Review Article

Novel Drug Delivery Approaches to Tuberculosis: A Review

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ABSTRACT

Tuberculosis (TB) remains the deadliest infectious disease. Tuberculosis is a ubiquitous, highly contagious chronic granulamatous communicable bacterial infectious disease caused by Mycobacterium tuberculosis and other species of same genera. Drug delivery, which takes into consideration the carrier, the route and the target, has evolved into a strategy of processes or devices designed to enhance the efficacy of therapeutic agents through modified or controlled release. This may involve enhanced bioavailability, improved therapeutic index, or improved patient acceptance or compliance. Clinical management of tuberculosis posses serious problem because the efficacy of chemotherapy has been reduced which may be attributed to the degradation of drugs before reaching the target, the low level of cell permeability to drugs, or primary drug resistance. Other reason for the failure of chemotherapy may be the difficulty in achieving adequately high concentration at the infection site, inadequate penetration of drug into macrophages and low level in cells. Designing and developing a site-specific delivery of antitubercular drug through various novel drug delivery systems may overcome these problems, which arise with conventional dosage forms of antitubercular drugs. The aim is to review briefly the problems related to treatment of drug-susceptible and drug-resistant tuberculosis (TB), describe recent advances in the development of new drug delivery approach for tuberculosis and thereby encouraging advances in TB drug research.

INTRODUCTION

Tuberculosis is a ubiquitous, highly contagious chronic granulamatous communicable bacterial infectious disease caused by Mycobacterium tuberculosis and other species of same genera. Tuberculosis, which is easily transmitted through the air, already infects 1.9 billion people, and takes the lives of about two million people each year. The situation has been excerbated because of the presence of numerous other complicating factors like multi drug resistant tuberculosis and HIV-coinfection. Tuberculosis is a leading cause of death amongst infectious diseases. Furthermore, this re-emerging disease has become one of the most important infections affecting human immunodeficiency virus (HIV)-positive patients worldwide. TB also is becoming increasingly resistant to existing drugs. In 1993, the World Health Association declared TB a “global emergency”, since almost one-third of the world population is infected with M. tuberculosis. Largely because it has been neglected as a public health issue for many years, it is estimated that between 1997 and 2020 nearly 1 billion people will become newly infected and 70 million will die from the disease at current control levels[1]. It is estimated by the World Health Organization (WHO) that more than 2 billion people in the world are infected with Mycobacterium tuberculosis [2].

History

Before the discovery of specific antibiotics for the treatment of tuberculosis, there was no cure. Mortality of those with pulmonary disease (disease of the lungs) was about 50%. The introduction of anti-tuberculosis drugs in the 1950s and the development of the various drug regimens meant that by the 1980s there was a 98% chance of cure. However, treatment had to be continued with good quality drugs for as long six months to ensure cure. The difficulties in ensuring this occurs, especially in resource poor countries, has resulted in an increasing incidence of tubercle bacteria resistant to the most effective drugs; so called multi-drug resistant tuberculosis[3].For these reasons, it is vital that new medications are developed to shorten the duration of therapy, increase the dosing interval of

intermittent regimens and replace agents lost to resistance. Other special considerations include identifying optimal therapy for persons with acquired immune deficiency syndrome, particularly noting the problems of drug/drug interactions for those receiving antiretroviral treatment[4].

Causes and symptoms

Two types of tuberculosis bacilli that affect the human.

- ✓ Mycobacterium tuberculosis (endemic in man) is transmitted by inhalation of the organism in droplets.
- ✓ Mycobacterium bovis (endemic in cattle) is transmitted by ingestion of infected milk.

Tuberculosis is either latent (dormant) or active.

- ✓ Latent tuberculosis means that patient have the causing bacteria in their body, but cannot spread the disease to other. However, you can still develop active tuberculosis.
- ✓ Active tuberculosis means the infection is spreading in the body and; if their lungs are infected, they can spread disease to others[5].

Symptoms

Tuberculosis pleuritis may occur in 10 % of people who have the lungs disease from tuberculosis. The pleural disease occurs from the receptor of diseased area into the pleural space, the space between your lungs and lining of abdominal cavity. These people have a non-productive cough, chest pain and fever; the disease may go away and then come back at a date.

In a minority of people with weekend immune system, tuberculosis bacteria may spread through their blood to various parts of their body. This is called miliary tuberculosis and produces fever, weakness, and loss of appetite.

