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Antibiotic Drug Delivery System for the Intracellular Targeting of Bacterial Pathogen

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Abstract: *Treatment of intracellular infections remains a serious pharmaceutical issue even with the introduction of a significant number of novel medicines. These specialized frequently have sub therapeutic antibiotic concentrations, necessitating the frequent administration of large antibiotic dosages. Not only is this expensive, but it could also have more systemic or localized adverse effects. Treatment for intracellular bacterial diseases is challenging due to the resistance of commonly used antimicrobial drugs such as macrolides, aminoglycosides, β-lactamases, and fluoroquinolones to enter, accumulate, or stay inside mammalian cells. The growing issue of antibiotic resistance makes treating illnesses brought on by these drugs increasingly difficult. Targeted drug delivery into the cell compartment that is the most vulnerable to effects of the appropriate drug is a difficult issue, and a proper resolution can greatly improve the therapeutic agents' delivery's effectiveness and minimize its negative effects. A drug delivery system that meets the requirements for usage in pharmaceutical and biomedical formulations should have multiple features, including antibacterial activity, biodegradability, and biocompatibility. Through this approach, outdated antibiotics rendered ineffective due to toxicity or resistance can be revived, last-line therapy antibiotics can be saved by raising the therapeutic index, the antimicrobial spectrum of antibiotic scaffolds that failed due to membrane permeability issues can be expanded, and the time between the emergence of new antibiotics and the increasingly drug-resistant pathogens can be shortened. The Purpose of this article is, to outline the key research directions for the development of drug delivery mechanisms for the intracellular release of antibiotics, as well as the limits of each class of antibiotics in targeting intracellular bacteria. This more efficient use of antibiotics may mitigate their downsides and provide the foundation for decreasing the present time required by traditional therapies. This will be concentrate on the role of DDS as a potential tool against intracellular microorganisms.*

Keywords: Intracellular targeting bacterial pathogen, Drug Delivery System, Antibiotic classes, Mechanism of cellular Targeting Antibiotic, Antibiotic Transporters for Intracellular Activity

I. INTRODUCTION

The incapacity of traditional antibacterial medicines to enter, concentrate, or remain within mammalian cells makes infections with intracellular bacterial pathogens difficult to treat [1,2]. Compounding the difficulty of treating infections caused by antibiotics is the growing issue of antibiotic resistance. In the treatment of many diseases, getting the therapeutic ingredient to the desired location is a significant challenge. Ineffectiveness, unwanted side effects, poor biodistribution, and a lack of selectivity are characteristics of conventional drug use [1,3]. A number of bacteria have discovered how to bypass their bactericidal defenses and cause a "silent" infection inside of cells. As a result, in these circumstances, cells may serve as reservoirs and aid in the infection's spread to neighboring cells and organs in addition to being unable to destroy the intracellular germs. A wide variety of antibiotics have been found to be active against isolated bacteria, disappointing results are obtained against these pathogens in the intracellular environment. This is because bacteria that are located inside the cell are shielded from both the immune system and the action of the antibiotics present in the extracellular milieu [4,5]. Although combined therapies are more successful than single ones, patients may find it more difficult to comply with them, which could result in poor patient compliance and treatment of antibiotic. By delivering antimicrobial drugs and specifically targeting intracellular regions of infection, these DDS can assist boost the therapeutic index of antimicrobials in intracellular niches without causing the side effects of systemically providing high dosages of antibiotics. These germs' internal positions shield them from the host defense

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mechanism and the action of antibiotics, which may have trouble entering phagocytic cells. Analyzing the many biological and non-biological delivery methods utilized to increase the absorption of medications by infected host cells is the primary goal [6,7].

II. LIFECYCLE OF INTRACELLULAR TARGETING LIFE CYCLE

Mucosal cells and blood vessel endothelial cells are examples of eukaryotic, typically nonphagocytic cells that can harbor a variety of harmful bacteria. The intracellular medium provides the bacteria with protection so they can proliferate [8,9]. Within the field of infectious illnesses, the intracellular environment of professional phagocytes represents a noteworthy niche that warrants consideration. Paradoxically, bacterial infections like Listeria, Brucella, Mycobacterium, or Salmonella find a happy home in these specialized cells designed to destroy and digest the material consumed. Among its many uses, the endocytic route is involved in protein recycling for the secretory pathway as well as nutrition uptake. Ingested bacterial phagosomes fuse with early endosomes to acquire markers that give phagosomes characteristics often associated with early endosomes, such as the capacity to fuse with other endocytic organelles. Invasins are a class of molecules that are primarily used by invasive organisms to attach to their host cells. These molecules direct the entry of bacteria into the cells by acting as adhesion proteins on the cell surface [9,10]. Adherence mechanisms either directly or indirectly facilitate bacterial penetration by inducing or promoting cellular signals.Two processes lead to bacterial invasion following adherence: (a) The "zipper" mechanism: adhering bacteria alter the cytoskeleton of the host cell after attaching.especially actin filaments, which cause the bacteria to become embedded, and (b) internalization by a mechanism unrelated to the membrane chemicals that facilitate adhesion. Here, however,The bacterial contact with the host cell membrane results in localized infiltration is succeeded by endocytosis [11,12,13].

