectively release antibiotics without having to build up the drug in the cell into the outside environment; the drug is released straight out of the cytoplasm or periplasm. These pumps are very productive and can carry a large variety of antimicrobials such as 2-lactams, tetracyclines, fluoroquinolones and chloramphenicol. Due to their capacity to eliminate several drugs at the same time, RND pumps have been attributed to be a significant source of multidrug resistance of clinically significant pathogens, including *Escherichia coli* and *Pseudomonas aeruginosa* (Li et al., 2023). The other minor but important group of efflux pumps is the Small Multidrug Resistance (SMR) transporters. These are comparatively small membrane proteins, which play the

role of proton-dependent antiporters. Though SMR pumps are simpler in structure as compared to other efflux systems, it can expel various toxic compounds such as disinfectants and some antibiotics. Their existence adds to the level of background resistance which is witnessed in most bacteria (Sreekantan et al., 2022).

Various biophysical processes control the functioning of efflux pumps facilitating the identification and association, as well as transportation of antibiotic molecules. Energy-dependent transport can be regarded as one of the most important facets of the efflux pump activity. In the case of pumps of ABC family, the energy to alter the conformation of the transporter and propel substrate movement across the membrane is supplied by ATP hydrolysis (Brindangnanam et al., 2022). Other efflux systems like MFS, RND and SMR, on the other hand, are based mostly on the proton motive force provided by electrochemical gradients on the bacterial membrane. This gradient provides a source of energy to be used in powering the antiport mechanism to exchange the drug molecules with protons and thus expel antibiotics. The effective utilization of cellular energy makes bacteria have a low concentration level of antibiotics in their intracellular environment despite high levels of antibiotics that are applied to them externally (Ahmad et al., 2024).

The other key part of the efflux pump functioning is the capacity to recognize and affinity to various substrates. Efflux pumps have special binding pockets that are capable of holding a wide variety of structurally unrelated compounds. This extensive substrate specificity has been greatly attributed to the flexibility and dynamism of the binding sites in the transporter proteins (Gaurav et al., 2023). Hydrophobic, electrostatic, and hydrogen bonding play a role in the recognition of antibiotics molecules and their further binding to the pump structure. After the drug molecule is bound to the transporter, the protein changes its structure allowing the substrate to cross the membrane. These changes in conformation comprise a cyclic mechanism called the transport cycle where the pump switches between the various structural variations to trap, transport and release the substrate. This synchronized process of binding substrate, conformational change and drug release in this way guarantees the constant elimination of antibiotics in the bacterial cell (Lin et al., 2025).

The efflux pump activity has significant clinical implications on antibiotic therapy. Through vigorous exportation of antibiotics, efflux pumps have an enormous impact in lowering the concentration of the drug in the intracellular environment, making the drug fail to reach its intended molecular target at effective levels (Avakh et al., 2023). Consequently, β -lactams, fluoroquinolones, tetracyclines, and macrolides are the antibiotics whose therapeutic effectiveness might be lost. Not only does the decrease in intracellular drug concentration cause an already failed treatment but also encourages the survival of partially resistant bacterial populations. These surviving bacteria can further develop more mutations or gain resistance genes by horizontal gene transfer and they are then able to grow more resistant to antimicrobial agents. The process over the years leads to the development and dissemination of multidrug-resistant strains of bacteria that are so hard to cure under the traditional antibiotic treatment (Haider et al., 2023).

4. Nanotechnology in Antibiotic Delivery

4.1. Laws of Nano- Encapsulation

Nanotechnology has become a revolution in contemporary drug delivery, especially in antimicrobial therapy. The conventional antibiotic formulations are usually characterized by a few shortcomings that include lack of stability, rapid degradation, non-selective dispensation, as well as inadequate concentration of the drug on the infection location. Such disadvantages have the potential to decrease treatment efficiency, and they can lead to the emergence of antimicrobial resistance (Wilkins et al., 2024). Nano-encapsulation has emerged as a bright solution to all these problems by loading antibiotics into nanofiled carriers. During the nano-encapsulation process, the drugs are enclosed, adsorbed, or chemically fixed on nanoparticles whose dimensions tend to be between 1 and 100 nanometers. These nanocarriers are designed to act as protective vehicles that deliver antibiotics via the biological environment without damaging their chemical stability and pharmacological activity (Kumar & Dutta, 2025).

