



ADVANCED METHODS TO TREAT TUBERCULOSIS

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Abstract: Tuberculosis (TB) remains a major global health concern, with increasing resistance to conventional antibiotics. This study explores the development of novel hybrid drug delivery systems incorporating inorganic components, such as metal nanoparticles and mesoporous silica, for enhanced TB treatment. These systems combine the benefits of nanotechnology and inorganic materials to provide improved drug loading, sustained release, and targeted delivery. Our results demonstrate that these hybrid systems exhibit enhanced antibacterial efficacy against *Mycobacterium tuberculosis*, reduced toxicity, and improved bioavailability. This study highlights the potential of novel hybrid drug delivery systems as a promising approach for improving TB treatment outcomes.

Keywords - Tuberculosis, Drug Delivery, Inorganic Components, Nanotechnology, Hybrid Systems.

I. INTRODUCTION

Tuberculosis (TB) is an infectious disease caused by the bacterium *Mycobacterium tuberculosis* and its spread through the air by people infected with the bacteria (by coughing). According to the World Health Organization (WHO), about a quarter of the world's population is infected with *M. tuberculosis* and may be at risk of developing the disease. TB usually affects a person's lungs (pulmonary TB), but it can spread to other parts of the body (extrapulmonary TB).

Tuberculosis is prevalent in low- and middle-income countries because it is associated with poverty, poor sanitation or hygiene practices, and is easily transmitted from person to person. However, high-income countries, including Canada, still report cases of tuberculosis, and the disease is considered an important public health problem. According to the Public Health Agency of Canada (PHAC), Canada has one of the lowest rates of active tuberculosis in the world. However, annual rates of tuberculosis have remained the same in the country since the 1980s rather than falling steadily. In 2017, PHAC reported 1,796 cases of active TB in Canada, with migrants and indigenous peoples having the highest rates of active TB in the country and about 70% of cases being pulmonary TB.

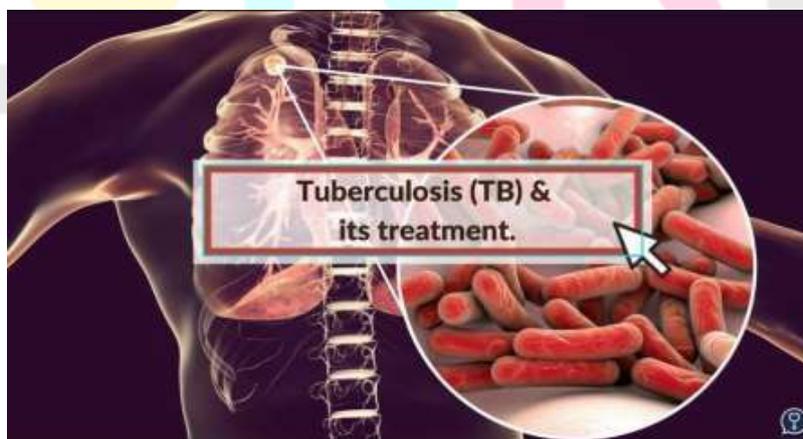


fig.1: tuberculosis and it's treatment

There are many published guidelines for the treatment of tuberculosis, and these guidelines can vary in quality and subject matter, which can make it difficult for healthcare professionals to choose the optimal treatment for patients with tuberculosis. The aim of this report is to review and critically appraise evidence-based guidelines for the treatment of tuberculosis.

In this review, we will discuss the advanced methods and technologies for the treatment of tuberculosis (TB).

This review is based on the study of various reviews and research, in this review the types of tuberculosis, the bacteria responsible and their treatment.

II. TYPES OF TUBERCULOSIS

Tuberculosis (TB) is an infectious disease that usually affects the lungs, but can also affect other parts of the body. When it affects the lungs, it is called pulmonary tuberculosis. Tuberculosis outside the lungs is called extrapulmonary tuberculosis. It can also be classified as active or latent. Active TB is contagious and causes symptoms. On the other hand, latent tuberculosis does not cause any symptoms.

Tuberculosis can be active or latent. Active tuberculosis is sometimes called tuberculosis disease. This is the type of tuberculosis that is contagious.