Escherichia coli pathogenic strains that selectively attach to the epithelial cells and interact with the M cells have the ability to colonize the intestinal mucosa. Following actin filament restructuring at the adhesion location, the adherence to intestinal epithelial cells and M cells causes the microvilli and M cell folds to disintegrate as well as the formation of certain unique structures known as pedestals.A facultative intracellular pathogen called Shigella sp. causes serious harm to the small intestine. Comprising the mucosa of the colon, together with the loss of the epithelial barrier. Following their attachment to the cellular membrane, Shigella sp. cells are phagocytosed, released into the cytoplasm, andthe phagosome membrane's breakdown. Shigella flexneri does not infiltrate the apical surface when epithelial tight connections are intact, according to in vitro investigations conducted using enterocytes. Only the basolateral membrane provides entry for the invasion. Shigella first enters the mucosa in vivo by M cells, then via the basolateral surface it invades epithelial cells. Because there are more lymphoid follicles and M cells in the ileum and colon, mucosal ulcerations are more common in these areas [14,15].

Drug Delivery System Against Intracellular Infections:

Monocytes have been demonstrated to sustain C. pneumoniae growth for several days; consequently, they can function as carrier systems for the bacteria and transfer the infection from the respiratory tract to other organs. Its inclusions localize in close proximity to the Golgi network and fuse to exocytic vesicles containing sphingomyelin, which appears to be essential for the intracellular replication of Chlamydia.

The facultative intracellular pathogen Legionella pneumophila mostly infects alveolar macrophages. It has also been demonstrated that L. pneumophila-containing vacuoles recruit endoplasmic reticulum (ER)-derived vesicles rather than endosomal and lysosomal markers suggesting that the bacteria live in an ER-surrounded compartment until the monocytes lyse and release the germs [16,17,18].

Through M cells—to which bacteria attach more readily—Yersinia sp. cells enter the intestinal mucosa, anchor themselves, and then transcytose—to traverse the cytoplasm.

A Peyer's patch infection is brought on by consuming Salmonella cells. In addition to immediately invading through epithelial villi, S. typhi and S. typhimurium attach to M cells quickly and preferentially.

Certain types of bacteria can enter host cells directly by means of localized enzymatic digestion of the host cell membrane, subsequent to their adhesion. To illustrate, phospholipases secreted by Rickettsia prowazekii govern and regulate the targeted breakdown of the host cell membrane [8,19]

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The effectiveness of various antibiotic classes against intracellular infections:

Antibiotics are chemicals with low molecular weight that are created either chemically or by microbial biosynthesis. They can be employed at low quantities to specifically restrict the growth of bacteria or to kill them. Antibiotics are highly specific, which causes them to function differently against different types of microorganisms.The activity spectrum of antibiotics can vary depending on the quantity and variety of impacted microbial species. For example, tetracycline's spectrum includes both Gram-positive and Gram-negative bacteria, such as Chlamydia sp. and Rickettsia sp., while penicillins are particularly active against Gram-positive species.Glycopeptides and bacitracin are active against Gram-positive bacteria, while nitroimidazoles are restricted (novobiocin is active on Gram-positive bacteria, mainly staphylococci, but also on Gramnegative species, such as Haemophilus sp. and Pasteurella sp. in opposition to anaerobic microbes)[20,21].

Certain types of antibiotics, including beta-lactams and aminoglycosides, exhibit no intracellular activity or very little, while others, like macrolides, fluoroquinolones, tetracyclines, and ansamycins, are known to be active against both facultative and obligate intracellular pathogens. On the other hand, facultative intracellular organisms like Mycobacterium tuberculosis are susceptible to these medicines' action [6,17].