Encapsulation of antibiotics into nanoscale carriers has been defined as one of the major applications of nano-encapsulation. The antibiotics included in this process include nanoparticles of lipids, polymers, or inorganic materials. The encapsulated drug can be well protected within the nanoparticle matrix or core until they get the intended

point of action. This is due to its smaller size (nanoscale) that enables the antibiotic to move around the body and to ensure that it is not degraded prematurely before reaching its target location (Taheri et al., 2024). Also, targeted nanoparticles can be designed with an ideal physical and chemical characteristics like size, charge and surface alterations to optimize drug loading and delivery performance. Consequently, nano-encapsulation can enhance the pharmacokinetic profile of antibiotics to a great extent (Ahmadi-Nouraldin et al., 2024; Eltaib, 2025).

Degradation protection is another significant concept of nano-encapsulation. The antibiotics used as traditional preparation can be rapidly degraded by enzymes, hydrolysis, or adverse physiological conditions like excessively high or low PH. As an illustration, some of the enzymes in bacteria can neutralize the antibiotics before they can reach the intended target. Nanoparticles encapsulate the antibiotic molecules and offer a protective layer that keeps these degrading factors off the antibiotic molecules (Feng et al., 2024; Shahid et al., 2023). This defense mechanism maintains structural integrity and biological activity of the drug in the blood stream and in the infected tissues. Nano-encapsulation helps to avoid the premature degradation of the drug, thus keeping a larger percentage of the drug administered intact to use as an antibacterial agent (Hallan et al., 2025).

The other important characteristic of nano-encapsulation systems is controlled and targeted release of drugs. Nanocarriers can also be programmed to deliver the compounded antibiotic slowly over a certain time keeping therapeutic concentrations of drugs in the site of infection. Controlled release eliminates the rapid changes in the drug levels and eliminates the need of having frequent doses (Nazir et al., 2022). Also, nanoparticles may be targeted (ligands on their surfaces, or on their cores) or modified to target infected tissues or respond directly to bacterial cells. This localized treatment improves the effectiveness of the antibiotics concentration at the site of the infection as well as reduces exposure to normal tissues. Nano-encapsulation will, therefore, enhance the efficacy of treatment and minimize systemic side effects of conventional antibiotic therapy (Abdelkawi et al., 2023; Song et al., 2023).

4.2 Nanocarrier Technologies of Ceftriaxone

There are a number of nanocarriers explored in the delivery of ceftriaxone and other antibiotics. One of the most extensively studied systems is one of the liposomes. Liposomes are spherical vesicles made of phospholipid bi-layers, more or less like biological membranes. They have a distinctive structure that enables them to entrap hydrophilic and hydrophobic drugs. By including ceftriaxone in liposomal preparation, the phospholipid layer prevents the breakdown of the antibiotic and also increases its contact with bacterial membranes. Liposomes are very biocompatible and have been extensively exploited in pharmaceutical preparations because they enhance the stability and biodistribution of drugs (Panthi et al., 2025; Teymouri et al., 2025).

Another type of nanoparticles that is significant in the delivery of antibiotics is polymeric nanoparticles. Such nanoparticles are mainly made of biodegradable polymers like poly (lactic-co-glycolic acid) (PLGA) or natural polymers like chitosan. The reason why PLA nanoparticles are gaining a lot of popularity is due to the fact that the nanoparticles are biodegradable in the body by hydrolysis which enables the encapsulated drug to be released over a long period of time (Kuperkar et al., 2024). Chitosan nanoparticles have other benefits because it is a natural product, biodegradable, and carries a favorable surface charge. Chitosan nanoparticles attract to negatively charged cell membranes of bacteria and the antibiotic is absorbed into the bacteria cell which enhances the effectiveness of antibiotics by means of the positively charged surface of chitosan nanoparticles (Modi et al., 2023).

Nanoparticles of solid lipid are also being seen with a growing level of interest as efficient vectors of delivery of antibiotics. Such nanoparticles are solid lipid matrices, which are stable at physiological temperatures. It is possible to incorporate antibiotic molecules in the lipid core and release it over time as the lipid matrix breaks down. Lipid nanoparticles made of solid lipids have the benefits of liposomes and polymeric nanoparticles since they offer high drug stability, controlled release, and high biocompatibility. Their lipid composition allows to interact with biological membranes successfully, improving the penetration of drugs into infected tissues (Arabestani et al., 2024; Madkhali, 2022).

