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NANOTECHNOLOGY DRIVEN DRUG DELIVERY APPROACHES FOR TUBERCULOSIS TREATMENT: A COMPREHENSIVE REVIEW

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ABSTRACT

Tuberculosis (TB), caused by *Mycobacterium tuberculosis,* continues to pose a worldwide health problem, particularly with the rise of multidrug-resistant (MDR) and extensively resistant to drug (XDR) strains. Inadequate the compliance of patients, long-term medication length, toxic effects of medicines, and inadequate bioavailability are among limitations of traditional TB therapies. Current developments in nanotechnology provide prospective answers to these issues by improving medication delivery, therapeutic effectiveness, and adverse effects. Various nanocarriers, including polymeric nanoparticles, liposomes, dendrimers, and niosomes, allow for targeted and prolonged drug release, higher bioavailability, and enhanced stability. These devices may encapsulate numerous medicines and are suitable for either pulmonary or oral delivery. Although its potential, nanotechnology-based TB medicines confront challenges such as large-scale manufacturing, approval by regulators, and long-term safety testing. Future initiatives include creating inhalable nanoformulations and stimuli-responsive nanocarriers for site-specific medication delivery. Further research and innovation are required to move these novel systems from experimental to clinical use, particularly in resource-limited settings where tuberculosis is most common.

KEYWORDS: *Mycobacterium tuberculosis*, Patient compliance, bioavailability, nanocarriers, Nanotechnology-based drug delivery systems (NDDS).

1. INTRODUCTION

The word “tuberculosis” was derived from the Latin word tubercula (meaning “small lump”) and the causative agent (tubercle bacillus) for the disease was discovered by Robert Koch in 1882.[1,2] After thousands of years, Causative agent of TB was established as the cause of TB in humans. Causative agent of TB is an intracellular bacterium with acid-fast properties that has evolved various mechanisms to evade destruction by macrophages.[3,4] Mycobacterium mainly targets the lungs; however, it is also capable of affecting other organs such as the kidneys, lymphatic system, central nervous system (causing meningitis), circulatory system (resulting in miliary tuberculosis), genitourinary tract, joints, and bones.[5] The effectiveness of tuberculosis treatment is influenced by several factors, including (a) the patient's adherence to the prescribed therapy, (b) nutritional deficiencies, (c) tobacco use, (d) concurrent illnesses such as HIV, and (e) insufficient monitoring by healthcare professionals."

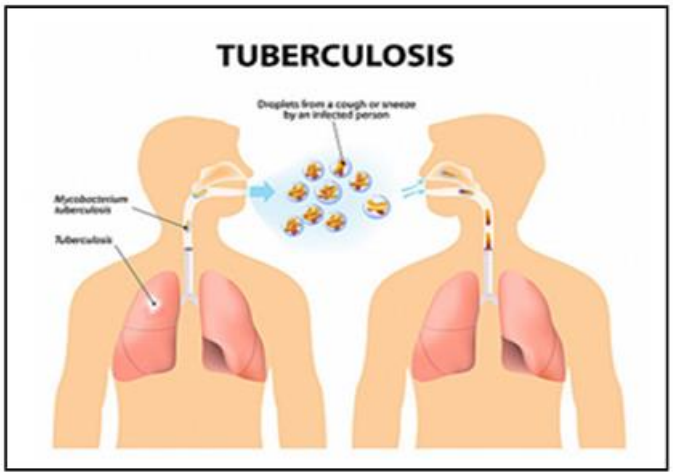

Figure 1: Mycobacterial infection.[6]

Tubercular disease is a contagious and potentially severe infection that primarily targets the lungs. It is transmitted from person to person through microscopic droplets expelled into the air when an infected individual coughs or sneezes. HIV compromises the immune system, making it less capable of defending against TB bacteria. In the United States, improved control efforts led to a decline in tuberculosis cases starting in 1993, though the disease still poses a public health concern. Numerous TB strains have developed resistance to commonly used antibiotics. To fully eliminate the infection and prevent drug resistance, individuals with active TB are required to undergo long-term treatment involving multiple medications.[7]

1.1 Forms of Tuberculosis (TB)[8]

- **Latent TB:** Bacteria stay inactive in the body for a long time without causing symptoms. Treated with a single medication for 9 months.
- **Active TB:** Bacteria grow and spread, leading to tissue damage and illness.