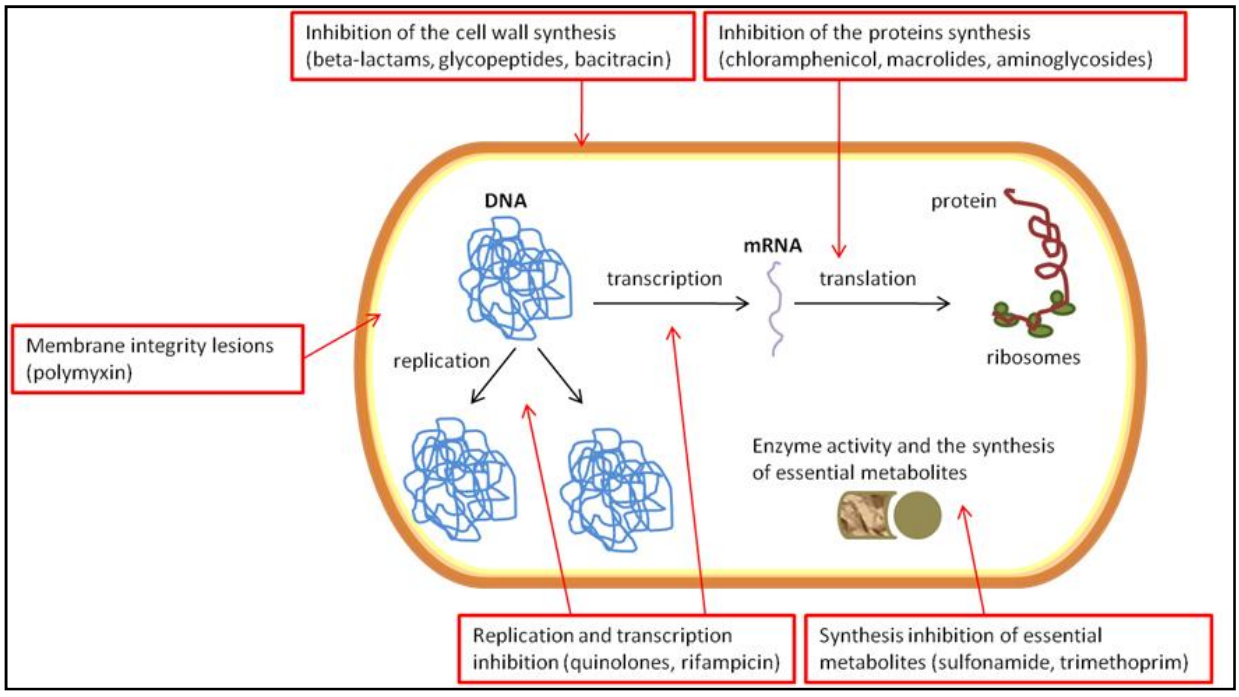

Fig.1: The mechanisms of action and cellular targets of antibiotics within the bacterial cell

Cell Wall Synthesis Inhibition:

The peptidoglycan cell wall is a closed structure made up of covalently linked units that permit the sequential insertion of new units on the outside of the cytoplasmic membrane. Autolysins act to shift the older units from the peptidoglycan's structure outward and release them. synthesis of the peptidoglycan takes place in three stages: (i) low-molecular-weightsoluble precursors are synthesized in the cytoplasm; (ii) the nonnucleotide region of the previously synthesized molecular precursor (intermediate N-acetyl glucosamine and N-acetyl muramic acid-penta- peptide) is attached to a lipid carrier, integrated in the membrane. (iii) the subunits of the peptidoglycan are polymerized by their insertion in the preexisting cell wall, by the reaction of transpeptidation, which takes place at the terminal Dala-D-ala residues. Some antibacterial agents interfere with the early steps of the cell wall synthesis (vancomycin, streptomycin, and cycloserine), while others (β-lactam antibiotics, penicillins, cephalosporins, monobactams, and carbapenems) inhibit the last steps of peptidoglycan synthesis, such as the formation of interpeptidic links. Glycopeptides (vancomycin and teicoplanin) inhibit the early stage of the peptidoglycan synthesis by binding to the carboxy-terminal dipeptide D-Ala-D-Ala[1,22].

