NANOTECHNOLOGY BASED APPROACHES FOR TUBERCULOSIS TREATMENT
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Edited by

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## Contents

### Contributors
- ix

### Preface
- xi

#### 1. Pathogenesis, biology, and immunology of tuberculosis
- 1

RAVI BANDARU, DEVIPRASAD SAHOO, RAMAKANTA NAIK, PRASHANT KESHARWANI AND RAMBABU DANDELA

1. Introduction
2. Mycobacterium tuberculosis and its transmission
   2.1 Scientific classification
   2.2 Transmission
3. Factors responsible for its transmission
   3.1 Patient-related risk factor
   3.2 Bacteriological factors
4. Pathogenesis
   4.1 Survival mechanisms of *Mycobacterium tuberculosis*
5. Mycobacterium tuberculosis capsule
   5.1 Cellular structure of *Mycobacterium tuberculosis* capsule
   5.2 Host-pathogen interaction from the capsule point of view
   5.3 Pharmaceutical methodology to target capsule
6. Immunology—Introduction
   6.1 Immunology of tuberculosis
   6.2 Innate immune system
   6.3 Inflammatory responses
   6.4 Adaptive immunity
   6.5 Granuloma formation
   6.6 Conclusion
7. References

#### 2. Tuberculosis: introduction, drug regimens, and multidrug-resistance
- 27

SIMA SINGH, NEELAM DHANKAR, ASHISH KUMAR GARG, NAGASHEKHARA MOLUGULU AND PRASHANT KESHARWANI

1. Introduction
2. Drug regimens for the treatment of tuberculosis
3. First line drugs for tuberculosis
4. Isoniazid
5. Rifampin
6. Pyrazinamide
7. Ethambutol
8. Streptomycin
9. Second-line antituberculosis drugs
10. Mechanisms of drug resistance
11. Conclusions
12. References

#### 3. Nanotechnology as a potential tool against drug- and multidrug-resistant tuberculosis
- 37

DAMIÁN EDUARDO PÉREZ-MARTÍNEZ AND ROBERTO ZENTENO-CUEVAS

1. Tuberculosis as an infectious disease
2. Nanotechnology-based systems and the administration of drugs against tuberculosis
   2.1 Solid-lipid forms
   2.2 Emulsion-based systems
   2.3 Vesicular drug-delivery systems
   2.4 Miscellaneous NPs
3. Factors affecting NPs properties
   3.1 Potential benefits and risks in the use of NPs
4. References

#### 4. Translational research for therapy against tuberculosis
- 53

YOLANDA GONZALEZ, SILVIA GUZMÁN-BELTRÁN, LAURA E. CARRETO-BINAGHI AND ESMERALDA JUÁREZ

1. Research for tuberculosis elimination
2. Advances in the therapy for tuberculosis
3. New drugs for tuberculosis or new regimens
   3.1 The issues
   3.2 Recent advances
   3.3 Future challenges
4. Drugs repurposed for tuberculosis
5. References
5. Vaccine delivery systems against tuberculosis 75
RUPAL OJHA, RAJAN KUMAR PANDEY AND VIJAY KUMAR PRAJAPATI

1 Introduction 75
2 TB vaccine candidates in the pipeline 77
2.1 Viral vectorized TB vaccines 78
2.2 Adjuvanted subunit TB vaccine 78
2.3 DNA TB vaccine 78
2.4 Whole-cell and live Mycobacteria TB vaccine 80
3 Vaccine administration routes for TB vaccine 80
3.1 Intradermal route of administration 81
3.2 The intramuscular route of administration 81
3.3 Subcutaneous route of administration 81
3.4 Intranasal (mucosal, sublingual) route of administration 81
4 Advanced TB vaccine delivery systems and their related immune responses 82
4.1 Nanoparticles-based TB vaccine delivery systems 82
4.2 Cationic nanoparticle-based TB vaccine delivery 83
4.3 Chitosan-based nanoparticle TB vaccine delivery 83
4.4 Polymers/polyester-based nanoparticle as a TB vaccine delivery system 84
4.5 Liposome-based TB vaccine delivery 85

4.6 Dendrimer-based TB vaccine delivery system 85
4.7 Immune stimulating complexes (ISCOMs) as a TB vaccine delivery system 86
4.8 Virus-like particles (VLPs)-based TB vaccine delivery system 86
4.9 Virosomes-based TB vaccine delivery system 87
4.10 Role of adjuvants in TB vaccine formulation and their delivery 87

References 88

6. Inhalable polymeric dry powders for antituberculosis drug delivery 91
SUNEERA ADLAKHA, KALPESH VAGHASIYA, ANKUR SHARMA, EUPA RAY AND RAHUL KUMAR VERMA

