

# Targeted Delivery of Nanoparticles for the Treatment of Lung Disease (Tuberculosis)

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**Abstract:** Tuberculosis, commonly known as TB, is the second most fatal infectious disease after AIDS, caused by bacterium called *Mycobacterium tuberculosis*. Prolonged treatment, high pill burden, low compliance, and stiff administration schedules are factors that are responsible for emergence of MDR and XDR cases of tuberculosis. Till date, only BCG vaccine is available which is ineffective against adult pulmonary TB, which is the most common form of disease. Various unique antibodies have been developed to overcome drug resistance, reduce the treatment regimen, and elevate the compliance to treatment. Therefore, we need an effective and robust system to subdue technological drawbacks and improve the effectiveness of therapeutic drugs which still remains a major challenge for pharmaceutical technology. Nanoparticle-based ideology has shown convincing treatment and promising outcomes for chronic infectious diseases. Different types of Nanocarriers have been evaluated as promising drug delivery systems for various administration routes controlled and sustained release of drugs is one of the advantages of Nanoparticle based Antituberculosis drugs over free drugs.

**Keywords:** Anti tuberculosis drug, Nano particles, MDR (Multi Drug Regimen), XDR (Extensively Drug Resistance), Nano carriers.

## 1. Introduction

Tuberculosis (TB) is a potentially serious infectious disease that mainly affects your lungs. The bacteria that cause tuberculosis are spread from one person to another through tiny droplets released into the air via coughs and sneezes.

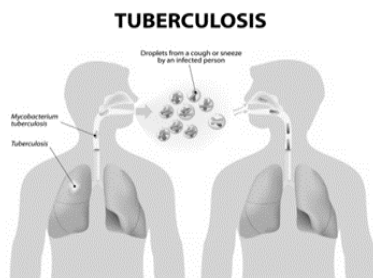


Fig. 1. Tuberculosis

Once rare in developed countries, tuberculosis infections began increasing in 1985, partly because of the emergence of

HIV, the virus that causes AIDS. (2) HIV weakens a person's immune system so it can't fight the TB germs. In the United States, because of stronger control programs, tuberculosis began to decrease again in 1993, but remains a concern.

Many strains of tuberculosis resist the drugs most used to treat the disease. People with active tuberculosis must take several types of medications for many months to eradicate the infection and prevent development of antibiotic resistance.

## 2. Symptoms

Although your body may harbor the bacteria that cause tuberculosis (TB), your immune system usually can prevent you from becoming sick. For this reason, doctors make a distinction between

- Latent TB. In this condition, you have a TB infection, but the bacteria remain in your body in an inactive state and cause no symptoms. Latent TB, also called inactive TB or TB infection, isn't contagious. It can turn into active TB, so treatment is important for the person with latent TB and to help control the spread of TB. An estimated 2 billion people have latent TB.
- Active TB. This condition makes you sick and in most cases can spread to others. It can occur in the first few weeks after infection with the TB bacteria, or it might occur years later

## 3. Signs and symptoms of active TB include



Fig. 2. Coughing up blood

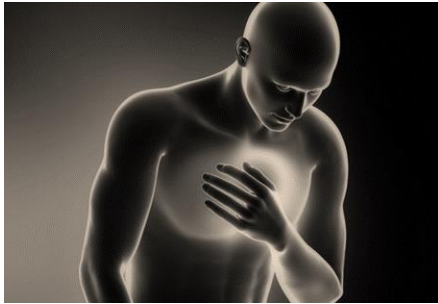


Fig. 3. Chest pain, or pain with breathing or coughing



Fig. 4. Unintentional weight loss



Fig. 5. Fatigue



Fig. 6. Fever

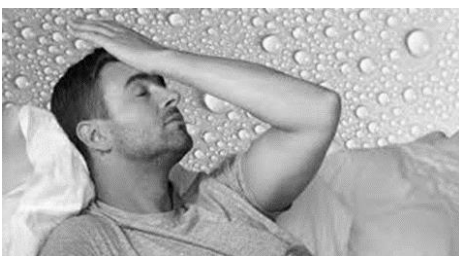


Fig. 7. Night sweats



Fig. 8. Chills



Fig. 9. Loss of appetite

Tuberculosis can also affect other parts of your body, including your kidneys, spine or brain. When TB occurs outside your lungs, signs and symptoms vary according to the organs involved. For example, tuberculosis of the spine may give you back pain, and tuberculosis in your kidneys might cause blood in your urine.