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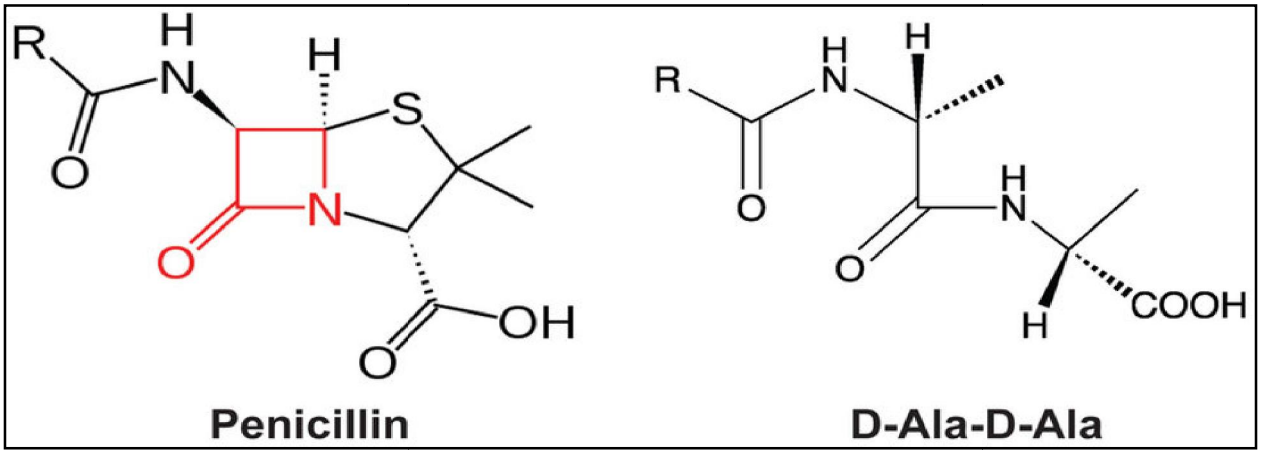
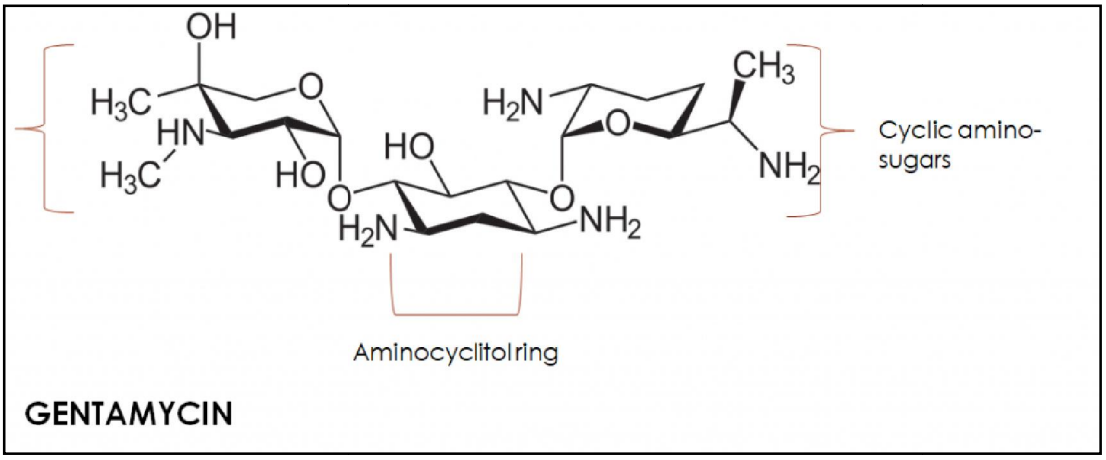


When treating gonococcal and meningococcal intracellular infections, penicillin G is the recommended medication. Since cefotaxime, ceftriaxone, cefotetan, ceftizoxime, cefoperazone, and cefixime are among the third-generation cephalosporins that may cross the blood–brain barrier, they are typically administered intravenously to treat meningitis brought on by Gram-negative bacteria.

Protein Synthesis Inhibition:

Antibiotics belonging to various classes have selective activity towards 70S ribosomes, hence impeding protein synthesis to varying degrees. Aminoglycosides are hydrophilic, low molecular weight cationic compounds that only build up within the cell via an energy-dependent transport mechanism [23]. The periplasmic proteins, whose synthesis is stimulated by the antibiotic, are thought to play a significant part in the intracellular buildup of aminoglycosides. Aminoglycosides are antibiotics that work quickly and have a wide range of effects. They are effective against both facultative and stringent Gram-positive and negative aerobic bacteria. By preventing the attachment of the aminoacyl-tRNA complex to the ribosome acceptor site A[24].



Tetracyclines are a class of antibiotics that inhibit the synthesis of proteins. In addition to killing normal gut microbiota and causing gastrointestinal issues, these antibiotics have a broad spectrum bacteriostatic effect, meaning they are active against both Gram-positive and Gram-negative bacteria as well as protozoa. Neutrophils are among the eukaryotic cells in which tetracyclines can build up. Tetracyclines are potent chelating agents, and the presence of metal ions affects their pharmacological characteristics. To maintain the antibiotic activity, only linear carbon atoms may be present in any one of the tetracycline core's rings. [23,24,25].