1 Introduction 91
2 Challenges with current anti-TB therapies 92
3 Rationale of pulmonary drug delivery in TB 92
4 Feasibility of lung as a portal for delivery of ATD 93
5 Pulmonary delivery of ATD 94
6 Formulations for DPIs 96
7 Drug carriers for pulmonary delivery 96
7.1 Polymeric nanoparticles 96
7.2 Hybrid nano-in-microparticles 98
7.3 Solid-lipid nano particles 98
7.4 Liposomes 98
7.5 Microparticles 99
8 Inhalation delivery devices for DPI 99
9 Clinical trials 100
10 Future of polymeric powder-based drug development for TB 101
11 Conclusions 101
References 102

7. Liposomes-and niosomes-based drug delivery systems for tuberculosis treatment 107
ALI IBRAHIM BEKRAKI

1 Introduction 107
2 Epidemiology 107
3 Nature of causative agent 108
4 Emergence of MDR and XDR TB 108
5 Drug regimens 109
6 Need for novel and sustained delivery systems 109
7 Nanodelivery systems 110
7.1 Introduction 110
7.2 Types of nanocarriers 110
7.3 Advantages of nanotechnology-based drug delivery system 110

8 Liposomes 111
8.1 Definition of liposomes 111
8.2 Types and uses of liposomes 111
8.3 Pulmonary TB and the importance of liposomal drugs 112
8.4 Si-RNA liposomes 113
8.5 Targeting of liposomes 114

9 Niosomes 115
9.1 Definition of niosomes 115
9.2 Advantages of niosomes 115
9.3 Various types of niosomes 116
9.4 Niosomes versus liposomes; which is superior? 116
9.5 Application of niosomes in drugs 116
9.6 Niosomes in the treatment of TB 117
9.7 Niosomal drug delivery system role in cerebral, drug-resistant TB 118

10 Pulmonary delivery of nanoparticle-encapsulated antitubercular drugs 118

11 The future of combating TB 119

References 120

8. Polymer-based nanoparticles as delivery systems for treatment and vaccination of tuberculosis 123

MOHSEN TAFAGHODI, FARZAD KHADEMI, FARIDEH SHIEHZADEH AND ZOHREH FIROUZI

1 Polymer-based nanoparticles as drug delivery systems of tuberculosis 123
1.1 Nanocarriers based on natural polymers 124
1.2 Nanocarriers based on synthetic polymers 128

2 Nanoparticle-based delivery systems for vaccination against tuberculosis 130
2.1 Tuberculosis vaccines 130
2.2 Adjuvants 135
2.3 Vaccine delivery systems 136
2.4 The future challenges 139

References 139

9. Nanotechnology-based approaches for tuberculosis treatment 143

MOHAMAD MOSA MUBARAK AND ZAHOOR AHMAD

1 Drug delivery systems 143
2 Tuberculosis: the need for antitubercular drug delivery systems 144
3 Nanomedicine and tuberculosis 146
4 Oral ATD-nanomedicine 148
5 Ligand-appended oral ATD-nanomedicine 149
6 Pulmonary delivery of ATD-nanomedicine 150
7 Injectable ATD-nanomedicine 151
8 Alginate-based ATD-nanomedicine 151
9 Lipid-based ATD-nanomedicine 153
9.1 Liposome-based drug delivery systems 153
9.2 Microemulsions as potential ATD delivery systems 154
9.3 Niosomes-based ATD delivery system 155
9.4 Solid lipid nanoparticles-based ATD-nanomedicine 155
10 ATD-nanomedicine for special situations: cerebral TB, drug-resistant TB, and latent TB 156
11 Potential toxicity of ATD-nanomedicine 157
12 ATD-nanomedicine: unresolved and upcoming issues 157
13 Conflict of interest 158

References 158

10. Dendrimer-based drug delivery systems for tuberculosis treatment 163

RAHUL SHUKLA, AAKRITI SETHI, MAYANK HANDA, MRADUL MOHAN, PRASHANT KESHRWANI AND PUSHPENDRA K. TRIPATHI

1 Introduction 163
2 Dendrimers 165
3 PAMAM dendrimers for tuberculosis treatment 166
4 PPI dendrimers for tuberculosis treatment 168
5 Melamine, PEHAM, and PEA dendrimers for tuberculosis treatment 170
6 Conclusion 170

References 171

11. Polymeric micelle-based drug delivery systems for tuberculosis treatment 175

BAPI GORAIN, HIRA CHOUDHURY, SREENIVAS PATRO SISINTHY AND PRASHANT KESHRWANI

1 Introduction 175
2 The structure of polymeric micelle 176
2.1 Corona of miceller structure 176
2.2 Core of miceller structure 178
3 Commonly used polymers in polymeric micelle 179
  3.1 Commonly used amphiphilic block copolymers 179
4 Polymeric micelles for enhanced permeability and retention effect 180
  4.1 Factors affecting EPR of micelle deliveries 182
5 Tuberculosis and urge of novel delivery approaches 183
6 Recent advances of polymeric micelles in tuberculosis 184
7 Conclusion 185
Conflict of interest 186
References 186