Another emerging technology associated with antibiotics delivery is metallic nanoparticles, like ceftriaxone. Nanoparticles constructed of gold or silver metals have special physicochemical properties which render them desirable in biomedical applications. Metallic nanoparticles in certain instances have inherent antimicrobial properties besides acting as drug carriers. Combining antibiotics with metallic nanoparticles, the resulting system can be more effective in antibacterial activities in a variety of ways, such as bacterial membrane disruption, reactive oxygen species creation, and better infiltration of bacteria by the drug. This combative activity can assist in addressing some form of resistance (Pasparakis, 2022).

4.3. Benefits of Nano-Encapsulation

Nano-encapsulation has a number of benefits that enhances the therapeutic efficacy of antibiotics to a large extent. Among the greatest advantages is the increase in stability. Confinement of antibiotics into nanoparticles avoids breakdown of the chemical, enzymatic and environmental stress. This protects the drug to have a longer half life and being in an active form of its biological activity will be more likely to reach the infection site (Kumar & Dutta, 2025; Fatima et al., 2026).

Better cellular invasion is also a major benefit of nanoparticle based drug delivery systems. Nanoparticles can more easily traverse biological barriers and are accumulated in the infected tissues as compared to standard drug preparations because of their small size and adaptable surface characteristics. This increased penetration will allow antibiotics to infiltrate intracellular pathogens or bacteria found within tissues that are deep-seated (Waheed et al., 2022).

Nano-encapsulation is also an advantageous method of delivering drugs into specific areas. Nanocarriers may be functionalized with certain ligands which identify bacterial cells receptors or tissue receptors in an infected tissue. This ability to target enables antibiotics to penetrate the location of infection maximizing treatment response and reducing the harm to normal cells (Kumar & Dutta, 2025).

5. Ligand–Receptor Dynamics in Nano-Encapsulated Ceftriaxone

5.1 Nanoparticle-Based Enhanced Drug Targeting

Drug delivery systems based on nanoparticles have enhanced the targeting efficacy of antibiotics like ceftriaxone through the promotion of ligandreceptor interaction in the

infected location. With traditional antibiotic therapy the drug molecules are dispersed all over the body in a more or less non-specific way, and this usually leads to under-optimal concentrations of the drug at the infected tissue. Such indiscriminate distribution decreases treatment effectiveness and can be a cause of antibiotic resistance. One of the potential solutions is nano-encapsulation as it has been found possible to deliver antibiotics specifically to the target by attaching certain ligands to the surfaces of nanoparticles. Such ligands are able to identify and bind to receptors on the bacterial cell or infected tissue hence targeting the nanocarrier to the target site of action (Alburyhi et al., 2023; Marzaman et al., 2023).

Surface modification with targeting ligands is one of such critical strategies that enhance nanoparticle-mediated drug delivery specificity. The combination of antibodies, peptides, carbohydrates, or other biomolecules that have the potential to selectively bind to bacterial surface receptors may be targeted. The attachment of such ligands to the surface (figure 2) of the nanoparticles that contain ceftriaxone facilitates bacterial cell recognition based on the interaction of the ligand-receptor (de Gomes Teixeira, 2022). These interactions cause the nanoparticles to be directed to the bacterial membranes and enhance the chances of the antibiotic being taken to the pathogen. This focal treatment minimizes the extraction of drug molecules in the blood capillaries and increases the antibiotic concentration in the infection area (Theivendren et al., 2025). The next significant benefit of nanoparticle-based enhancement of targeting is the capability to elevate the concentration of drug in the area of infected tissues. Alterations of the vascular permeability and tissue microenvironment allow nanocarriers to be concentrated in inflamed or infected foci. When nanoparticles arrive at the site of infection they can deliver ceftriaxone slowly so that the antibiotic stays at a low concentration around bacterial cells. This localized concentration of drugs enhances the likelihood of the effective interaction of ligands/receptors between ceftriaxone and bacterial target proteins. Consequently, the antibiotic is able to perform the antibacterial effect more effectively and at the same time reduce interference with normal tissues (Qin et al., 2023).