Symptoms of active tuberculosis include

Ongoing cough, that brings up thick cloudy and sometimes bloody mucus (sputum) from the lungs. Fatigue, weight loss, night sweats and fever, rapid heartbeat, swelling in the neck, shortness of breath and chest pain (in rare cases)[6].

Mycobacterium Tuberculosis

Pathogenic mycobacteria cause diseases of diverse nature and varying severity[7] .The term mycobacteria is used to designate 3 species of same the genus: M tuberculosis, M bovis, M africanum. Humans are the only reservoir for Mycobacterium tuberculosis. The organism is an aerobic, nonmotile, non-spore-forming bacillus. The cell wall is complex and contains a large amount of high-molecular-weight lipids. This makes mycobacteria resistant to many disinfectants as well as to common laboratory stains such as Gram's stain. The organism is slow growing, with visible growth on appropriate media taking from 4 to 6 weeks[8]. One characteristic but not distinctive morphologic property of M. tuberculosis is the tendency to form cords or dense clusters of bacilli aligned in parallel[9].

Structure of Mycobacterium tuberculosis

Mycobacterium tuberculosis is a rod-like obligate aerobe (Fig. 1 and 2) with filaments; clumped growth. It is a complex bacteria having a mold-like appearance (mycobacterium means fungus-like bacteria).