1.2 Types of Tuberculosis (TB)[9]

1. Pulmonary TB (Affects Lungs)

- **Primary TB Pneumonia:** Rare but highly infectious; causes fever and cough, common in young children, elderly, and immunocompromised individuals.
- **TB Pleurisy:** Infection spreads to the space between lungs and chest wall, causing fluid buildup, chest pain, and breathing difficulty.
- **Cavitary TB:** Forms lung cavities, Chronic cough, sweating at night, febrile episodes, and unintended weight loss.
- **Miliary TB:** Spreads throughout lungs, appearing as small nodules on X-ray; can be life-threatening.
- **Laryngeal TB:** Affects the voice box, highly contagious.

2. Extrapulmonary TB (Affects Other Organs)

- **Lymph Node TB:** Enlarges lymph nodes, may form skin fistulas.
- **TB Peritonitis:** Affects abdominal lining, causing fluid buildup and pain.
- **TB Pericarditis:** Causes fluid accumulation around the heart, affecting function.
- **Bone TB:** Often affects the spine, causing fractures and deformities.
- **Renal TB:** Affects kidneys, may impact reproductive organs.
- **Adrenal TB:** Can lead to adrenal gland failure, causing weakness and collapse.
- **TB Meningitis:** Infects brain lining, causing headaches, coma, and possible stroke-like symptoms.

1.3 Symptoms of Tuberculosis (TB)[10]

- Persistent cough (sometimes with mucus or blood).
- Chills and fever.
- Fatigue and loss of energy.
- Unexplained weight loss.
- Loss of appetite.
- Night sweats.
- Blood in sputum.

1.4 Serious TB Warning Signs (Seek Immediate Medical Attention)

- **Neurological symptoms**: Headache, vomiting, drowsiness, irritability, neck stiffness, or seizures (possible TB meningitis).
- **Persistent meningitis**: Symptoms not improving with treatment, or signs of increased brain pressure.
- **Organ enlargement**: Enlarged liver and spleen (indicating widespread TB infection).
- **Abdominal swelling**: Fluid buildup (ascites).
- **Respiratory distress**: Shortness of breath and swelling in the limbs (pericardial effusion).

1.5 Causes of Tubercular disease

- TB is transmitted through tiny droplets in the air when an infected individual coughs or sneezes.
- It is not as easily transmitted as the flu or a cold.
- Infection requires prolonged close contact, typically for several hours.
- TB is more likely to spread among household members living together.
- Casual contact, such as sitting next to an infected person on public transport, rarely leads to infection.
- Not all TB cases are contagious.
- TB in children or infections outside the lungs (extrapulmonary TB) do not spread to others.

1.6 Key Risk Factors for TB[11]

- **Exposure Risk:** Depends on air contamination and duration of exposure.

- **High-Risk Groups**

➢ Close contact with TB patients.
➢ People from high TB regions (Latin America, Caribbean, Africa, Asia except Japan).
➢ Residents/workers in nursing homes & prisons.
➢ Recent TB infection (within 2 years).
➢ Substance abusers (alcohol/drugs).
➢ Certain medical conditions (diabetes, cancer, kidney disease, underweight, lung diseases, immune disorders).

1.7 Modes of Transmission

- **Ingestion:** Consuming infected material can lead to throat or intestinal TB. This can happen through swallowing infected sputum or drinking contaminated milk from diseased cows.
- **Skin Contact:** Rarely, TB bacteria can enter through skin wounds from infected pus or tissue.
- **Transplacental:** In rare cases, an infected mother can pass TB to her baby before birth.

1.8 Diagnosis of Tuberculosis[12]

A. Screening (High-Risk Groups)

- Children living with a person diagnosed with infectious TB.
- HIV-positive children.
- Children under five years old.
- Children with severe malnutrition.

B. Clinical Diagnosis of TB

1. Pulmonary TB is identified by

- A cough lasting three or more weeks
- Coughing up blood
- Breathing difficulties
- Chest discomfort
- Reduced appetite and Loss of body mass
- General weakness and fatigue
- Nocturnal perspiration and fever

2. For extrapulmonary TB; diagnosis is based on the specific symptoms associated with the affected organ.

C. Radiological Diagnosis

Pulmonary tuberculosis can be detected using chest X-rays, which help identify lung abnormalities.