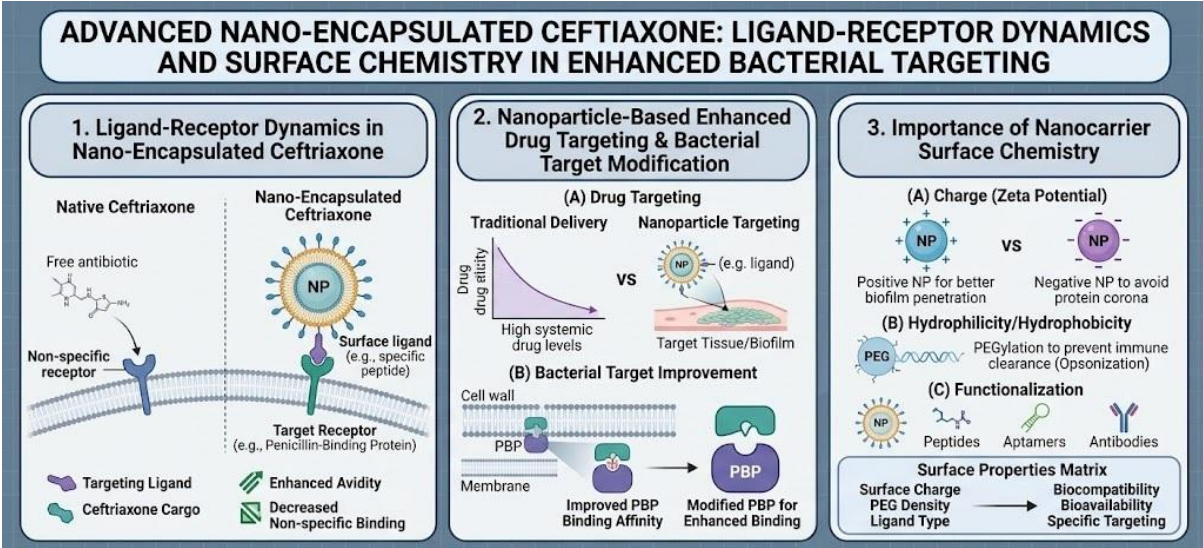


Figure 2: Ligand-Receptor Dynamics in Nano-Encapsulated Ceftriaxone

5.2. Optimization of Bacterial Targets for Enhanced Protein Binding

The binding effectiveness of ceftriaxone to its bacteria targets can also be increased by nano-encapsulation of ceftriaxone. The main antigens of the β -lactam antibiotics are penicillin-binding proteins (PBPs) which are vital enzymes in the synthesis of the bacterial cell wall. In traditional drug preparations, ceftriaxone molecules do not necessarily penetrate into PBPs because of obstacles like bacterial membranes, efflux pumps or enzymatic degradation. The delivery systems based on nanoparticles will be able to overcome these barriers by enabling the better access of antibiotic to its molecular targets (MISHRA, 2025).

The possibility of interacting with bacterial cell surfaces closely is what improves the access of PBPs. Nanocarriers are more effective in targeting bacterial membranes compared to the free drug molecules because of their small size (nanoscale) and the ability to tune the surface properties. As soon as the nanoparticles enter the close range of the bacterial cells, ceftriaxone may be discharged in the immediate surroundings of PBPs, and the chances of effective drug-target interaction are more likely to occur. This increases its accessibility enabling the antibiotic to bind more effectively to PBPs and block any transpeptidation reactions needed to produce cell walls (Osman et al., 2022). The other significant parameter that has an effect in ligand-receptor interaction is the residence time of the antibiotic in the proximity of the bacterial membrane. Molecules

of the drug might in the traditional formulations diffuse off quickly out of the site of the infection, shortening the time spent in interaction with bacterial targets. However, nano-encapsulated ceftriaxone can be kept localized around bacterial membranes because it has a longer retention time at the nanocarrier because of prolonged release (Faghihkhorsani et al., 2023). This lengthens the residence time of the antibiotic to provide increased time of contact with PBPs, which results in an increase in binding affinity and better antibacterial activity. The long length of stay of the drug around the bacterial surface also raises the chances of overcoming mechanisms of resistance like the efflux pump activity which normally demands speedy elimination of the antibiotic out of the cell (Martins et al., 2022).

5.3 Importance of Nanocarrier Surface Chemistry

Surface chemistry of nanocarriers is important to show how it will interact with bacterial cells and their capacity to bind ligand with receptor. The surface charge of the nanoparticles is one of the most crucial aspects that affect such interactions. The cell membranes of bacteria tend to be protected with negativity, which is attributed to the occurrence of phospholipids, lipopolysaccharides, and other components that are anionic. These negatively charged bacterial membranes can react electrostatically with nanoparticles bearing positively charged surfaces and therefore ensure a close contact between the nanocarrier and the bacterial cell. This electrostatic force adds to the delivery of ceftriaxone to the bacterial surface and adds to the effectiveness of drug-target interactions (Balog et al., 2024).