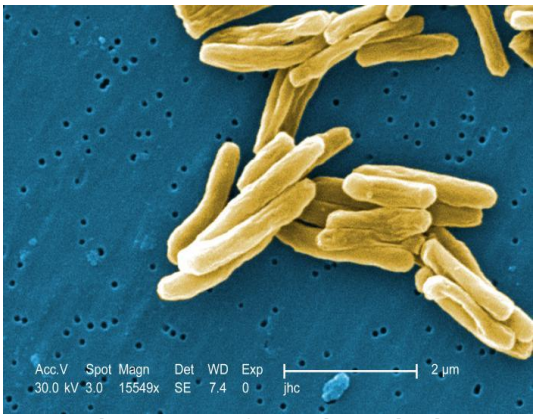


Fig.1: SEM of *M. tuberculosis*

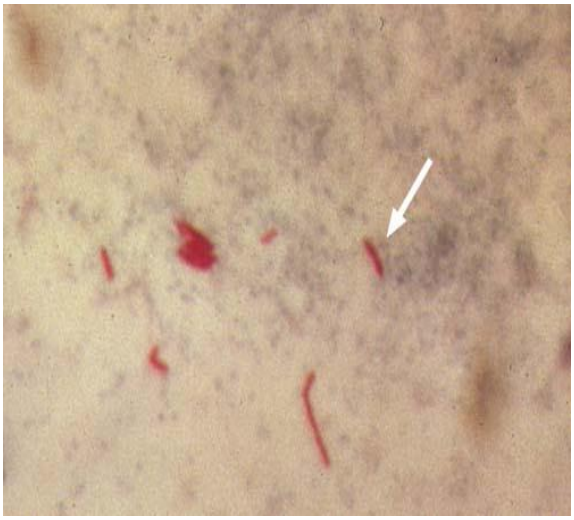
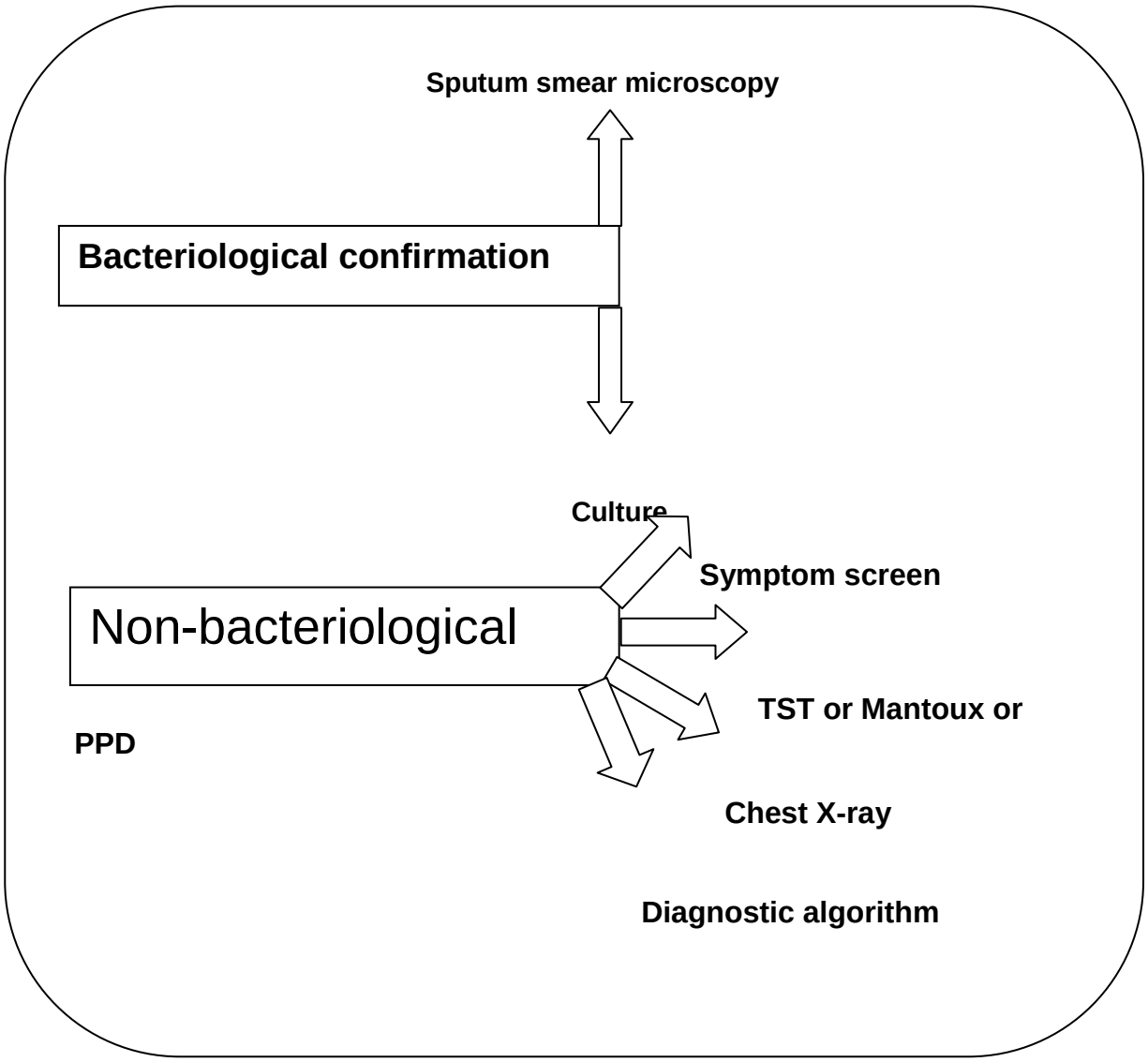


Fig. 2: Acid-fast stain of *M. tuberculosis*

PATHOGENESIS AND LIFE CYCLE OF TUBERCULOSIS

Tuberculosis is a disease that is almost exclusively transmitted by the aerosolized droplets containing infectious M. tuberculosis. These droplets are generated by the cough of a person with M. tuberculosis lung infection and are inhaled by an uninfected person. The inhaled bacilli lodge in the terminal air spaces of lung where they enter and replicate within alveolar macrophages. The initial, or primary, infection with M. tuberculosis involves replication of the organism at the initial primary pulmonary site of infection, spread to local lymph nodes within the lung, and eventual dissemination of infection to remote site in the body. Despite this successful initial parasitization of the human host, the primary infection is almost invariably asymptomatic in adults. With the onset of human immune response, active bacterial replication and dissemination are controlled. Although the immune response against M. tuberculosis is highly effective in controlling the primary infection, the organism is almost never eradicated. Thus, M. tuberculosis is foremost among bacterial pathogen in its ability to establish and maintain latency, a clinical period during which the infected person do not have clinically apparent tuberculosis, but harbors M. tuberculosis organism able to reactivate at a later date. Reactivation of the latent M. tuberculosis infection often occurs in apparently healthy people, and very frequently in people who are immunosuppressed as a result of diseases such as AIDS[10].

