REVIEW ARTICLE

Rifampicin-Loaded Nanoparticles for Targeted Tuberculosis Therapy: Enhancing Delivery and Efficacy

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Abstract

Tuberculosis (TB) remains a major global health challenge, with limitations in the present drug regimens, including poor bioavailability, systemic side effects, and the emergence of multidrug resistance. Rifampicin (RMP), a first-line anti-TB drug, suffers from rapid metabolism, limited tissue penetration, and poor targeting, necessitating frequent dosing. Nanoparticle-based drug delivery systems offer a promising strategy to address these challenges by enhancing targeted delivery, reducing toxicity, and improving therapeutic efficacy. A disruptive solution to these challenges is presented by nanotechnology-based drug delivery systems. In this review, we examine various studies on RMP-loaded nanoparticles, including polymeric nanoparticles, lipid-based nanocarriers (such as liposomes and solid lipid nanoparticles), metallic nanoparticles, dendrimers, and micelles. These carriers enhance the stability of the drug, facilitate its controlled release, and target its delivery to TB-infected tissues and macrophages. Nanocarriers loaded with RMP have a high potential for transforming TB treatment because they are more effective, have fewer systemic adverse effects, and are part of combating TB drug resistance on a global scale.

Key words: Multidrug resistance, nanoparticles, rifampicin, targeted drug delivery, tuberculosis

INTRODUCTION

Tuberculosis (TB) is a chronic infectious disease caused by the bacterium *Mycobacterium tuberculosis* (Mtb), which is an acid-fast bacillus. The lungs are most commonly affected, but TB can also spread to other organs, such as the brain, bones, and kidneys. Although TB is preventable and treatable, it continues to be a significant global health problem, particularly in low- and middle-income countries. Factors, such as poor nutrition, HIV co-infection, smoking, and overcrowded or unhygienic living conditions increase the risk of TB infection and progression to active disease. Another challenge in TB management is the rise of drug-resistant strains, which makes treatment more complicated and less effective.[1] Every year, the World Health Organization (WHO) publishes a report on worldwide TB control. On October 29, 2024, the Global TB Report 2024, based on 2023 statistics, highlighted the worldwide TB burden. According to the report, 10.8 million new TB cases were registered, corresponding to 134 cases/100,000 population. Among these, 662,000 individuals (6.1%) were co-infected with HIV, underscoring the strong association between TB and HIV. What's more, 400,000 (3.7%) of the patients were resistant to multiple drugs, and others to rifampicin (RMP) as well. Multidrug-resistant tuberculosis / Rifampicin-resistant tuberculosis (MDR/RR-TB) was especially worrying since

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16% of people who were previously treated and 3.2% of new patients were identified as resistant, proving that there are difficulties with diagnosis, treatment, and compliance with medications. The case count of TB worldwide in 2023 amounted to 1 million cases, which remains the top cause of infections leading to death. This means TB is responsible for many more deaths than HIV/AIDS, which shows how significant a threat it is to the world. Even if there have been some advancements in TB detection, treatment, and what we know about it, the situation is not improving fast enough to eradicate TB. It notes that we will need to spend significantly more on advanced healthcare solutions, newer technologies, and strengthen health systems in the coming years to address TB.[2]

TB bacteria are rapidly killed by RMP, making it a vital drug in treating the first stage of this disease. It achieves this action by hindering the process through which bacterial RNA polymerase carries out its function. Resistance to RMP mostly takes place when there are alterations in the *rpoB* gene that reduce the drug's attraction to the RNA polymerase β-subunit. Observers show different levels of the drug in their blood, and, on average, RMP reaches peak levels in approximately 2 h after a patient takes it orally. The absorption of RMP varies depending on factors, such as food intake, stomach acidity, and other medications taken concurrently. The body's response to RMP lowers the amount of antibiotic in the blood as time goes by. TDM may be recommended by doctors who aim to achieve the most effective outcomes, particularly when treating patients who are slow responders. Adequate RMP in the body kills the bacteria, prevents them from becoming resistant, and boosts the patient's health.[3] Still, achieving the proper RMP levels is a challenge when it is included in the combination drugs prescribed for TB. Different TB mutations may complicate the treatment of patients, increasing their likelihood of developing drug resistance. Experts do not fully understand the main reasons, but factors they have suggested include problems during RMP production and changes in its structure.[4] Various studies indicate that the breakdown of RMP and isoniazid in the stomach due to acidic juices is the reason why these medications are not as readily available to the body as they should be. Perhaps lower performance is caused by the recent changes in the FDC. TB is a significant health problem across the world since patients may not cooperate, often therapy takes a long time, several drugs become resistant, and key agents are not always delivered to the correct site in the body.[5]

Scientists are showing great interest in using nanoparticles to deliver TB drugs, as they help these drugs work more effectively. Nanoparticles that are <1 μm big are particularly created to safely hold medicine inside their structure or link it to their surface. Most of the time, they use safe and natural items, such as gelatine, albumin (both known as natural polymers), polylactides, polyalkylcyanoacrylates (synthetic polymers), as well as solid lipid nanoparticles and nanostructured lipid carriers containing lipids. With their tunable properties, they can regulate drug administration, sustain release over time, and act specifically at infection sites, thereby minimizing off-target side effects.[5,6] Although positive outcomes have been observed in pre-clinical research, the currently used animal models are unable to represent human TB as it occurs in the body entirely. As a result, we need more studies to demonstrate the potential benefits of these nanotechnologies for patient care. Using this review, we provide a clear picture of modern studies on RMP -loaded nanoparticles and their potential for better and more directed treatment of TB. The primary purpose is to bridge the gap between nanotechnology's present achievements and its potential to aid in combating severe infectious diseases.[6]