Besides the interaction of charges, another significant way of enhancing receptor targeting of nanocarriers is the functionalization of the ligand. Functionalization is an enhancement technique that can be used to apply certain ligands or recognition molecules to the nanoparticle surface in order to allow it to selectively bind to bacterial receptors or cell surface structures (Bhattacharjee & Prasad, 2023). These ligands can be antibodies that identify bacterial antigens, peptides that bind to membrane proteins or other biomolecules that can identify selective molecular recognition. Functionally loaded nanoparticles When nanoparticles are functionalized with such ligands, they can actively differentiate bacterial cells and bind them on the surface via ligand-receptor interactions.

Optimized surface charge and ligand functionalization leads to the targeting of bacterial pathogens in nanoparticles with a high degree of efficiency. When the nanocarrier attaches itself to the bacterial cell surface, the entrapment ceftriaxone can be discharged directly in the region where the PBPs are found so that the cell wall synthesis can be inhibited efficiently. This is a specific strategy that enhances antibacterial efficacy, as well as minimizes the chances of off-target and systemic toxicity. On the whole, the dynamics between ligands and receptors that may take place in the nano-encapsulation of ceftriaxone delivery are indicative of the significance of designing nanoparticles to enhance antibiotic functionality and circumvent bacterial resistance strategies (Wang et al., 2023).

6. Mechanisms by Which Nanocarriers Overcome Efflux Pump Resistance

6.1 Recognition Approval

One of the most significant mechanisms of bacteria resistance to antibiotics therapy is efflux pumps. Such membrane proteins actively expel antibiotics out of the bacterial cell and hence lower the intracellular concentrations of the drug and does not expose the antibiotic to its target site. The pumps usually recognize and quickly reject standard antibiotic molecules, which result in a decrease in the efficacy of treatment (Huang et al., 2022). Drug delivery systems based on nanocarriers offer an attractive way to circumvent this efflux recognition mechanism. Once antibiotics like ceftriaxone are bound to nanoparticles, the drug molecules are covered by the nanoparticles so that the first contact is not exposed to efflux pump proteins when they first encounter the bacterial cell (Gaurav et al., 2023).

Nanoparticles may invade the bacterial cell via other mechanisms other than the one that is followed by the free antibiotic molecules. Tunable surface properties and nanoscale size of nanocarriers enable nanocarriers to engage with bacterial membranes and lead to increased penetration of the nanocarrier into the cell envelope. Under certain circumstances, the nanoparticles can also merge with bacterial membranes or cause local perturbations that enable the drug that was encapsulated to gain access to the bacterial cytoplasm (Modi et al., 2023). Since the antibiotic is entrap within the nanocarrier at the earlier stages of cellular ingestion, efflux pumps might not be able to detect and shed out the drug successfully. After being incorporated into the bacterial

setting, the nanoparticle progressively releases ceftriaxone that will engage the molecular targets of the antibiotic prior to its elimination by efflux apparatus. This efflux recognition avoidance capability goes a long way in increasing intracellular concentration of antibiotics and their antibacterial effect (Modi et al., 2023).

6.2 Sustained Drug Release

Sustained drug release is another significant process through which nanocarrier can evade efflux pump resistance. The classical antibiotic preparations are usually used to produce large doses of the drug within a limited duration of time, and this drug is then quickly excreted or effluxed away. Such variation can lower the overall efficacy of the antibiotic because bacteria can survive in cases when the drug concentration is below the minimum inhibitory concentration. Drug delivery systems based on nanoparticles overcome this drawback and have controlled and sustained release of the encapsulated antibiotic (Baryakova et al., 2023).

In cases where ceftriaxone is loaded into nanoparticles the drug is released slowly throughout a prolonged time period as the nanocarrier matrix breaks down or diffuses into biological conditions. This slow release provides the constant exposure of the bacterial cells to therapeutic quantities of the antibiotic. Although efflux pumps may eliminate a certain fraction of the drug in the bacterial cytoplasm, the continuous release of extra antibiotic molecules by the nanoparticle keeps the bacterial cell intracellular concentration high enough to prevent bacterial growth. The efficient efflux pumps may be overloaded with continuous exposure to antibiotics, which decreases their efficiency and lets the antibiotic exercise its bactericidal effect more effectively. Consequently, prolonged drug delivery does not only enhance the effects of antibacterial action, but also decreases the chances of resistance development (Huang et al., 2022).