How is TB diagnosed



TUBERCULOSIS THERAPY

Classes of antitubercular drugs

The goals of tuberculosis treatment are to ensure cure without relapse, to prevent death, to impede transmission, and to prevent the emergence of multi drug resistance[11]. According to their clinical utility against Mycobacteria, the antitubercular drugs can be classified into

First line

These drugs have high antitubercular efficacy as well as low toxicity; are used routinely. For example, rifampicin, isoniazid, pyrizinamide, rifabutin, ethambutol, aminoglycosides (injectables), streptomycin, kanamycin, amikacin, capreomycin, and flouroquinolones.

Second line

These drugs have either low antitubercular efficacy or high toxicity or both; are used in special circumstances only. For example, ethionamide, cycloserine, p-aminosalicylic acid, clofazimine, amoxicillin, clarithromycin and thiacetazone [12].

DOTS (Directly Observed Therapy, Short Course)

DOTS are an inexpensive and highly effective means of treating patients already infected with *Mycobacterium tuberculosis* and preventing new infections and the development of drug resistance. The DOTS is a systematic strategy, which has five components, and each of these components is a part of management package provided by WHO [13].

Standard Tuberculosis Treatment Regimen-6 Months

Initial phase - 2 months, drugs: INH, RIF, PZA, EMB, 2 weeks daily, then 6 weeks twice weekly (14 daily doses, then 12 twice-weekly doses).

Continuation phase - 4 months, drugs: INH, RIF, 18 weeks, twice weekly, (36 twice-weekly doses).

INH=isoniazid, RIF=rifampin, PZA=pyrazinamide, EMB=ethambutol (Management of Tuberculosis, 2007).

Drawbacks of DOTS therapy

- Poor patient compliance: Access of antimycobacterial agents to M. tuberculosis bacilli inside host macrophages is limited due to the low levels of drug permeation, making it difficult to achieve effective drug concentrations. In addition, degradation of drugs may occur before they reach target tissues. Therefore, conventional treatments for TB include daily therapy with high doses of antimycobacterial drugs for at least 6 months. These long treatment schedules are associated with severe side effects and result in poor compliance.
- Toxicity: It occurs due to long term use of drug. Toxicity mainly occurs in the organs which are not associated with therapy, eg. Spleen, liver etc.

Novel drug delivery system for the treatment of tuberculosis

Drug delivery, which takes into consideration the carrier, the route and the target, has evolved into a strategy of processes or devices designed to enhance the efficacy of therapeutic agents through modified or controlled release. This may involve enhanced bioavailability, improved therapeutic index, or improved patient acceptance or compliance[14].The mycobacterium cell wall, lipid (e.g. mycolic acid) are linked to the underlying arabinogalactan and peptidoglycan. The structure is responsible for very low permeability of cell wall and thus for ineffectiveness of most of antibiotic against the organism. Clinical management of tuberculosis posses serious problem because the efficacy of chemotherapy has been reduced which may be attributed to the degradation of drugs before reaching the target, the low level of cell permeability to drugs, or primary drug resistance. Other reason for the failure of chemotherapy may be the difficulty in achieving adequately high concentration at the infection site, inadequate penetration of drug into macrophages and low level in cells. Designing and developing a site-specific delivery of antitubercular drug through various novel drug delivery systems may overcome these problems, which arise with conventional dosage forms of antitubercular drugs. These drug delivery systems are given in table 1.

Table 1: Various Novel Antitubercular Drug Delivery Systems

S.No	Delivery System and polymer/ligand employed	Drug	Route of Administration	Study Description	Reference
1.	**Liposomes**				
a.	Liposomes	Rifabutin	Intravenous	High concentration of antibiotic was achieved in lung, liver and spleen.	15
b.	Liposomes	Rifampicin	Intravenous	Produced better chemo-therapeutic efficacy when investigated in mice.	16
c.	Liposomes	Isoniazid and rifampicin	Intravenous	Reduced the myco-bacterial load significantly in lungs, liver and spleen of infected mice compared with untreated animals	17
2	**Microparticles**				
a.	PLG Microparticles	Isoniazid and rifampicin	Subcutaneous	Sustained release of drug over 6-7 weeks when tested in mice.	18
b.	Solid lipid microparticles (SLMs)	Isoniazid and rifampicin	Intrathecal	Does not induce significant airway response in rats. SLMs might be potential carrier for encapsulated drug via the pulmonary route.	19
3.	**Microspheres**				
a.	Microspheres employing PLG	Rifampicin	Inhaled	21 and 12% cumulative drug release respectively after 6 days.	20
b.	Microspheres	Rifabutin	Intravenous	Intracellular release of rifabutin formulations caused significant reduction of intra-cellularly replicating *Mycobacterium avium* (MAC).	20