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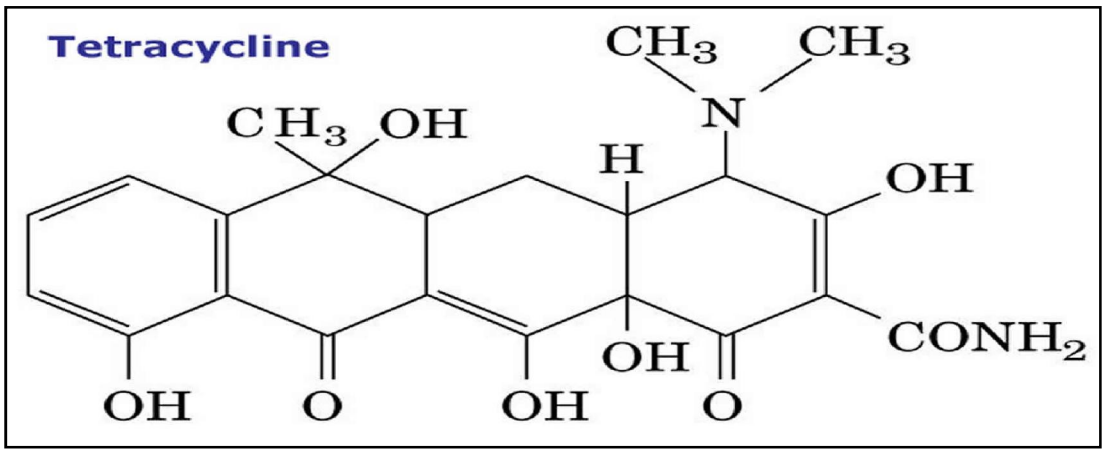

Cytoplasmic Membrane Inhibition:

The cytoplasmic membrane serves as a barrier with selective permeability for nutrients and ions. It is also the main structural transport mechanism that regulates the cytoplasm's chemical composition. Ion-selective permeability is altered and ionic or macromolecular equilibrium is lost when structural integrity and/or functional characteristics are compromised.

Because the cellular membranes of bacteria and fungus differ significantly from those of mammal cells, they can be damaged more quickly by certain therapeutic chemicals, allowing for the use of selective therapy. Polymyxins are high molecular weight polypeptide antibiotics that possess distinct chemical and biological characteristics. Polymyxins A, B, C, D, and E are the five major chemically different types of polymyxins that are now recognized. Bacillus polymyxa is the synthetic source of all polymyxins, which share an identical antibacterial range [26,27].

Antibiotic Transporters for Intracellular Activity:

Treatment for intracellular bacterial illnesses is challenging due to the lipidic membrane's resistance to traditional antibacterial drugs from commonly utilized classes. They gather in various cell compartments and encounter the phagocytic cells' limiting conditions, which include low oxygen pressure, lysosomal acidic pH and inactivating enzymes, etc. This calls for the development of effective delivery systems that could release the antimicrobial agent intracellularly in active concentrations, thereby enhancing its efficacy. while lowering the systemic toxicity, the likelihood of selection resistance, and the necessary therapeutic dosages. Antibiotics loaded into liposomes and other lipid formulations, microspheres, polymeric carriers, fullerenes, dendrimers, and nanoplexes are only a few of the better drug carriers that have been created for the treatment of intracellular pathogens. The benefits of using drug delivery systems include the ability to modify the surface, size, shape, and functionalization properties of the drug depending on its structure; immune system evasion; the ability to transport multiple drugs on the same carrier; enhanced drug biodisponibility, biodistribution, and pharmacokinetics; the availability of drug carriers for various administration routes; and the low likelihood of resistance being selected [3,28,30].

III. CONCLUSION

In this article we have concluded that, Enhancing the drug delivery methods to combat intracellular bacterial infections saw significant advancements. With the help of the suggested remedies, there was a decrease in toxicity, an improvement in bioavailability, a prolonged and sustained release that was linked to less frequent dosing and increased antibacterial activity. Antibiotic Drug Delivery System have an important role in the management of intracellular infections. By improving patient compliance and lowering the adverse effects of antimicrobial drug delivery system formulation can save healthcare delivery costs. One of the most significant therapeutic developments in intracellular bacterial disease therapy in recent years may be the possible application of DDS loaded with antibiotics. The determination of the intracellular kinetics (distribution, accumulation, and degradation in various intracellular compartments and activities) of the individual medications should be the foundation for designing the best drug carrier for the intracellular release of various antibiotics.

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