D. Methods for Detecting Mycobacterium Species[13]

1. Microscopy

- Uses Acid-Fast Staining to identify mycobacteria, which retain dye even after acid-alcohol treatment.
- Ziehl-Neelsen (Carbol-Fuchsin) Staining: Mycobacteria appear red against a blue background.
- Fluorochrome Staining (Auramine-O, Auramine-Rhodamine): Mycobacteria appear as fluorescent yellow-orange rods against a pale background.
- Detects 5,000–10,000 bacteria per ml with a sensitivity of 46–78% and nearly 100% specificity, depending on sample type and bacterial strain.

1.8 Multidrug-Resistant Tuberculosis (MDR-TB)

- MDR-TB occurs when TB bacteria become resistant to at least two primary TB drugs.
- It develops due to improper or incomplete treatment.
- Treatment lasts nearly two years, using second-line drugs**,** which are costly, complex, and have severe side effects.
- Many second-line drugs are highly toxic and cause severe side effects.

A. Extensively Drug-Resistant TB (XDR-TB)

XDR-TB is an even more severe form of MDR-TB, posing a serious public health threat. It is resistant to fluoroquinolones and at least one of the three injectable second-line drugs.

B. TB Drug Regimens

1) First-Line Drugs

- TB is primarily treated with a combination of **isoniazid, rifampin, pyrazinamide, and ethambutol** for several months.
- These oral medications are highly effective against *Mycobacterium tuberculosis* (Mtb).

2) Second-Line Drugs:

- When TB becomes resistant to isoniazid and rifampin, it develops into MDR-TB**,** requiring stronger medications.

- Second-line drugs include:
- **Aminoglycosides**: Amikacin, Kanamycin
- **Polypeptides**: Capreomycin, Viomycin, Enviomycin

- **Fluoroquinolones**: Ciprofloxacin, Levofloxacin, Moxifloxacin
- **Thioamides**: Ethionamide, Prothionamide, Cycloserine

- These drugs are more toxic, costly, and require longer treatment durations than first-line drugs.

2. Nanotechnology-Based Drug Delivery for TB Treatment[14]

In recent years, researchers have explored the emerging use of nanotechnology-based therapy as an alternative to administering antibiotics or other drugs in their free form. This approach involves delivering medications encapsulated within nanoparticles. Nanocarriers are a promising approach for drug delivery, offering benefits like improved bioavailability, drug protection, controlled release, and reduced dosage with fewer side effects. Various nanocarriers, including polymeric nanoparticles, micelles, liposomes, and solid lipid nanoparticles, have been developed to target Mtb reservoirs.[15]

2.1 Nanoparticles and Tuberculosis

Nanotechnology-driven drug delivery systems primarily comprise various formulations, each possessing distinct functional and structural characteristics. These include colloidal drug delivery systems.[16] Nanoparticles, classified as submicron (<1 µm) colloidal particles, serve as carriers for drug delivery. For therapeutic applications, drugs can either be chemically attached to the particle's surface or integrated into its matrix. These nanoparticles are composed of biocompatible and biodegradable materials, including natural polymers (such as gelatin and albumin), synthetic polymers (like polylactides and polyalkylcyanoacrylates), or solid lipids (SLNR and NLCR).[17]

3. Benefits of Nanoparticle-Based Drug Delivery for Tuberculosis Treatment[18]

- Enhanced stability and prolonged effectiveness over time.
- Greater drug-loading capacity, allowing multiple medications to be encapsulated within the matrix.
- Reduced adverse effects compared to traditional drug formulations.
- Improved bioavailability through slow, sustained, and controlled drug release.
- Compatibility with various administration routes, such as oral intake and inhalation.
- Fewer side effects and better patient adherence to treatment.

4. Polymeric Nano-Carrier

1. Dendrimers: Dendrimers are artificial nanoparticles composed of multiple atoms organized into long, repetitive chains in a three-dimensional structure. These molecules have a diameter ranging from 5 to 10 nanometers and are highly versatile due to their unique shape and multifunctional properties. Dendrimers have been explored in combination therapy for tuberculosis (TB). Scientists have studied their use in delivering multiple drugs simultaneously to improve treatment outcomes and minimize the risk of drug resistance. By functionalizing dendrimers with various drugs or drug combinations, their effectiveness against tuberculosis can be significantly enhanced.[19]