PHARMACOLOGICAL PROFILE OF RMP

RMP acts by inhibiting DNA-dependent RNA polymerase, which is required for DNA to be transcribed into mRNA, thereby combating bacterial growth [Figure 1]. When a drug forms a stable drug-enzyme complex with a strong binding affinity, its inhibitory effect is achieved (the dissociation constant is about 10^{-9} M at 37°C). Units of the β-subunit of RNA polymerase form a bond with RMP at the enzyme's active site; this stops the further elongation of nascent RNA chains and formation of phosphodiester bonds.[7] RMP selectively inhibits bacterial RNA polymerases while sparing those in animals, making it a safe and effective treatment for Mtb and related infections. Still, there is a significant clinical problem with bacterial resistance, mainly due to mutations found in the *rpoB* gene, which encodes the β-subunit of RNA polymerase. These changes make the bacteria resistant to the drug by reducing the amount of RMP that binds to the enzyme. RMP resistance can be present in varying degrees, rather than being either present or absent. The response to RMP is not a simple on-off situation; bacterial RNA polymerases are affected in different ways by various types and locations of mutations. In addition, the correlation between sensitivity in the test tube and the MIC values obtained using microbiological methods is not perfect. Since RNAs perform different tasks in each case, the reasons bacteria are inhibited either increase or do not increase during enzyme assays compared to bacterial growth in the lab.[8]

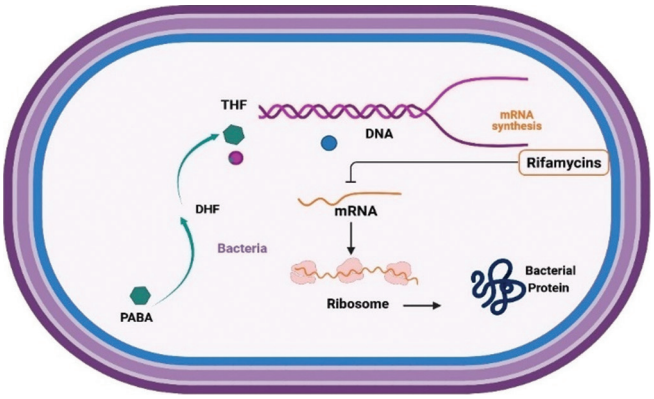

Figure 1: Mechanism of action of rifampicin

RMP has a complicated way it is handled by the body, which causes vast differences in drug levels from person to person. Oral administration of antibiotics typically results in peak plasma concentrations within approximately 2 h, and fasting enhances absorption.[9] Still, how well the body absorbs a medication may depend on factors, such as malnutrition, HIV infection, diabetes, hepatic cirrhosis, dose amount, variations in genes, and the quality of the formulation. It is essential to note that renal impairment does not alter the absorption of RMP at standard doses (600 mg). As you keep using RMP, your liver starts processing more of it, and so C_{max} and the medication's half-life are reduced. As a result, the drug level may remain too low, which is why TDM would be important, especially in people whose illness has not improved with the usual dosage. Administering TDM at 2, 4, and 6 h allows for the optimal concentration of the drug. An exposure level of $C_{max} > 8.2$ µg/mL is considered to have sterilizing activity. Patients with higher exposures (Cmax ≥ 22 µg/mL) and AUC0–6 ≥ 70 µg/mL tend to fare better with severe TB, such as meningitis. Fortunately, using high-dose RMP (up to 35 mg/kg/day) has been seen to be safe and digestible, and it may improve treatment, shorten the therapy, and lead to fewer relapse cases. Future investigations should utilize the ratios of C_{max}/MIC and AUC/MIC as rough measures to determine the optimal dosage of a drug.[10]

TYPES OF NANOPARTICLES USED FOR RMP DELIVERY

Nanoparticles are small carriers (1–1000 nm) that can entrap drugs, enhancing their stability, bioavailability, and target specificity. Nanoparticles are also valuable for TB treatment, as they facilitate the delivery of RMP to infected cells with minimal side effects and enhance the treatment's efficacy.[11]

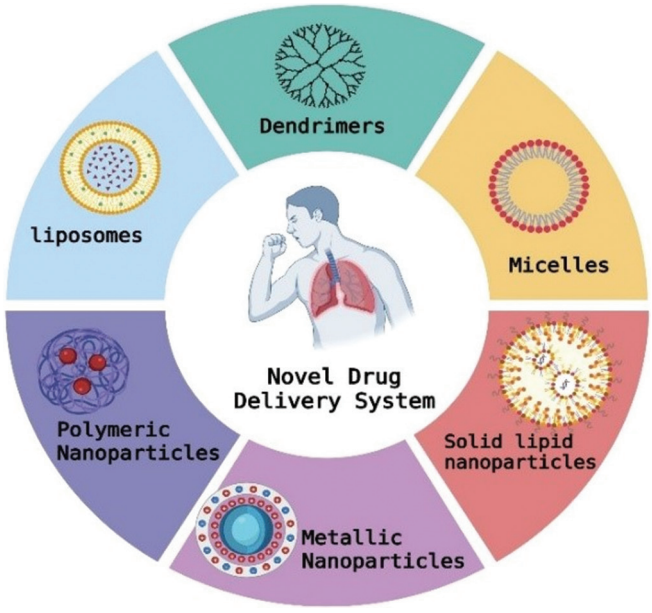

Figure 2: Various types of nanoparticles are utilized for rifampicin delivery in tuberculosis treatment

The most common are shown in Figure 2, such as polymeric nanoparticles (sustained and controlled release), lipid-based carriers (liposomes, solid lipid nanoparticles, etc.), metallic nanoparticles (gold, silver, etc.) with antimicrobial activity, dendrimers (high drug loading), and micelles (poorly soluble drugs). Such systems are a significant improvement in the RMP-based TB treatment since they deliver the drugs effectively and accurately.