SIMONE PINTO CARNEIRO AND ORLANDO DAVID HENRIQUE DOS SANTOS

1 Methods of production 196
  1.1 Hot homogenization method 196
  1.2 Cold homogenization method 196
2 Excipients used in lipid nanocarriers 198
  2.1 Lipids 198
  2.2 Emulsifiers 198
3 Challenges for current tuberculosis therapy 198
4 Lipid nanoparticles for TB treatment 198
5 Solid lipid nanoparticles and nanostructured lipid carriers as alternative nanomedicines for TB treatment 199
6 Lipid nanoparticles functionalization 200
References 202

13. DNA markers and nano-biosensing approaches for tuberculosis diagnosis 207
AMAL RABTI, AMAL RAOUAFI AND NOUREDDINE RAOUAFI

1 Introduction 208
2 DNA structure 208
3 Carbonaceous nanomaterials-based DNA biosensors 210
  3.1 Graphene derivatives 210
  3.2 Carbon nanotubes 213
4 Nanoparticles based-DNA biosensors 215
  4.1 Noble metal nanoparticles 215
  4.2 Metal oxide nanoparticles 222
  4.3 Magnetic beads 223
  4.4 Quantum dots 224
5 Conclusion 226
References 227

14. Recent advancement and future perspective for the treatment of multidrug-resistant tuberculosis 231
NOORSUZANA MOHD SHARIFF

1 Multidrug-resistant tuberculosis (MDR-TB): the emergence of new global threat to tuberculosis (TB) eradication 231
2 The progression of treatment guidelines for MDR-TB: the past and present 233
3 The advancement in MDR-TB treatment: the recent, on-going, and future direction 233
  3.1 The promising new all-oral drugs versus the extensively use injectable drugs 233
  3.2 Other ongoing trials for new treatment regimen for MDR-TB/XDR-TB 239
4 Host-directed therapies as a future option in treating MDR-TB 240
5 Conclusion 246
References 246

15. Nanotechnology approach in conquering anti-TB resistance 251
BERNADETTE DIAN NOVITA

1 Mycobacterium: pathogenesis and its problem in the resistant 251
2 Antituberculosis and the mechanism of antituberculosis resistant 253
3 Nanoparticle and its use to conquer tuberculosis infection 258
4 Function nanoparticle for overcoming resistance tuberculosis treatment 260
5 Nanoparticle for diagnose tuberculosis 263
References 266

Index 267
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Tuberculosis (TB) is a leading chronic bacterial infection. Despite potentially curative pharmacotherapies being available for over 50 years, the length of the treatment and the pill burden can hamper patient lifestyle. Prolonged treatment, high pill burden, low compliance, and stiff administration schedules are factors that are responsible for the emergence of multidrug-resistant strains. According to WHO reports, 53 million TB patients died from 2000 to 2016. Therefore, early diagnosis of the disease is of great importance for global health care programs. 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 remains a major challenge for pharmaceutical technology.

Regarding TB treatment, nanoparticles can be a useful strategy for two distinct applications: (1) for their intrinsic antimycobacterial activity and (2) as vehicles for known antitubercular drugs to allow the reduction of dose- and drug-associated side-effects and administration via user-friendly administration routes such as pulmonary or oral ones.

This book will summarize the types of nanodrugs, their synthesis, formulation, characterization, and applications, with the most important administration routes. Thus, this book will discuss various nanotechnology-based approaches which may help overcome persisting limitations of conventional/traditional treatment. Also, recent advances and achievements regarding therapeutic efficacy provide possible future applications in this field. In this scenario, this book will directly address all translational aspects and clinical perspectives of TB nanomedicine from a comprehensive and multidisciplinary perception. This book is thus (1) an unrivalled, comprehensive summary of the field and (2) rationally conceived clinical stage of TB nanomedicines. The editor and contributors (authors) cover a wide range of expertise in the nanomedicine and TB and all of them are already proven their international acclaim.

We thank all the authors for their valuable and timely contributions. We believe that the book, with its comprehensive coverage of fundamental and applied aspects of the subject, will prove immensely useful to its readers and stimulate further interest.

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Nanotechnology approach in conquering anti-TB resistance

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Abbreviations

AFB Acid Fast Basil
MDR-TB multidrug resistant tuberculosis
M.tb Mycobacterium tuberculosis
TB tuberculosis
XDR-TB extra-drug resistant tuberculosis
RIF rifampicin
INH isoniazid
PYR pyrazinamide
ETB ethambutol

1 Mycobacterium: pathogenesis and its problem in the resistant

Tuberculosis (TB) is an air-borne chronic infection caused by Mycobacterium tuberculosis (M.tb). It has a high affinity to the parenchymal tissue of lungs due to the high oxygen level. Mycobacterium tuberculosis (M.tb) is a Gram-positive acid-resistant stem and called Acid Fast Basils (AFB). The golden standard in identified TB infection is the count of AFB smears from sputum, for TB in the lung or other specimens, for extrapulmonary TB [1].