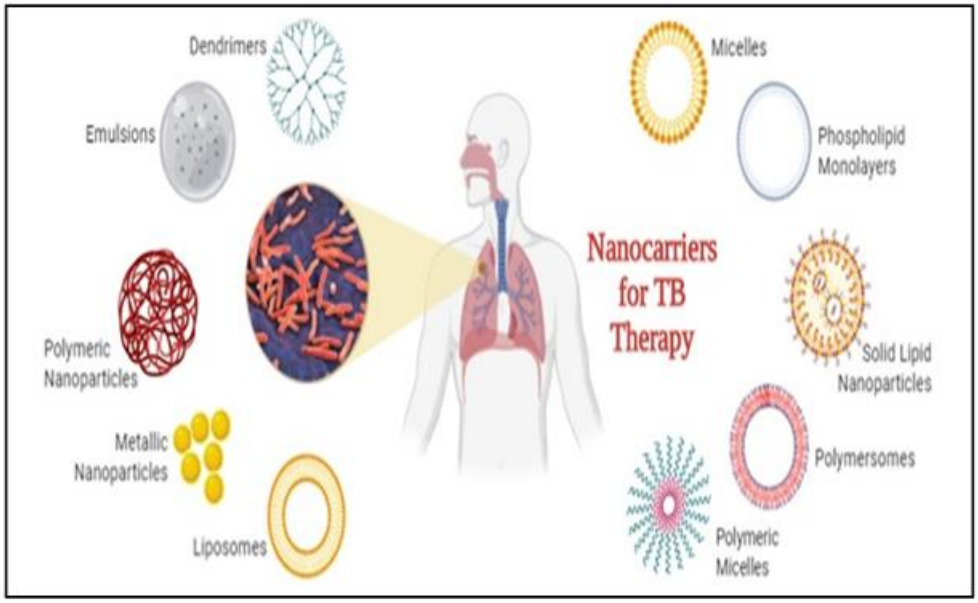

Figure no. 2: Nanomaterials that can serve as drug delivery platforms in tuberculosis therapy.[20]

2. Nanoemulsions

Nanoemulsions are stable oil-in-water (o/w) systems with particle sizes ranging from 10 and 100 nanometers. These systems have distinct advantages, such as their spontaneous generation, the ability to be produced on a large scale without demanding significant energy for homogenization, and their suitability for sterilization through filtration. Additionally, Nanoemulsions, which consist of lipid emulsions, are known to be readily taken up by the cells of the phagocytic system. Due to these properties, nanoemulsions hold promise as novel antimicrobial agents, particularly in enhancing the delivery and efficacy of drugs.[21]

3. Niosomes

Niosomes are membrane-bound vesicles that are biocompatible, non-immunogenic, and biodegradable, with the added benefit of flexibility in their structural design. These stable vesicles, similar to liposomes, are generated by various processes, such as hydrating cholesterol, incorporating charge-inducing components like charged phospholipids, and utilizing non-ionic surfactants. The merits of niosomes include improved stability, the ability to encapsulate a larger number of substances, and the convenience of not requiring special storage or handling conditions. Niosomes can trap hydrophilic drugs within their structure in central core, whereas, the water-loving drugs are trapped within their lipophilic domains, making them effective carriers for a variety of therapeutic agents.[22]

4. Lipid vesicles

Lipid vesicles are vesicular structures that vary in size from nano to microscale, consisting of a phospholipid bilayer that surrounds an aqueous core). In these vesicles, the core is designed to encapsulate water-soluble drugs, while the hydrophobic regions trap insoluble compounds. After administration, liposomes are typically recognized by phagocytic cells, leading to their fast elimination from the bloodstream.[23] To enhance their therapeutic effectiveness, liposomes are often modified with polyethylene glycol (PEGylation). Recent investigations have centered around the development of liposomes containing pyrazinamide and rifabutin. Research on liposomes encapsulating isoniazid (INH) and rifampin for lung-targeted delivery against *Mycobacterium tuberculosis* (MTB) infection has shown that these liposome-encapsulated drugs, even at or below therapeutic concentrations, are more effective than the free drug forms in treating TB.[24]

5. Polymeric and Non-Polymeric Nanoparticles

Polymeric nanoparticles (PNPs) are Frequently applied in drug delivery due to their ability to enhance drug solubility, improve stability, and enable targeted delivery. These systems offer high drug-loading capacity and are suitable for administration through various routes, making them a highly effective tactic for drug encapsulation.[25] Based on their configuration and purpose, PNPs can be sorted into two main types: **nanocapsules**, where the drug is enclosed within a polymeric shell, and **nanospheres**, where the drug is dispersed throughout the polymer matrix. These nanoparticles can encapsulate drugs dissolved in either water-based or oil-based environment, wrapped in a polymeric membrane. A wide range of biocompatible

materials is available for fabricating PNPs. Once administered, these nanoparticles are typically cleared from the body through opsonization followed by phagocytic removal.[26]