Polymeric nanoparticles

To overcome the problems associated with RMP, such as low aqueous solubility and variable bioavailability, Rani *et al*. developed a nanoparticle system composed of N-(2-hydroxypropyl) methacrylamide (HPMA) and poly(lactic-co-glycolic acid) (PLGA). The HPR-NPs prepared are designed to make RMP more long-lasting and improve its ability to reach and function within the body. It was found that the nanoparticles had a mean size of 260.3 ± 2.21 nm, a zeta potential of −6.63 ± 1.28 mV, and a polydispersity index (PDI) of 0.303 ± 0.22, indicating that they were uniform and relatively stable. According to TEM, each carbon dot is round, with no sign of clumping. A high drug capacity was observed in the nanocarrier, with entrapment efficiency and drug loading at 76.25 ± 1.28% and 26.19 ± 2.24%, respectively. Sustained drug release over a long period was observed, as the *in vitro* drugs were released according to the Higuchi and Korsmeyer-Peppas models. More importantly, when human red blood cells were used in interaction studies, the nanoparticles loaded with RMP had less hemolytic toxicity than the free medicine ($P < 0.05$). HPMA-PLGA-based nanoparticles are shown to enhance RMP solubility, making it available to as many cells as possible, and reduce side effects, which may make them useful in TB treatment.[12]

Similarly, given the problems with RMP solubility in water, Petkar *et al*. came up with a new water-repelling (hydrophobic) chitosan derivative, octanoyl chitosan (OC), that dissolves well in organic solvents. Thanks to this improvement, my team was able to develop nanoparticles that contain RMP and are intended for pulmonary administration. It was confirmed that the OC polymer had a substitution degree of 44.05 ± 1.75%, indicating successful acylation and demonstrating non-toxic behavior with A549 human lung epithelial cells after 24 h. A solvent evaporation method was employed to prepare the nanoparticles, eliminating the need for chemical crosslinkers. An improved formulation with a similar spherical morphology, an average size of 253 nm, and a modest variation in size was achieved using a 32 complete factorial design. The encapsulation efficiency of RMP in the formulation was 64.86 ± 7.73%. A two-stage impinger was used to determine that the optimized nanoparticles have a fine particle fraction of up to 97%, which demonstrates high performance when delivered to the lungs using a nebulizer. During the 72-h test, 73.14 ± 3.17% of RMP was released, and the nanoparticles remained physically unchanged for at least 2 months under storage conditions. It was found

that OC-based nanoparticles are effective as a platform for delivering RMP to the lungs of individuals with TB, remaining effective for a more extended period, possessing good aerodynamic properties, and being safe for human use.[13]

Similarly, Hakkimane *et al*. conducted a fourth study to test the administration of RMP and a produced isoniazid benzhydrazone derivative inside biodegradable polymer nanoparticles against Mtb. The purpose of the study was to assess the effectiveness of the medicine in combating the virulent H37Rv strain of Mtb. Drugs were encapsulated in PLGA nanoparticles, a polymer type endorsed by the FDA, which allows them to remain in the body for an extended period. The research showed that the nanoparticles had a small size, designed release patterns, and were stable. The *in vitro* test demonstrated that administering the dual drugs together in nanoparticles was more effective against Mtb than administering them separately. MICs were remarkably decreased, indicating that the use of nanoparticles enhanced the potency of the drugs. This research demonstrates that loading biodegradable nanoparticles with multiple medications may improve the delivery of these medications, reduce the frequency of doses, and mitigate some of the challenges associated with TB resistance.[14]

Similarly, to support intracellular drug delivery, Smitha *et al*. used amorphous chitin nanoparticles loaded with RMP (RIF-ACNPs) to target the primary immune cell of the first response to bacterial infections (polymorph nuclear leukocytes). Even though PMNs release ROS and agents that destroy microbes, some pathogenic organisms remain safe inside the PMNs and are protected against the immune system's actions. It was demonstrated that RIF-ACNPs, with an average size of 350 ± 50 nm, are non-toxic to host cells and do not induce blood cell destruction. Most RMP was released within 24 h, and only a little was released in the next 48 h. Most importantly, nanoparticles caused up to 6 times more RMP to be taken up by PMNs in comparison with the free drug. They exhibited antimicrobial effects against pathogens, such as *Escherichia coli* and *Staphylococcus aureus*. It was found that these particles enhance the effectiveness of RMP in killing bacteria within cells, highlighting its potential usefulness against infections, such as TB.[15]

Another study by Sung *et al*. produced RMP nanoparticles to improve their solubility, stability, and delivery to the lungs. The nanoparticles were designed for inhalation, aiming to increase the level of drugs in the lungs without exposing the entire body, which is crucial in treating pulmonary TB. Such systems were formed by using biocompatible substances to hold RMP, without the use of surfactants or hazardous solvents. The particles made from biostable polymers showed a high capacity for loading drugs, were easily formed into aerosols, and maintained sustained release. It was found that, compared to the usual RMP types, Boehringer Ingelheim's formula increases the amount retained in the lungs, providing a more substantial local effect over a more extended period. The feature of non-invasive, localized drug delivery for this platform may improve treatment outcomes and reduce side effects. The findings support the use of nanotechnology-based pulmonary methods in the development of simple and effective TB treatment strategies.[16]