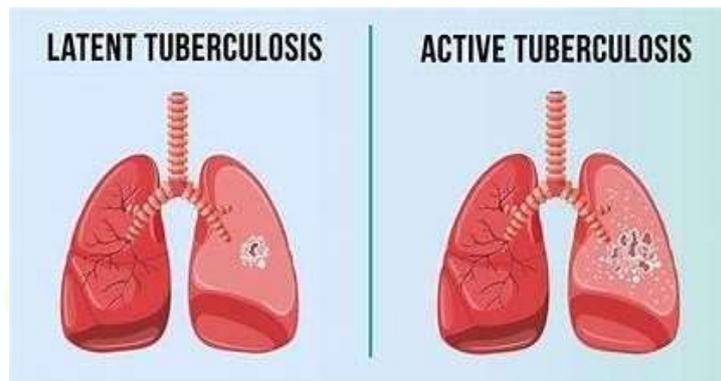


fig.2: types of tuberculosis

2.1 Active tuberculosis

Active TB, sometimes called TB disease, causes symptoms and is contagious. The symptoms of active tuberculosis vary depending on whether it is pulmonary or extrapulmonary.

But general symptoms of active tuberculosis include:

- unexplained weight loss
- loss of appetite
- fever
- cold
- fatigue
- night sweats

Active TB can be fatal if not treated properly.

2.2 Latent tuberculosis

If you have a latent TB infection, you have TB bacteria in your body, but they are inactive. This means you have no symptoms. You're not stuck yet. However, you will get a positive result in the blood and skin tests for tuberculosis.

Latent TB can develop into active TB in 5-10% of people. This risk is higher for people whose immune system is weakened by medication or an underlying disease.

2.3 Pulmonary tuberculosis

Pulmonary tuberculosis is active tuberculosis that affects the lungs. This is probably what most people think of when they hear about tuberculosis.

2.4 Extrapulmonary tuberculosis

Extrapulmonary TB is tuberculosis that affects parts of the body outside the lungs, such as the bones or organs. Symptoms depend on the part of the body affected.

2.5 Tuberculous lymphadenitis

Tuberculous lymphadenitis is the most common type of extrapulmonary tuberculosis and affects the lymph nodes. Skeletal tuberculosis

Skeletal tuberculosis, or bone tuberculosis, is tuberculosis that spreads to the bones from the lungs or lymph nodes. It can affect any of your bones, including your spine and joints.

2.6 Hepatic tuberculosis

Hepatic tuberculosis is also called hepatic tuberculosis. It occurs when tuberculosis affects the liver. It accounts for less than 1% of all tuberculosis infections.

2.7 Gastrointestinal tuberculosis

The symptoms of gastrointestinal tuberculosis depend on the area of the tract infected

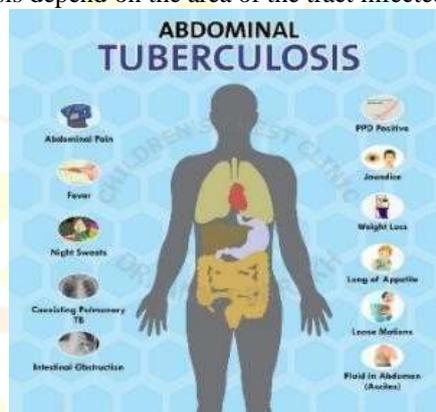


fig.3 abdominal tuberculosis

2.8 Tuberculosis meningitis

Also called meningeal tuberculosis, tuberculous meningitis spreads to the meninges, which are the membranes that surround the brain and spinal cord.

III. DIAGNOSIS

3.1 MEDICAL HISTORY

A healthcare professional will ask you questions about your medical history. For example, your healthcare professional may ask if you have:

- Symptoms of active tuberculosis
- Spend time with someone with active TB
- Have you ever had a positive blood or skin test for tuberculosis
- Have you ever been diagnosed with inactive TB or active TB in the past
- Factors that can increase your risk of infection with tuberculosis germs

3.2 PHYSICAL EXAMINATION

A physical examination is an essential part of every visit to your healthcare provider. She can:

Provide valuable information about your overall health,

Assist with diagnosis, and

Find out other factors that may affect TB treatment.

Tuberculosis infection screening test

There are two types of tests for TB infection: the TB blood test and the TB skin test. Ask your doctor which TB test is best for you.

Tuberculosis blood test

Tuberculosis blood tests (also called interferon gamma release assays or IGRAs) use a blood sample to determine if you are infected with tuberculosis germs. The tests measure how your immune system reacts when a small amount of blood is mixed with tuberculosis proteins.