5. Drawbacks of Traditional Tuberculosis Treatment

Conventional tuberculosis treatment presents multiple challenges that hinder its effectiveness:

- **Extended duration of therapy**: Standard TB treatment typically spans 6 to 9 months, which can be difficult for patients to complete, increasing the risk of non-compliance.
- **Poor aqueous solubility**: Key anti-TB drugs such as rifampin and isoniazid exhibit limited solubility in water, which can affect their absorption and therapeutic performance.[27]
- **Low bioavailability**: Inefficient absorption of drugs can result in insufficient drug concentrations at the target site, particularly in pulmonary tissues.[28]
- **Unwanted effects and toxicity**: The administration of multiple drugs often leads to adverse effects, discouraging patients from maintaining the full course of therapy.[29]
- **Emergence of drug resistance**: Irregular adherence and incomplete treatment contribute to the rise of MDR and XDR tuberculosis strains resistant to multiple drugs.[30]

6. Current Research and Clinical Status

Although many nanotechnology-based TB drug delivery systems are still in the preclinical or early clinical development phases, a growing body of research has shown promising outcomes:

- **Increased drug absorption**: Nano formulations have significantly improved the bioavailability of anti-TB medications.[31]
- **Greater therapeutic effectiveness**: Enhanced performance has been observed, particularly against multidrug-resistant tuberculosis (MDR-TB) strains.
- **Lower dosing requirements and minimized side effects**: Controlled release mechanisms have led to reduced dosing frequency and better patient tolerance.[32]

However, there are still numerous hurdles that need to be overcome:"

- **Challenges in large-scale production**: Ensuring consistency and stability during manufacturing remains a key issue.
- **Complex regulatory hurdles**: Gaining approval for clinical use of nanomedicines involves navigating stringent and evolving regulatory frameworks.

- **Uncertainty regarding long-term safety and economic viability**: More data are required to assess the safety profile over time and determine cost-effectiveness in resource-limited settings.[33]

7. Prospective Advances in Nanotechnology for TB Treatment

The continued progress of nanotechnology in tuberculosis (TB) treatment hinges on addressing the existing challenges. Key areas of future development include:

1. Pulmonary Drug Delivery Systems

A promising area of research focuses on designing nanocarriers specifically for pulmonary administration. By developing inhalable nanoformulations, Drugs can be targeted straight to the lungs, the primary site of TB infection, ensuring more targeted and effective treatment.

2. Smart and Stimuli-Responsive Nanocarriers

Another exciting direction involves the creation of nanocarriers that release their drug payloads in response to specific environmental stimuli, such as changes in pH or temperature. These "smart" systems would enhance drug targeting while minimizing side effects by ensuring that the drug is released only in the infected areas.

3. Cost-Effective and Scalable Production

To make nanocarrier-based therapies viable for widespread clinical use, the development of affordable and efficient manufacturing processes is essential. Researchers are exploring methods to scale up production while keeping costs manageable, which would enable large-scale deployment of these advanced treatments.[34]

CONCLUSION

Tuberculosis (TB) continues to be one of the most persistent infectious diseases globally, especially in low- and middle-income countries. Despite the availability of conventional anti-TB drugs, the treatment is often complicated by long therapy durations, poor bioavailability, and the emergence of drug-resistant strains like MDR-TB and XDR-TB. These challenges have created an urgent need for innovative therapeutic strategies. Nanotechnology has emerged as a promising approach to address these limitations. By utilizing nanocarriers such as polymeric nanoparticles, liposomes, dendrimers, nanoemulsions, and niosomes, drug delivery can be more efficient and targeted, ensuring higher drug concentration at the site of infection with minimal systemic toxicity.

These nano-based systems offer numerous advantages, including controlled drug release, improved solubility, reduced dosing frequency, and enhanced patient compliance. Furthermore, targeted pulmonary delivery through inhalable nanoparticles shows particular promise for treating lung infections like TB. However, despite encouraging laboratory results, there are still several hurdles to overcome, such as large-scale production, cost-effectiveness, complex regulatory processes, and safety concerns over long-term use.

In conclusion, nanotechnology holds great potential to revolutionize TB treatment. Continued research, along with efforts to make these technologies clinically viable and accessible, is essential for effectively managing and eventually eradicating tuberculosis.

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