A 2020 study by Haopeng Luan created nanoparticles that carry mannosamine and target rifapentine – a rifamycin drug – to macrophages infected with Mtb. Researchers designed these nanoparticles to rely on mannose receptor-mediated endocytosis, enabling them to be more effectively absorbed by macrophages, which are crucial to the development of TB disease. The nanoparticles were highly suitable because they had a narrow size distribution, an even surface layer, and high encapsulation. Experiments with mannosylated nanoparticles in the lab demonstrated that macrophages absorbed more rifapentine than non-targeted nanoparticles, resulting in higher drug levels within the cells. In addition, investigating the drug's antimycobacterial activity confirmed that it reduced the burden of Mtb in infected macrophages, indicating its potential success in treating TB within cells. The platform also showed positive biocompatibility and negligible toxicity. The study highlights that targeted nanocarriers carrying antibiotics may enhance the efficacy, safety, and specificity of treatments for TB.[17]

Lipid-based nanocarriers (liposomes, solid lipid nanoparticles)

It is possible to deliver RMP and other drugs using lipid-based nanoparticles, such as liposomes and solid lipid nanoparticles. As a result of these aspects, these systems allow for better treatment of TB and control of toxic exposure elsewhere.[18] To improve the body's uptake and release of RMP (RIF), Hussain *et al.* developed elastic liposomes for transdermal applications. The best formulations of F3, F5, and F7 (optimized with varying Tween 80 and Phospholipon® 90 G) allowed the gel to release the drug more effectively and over a much longer time than the oral suspension did in experiments involving rats and people. More drug was released from F5 gel (56.23 µg/h on average) than reached from oral RIF (41.71 µg/h on average), as seen by the lower Cmax value for F5 gel. The simulations and histopathological analyses yielded these results, suggesting that this system could be a suitable choice for treating cutaneous TB and enhancing patient adherence to antibiotics.[19]

Similarly, a study on Dual Antitubercular Drug-Loaded Liposomes for Macrophage Targeting was conducted. The researchers involved in this research are Shrivastava *et al*. They designed liposomes that carry both rifampin and isoniazid in one package for delivery specifically to macrophages, where Mtb usually hides. To increase the uptake and retention of liposomes by cells, the liposomes were appropriately sized, charge-balanced, and loaded with

the desired cargo. It was found in the lab that dual-drug liposomes were taken up better by alveolar macrophages than the drugs used separately. When administered to rats, the drug had a prolonged circulation time and enhanced delivery to the bloodstream. The study revealed that more drugs are detected in lung tissue when using the liposomal system, making it a more effective treatment for pulmonary TB. To summarize, dual-loaded liposomes are effective at targeting treatment to specific cells and maintaining the drug's activity for an extended period, making them suitable for treating TB within cells.[20]

Similarly, Garcia-Contreras *et al*. compared two methods of administering RMP through pulmonary delivery. Liposomal particles were incorporated into the RIF-NEB formulation to enhance the encapsulation of RMP and improve its stability during inhalation therapy. When using guinea pigs with TB, the inhaled medication was deposited more in lung tissue, killed more bacteria, and reduced pathology in the lungs compared to when it was given orally. Liposomal carriers enabled the drug to be released slowly, allowing it to reach the affected part of the body and result in better healing with fewer side effects elsewhere.[21]

Metallic nanoparticles

Metallic nanoparticles made of silver, gold, or iron oxide have garnered attention as drug carriers due to their unique properties, including a large surface area, high stability, and the ability to modify their surface, making them suitable for carrying RMP. Thanks to the nanoparticles, RMP can work more effectively by targeting the expected site, entering more bacterial cells, and releasing inside the primary Mtb host cells.[22] By combining RMP with metallic nanoparticles, one can enhance the bactericidal effect, as the drug acts on its own, and metallic nanoparticles also possess a natural ability to inhibit microbial growth. In addition, metallic drug carriers can be tailored to deliver drugs in response to changes in the local environment's pH or enzyme activity. Several studies have found that combining RMP with metal-based nanoparticles results in improved absorption, reduced dosing frequency, and potential additional benefits.[23] A survey by Kiria *et al*. investigated the mechanism by which Silver Nanocomposites (AgNCs) affect RMP-resistant Mtb strains. These nanocomposites are made using a polymer that allows the material to be stable and helps the controlled release of silver ions. AgNCs were observed to be more effective against drug-resistant TB, requiring lower doses (MICs) than traditional silver salts. Some mechanisms suggested are destroying bacteria's outer membrane, producing harmful oxygen in the body, and interfering with their important biomolecules, such as DNA and proteins. Tests showed that at therapeutic doses, AgNCs posed little danger to cells in the body and caused minimal destruction of red blood cells. This study highlights the potential role of silver nanocomposites in addressing multidrug-resistant TB, particularly in cases where RMP monotherapy proves ineffective.