IV. ADVANCE DRUG DELIVERY SYSTEM FOR TUBERCULOSIS

Various system can be used and these are as follows:

4. NDDS

NDDS are used to treat tuberculosis and include

4.1 NIOSOMES AND LIPOSOMES

Non-ionic surfactant-based vesicles (niosomes) are structures formed by the self-assembly of non-ionic amphiphiles in an aqueous environment, resulting in a closed bilayer structure. The assembly is rarely spontaneous and usually involves an input of energy such as physical agitation or heat

The result is an assembly in which the hydrophobic parts of the molecule are protected from the aqueous solvent and the hydrophilic head groups benefit from maximum contact with it. Rifampicin encapsulated in a Span 85 (sorbitan trioleate) ring in the range of 8-15 mm was found to accumulate in the lungs of mice, offering the possibility of improved anti tuberculosis therapy.

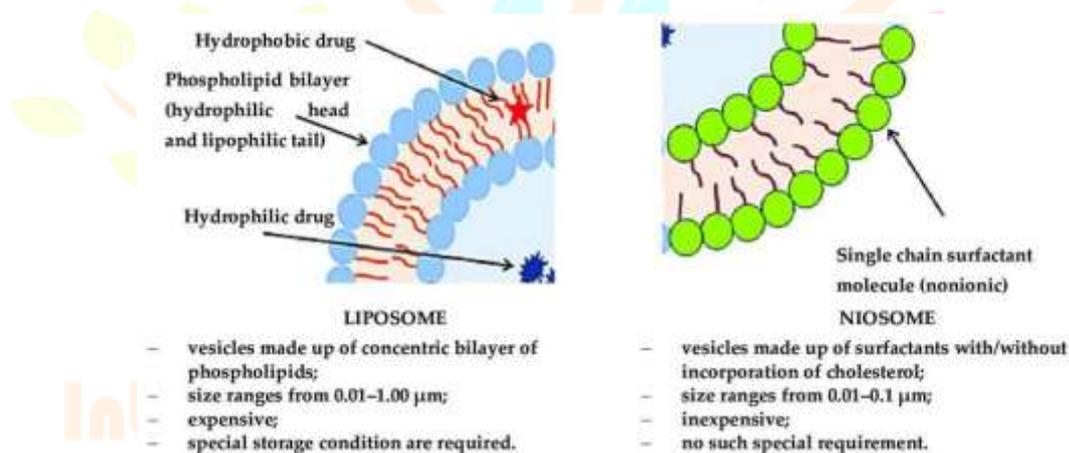


fig.4 niosome and liposome

Liposomes are concentric bilayer vesicles in which an aqueous volume is completely surrounded by a lipid bilayer membrane. These are the most studied systems for controlled drug delivery to the lung because they can be prepared using endogenous lung phospholipids as surfactants. They can bind a wide range of hydrophilic and hydrophobic drugs. Pulmonary delivery has been improved and even tested in animals and humans. Incorporation of drugs into liposomes increases bactericidal activity compared to free drug, particularly for the treatment of monocytes and macrophages. Drug delivery depends on the release of drug from the liposome, which can serve to retain the drug in the lungs and minimize its distribution to other organs. When administered intratracheally to sheep daily, amikacin in solution exhibits a half-life of approximately 2 hours with a peak plasma level of 8.3 μg/ml, whereas the half life of the drug encapsulated in a phosphatidylcholine/phosphatidylglycerol/cholesterol (4:3:3) liposome was found to last more than 10 hours with a plasma level of 3.3 μg/ml. Applications of liposomes include relatively low toxicity, preparation in a wide range of sizes (20 nm-1 μm), the ability to dissolve poorly water-soluble drugs, facilitating their nebulization, serving as a biodegradable pulmonary reservoir with an extended residence time. Due to their reduced mucociliary clearance of drugs due to their surface viscosity, they can be used as a targeting device in a specific population in the lung, particularly macrophages, infected or damaged alveolar cells, and pulmonary epithelium.