Rationale of Drug targeting

- The site-specific targeted drug delivery negotiates an exclusive delivery to specified pre-identified compartment with maximum intrinsic activity of drug and concomitantly reduces access of drug to irrelevant non-target cells.
- The targeted delivery to previously in-accessible domains, offers distinctive therapeutic benefits. The controlled rate and mode of drug delivery to pharmacological receptors and specific binding with target cells is the specific feature of targeting. Invariably, every event stated contributes to higher drug concentration at the site of action and resultant lower concentration at non-target tissue where toxicity might crop-up. The high drug concentration at the target site is a result of the relative cellular uptake of drug vehicle, liberation of drug and efflux of the free drug from the target site.
- Targeting is signified if the target compartment is distinguished from the other compartments where toxicity may occur, and also if the active drug could be placed predominantly on the proximity of target site. The restricted distribution of the parent drug to non-target site(s) with effective accessibility to the target site(s) could maximize the benefits of targeted drug delivery [21].

Levels of Drug Targeting

Targeted drug delivery may be achieved by using carrier systems, where reliance is placed on exploiting both, intrinsic pathways that these carriers follow, and the bioprotection that they can offer to drugs during transit through the body. The various approaches of vectoring the drug to the target site can be broadly classified as:

- Active targeting (Ligand mediated targeting and Physical targeting)
- Passive targeting
- Inverse targeting
- Dual targeting
- Double targeting
- Combination targeting

Active Targeting

Active targeting is accomplished by attachment of specific molecules on the carrier's surface, which enhance the binding and interactions with antigens or receptors

expressed on specific cell populations. Targeting ligands explored for tuberculosis therapy include *O*-palmitoyl mannan (OPM)[21], maleylated bovine serum albumin MBSA and O-stearyl amylopectin[22-23], tetra-pentylammonium (TPA) and tetra-heptyl ammonium (THA) [24]. The choice of appropriate ligand is based on its specificity, stability, availability and selective display of its corresponding pair on the target cells, as well as its cost. In addition to the above considerations, conjugation chemistry, density and accessibility of the ligand[25], need to be properly designed for efficient targeting.

Active targeting complements passive accumulation into macrophages; selectivity and retention are improved as a result of specific interactions with target cells, at the expense of increased complexity, cost and risks (e.g. adverse biological reactions to ligand).

Passive targeting

Systems that target the systemic circulation are generally characterized as passive delivery system i.e. targeting occurs because of body's natural response to the physicochemical characteristics of the drug or drug carrier system. It is a sort of passive process that utilizes the natural course of biodistributinon of the carrier system through which, it eventually accumulates in the organ compartment(s) of body. The ability of some colloids to taken up by the RES especially in liver and spleen has made them ideal vectors for passive hepatic targeting of drug to these compartments.

Advantages of Targeted drug delivery system

- Reduction of adverse side effects. Because there are seldom peak drug blood levels above the drug therapeutic range and into the toxic range, adverse side effects are less frequently encountered.
- Targeted drug delivery system provides a reduction in drug blood level fluctuation. It provides control in the rate of drug release in case of controlled drug delivery system i.e. the "peak and valleys" of drug in blood or serum level are eliminated.
- Enhanced patient compliance.
- There is reduction in dosing frequency.
- Reduction in healthcare cost.
- The duration of action can be extended for days or month.

CONCLUSION

Treatment of tuberculosis is complicated by the need of multi-drug regimens that need to be administered over long periods. Poor patient compliance and toxicity is the most common reasons for chemotherapy failure in tuberculosis [26]. To minimize toxicity and improve patient compliance, extensive progressive efforts have been made to develop various novel drug delivery systems, which either target the site of M. tuberculosis infection or reduce the dosing frequency. TB continues to be one of the greatest challenges in global health. Current therapeutic agents against TB are life-saving for many patients, but cannot overcome increasing new challenges, including the creation and dissemination of MDR-TB/XDR-TB and the need for simultaneous treatment ofTB and HIV. Recent advances in drug delivery system encouraging the TB drug research and development. It requires the wide involvement of all relevant parties (industry, academia, drug regulatory agencies, and international policy-making agencies) who must collaborate effectively to deliver optimal future therapies for TB.

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