Similarly, a recent study by Bano *et al*. developed a novel nanocomposite that utilizes superparamagnetic iron oxide nanoparticles (SPIONs) and carbon nanotubes (CNTs). This nanocomposite is used to detect RMP with high sensitivity in amperometric tests. The nanocomposite of SPIONs-CNT was developed through simple co-precipitation and then established on a glassy carbon electrode through functionalization. Due to its high surface area, good conductivity, and excellent electrocatalytic properties, the hybrid nanomaterial is suitable for use in electrochemical sensing. Techniques FTIR, TEM, XRD, and electrochemical impedance spectroscopy confirmed that the nanocomposite was successfully prepared and had the desired structure. Modifying the electrode with SPIONs-CNTs enabled the fast and isolated detection of RMP, requiring a low concentration and providing a highly sensitive response. The sensor performed very well, exhibiting stability, reproducibility, and responsiveness in samples taken from human serum and pharmaceutical products. It highlights that nanotechnology-based platforms can facilitate on-the-spot monitoring and quality assurance of RMP, providing support for both therapeutic and environmental management.[24]

Dendrimers and micelles

Researchers have discovered that dendrimers and micelles can be used to carry RMP and increase its treatment of TB. RMP is efficiently incorporated onto the surface of dendrimers due to their fixed structure and numerous functional groups on their surface. Due to their specific design, these nanoparticles can slowly and accurately release drugs, are more soluble, and are readily taken up by macrophages, which are the primary host cells for Mtb.[25] Meanwhile, micelles form amphiphilic structures that feature a hydrophobic region, which is ideal for incorporating drugs, such as rifampin. The use of polymeric micelles offers the gradual delivery of the drug, improved stability, and possibilities for administration through inhalation or injection, thereby maintaining the correct drug level at the site of infection. They have both been shown to be less toxic, work more effectively in the body, and help overcome resistance to medicines by maintaining high levels within cells.[26]

Bellini *et al*. urged the study of interacting RMP and PAMAM dendrimers to check their potential as nanocarriers for TB medicine. Experiments demonstrated that electrostatic and hydrophobic interactions enabled the successful attachment of RMP to G4 PAMAM dendrimers, resulting in the formation of stable nanostructures. Measurements using UV-Vis spectroscopy and fluorescence provided conclusive evidence that RMP was well encapsulated by the dendrimer, with little to no RMP degradation. The combination of RMP and PAMAM dendrimer exhibited improved stability and

higher solubility compared to RMP alone. Furthermore, drug release studies in a recipient system revealed that there was a steady decline of RMP, suggesting it may continue to offer therapeutic results for a long duration. It was also found that the cytotoxicity of Vero cells decreased with the addition of the dendrimer–RMP complex, proving that it is safer than RMP alone. As a result, it can be said that PAMAM dendrimers can be used effectively and safely for treating TB, and specifically help in cases of drug resistance or for additional doses.[27]

According to Tripodo *et al*., natural inulin forms micelles that enhance the delivery of RMP to cells, allowing for higher amounts. Inulin was chemically modified to incorporate hydrophobic parts, resulting in amphiphilic copolymers that can self-assemble into stable micelles in water. The mixture of micelles loaded with RMP exhibited favorable properties, including a particle size of approximately 120 nm and a narrow PDI, indicating uniformity. Micelles demonstrated a significant capacity for transporting drugs and releasing medicines in a sustained manner. It was established through studies that the formulation maintained effective action against Mtb and was efficiently absorbed by human macrophages. Because the bacteria hide within cells, effective intracellular delivery becomes crucial in combating TB. All in all, the method based on micellar inulin appears to be safe, biodegradable, and effective, potentially making RMP delivery more successful.[28]

Similarly, Yuan *et al*. developed a novel method for delivering RMP using a mucoadhesive guar gum hydrogel combined with CS-g-PCL micelles. This way, the nano-scale structure of micelles is combined with the stickiness of guar gum hydrogel. Due to its complex interpenetrated structure, the tablet adheres well to mucus membranes, is strong, and delivers anti-TB medicines in small increments. As a result, the developed micellar hydrogel exhibits a high percentage of drugs within its core, is cell-friendly, and provides a steady release of the drug over an extended duration. Tests conducted in the laboratory demonstrated that the nanovesicle is safe in the body and does not release the medicine immediately, making it suitable for administering TB treatment orally or through mucous membranes.[29]

Rani *et al*. further developed PEGylated diblock nanopolymeric micelles to facilitate the co-delivery of isoniazid and RMP, thereby enhancing treatment for Mtb. The drugs were highly encapsulated by the micelles, which ensured the nanocarrier functioned effectively. The *in vitro* studies indicate that the drug is released slowly and steadily over a prolonged period, making it easier to maintain proper drug levels in the body and reduce the frequency of administration. Tests using antimicrobial assays demonstrated that mixing the two drugs in micelles yielded greater synergy than using the drugs individually against Mtb. Determining the level of cytotoxicity demonstrated that the nanomicelles are suitable for therapeutic use. Adding PEG to the micelles resulted in greater stability and more prolonged survival in the body since they were not removed quickly by the immune system. All in all, the findings suggest that these special micelles are suitable for co-delivering anti-tubercular drugs, which could enhance both patient adherence and therapeutic outcomes.[30]

In the same way, Gao *et al*. used hyaluronic acid (HA) conjugated with tocopherol succinate (TS) to generate self-assembling micelles that enabled RMP to be delivered to the primary host cells of Mtb – alveolar macrophages. The HA-TS conjugate forms small, spherical micelles that are easily inhaled into the lungs and can be readily taken up by cells. Because the micelles included a high amount of RMP, the drug was released slowly and steadily. With the help of the CD44 receptor, macrophages present in the lungs processed the HA moiety, allowing selective targeting. Research performed on dishes showed that the science formula was more active against Mtb within macrophages, and this activity was superior to that seen with free RMP. It was confirmed that the micellar system is biocompatible toward both lung epithelial and macrophage cells, as determined by cytotoxicity assays. Overall, it has been found that targeting RMP to alveolar macrophages using HA-TS-based micelles may lead to a better treatment of TB with fewer side effects.[31]

Figure 3 illustrates the nanomedicine-based solution designed to enhance RMP delivery in TB disease conditions, particularly in addressing challenges, such as antimicrobial resistance, poor aqueous solubility, and variable bioavailability of RMP. Nanoparticle systems, such as metallic nanoparticles (e.g., silver and gold), lipid-based carriers, polymeric nanoparticles, and dendrimers, are utilized to enhance drug solubility, stability, and targeted drug delivery. The action of these nanocarriers involves specific mechanisms, including membrane disruption and controlled drug release at the site of infection. Such a particular method of action enables the effective concentration of RMP in cells infected with TB. It blocks the DNA-dependent RNA polymerase in bacteria, thereby preventing the synthesis of RNA and enhancing therapeutic efficacy.