Pathogen M.tb is easily to die with direct sunlight. However, it survives in dark and damp places, even it is outside the host. Mycobacterium tuberculosis transmits through aerosol droplets from coughing, sneezing, or saliva splashes of people infected TB lungs. The droplet diameter is very small (0.5-5 \( \mu \)m) and around 40,000 bacteria are produced each sneezing, therefore M.tb eases to transmitted [1].

After the inhalation of M. tuberculosis, innate immune responses involving alveolar macrophages and granulocytes begin to combat the infection; in some persons, the bacilli are cleared, whereas in others, infection is established [2]. The replication of bacilli in macrophages and regional lymph nodes leads to both lymphatic and hematogenous dissemination, with seeding of multiple organs, which may eventually give rise to extrapulmonary disease. The containment of bacilli within macrophages and extracellularly within granulomas limits further replication and controls tissue destruction, resulting in a dynamic balance between pathogen and host. The classic interpretation of this as a binary
Nanotechnology approach in conquering anti-TB resistance

process with either truly latent *M. tuberculosis* infection or active tuberculosis disease has recently been challenged as an oversimplification. Instead, a spectrum of immunologic responses that are both protective and pathogenic and correlate with a range of bacterial activation has been suggested. This continuum encompasses a variety of host-microbe interactions, which are characterized by clinical latency when host responses predominate and by disease when bacterial replication exceeds the threshold required to cause symptoms [2-4]. Recent evidence suggests that host inflammatory responses, particularly with interleukin-1β, may actually enhance mycobacterial replication, which illustrates that the double-edged sword of immune responses seen in tuberculosis disease may also be present in latent infection (as shown in Fig. 15.1).

*Mycobacterium tuberculosis* forms into an active, clinically silent, and latent infection. It said that one-third of the world’s population infected by *M. tb*, most of them are asymptomatic and become latent tuberculosis infection especially in people with immunocompromised conditions, for example, HIV/AIDS, DM, malnutrition, on chemotherapy or steroids therapy, and antitumor therapy necrosis factor. Only about 5%-10% suffer from active tuberculosis infection [1].

Tuberculosis (TB), the infection caused by *Mycobacterium tuberculosis* (*M. tb*), remains a problem to overcome in Indonesia. In East Java Province Indonesia 2018, the incidence of new TB cases reached 767 from 100,000 population [6]. This phenomenon was similar to TB incidence in the world. According to the World Health Organization (WHO) data in 2013, it states that the incidence of new TB cases in the world has increased 50%, and therefore WHO has declared for TB as a “global health emergency” [7]. The pathology mechanism of TB could be seen in Fig. 15.2.

Mycobacteria, especially *Mycobacterium tuberculosis* (*M. tb*), are intrinsically resistant to most antibiotics [9]. They have the ability in growing slower than other bacteria. There is no single antibiotic that is relatively effective against *M. tb*, therefore for tuberculosis (TB) multidrugs therapy (MDT) is required to avoid bacterial resistant [9,10]. Mycobacterial cells are lipid-rich and also able to be dormant that causes impermeable and poorly penetrate for many agents, including macrophages.
Finally, *M. tuberculosis* has the ability to manipulate both innate and adaptive immune response and called TB’s escape mechanism. In this mechanism, M.tb has a high ability to avoid intracellular killing process and macrophage phagocytosis process [11,12]. Mycobacteria are notorious for their ability to develop resistance [9,10]. Moreover, phagosome maturation, which is activated during M.tb recognition process, is the decrease of intra-vacuole pH, from ~7 to 5. This acidification represents a fundamental blocking step in the process of bacterial elimination [5].

### 2 Antituberculosis and the mechanism of antituberculosis resistant

The aims of antituberculosis (anti-TB) are (1) to cure the patient; (2) to prevent death; (3) to prevent recurrence; (4) to break the chain of transmission; and (5) to prevent M.tb resistant. Mycobacterium has ability to grow very slowly and develop resistance rapidly. Therefore, to treat TB, several combinations or TB-MDT are needed.

Tuberculosis MDT is classified into two lines: the first line of TB MDT is rifampicin (RIF),
isoniazid (INH), pyrazinamide (PYR), ethambutol (ETB), and streptomycin. This group of drugs exhibits high effectiveness with acceptable toxicity [9,10,13]. The second line of TB-MDT is the antibiotics fluoroquinolones (such as ciprofloxacin, ofloxacin, levofloxacin, moxifloxacin), macrolides (such as erythromycin, clarithromycin), and aminoglycosides (such as amikacin, kanamycin, and capreomycin) [9,10,13].