6.3. Efflux Pump Inhibition Strategies in Oil Spill Remediation

Besides avoiding efflux recognition and ensuring a prolonged release of the drug, nanocarriers may also be created to specifically block the operation of the efflux pumps. A potential opportunity is co-delivery of efflux pump inhibitors with the antibiotics like ceftriaxone in the same nanoparticle system. The efflux pump inhibitors are substances that have the ability to inhibit the functions of the membrane transport proteins that

mediate the extrusion of antibiotics. These pumps can be blocked to raise the concentration of the antibiotic, which is in the cell, to a great degree (Devi Thillai et al., 2025).

Nanocarriers are the best medium to deliver the antibiotic as well as the efflux inhibitor into the bacterial cell. Upon landing the nanoparticle on the location of the infection, both parts are released near the bacterial membrane. The first effect of the inhibitor is to inhibit the action of efflux pumps, which decreases the expulsive capability of bacteria against the antibiotic. Later on, the release of ceftriaxone occurs, and it can be concentrated in the bacterial cytoplasm at higher levels. This synergistic mechanism increases the antibacterial activity of the drug and reinvigorates the action of the antibiotics otherwise ineffective against the resistant strains of bacteria. Combination of efflux pump inhibitors with nano-encapsulated antibiotics is thus a promising approach to surmount multidrug resistance as well as enhance the treatment results of antimicrobial therapies (Ma et al., 2022).

Table 2: *Nanocarrier Strategies for Overcoming Efflux Pump Resistance in Antibiotic Therapy*

Mechanism	Nanocarrier Strategy	Description	Effect on Efflux Pump Activity	Impact on Ceftriaxone Efficacy	Reference
Efflux Recognition Avoidance	Nano-encapsulation	Antibiotics enclosed in nanoparticles to prevent direct recognition by efflux pumps.	Reduces immediate drug expulsion from bacterial cells.	Increase intracellular drug availability.	(Modi et al., 2023)
Membrane Interaction	Lipid-based nanoparticles	Lipid nanocarriers interact with bacterial membranes	Bypasses conventional drug transport pathways.	Enhances ceftriaxone penetration.	(Wang et al., 2023)

		and facilitate drug entry.			
Alternative Cellular Entry	Polymeric nanoparticles	Nanoparticles enter bacterial cells through membrane interactions or diffusion pathways.	Efflux pumps may fail to detect encapsulated drug molecules.	Improves intracellular antibiotic concentration.	(Modi et al., 2023)
Sustained Drug Release	Controlled release nanocarriers	Nanoparticles gradually release the antibiotic over time.	Continuous drug exposure overwhelms efflux pump capacity.	Maintains therapeutic drug levels.	(Amarnani et al., 2023)
Targeted Drug Delivery	Surface-modified nanoparticles	Functionalized nanoparticles accumulate at infection sites.	Increases local drug concentration near bacteria.	Enhances drug–target interaction.	(Osman et al., 2022)
Efflux Pump Inhibition	Co-delivery systems	Nanocarriers deliver both antibiotics and efflux pump inhibitors simultaneously.	Direct inhibition of efflux pump activity.	Restores antibiotic sensitivity.	(Zhang et al., 2024)
Membrane Disruption	Metallic nanoparticles	Metallic nanocarriers disrupt bacterial membrane integrity.	Impairs efflux pump function.	Improves antibiotic uptake.	(Amarnani et al., 2023)
Electrostatic	Positively	Nanoparticles	Facilitates	Enhances	(Balog et

Interaction	charged nanoparticles	interact electrostatically with negatively charged bacterial membranes.	nanoparticle attachment to bacteria.	ceftriaxone delivery.	al., 2024)
Increased Residence Time	Nanoparticle adhesion	Nanocarriers remain longer near bacterial surfaces.	Sustains antibiotic exposure despite efflux activity.	Strengthens bactericidal action.	(Modi et al., 2023)
Combination Therapy	Multifunctional nanoparticles	Nanocarriers incorporate multiple therapeutic agents.	Targets multiple resistance mechanisms simultaneously.	Improves treatment effectiveness.	(Mir et al., 2022)