4.2 LIQUID CRYSTAL

4.2.1 Liquid Crystal Development

Three different phase diagrams were developed, differing only in the oil phase. All diagrams contained ethoxylated and propoxylated cetyl alcohol (Procetyl® AWS) as surfactant, deionized water for the aqueous phase and the oil phase, soy

phosphatidylcholine, oleyl amine and a 1:1 (m/m) oleyl amine/soy phosphatidylcholine mixture, each labeled D diagram, E diagram and F diagram respectively. For each diagram, 36 different formulations were prepared, with sizes ranging from 10 to 100 nm. 80% (w/w) of the above-mentioned ingredients. After adding all the ingredients, the formulations were homogenized with an Ultra Turrax (IKA-T25 base) at 13,000 rpm for 3 minutes, then left for 24 hours.

4.2.2 Incorporation of rifampicin into liquid crystal systems

Rifampicin incorporation occurred after addition of the drug at a concentration of $0.15 \mu\text{g mL}^{-1}$ soluble in the oil phase of the systems; then, other ingredients were added and homogenized as described previously. This concentration of rifampicin corresponds to 10 times the MIC value for Mtb strains

4.3 CHITOSAN-BASED POLYMER DRUG DELIVERY SYSTEM

Chitosan-based nanoparticles (chitosan-based nanocomposites; chitosan nanoparticles; ChNPs) are promising materials that have attracted much attention in the last decades. ChNPs have great potential as nanocarriers. They are able to encapsulate drugs as active ingredients and deliver them to a specific location in the body ensuring a controlled release. In the article, an overview of the most widely used preparation methods and applications developed in medicine was given. The presentation of the most important information about ChNPs, in particular the properties of chitosan in drug delivery systems (DDS), as well as the way to produce NPs, was mentioned. Furthermore, the specification and classification of the morphological characteristics of NPs determine their application, as well as the methods of binding drugs to NPs. The most recent scientific reports on DDS using ChNPs administered orally, ocularly, dermally and transdermal are considered.

4.3.1 Methods of manufacturing CHITOSAN

the steps and method to manufacture chitosan is described as diagrammatically as follow-

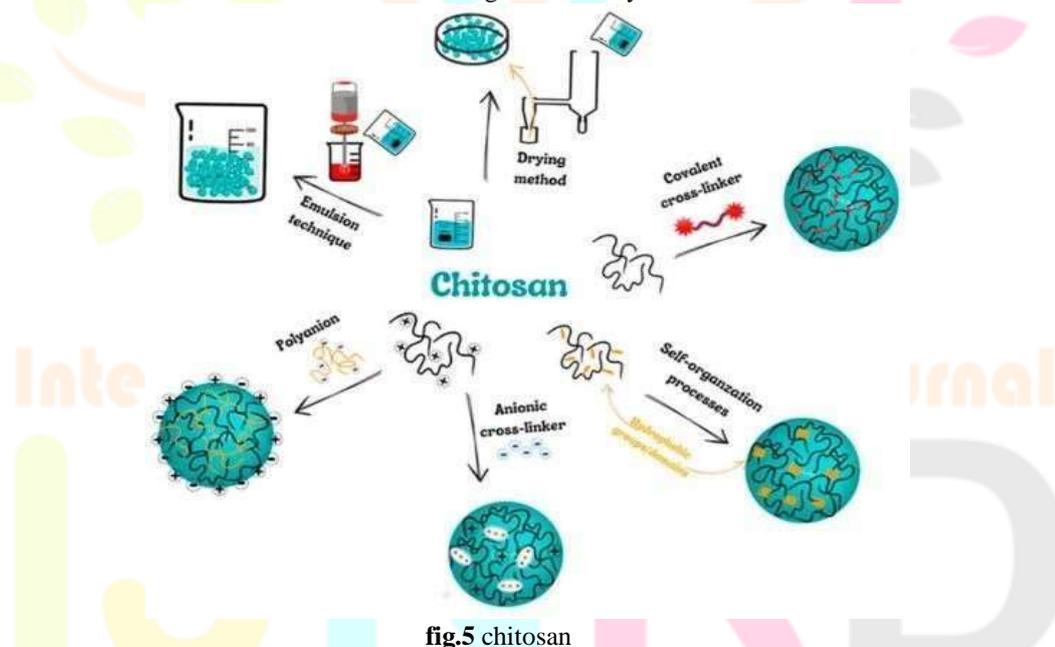


fig.5 chitosan

V. INORGANIC NANOPARTICLES

Inorganic nanoparticles play an important role in TB treatment and they are as follows:

5.1 GOLD NANOPARTICLES

Nanoparticles can cause oxidative stress, cell apoptosis, and damage to DNA, mitochondria, and cell membranes, which can have a negative effect on cells [52]. The great importance of nanomaterials is due to the strong dependence of properties on the size and shape of particles in the range of 1–100 nm, which is of interest for biological interactions. For example, particles with a diameter of less than 12 nm can cross the blood-brain barrier [53,54], and those with a diameter of 30 nm or less.