The aims of TB-MDT are (1) to increase bactericidal activity, starting from the beginning of therapy phase; (2) to prevent drug resistant; and (3) to enhance the process of eliminating *M. tuberculosis* in the sites of TB infection [9,10,13].

*Isoniazid* is the primary drug for chemotherapy of TB infection with the highest bactericidal activity at the beginning of TB treatment. All patients infected with isoniazid-sensitive strains of the tubercle bacillus should receive the drug if they can tolerate it. The use of combination therapy (isoniazid + pyrazinamide + rifampin) provides the basis for “short-course” therapy and improved remission rates [9,10]. The mechanism of action of anti-TB could be seen in Fig. 15.3.

![FIGURE 15.3 Mechanism of pharmacotherapy in tuberculosis [8].](image-url)
The isoniazid’s efficacy gets higher when it combined with ethambutol, rifampicin, pyrazinamide, and streptomycin. Rifampicin has the highest elimination ability of *M. tuberculosis*. Isoniazid enters bacilli by passive diffusion. The drug is not directly toxic to the bacillus but must be activated to its toxic form within the bacillus by KatG, a multifunctional catalase-peroxidase. KatG catalyzes the production from isoniazid of an isonicotinoyl radical that subsequently interacts with mycobacterial NAD and NAPD to produce a dozen adducts. One of these, a nicotinoyl-NAD isomer, inhibits the activities of enoyl acyl carrier protein reductase (InhA) and -ketoacyl acyl carrier protein synthase (KasA). Inhibition of these enzymes inhibits synthesis of mycolic acid, an essential component of the mycobacterial cell wall, leading to bacterial cell death. The products of KatG activation of INH include superoxide, $\text{H}_2\text{O}_2$, alkyl hydroperoxides, and the NO radical, which may also contribute to the mycobactericidal effects of INH. *M. tuberculosis* could be especially sensitive to damage from these radicals because the bacilli have a defect in the central regulator of the oxidative stress response, *oxyR*. Backup defense against radicals is provided by alkyl hydroperoxide reductase (encoded by *ahpC*), which detoxifies organic peroxides. Increased expression of *ahpC* reduces isoniazid effectiveness [10]. The antibacterial effect of isoniazid against clinical *M. tuberculosis* strains varies between 0.025 and 0.05 mg/L. Activity against *Mycobacterium bovis* and *M. kansasii* is moderate. Isoniazid has poor activity against MAC. It has no activity against any other microbial genus [10]. The prevalence of drug-resistant mutants is ~1 in $10^6$ bacilli.

 TB cavities may contain as many as $10^7$ to $10^9$ microorganisms; preexistence resistance can be expected in pulmonary TB cavities of untreated patients. These spontaneous mutants can be selected by monotherapy; indeed, strains resistant to isoniazid will be selected and amplified by isoniazid monotherapy. Thus two or more agents are usually used. The mutations resulting in drug resistance are independent events, the probability of resistance to two antimycobacterial agents is small, ~1 in $10^{12}$ ($1 \times 10^6 \times 10^6$), a low probability considering the number of bacilli involved. Resistance to INH is associated with mutation or deletion of katG, overexpression of the genes for inhA (confers low-level resistance to INH and some cross-resistance to ethionamide), and *ahpC* and mutations in the *kasA* and *katG* genes. KatG mutants exhibit a high level of resistance to isoniazid (as shown in Fig. 15.4).

*Rifampicin* inhibits the growth of most Gram-positive bacteria as well as many Gram-negative microorganisms such as *Escherichia coli*, *Pseudomonas*, indole-positive and indole-negative *Proteus*, and *Klebsiella*. Rifampicin is very active against *Staphylococcus aureus* and coagulase-negative staphylococci. The drug also is highly active against *Neisseria meningitidis* and *Haemophilus influenzae*. Rifampicin inhibits the growth of many *M. tuberculosis* clinical isolates in vitro at concentrations of 0.06-0.25 mg/L [10]. The prevalence of rifampicin-resistant isolates is 1 in every $10^7$ to $10^8$ bacilli. Microbial resistance to rifampin is due to an alteration of the target of this drug, *rpoB*, with resistance in 86% of cases due to mutations at codons 526 and 531 of the *rpoB* gene [10].

*Pyrazinamide* is the synthetic pyrazine analog of nicotinamide. Pyrazinamide is also known as pyrazinoic acid amide, pyrazine carboxylamide, and pyrazinecarboxamide. Pyrazinamide is “activated” by acidic conditions. Initially it was assumed that the acidic conditions under which pyrazinamide works were inside macrophage phagosomes. However, pyrazinamide may not be very effective within macrophages; rather, the acidic conditions for activation may be at the edges of necrotic TB cavities where inflammatory cells produce lactic acid. *M. tuberculosis* nicotinamidase or pyrazinamidase deaminates pyrazinamide to pyrazinoic acid (POA), which is then transported to the extracellular milieu by an efflux pump. In an acidic extracellular milieu, a
fraction of POÄ is protonated to POAH, a more lipid-soluble form that enters the bacillus. The actual mechanism of pyrazinamide microbial kill is still unclear; three mechanisms have been proposed [10]:

1. inhibition of fatty acid synthase type I leading to interference with mycolic acid synthesis,
2. reduction of intracellular pH, and
3. disruption of membrane transport by HPOA.