7. Experimental and Computational Methods

7.1 Biophysical Techniques

Biophysical methods are significant in determining the interaction of antibiotics with the biological targets especially in the research on nano-encapsulated drug systems. Such methods enable scientists to study the ligand-receptor interactions, binding kinetics and thermodynamic constants which define the efficacy of interest antibiotics like ceftriaxone. Surface plasmon resonance (SPR) is one of the most popular methods of studying the interactions between molecules (Paramanick et al., 2025). SPR is an optical technique which is very sensitive and quantifies the binding interactions among the molecules in real time without the requirement of labelling. Ceftriaxone and other antibiotic interactions with bacterial target proteins, including penicillin-binding proteins (PBPs), can be studied with the help of SPR in antibiotic studies (Figure 3). SPR is useful in determining the affinity of binding, association and dissociation rates by measuring changes in the refractive index as a function of distance away the sensor surface. This

data assists the researcher to learn the strength with which the antibiotic attaches itself to its target and the duration of interaction (Hiep et al., 2024).

Isothermal titration calorimetry (ITC) is another significant biophysical technique and is applied in the determination of thermodynamics of molecular interactions. ITC measures the binding enthalpy, entropy and equilibrium constants through direct measurement of the amount of heat released or absorbed when a ligand binds to a receptor. ITC could be useful in the study of antibiotics, to give in-depth information about the energetic behavior of the ceftriaxone-bacterial proteins interaction. Knowledge on these thermodynamic properties will help design drugs in the most efficient way and enhance the efficiency of nano-encapsulated antibiotic systems (Bastos et al., 2023).

The other potent method that is usually applied to analyze interactions between molecules and unravel structural changes in biological systems is the fluorescence spectroscopy. This technique is based on the fact that emitted light by fluorescent molecules following the excitation of these molecules by a certain wavelength. Influences of the protein structure can be monitored using fluorescence-based methods, the process of ligand binding can be detected, and the uptake of drugs by bacterial cells can be assessed with the help of fluorescence-based techniques. Frequently, the use of fluorescence spectroscopy in nanoparticles studies is to trace the movement and location of drug-containing nanoparticles in the biological system. The method allows one to obtain useful data regarding the efficiency of nano-encapsulated ceftriaxone in its interaction with bacterial targets and cellular penetration of microbes (Pandey & Pandey, 2025).

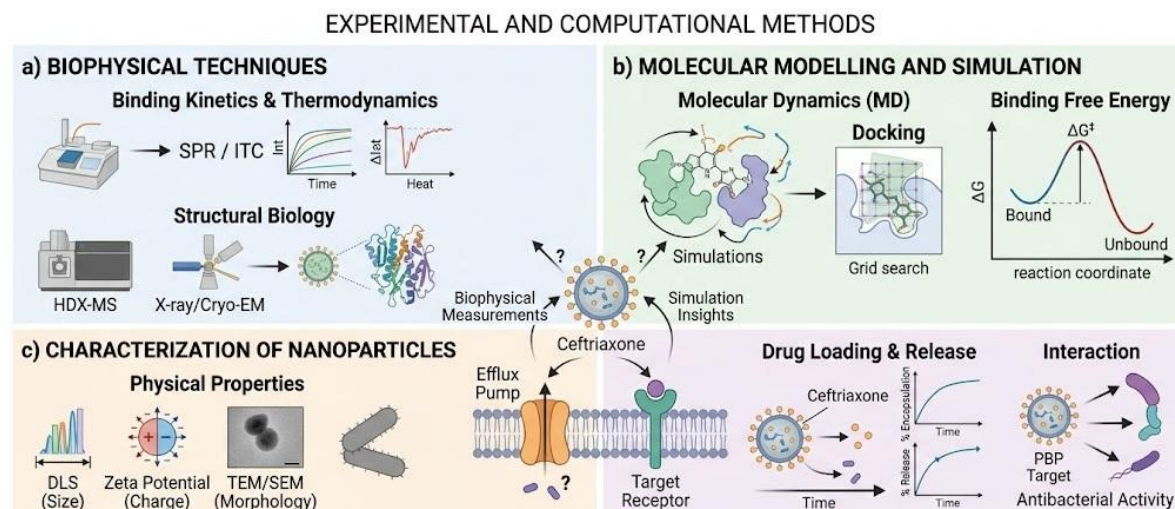


Figure 3: Experimental and Computational Methods.