#### A. Causes

It's spread when a person with active TB disease in their lungs coughs or sneezes and someone else inhales the expelled droplets, which contain TB bacteria. Although TB is spread in a similar way to a cold or the flu, it isn't as contagious.

You would have to spend prolonged periods (several hours) in close contact with an infected person to catch the infection yourself.

For example, TB infections usually spread between family members who live in the same house. It would be highly unlikely for you to become infected by sitting next to an infected person on a bus or train.

Not everyone with TB is infectious. Children with TB or people with a TB infection that occurs outside the lungs (extra pulmonary TB) don't spread the infection.

#### 4. History

In 1867, tuberculosis (TB) was the leading cause of death in Canada. The bacterium that causes TB, the tubercle bacillus, was discovered by a German scientist, Robert Koch, in 1882. Proof that TB was contagious led to organized efforts to isolate those infected in sanatoria -- special hospitals where patients could rest and get fresh air and a good diet. The "rest cure" was the most common treatment for TB until antibiotic treatment was developed in the 1950s. (3)

Another form of treatment was "collapse therapy." Surgeons

pumped air into the chest cavity so the lung could relax and the tuberculosis lesion could heal. The use of collapse therapy was first recorded in Ingersoll, Ontario in 1898, but it did not become standard Canadian practice until 1919.

The first tuberculosis survey in Canada was conducted in 1921 by the Saskatchewan Anti-Tuberculosis Commission to determine the rate of infection among school children. The survey found that more than half of the children were infected with TB.

Travelling TB clinics began in Ontario in 1923 and were soon used in every province. The clinics could diagnose, treat and follow-up with TB patients and their contacts.

Mobile x-ray machines could to find TB before people showed external symptoms, which made treatment far more effective.



Fig. 10. Woman being tested for tuberculosis on the Ontario Tuberculosis Association Chest X-Ray Train, Northern Ontario [ca. 1950]

*Streptomycin* was discovered in 1946 -- the first specific antibiotic that could kill the TB-causing bacterium. This and other antibiotics became widely used against TB in the 1950s.

Antibiotic treatment and a gradual decline in the incidence of tuberculosis led to shorter stays in sanatoria. The number of TB beds in Canada dropped from 18,977 in 1953 to 9,722 in 1963 and by the 1970s, only a small number of TB patients were admitted to hospital. Today, drug therapy is the only type of treatment prescribed by doctors. However, ensuring that patients take the full-course of drugs, which usually requires several months, remains a problem.

TB is still considered one of the deadliest infectious diseases, especially in developing countries.

#### A. Pathogenesis of tuberculosis

Progression of the tuberculosis granuloma. (4) The cycle of TB infection begins with dispersion of *M. tuberculosis* aerosols. A dose of one to 10 bacilli is dispersed throughout the air, making the risk of transmission likely. In the patient's lung, the bacilli are phagocytized by alveolar macrophage cells, which then invade the underlying epithelium. Here, monocytes from nearby blood vessels form the beginning of a granuloma, as the immune system attempts to ward off the disease. This is a hallmark characteristic of tuberculosis.

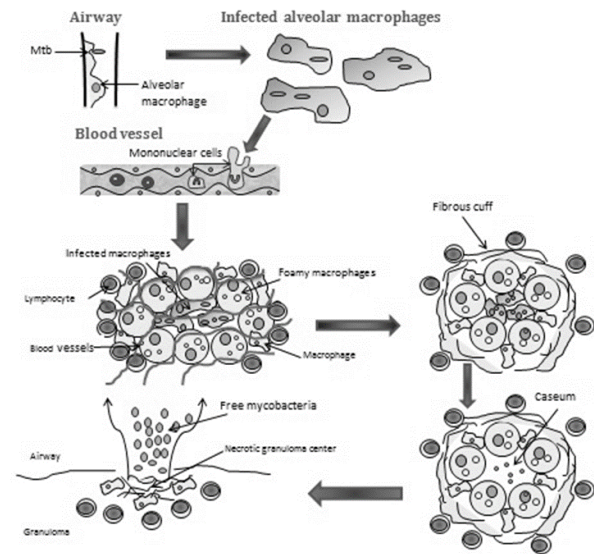


Fig. 11. Tuberculosis

Within the granuloma, a core of infected macrophages is surrounded by foamy macrophages, mononuclear phagocytes, and lymphocytes. The result is a fibrous capsule with increased foamy macrophages, presumed to create the typical caseous debris (necrotic tissue resembling cheese) in the center of the granuloma. Although it appears contained immunologically, the caseous center tends to liquefy and cavitate as it empties thousands of *M. tuberculosis* bacilli into the airway. The cycle is complete as the damaged lungs produce a cough that, once again, contains the highly transmissible infectious droplet nuclei.