Antibacterial activity of pyrazinamide in vitro only at acidic pH. At pH of 5.8-5.95, 80%-90% of clinical isolates have a MIC of 100 mg/L. Pyrazinamide-resistant occurs when M.tb has pyrazinamidase to reduce affinity for pyrazinamide. This reduced affinity decreases the conversion of pyrazinamide to POA. Single point mutations in the pncA gene are encountered in up to 70% of resistant clinical isolates. The mechanisms contributing to resistance in 30% of resistant clinical isolates is unclear [10].

*Ethambutol* inhibits arabinosyl transferase III, thereby disrupting the transfer of arabinose into arabinogalactan biosynthesis, which in turn disrupts the assembly of mycobacterial cell wall. The arabinosyl transferases are encoded by embAB genes. Ethambutol has activity against a wide range of mycobacteria but no activity against any other genus. Ethambutol MICs are 0.5-2 mg/L in clinical isolates of M.tb [10]. In vitro, mycobacterial resistance to the drug develops via mutations in the embB gene. In 30%-70% of clinical isolates that are resistant to ethambutol, mutations are encountered at codon 306 of the embB gene. However, mutations in this codon are also encountered in ethambutol-susceptible mycobacteria, as though this mutation is necessary, but not sufficient, to confer ethambutol resistance [10].
A combination of isoniazid-rifampicin for 9 months administration will cure 95%-98% of cases of tuberculosis infection caused by susceptible strains [9]. An initial intensive phase of treatment is recommended for the first 2 months due to the prevalence of resistant strains. The addition of pyrazinamide during this intensive phase allows the total duration of therapy to be reduced to 6 months without the loss of efficacy. In practice, therapy is usually initiated with a four-drug regimen of isoniazid, rifampicin, pyrazinamide, and ethambutol until susceptibility of the clinical isolate has been determined. In susceptible isolates, the continuation phase consists of an additional 4 months with isoniazid and rifampicin [9]. However, isoniazid and rifampicin are the TB-MDT that experiences resistant frequently.

The resistance of TB-MDT arises through several mechanisms [10] (as shown in Fig. 15.5), including:

1. The inability of TB-MDT to penetrate into M. tuberculosis' wall cells by reason of its rich lipopolysaccharide and mannose.
2. The anaerobic conditions in the site of infection enable M. tuberculosis to become dormant. The TB-MDT, especially isoniazid, is ineffective in dormant conditions.
3. Alteration of enzymes that produced by M.tb. These enzymes prevent the conversion of prodrugs into active drugs. Isoniazid inhibits the synthesis of mycolic acids, which are essential components of mycobacterial cell walls. Isoniazid is a prodrug that is activated by KatG, the mycobacterial catalase-peroxidase. The activated form of isoniazid forms a covalent complex with an acyl carrier protein (AcpM) and KasA, a beta-ketoacyl carrier protein synthetase, which blocks mycolic acid synthesis. Resistance to isoniazid is associated with mutations resulting in overexpression of

![FIGURE 15.5 Mechanism of TB-MDT resistance [10].](image-url)
inhA, which encodes an NADH-dependent acyl carrier protein reductase; mutation, or deletion of the katG gene; promoter mutations resulting in overexpression of ahpC, a gene involved in the protection of the cell from oxidative stress; and mutations in kasA. Overproducers of inhA express low-level isoniazid resistance and cross-resistance to ethionamide. KatG mutants express high-level isoniazid resistance and also pyrazinamide resistance.

4. Alteration of target protein structures. This prevents drug recognition (rifampicin, ethambutol, fluoroquinolones, macrolides).

5. Drug exported from the cell before reaching the sites of infection (isoniazid, ethambutol, streptomycin).

6. Mutation in DNA repair gene that leads the multidrug resistance (MDR)-TB.

Those all aforementioned mechanisms reduce the efficacy of TB-MDT.

3 Nanoparticle and its use to conquer tuberculosis infection

Nanotechnology is an innovative use of the latest technological developments or nanoparticle sized. Nowadays, it has a major impact for health and therapeutic development. The nanoparticle now is known as a drug delivery system, thus it enhances the drug efficacies [14].

In the process of diagnosis, nanotechnology may play a role in the diagnostic kit. For example in India, The aid of TB diagnosis created diagnostic kits in an optical biosensor for rapid detection of M.tb bacilli [14,15].