7.2 Molecular Modelling and Simulation

Besides experimental methods, computational methods have gained more significance in examining antibiotic interactions on the molecular level. The use of molecular modelling and simulation enables scientists to forecast and visualize drug-biological interactions through computerised modelling and simulation. Molecular docking is one technique that is widely used and it predicts the preferred binding orientation of the drug molecule on interaction with a given receptor. Molecular docking may be applied to studies that deal with ceftriaxone to understand the binding process of the antibiotic to penicillin-binding proteins and other bacteria targets. Docking studies aid in the identification of the main amino acid residues to participate in the binding process and approximate the strength of the interaction. This fact can be useful in the study of the molecular principle of antibiotic action and the development of more efficient drug delivery platforms (Lv et al., 2022).

Molecular dynamics simulation is another method that is important in computation. Whereas molecular docking gives a picture of the drug-receptor interactions as it is, molecular dynamics simulations is the picture of the interaction as it moves with time through the movements of atoms and molecules. Such simulations enable the researcher to take a look at the interaction between antibiotic molecules and their targets in a realistic biologic environment. Molecular dynamics simulations will be able to provide the insights on the conformational change in proteins, assess the

stability of ligand receptor complexes, and give the pointers to the mechanism of drug binding and release. The interactions between nanoparticles, antibiotics and bacterial membranes can also be studied with the help of molecular dynamics simulations in the framework of nanotechnology-based drug delivery (Xie & Zhu, 2025).

7.3. Characterization of Nanoparticles

The effective and safety of nano-encapsulated antibiotic systems require accurate characterization of nanoparticles. There are various analytical methods that are usually applied to measure the physical and chemical characteristics of nano particles. A popular technique in the measurement of size distribution and stability of nanoparticles in suspension is the dynamic light scattering (DLS). This method examines the variations in the light scattering induced by the Brownian movement of particles enabling the researchers to ascertain the mean size of the particles and the polydispersity index. These parameters are of significance since the size of nanoparticles determines the uptake into cells, the behavior of drug release, and the overall treatment outcome (Verma & Pandey, 2025).

Another significant method of characterizing nanoparticles is transmission electron microscopy (TEM). TEM can be used to give images of high quality that indicates morphology, shape, and structural features of nanoparticles at the nanoscale level. With the help of TEM, researchers will have the opportunity to see directly the size and structural integrity of nanocarriers utilized in the delivery of ceftriaxone. The information is critical in ensuring the successful synthesis of nanoparticles and uniform formulation (Tewabe et al., 2021).

Besides structural characterization, assessment of drug loading capacity and release behaviour is also vital in the drug delivery systems of nanoparticles. Drug loading analysis is used to identify the quantity of antibiotic that is properly loaded into the nanoparticle matrix. This parameter has a direct effect on the therapeutic dose and efficiency of the nanocarrier system in general. Drug release experiments are done to determine the release of the antibiotic out of the nanoparticle as time passes under physiological conditions. The desired attributes of controlled and sustained release include the profiles that ensure the effective concentration of the drug at the site of infection and decreases the number of drug doses. When combined, the techniques of

characterization give complete information about the design, functionality, and performance of nanoparticle-based antibiotic delivery systems (Drusano, 2004).

Conclusion

The increasing problem of antimicrobial resistance has led to the emergence of a pressing necessity to develop new measures to enhance the effectiveness of the available antibiotics including ceftriaxone. Traditional formulations are becoming more restricted due to bacterial resistance mechanisms such as efflux pumps, enzymatic degradation and decreasing membrane permeability, which markedly lower the level of intracellular drugs and hamper therapeutic results. The drug delivery systems based on nanotechnology provide a viable option as it will overcome these problems by entrapping the antibiotics in nanoscale carriers. Nano-encapsulation provides better drug stability, preservation of antibiotics, and controlled and targeted delivery of drugs to maintain prolonged therapeutic levels at the point of infection.

The dynamics of ligand-receptor are central in the increased efficacy of ceftriaxone nano-encapsulated. Bacterial targeting, enhancement of local drug concentration, and the ability of nanoparticles to interact more extensively with penicillin-binding proteins are improved by surface functionalization of nanoparticles with ligands that are specific. Nanocarriers are further optimised by the surface chemistry of the nanocarrier such as charge and ligand composition, which enhances drug-membrane interactions, to increase intracellular delivery and residence-time below bacterial targets. All of these properties augment the chances of effective drug-target interactions, despite resistance mechanisms like efflux pumps.

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