MECHANISMS OF TARGETED DELIVERY

These types of drug delivery systems aim to apply treatment only where it is needed, thereby reducing the risks of side effects and making the treatment more effective. RMP nanoparticles are used in TB therapy because they utilize both physical principles and targeted biological entities. After they are given, nanoparticles enter the bloodstream and can either be guided by natural body functions or directed with the help of external tools. After reaching the chosen site, the medication is released steadily or in a controlled way. When RMP is encapsulated inside nanocarriers, its water solubility increases, it is protected from early damage, and it can be readily taken up by macrophages, the primary hosts for Mtb.

More drugs are deposited in granulomas and infected cells, leading to additional bactericidal effects at the infection site.[32]

Passive targeting utilizes altered blood flow and tissue barriers in TB sites, similar to enhanced permeability and retention (EPR)-like behavior, as illustrated in Figure 4. In TB, disruption of blood vessels, increased leakiness of capillaries, and impaired lymphatic drainage result in nanoparticles (approximately 100–300 nm) being collected at the sites of infection. Those nanocarriers have been developed to exploit the enhanced permeability observed in the lungs and damaged regions. In addition, nanoparticles in the tumor area may remain for a prolonged period, resulting in slower drug release and potentially better outcomes. Targeting using a passive mechanism is crucial for enhancing the delivery and efficacy of RMP, particularly in the treatment of pulmonary TB.[33]

Active targeting utilizes the strong bonds formed between a

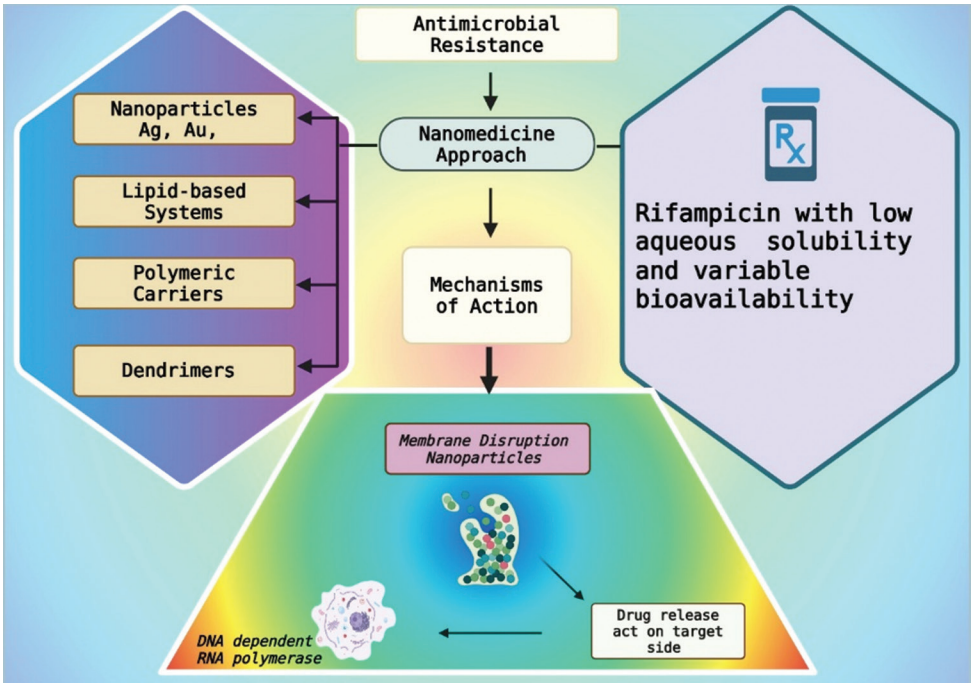

Figure 3: Nanomedicine approach for targeted rifampicin delivery in tuberculosis treatment