In the TB treatment, nanotechnology has a huge improvement in pharmacology, especially in the delivery system. The TB-MDT is able to reach the site of infection and impact to the function of macrophage and other phagocyte cells. Nanoparticle gives advantages such as combining MDT into one form, reducing the frequency of drugs, increasing the therapeutic index of anti-TB, increasing the solubility of hydrophobic agents capability, and reducing the administration of higher doses [16]. As drug delivery, nanoparticles also give other advantages such as, improve drug stability, improve the ability of carrier molecules, and the feasibility of incorporation of both hydrophilic and hydrophobic substances. Reviewing these carriers can also be designed to enable controlled (sustained) drug release from the matrix [16].

Nanoparticles as a therapeutic include; nanoemulsions, nanosuspensions, niosomes, polymeric micelles, and other self-assembled structures, are roommates antituberculosis drug nanocarriers, and polymeric and nonpolymeric nanoparticles. Nanoparticles can penetrate the intestinal permeability barrier directly through the transcellular or paracellular pathways into the circulation. This work makes drugs more and more effective. Nanosuspensions are a potential and promising new anti-TB drug formulations for intravenous way. Nanoparticles are able to achieve the higher stability and ability of the drugs, the feasibility of incorporating both hydrophobic and hydrophilic substances, and the feasibility of any administration routes such as parenteral, oral, and inhalation [15].

Nanotechnology increases the bioavailability of drugs as a result of a special absorption such as the absorption mechanism of endocytosis. The nanoparticles are also able to remain in the blood for a longer period of time and in controlled release manner into the target tissue. The self-control system of release of the drug helps reduce fluctuations in plasma and minimize side effects of the drug. In the case of TB adverse effects of tuberculosis drugs became one of the causes in poor compliance [17].

Nowadays, nanoparticle also develops in order to diminish the number of MDR-TB cases. There is a strong urge to develop novel ways of delivering the therapeutic compounds to the specific target of making the drug more effective [14].
Currently, the basic mechanism of controlled drug release was established and most drug delivery formulations were oral and transdermal administration. The effectiveness and stability were low in these drug systems. The effectiveness and stability of the drug will affect drug action and its effect on the patient’s body. The drug is incorporated into the nanoparticle that easily diffused through biological membranes and cells take up. These particles for the efficiency in drug delivery to the site of action. Nanotechnology improves the performance of the effectiveness of the drug, in patients taking the drug longer, and cost-effectiveness. Nanotechnology can produce biodegradable, biocompatible polymers, stimulate, and targeted by following the intended target organs, such as liposomes deliver responsive, nanofabricated materials (fullerenes, carbon nanotubes, silicon, silica), metals (gold, silver, iron, platinum, quantum dots), and polymers (micelles, dendrimers). Nanoparticles shape assortment such as spherical, rods, wires, discs, hemispherical, and ellipsoidal [17].

The size of the nanoparticles that less than submicron (<1 µm) colloidal particles are used as drug delivery vehicles. For therapeutic purposes, drugs can be covalently embedded to the particle surface or can be incorporated in the matrix of the particle. Nanoparticles comprise biocompatible and biodegradable materials such as polymers, which can be natural (e.g., gelatin and albumin), synthetic (e.g., polylactides and polyalkylycyanoacrylates), or solid lipids. Nanoparticles have a higher efficiency of the cells compared to the molecules in the case of a delivery system. Nanoparticle delivery system has capabilities that are more specific and faster. These carriers that are adapted to enable controlled, slow, and persistent drug release from the matrix [18]. The nanoparticle expresses in the gene and able to trace into the DNA complexes track (in vivo), this advantage is important in simultaneously dosage administration and determination. In this determination system, the nanoparticle has a high sensitivity to measure the level of gene expression (in vivo imaging) and is also able to target the specific/diseased cell types [14].

Nanoscience is a new perspective in making early detection, prevention, diagnosis, and treatment in TB became easier and more effective. This is because nanoscience has the potential to empower local responses to specific targets and other benefits to save costs. Nanoparticle-based gene therapy and drug delivery hold a great promise for the sound management of diseases in terms of improved drug bioavailability and reduced dosing frequency, though it is extremely important to investigate the toxic effects nanoparticles according to chemistry, size, and other physical properties [14].

Future holds up in designing of drug-delivery systems or formulations roommates can resolve all the limitations of tuberculosis drug therapy and making them affordable to all patients. Several antitubercular drugs encapsulated in natural or synthetic carrier-based controlled release formulations have been explored and nanoparticles appeared to be the best in terms of therapeutic efficacy [14].

Developing research related to vector-based delivery systems could combine roommates colloidal carriers such as large payloads of drug with the active targeting to improve the effectiveness and efficiency of drug action based on the nanoparticle-based formulations. Understanding the fate of nanocarriers and their polymeric constituents along with the elimination of any residual organic solvents is a must for dealing with any toxicological issues associated with these nanoformulations [14].