Infected macrophages may be carried by the lymphatic system to the lungs, lymph nodes, kidneys, epiphyses of the long bones, and other areas of the body. Infected macrophages may also be carried in the blood of an immunocompromised host (eg., AIDS patient). After three to eight weeks, despite widespread infection, there are no immediate symptoms or signs other than a positive TB skin test (TST). In children, the elderly, non-white races, and AIDS patients, the disease progresses quickly to pneumonia from hilar or mediastinal lymph nodes to cavitation in the bronchi. It is here that the distribution of caseous material occurs, such as in acute miliary TB (disseminated disease) or TB meningitis, particularly in children. Patients infected at ages over 30 years and less than 65 years have a better prognosis compared to children, adolescents, young adults, and the elderly because they have a lower risk of tissue necrosis.

In general, hypersensitivity develops during the three-to-eight-week period after infection, signaling the action of cellular immunity and control of the infection. At this time, a skin test reaction will be positive indicating latent infection exists. However, as previously stated, in high risk groups, progression of disease to cavitation in the lung and

hematogenous dissemination are likely to occur.

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### 5. Multidrug-Resistant Tuberculosis (MDR-TB)

This is onerous form of tuberculosis (TB) defined by resistance to at least two of the standard four drug anti-TB medicines (first-line antituberculosis drugs) (7).

Inadequate or inconsistent treatment has allowed MDR-TB to emerge and spread quickly. Today, the treatment for drug-resistant TB takes almost two years and, in addition, the treatment is so complex, expensive, and toxic that MDR-TB patients struggle to live (8) Treatment of MDR-TB consists of second-line drugs. Many second-line drugs are lethal and have

harsh side effects. Treatment for MDR-TB is administered for 2 years or more than that and involves daily injections. All these components hold a significant challenge to governments and health care departments. World Health Organization aims to treat 80% of the MDR-TB cases by 2015. Without unique, simple, and inexpensive treatments for MDR-TB, this is next to impossible. WHO predicted that more than 2 million people would have developed MDR-TB between 2011 and 2015 (9).

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

XDR-TB poses a major risk to public health. This is more brutal form of MDR-TB and is characterized by resistance to any fluoroquinolone and at least one of the three injectable second-line drugs (10). This makes this XDR-TB treatment extremely problematic. In the year 2006, XDR-TB outbreaked in KwaZulu-Natal, South Africa; 52 out of 53 people who contracted the disease died within few months (11) 70% of XDR-TB patients were estimated to die within a month of diagnosis. Estimation by WHO suggested that roughly 5% of MRD-TB cases are XDR-TB.

#### B. Drug regimens

##### 1) First-line drugs

In general, tuberculosis is treated with first-line drugs as a combination therapy with isoniazid, rifampin, pyrazinamide, and ethambutol for several months. These drugs are administered orally and have outstanding effectiveness against *Mtb* (12).

##### 2) Second-line drugs

When *Mtb* strain is resistant to isoniazid and rifampin, two of the most powerful first-line drugs, it develops into more complex form of TB known as MDR-TB. A combination of second-line drugs used to cure MDR-TB is aminoglycosides such as amikacin and kanamycin, polypeptides such as capreomycin, viomycin, and enviomycin, fluoroquinolones such as ciprofloxacin, levofloxacin, and moxifloxacin, and thioamides such as ethionamide, prothionamide, and cycloserine. Second-line drugs are more lethal and are more expensive than first-line drugs, and treatment may last much longer (13).

### 6. Nanotechnology-Based Therapies

Over the past few years, the budding use of nanotechnology-based therapy has been researched for replacing the administration of antibiotics or other drugs in the free form with an access using drugs that are encapsulated with nanoparticle (14).

#### 1) Nanoparticles and tuberculosis

Nanotechnology-based drug-delivery systems are mainly consists of different formulations, each of them contains different functional and structural properties Colloidal drug delivery systems (15).