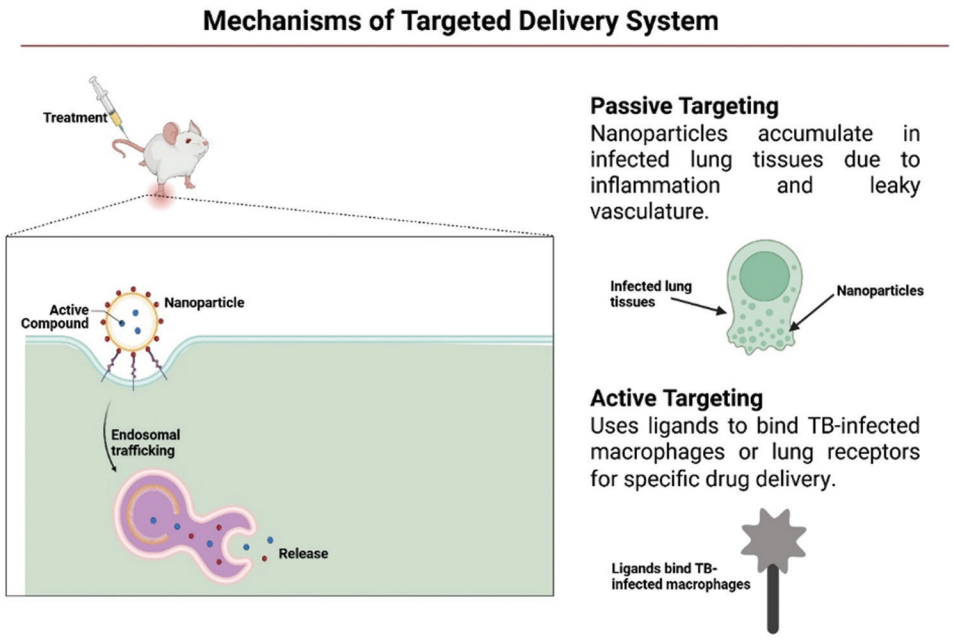

Figure 4: Passive and active targeting mechanisms in rifampicin-loaded nanoparticle delivery

molecule and a protein to enhance the ease with which a drug can enter a cell. For TB, Macrophages found in the alveoli mainly keep Mtb, and these cells also contain mannose, lectin, and scavenger receptors that allow ligand-targeted delivery of RMP using nanocarriers. A notable example is represented by mannosylated solid lipid nanoparticles (Man-RIF SLNs). They are coated with mannose groups that are meant to stick to the mannose receptor found on infected macrophages. Evidence shows that targeting Man-RIF to SLNs significantly enhances uptake by alveolar macrophages, resulting in a RMP concentration that is more than 4 times higher within these cells and a greater ability to kill bacteria compared to these same antibiotics in non-SLNs.[34]

These studies in living animals demonstrated that after inhaling mannosylated SLNs, most of the particles remained in the lungs, with minimal spread to other parts of the body. Additional ligands being investigated for targeting macrophages include O-steroyl amylopectin (O-SAP), maleylated bovine serum albumin, and tuftsin, when incorporated into liposomal or nanoparticle carriers. Using these systems, decorated with ligands, resulted in greater drug delivery to lung macrophages, which in turn led to higher RMP levels in the body and a more effective fight against TB compared to non-targeted versions.[35]

Once macrophages have nanoparticles carrying RMP inside them, the medication must be released at the proper time and within the proper internal cells. It is necessary to destroy Mtb that is hidden inside phagosomes and belongs to other cellular compartments. Nanocarriers are mostly absorbed into cells through endocytosis or recognized and engulfed by macrophages through phagocytosis.[36] Adding mannose, HA, or tuftsin ligands to vaccine surfaces results in enhanced binding to particular macrophage receptors (e.g., mannose, CD44, Fc). Once nanoparticles enter, they reach acidic environments (~5), where specific enzymes and redox conditions exist in endo-lysosomes, unlike those found outside.[37]

CLINICAL POTENTIAL AND TRANSLATIONAL CHALLENGES

Even with all the improvements in pre-clinical studies, there still aren't any RMP-based nanoparticle formulas in clinical trials. Several inhalable systems, including liposomes, polymeric nanoparticles, microspheres, and solid lipid nanoparticles, have shown positive outcomes when administered to animals, demonstrating proper distribution, favorable kinetics, and safety.[38] Nevertheless, due to the lack of strong pre-clinical tests at adequate doses and insufficient direct information on the toxicity and efficacy of the injectable form compared to oral or intravenous drugs, progress in its use has been delayed. Due to their varying structure, RMP-loaded nanoparticles are classified as non-biological complex drugs (NBCDs). That is why both the FDA and EMA want extensive investigations and assessments related to the unique features of nanoscale substances.[39] Due to these issues, it takes longer to develop and comply with additional regulations. It is also challenging to develop RMP nanoparticles due to economic and logistical constraints. Most of the time, advanced formulations lack appeal because they tend to be costlier than typical oral medicines. Besides, it is often hard to use targeted delivery (inhalation or intravenous) in places affected by TB, since such areas usually lack both advanced equipment and trained staff. Addressing these challenges requires the use of particular strategies.[40] Examples include interacting with regulatory agencies early on, creating scalable and thermostable medicines, and adopting affordable and field-ready methods of vaccine delivery. Laboratory research can be transformed into effective drugs only with the help of public–private partnerships, individuals who donate funds, and innovative manufacturing techniques. Such new tools could lead to better medication compliance, fewer frequent doses, and improved results in TB management worldwide.

SAFETY, TOXICITY, AND BIOCOMPATIBILITY

Cytotoxicity assessment is crucial when developing RMP-based nanoparticles as treatments for patients. It has been demonstrated that the safety testing of polymeric nanoparticles, liposomes, solid lipid nanoparticles, dendrimers, metallic nanoparticles, and micelles yields acceptable results in laboratories. However, this depends on the nanoagent's composition, surface charge, and size. Nanoparticles composed of PLGA or chitosan have a low potential for toxicity. HPMA-PLGA nanoparticles carrying RMP exhibited a slight hemolytic effect and did not induce toxicity in human red blood cells or alveolar epithelial cells.[12] Similarly, optimized OC nanoparticles for pulmonary use did not induce toxicity in A549 lung cells over a 24-h period. Elastic liposomes and liposomal gels have been demonstrated to be safe for the skin and mucosal surfaces in transdermal and pulmonary models. In particular, it was shown that the bioavailability of nanoformulations improved, with no adverse effects observed on skin tissue in rats.[41]