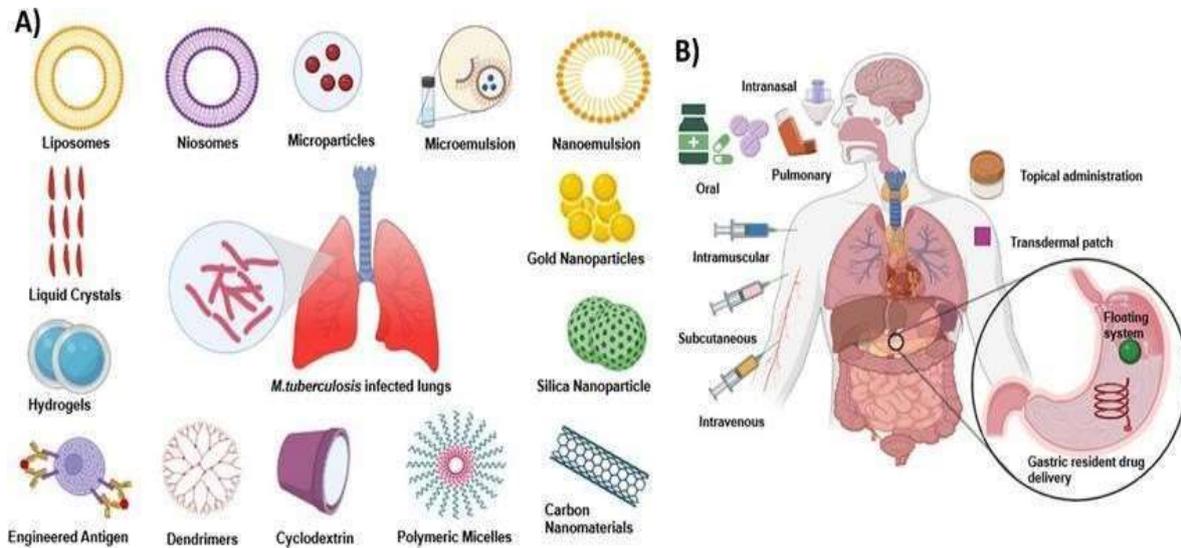


fig.6 gold nanoparticle

5.2 SILICA NANOPARTICLES

The synthesis of mesoporous silica nanoparticles containing silver bromide nanoparticles (MSNs- AgBrNPs) was carried out using a one-pot route for incorporation of silver ions followed by thermal treatment (Fig. 1A). Hybrid organic-inorganic mesoporous silica nanoparticles were first formed by the co-condensation of the silica precursor TEOS and the alkoxy silane TSD containing primary and secondary amine functional groups as anchor points for Ag⁺-complexation.

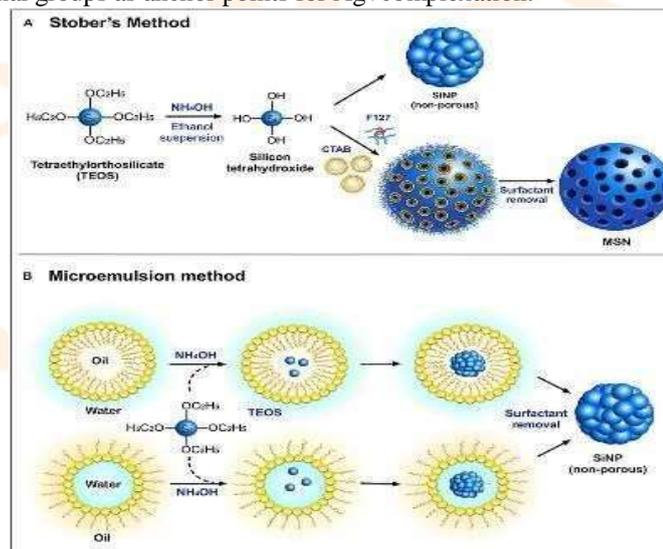


fig.7 silica nanoparticles

5.3 CARBON NANOTUBES

Carbon nanotubes (CNTs) have been studied as a potential tool in the treatment of tuberculosis (TB). Here are some ways in which CNTs can be used:

5.3.1 Drug delivery:

CNTs can be used as carriers for anti-tuberculosis drugs, improving their solubility, stability, and targeting ability. This can lead to more effective treatment and reduced side effects.