Problems with conventional drug delivery systems:

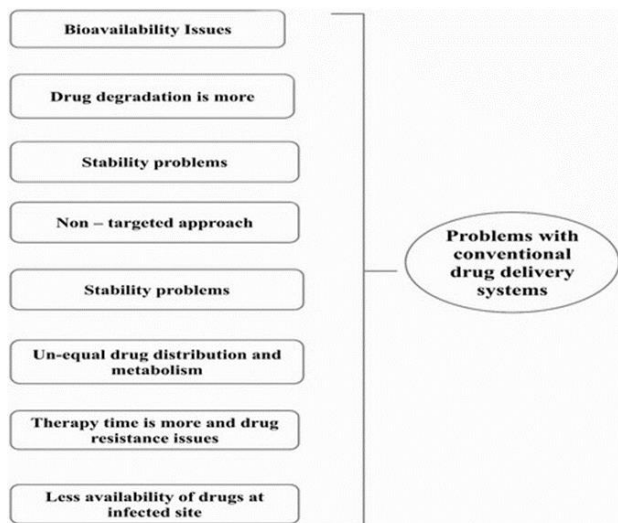


Fig. 12. Advantages of nanotechnology-based drug delivery systems

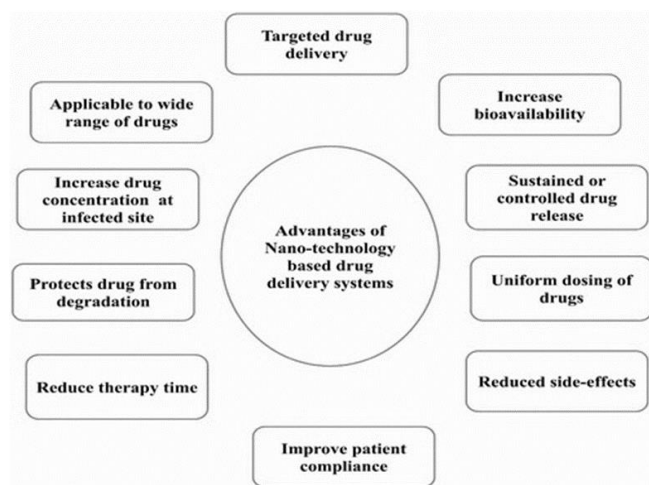


Fig. 13. Tuberculosis

**B. Novel carrier system in MDR-TB and XDR-TB**

**1) Nano dispersions**

Nano dispersions are submicron dispersions which are generally colloidal in nature of pure drugs which is stabilized via use of different surfactants. They also improve the solubility profile drugs. They are thermodynamically stable with the size of droplet mostly ranges between 10 and 100 nm. They can host hydrophilic drugs inside core and lipophilic drugs within hydrophobic domains respectively.

**C. Polymeric micelles**

These are nanocarrier systems which are generated by the self-assembly or self-arrangement of a polymers in water above its critical micellar concentration (CMC). They are also effective in high drug-loading and drug release, specifically in the case of anti-tubercular drugs. It was found during study that large micelles were found by increasing the poly-ethylene glycol concentration. Rifampicin was found to be entrapped within the system appropriately.

**7. Conclusion**

There is no magic bullet for surmounting the TB and DR-TB epidemics. However, given our current trajectory in TB programs, research, and drug development, there is little reason to believe that we will turn the tide against the rising DR-TB epidemic in the near future. Though development of novel TB drugs remains a priority, the scarcity of drug candidates in the development pipeline combined with the exponential increase of DR-TB incidence and prevalence forces the medical community to consider plausible alternatives. Nanotechnology is this alternative: it takes current chemotherapy and utilizes it more efficaciously.

The primary advantages are decreased frequency and duration of treatment via sustained concentration profiles and targeted delivery. These advantages will likely improve completion rates by reducing the burden on both the patient and to health infrastructure itself, such as making the DOTS program more manageable and affordable. In contrast to high-income countries where death from DR-TB is virtually non-existent, the importance of this technology in reducing treatment burden in low-income countries cannot be overstated: DR-TB is a death sentence to people in these communities. Moreover, DR-TB is often allowed to run unchecked throughout these regions, perpetuating a deadly and worsening cycle of drug resistance. By using readily available technology, nanoparticle delivery of ATDs provides a logical, cheap, and attractive solution.

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