Different kinds of cells have not exhibited problems from contact with both SLNs and micellar systems. These micelles are preferred because they are stealthy and hydrophilic, allowing them to remain hidden from the immune system and facilitating the drug's delivery to other parts of the body.[42] Unlike organic nanoparticles, metallic nanoparticles (e.g., silver, copper oxide) exhibit strong antimicrobial effects; however, their use should be carefully evaluated, as they may be harmful. Using CuO nanoparticles created by a green approach, RMP was degraded to a high extent, but there may be safety concerns if they are used in the body.[43] Silver nanocomposites exhibited a distinctive action against RMP-resistant Mtb, so the effect on host cells should be tested under *in vivo* conditions.[44] In particular, PAMAM

dendrimers can nicely carry drugs and reach cells, but they are more toxic with increasing concentrations, thanks to their positive surface. PEG or other similar treatments help to lessen potential side effects significantly.[45] Overall, the majority of RMP nanoparticle carriers exhibit little to medium toxicity, and both polymeric and lipid-based systems are more biocompatible than other types. It is essential to carefully modify the surface of metallic and dendrimeric systems to mitigate toxic side effects while achieving favorable treatment outcomes.

The safe and long-term use of RMP nanoparticles requires that biodegradability be made a top priority. PLGA and chitosan are recognized as biodegradable materials because PLGA typically releases lactic and glycolic acids and chitosan is degraded in the body by enzymes. The polymers have been designed to degrade in a controlled manner, ideal for effective TB therapy that can last several months. On the other hand, the use of lipid nanoparticles (such as liposomes and solid lipid nanoparticles) leads to removal through normal lipid clearance, making them safe for the body – unless PEGylation is added, as repeated doses can then result in faster-than-expected clearance from the bloodstream. If anti-PEG antibodies develop, the nanoparticles' clearance time is shortened, and this may trigger a reaction from the immune system.[46]

On the other hand, non-biodegradable nanoparticles, such as silver, copper oxide, or iron oxide, often accumulate in organs, such as the liver, spleen, and lungs, which may cause oxygen damage, irritation, and serious side effects in the future.[47] Even though "green" techniques are designed to ensure safety, all nanomaterials must undergo *in vivo* clearance studies before being used clinically. Similarly, unless designed with breakable bonds, dendrimers and carbon-based carriers may remain in tissues, potentially causing problems due to prolonged retention and unexpected interactions with the body.[48] With these worrying points in mind, biodegradable polymers and lipid carriers appear to be the most suitable means for delivering RMP, as they are safer for use. To prevent build-up in less breakable parts, new engineering methods (such as chemistry that allows coating to be removed) and dosing plans should be employed. Researchers should pay more attention to how medicines spread throughout the body, how long they remain, and how they degrade when similar treatment durations are used.

CONCLUSION AND FUTURE PERSPECTIVE

RMP-loaded nanocarriers, including polymeric nanoparticles, such as PLGA and HPMA PLGA, lipid-based systems, such as liposomes, solid lipid nanoparticles, and elastic liposomes, as well as dendrimers, micelles, and selected metallic platforms, consistently improve physicochemical stability, enable controlled release, and enhance delivery to TB-relevant compartments, particularly alveolar macrophages and granulomatous lesions. Across the reported studies, these systems enhanced intracellular uptake, prolonged pulmonary residence in inhaled formats, reduced hemolysis or epithelial toxicity *in vitro*, and often potentiated antimycobacterial activity compared with free drug or non-targeted formulations. Targeting approaches have made use of EPR-like leakiness at TB sites and receptor-mediated uptake mechanisms, such as mannose and HA/CD44 interactions. At the same time, co-delivery strategies combining RMP with isoniazid demonstrated synergistic effects and the potential to reduce dosing frequency. Despite these advantages, translation remains a significant challenge. No RMP nanoformulation has reached clinical trials, and evidence is limited mainly to preclinical settings in small animal models, which do not fully reflect human TB pathology. A tendency to over-generalize EPR-like behavior, insufficient characterization of long-term immunotoxicity or RES accumulation (especially for cationic dendrimers and metals), and the absence of standardized Pharmacokinetic/Pharmacodynamic (PK/PD) and exposure–response comparisons with optimized oral regimens limit progress. In addition, challenges of large-scale manufacturing, cost, inhalation device compatibility, thermostability, and the complex NBCD regulatory framework create further obstacles to adoption in high-burden regions.

Moving forward, RMP nanomedicine requires integration of translational PK/PD frameworks that clearly link lung and macrophage exposure to sterilizing activity, supported by harmonized *in vitro* release, bioaccessibility, and macrophage uptake assays validated against *in vivo* outcomes. Instead of relying solely on surrogate endpoints, robust head-to-head efficacy studies in appropriate TB models and carefully designed early-phase clinical trials must benchmark performance against optimized high-dose RMP and standard fixed-dose combinations. Co-loaded regimens and applications in latent and drug-resistant TB represent particularly promising directions. Equally important is the focus on manufacturability, with scalable, solvent-minimized processes that yield stable dry-powder inhalers or lyophilized products compatible with resource-limited settings, alongside co-development of devices to ensure consistent dosing and patient usability. Safety-by-design principles must guide the selection of biodegradable polymers and lipids, as well as the careful monitoring of immunogenicity and thorough evaluation of long-term tissue retention, particularly for metallic or dendrimer-based systems. Targeting strategies, such as ligand-decorated carriers for macrophage and lesion-specific delivery, combined with stimuli-responsive release inside phagolysosomes, hold promise for improving precision. Co-delivery with host-directed therapies targeting inflammatory pathways, such as NLRP3 or RIPK1, could help mitigate tissue damage. Long-acting injectable or implantable formats may further strengthen adherence and treatment completion.

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