5.3.2 Targeted therapy:

CNTs can be functionalized to target specific cells or tissues, such as macrophages infected with Mycobacterium tuberculosis (M. tuberculosis). This targeted approach can improve the efficacy of treatment.

5.3.3 Immunotherapy:

CNTs can be used to deliver immunomodulatory molecules, such as cytokines or antigens, to stimulate an immune response against *M. Tuberculosis*.

5.4 MICROEMULSION IN THE TREATMENT OF TUBERCULOSIS

Microemulsions have been investigated as a potential tool in the treatment of tuberculosis (TB). Here is some information about their application:

5.4.1 Benefits of microemulsion in the treatment of tuberculosis

5.4.1.1 Improved Bioavailability:

Microemulsions can improve the solubility and bioavailability of anti-TB drugs, leading to better therapeutic outcomes.

5.4.1.2 Targeted Delivery:

Microemulsions can be designed to target specific sites in the body, such as the lungs, where *M. Tuberculosis* resides.

5.4.1.3 Reduced toxicity:

Microemulsions can help reduce the toxicity of anti-TB drugs by encapsulating them in a lipid-based carrier.

5.4.1.4 Improved patient compliance:

Microemulsions can be formulated as an oral or inhaled dose, making treatment more convenient and improving patient compliance.

5.4.2 Mechanism of microemulsions in the treatment of tuberculosis

5.4.2.1 Increased permeability:

Microemulsions can increase the permeability of anti-TB drugs across biological membranes, allowing for more effective treatment.

5.4.2.2 Inhibition of *M. tuberculosis* growth:

Some microemulsions have been shown to inhibit the growth of *M. tuberculosis* by disrupting the cell membrane or interfering with its metabolic processes.

5.5 NANOEMULSION IN THE TREATMENT OF TUBERCULOSIS

Nanoemulsions show promise in the treatment of tuberculosis, offering improved bioavailability, targeted delivery, and reduced toxicity.

- **Improved Bioavailability:** Nanoemulsions can improve the solubility and bioavailability of anti-TB drugs, leading to better therapeutic outcomes.
- **Targeted Delivery:** Nanoemulsions can be designed to target specific sites in the body, such as the lungs, where *M. tuberculosis* resides.
- **Reduced toxicity:** Nanoemulsions can help reduce the toxicity of anti-TB drugs by encapsulating them in a lipid-based carrier.
- **Improved patient compliance:** Nanoemulsions can be formulated as an oral or inhaled dose, making treatment more convenient and improving patient compliance.

5.5.1 Mechanism of nanoemulsions in the treatment of tuberculosis

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- **Inhibition of *M. tuberculosis* growth:** Some nanoemulsions have been shown to inhibit the growth of *M. tuberculosis* by disrupting the cell membrane or interfering with its metabolic processes.

VI. CONCLUSION

Tuberculosis is a potentially fatal disease affecting the human lungs. It is caused by the bacterium *Mycobacterium tuberculosis*.

The integration of inorganic components, such as metal nanoparticles, carbon nanotubes, and mesoporous silica, into novel drug delivery systems offers a promising approach to improve the treatment of tuberculosis. These hybrid systems provide improved drug loading, sustained release, and targeted delivery, leading to increased antibacterial efficacy and decreased toxicity. The incorporation of inorganic components can also provide additional functionalities, such as imaging and diagnostics, to the drug delivery system. However, more research is needed to fully explore the potential of these hybrid systems and to address the challenges associated with their development and clinical translation. Future directions

- Scalability and cost effectiveness: Development of efficient and scalable methods for the production of hybrid drug delivery systems.
- Toxicity and biocompatibility: assessment of toxicity and biocompatibility of inorganic components and their impact on the overall safety of the drug delivery system.
- Targeted delivery and imaging: investigate the potential of hybrid drug delivery systems for targeted delivery and imaging in the treatment of tuberculosis.
- Combination therapies: investigate the potential of combining hybrid drug delivery systems with existing anti-TB drugs to improve treatment outcomes.

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