Nanoparticle delivery system is a promising key for the media but it is also against drug-susceptible tuberculosis and drug resistance. Nanoparticles are also useful for reducing the burden on the patient’s dose but have the same benefits, but simultaneously. Nanotechnology still has a lot of homework for future challenges especially for TB. Lots of health gaps need to be filled along with global sustained efforts to
overcome TB infection, in order to reach the site of infection in the secondary lymphoid organs [14].

Increasing incidence of multidrug-resistant strains make research related to ways of delivering the therapeutic compounds to the specific target of growing. Many delivery systems, such as nanoemulsions, nanosuspensions, polymeric and nonpolymeric particles, liposomes, niosomes, and dendrimers, have been developed in the past, overcoming many of the shortcomings of the delivery of conventional drugs [14].

4 Function nanoparticle for overcoming resistance tuberculosis treatment

TB drug resistance is the inability of the existing TB drugs to phagocyte mycobacterium that exists in the patient’s body, due to the growing strength of Mycobacterium tuberculosis that is inside the patient’s body TB [19].

Mycobacterium tuberculosis is one of the most infection disease which successful human pathogens, due to its ability to carry a primary infection to a state of dormancy (latents), persisting in the body even in immune-competent people. In this regard, it is important to mention that there are two billion people infected worldwide by M.tb, and only nine million people develop into TB clinical diseases, for example: from 100 people whom were exposed with M.tb, only 2 persons grow into clinical TB infection, this phenomenon is due to immune response. TB is usually a lung disease, due to the fact that these organs are the gateway and provide optimal conditions for the infected of this disease. The primary infection begins with the inhalation of the particles of Mycobacterium tuberculosis. Approximately 10% of this invasion due to respiratory tract that are in alveoli and bronchioles, where the bacteria is recognized and phagocyted by alveolar macrophages (AMs) or dendritic cells (DCs). Macrophages exposed to Mycobacterium tuberculosis secrete pro-inflammatory cytokines (IL-1, TNF-α, and IL-6) that will contribute to the subsequent formation of focal granulomatous lesions, a process that takes 2-3 weeks, and which generally leads to the containment of the pathogen [8].

Pharmacotherapy of tuberculosis therapeutic regimen is recommended by the WHO for susceptible pulmonary TB rifampicin, isoniazid, pyrazinamide, ethambutol, and streptomycin. The therapy in tuberculosis consists of a short-term treatment of 6 months (divided into two stages), intensive phase and continue phase [8,10,20]. Drug chemical structures could be seen in Fig. 15.6.

Tuberculosis drug resistance or multidrug resistant tuberculosis (MDR TB) is a condition in which a patient is resistant to first-line TB treatment. The first-line drug is a list of the first drug given to patients with TB occurrence. This is because of the resistance of patients who dropped out treatment or in patients who are infected with Mycobacterium tuberculosis for the umpteenth time. The inability of antituberculosis (anti-TB) has become one of the causes in which a patient MDR-TB or now known by extra-drug resistant tuberculosis (XDR-TB) must increase the dosage of antituberculosis drugs and make the treatment of TB becomes longer. The efficacy of antiinfective drugs is not only dependent on the pathogens related to MIC, but also on the exposure of the drug in the patient [21].

Combination of nanomaterials with the understanding of differentiation of biological processes, nanotechnology could ameliorate and trigger the usage of brand new drug/antigen in delivery systems. Based on evidence nanomaterials have a result better than liposomes, there about stabilization and drug loading capacity. The differentiation of nanoformulations, like lipid-based and (branched) polymeric ones, is being explored to deliver different types of drugs. In recent years, many efforts have been directed to the encapsulation of anti-TB drugs within nanoparticles [8].

Low compliance, the main cause that makes the incidence of drug resistance to anti-TB
against *Mycobacterium tuberculosis*, is increasing. Now it has become clear that pharmacokinetic variability is much more likely to be the driving force of drug resistance. The development of pharmacokinetic required in the case of antituberculosis drug resistance (anti-TB). If the existing infection with TB addressed adequately, then the bacteria will not occur and can be treated. However, in the case of anti-TB drugs, a therapeutic range or the target has not been established.[21]

Nanoparticles are believed to increase the significance of the treatment of TB from diagnosis, treatment, and prevention. Nanotechnology is one of the functions that improve nanomedicine. Due to reviews, their size, shape, and morphology (less than 100 nm in one aspect) nanoparticles exhibit different properties of the same material when they are in bulk size. New diagnostics and therapeutics for application in organ systems have been developed due to the unique properties of nanopharmaceuticals [22].

Nanomedicine approaches are being used as effective carriers of drugs to different parts of the body that were previously difficult to access. Nanomedicine approach in anti TB enhances the efficacy of the drugs. It may possible to the target nanoparticles to specific organs by modifying

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**FIGURE 15.6** Pharmacotherapy of tuberculosis [10].

![Chemical structures of antituberculosis drugs](image-url)
the elemental composition, size, shape, charge, and surface modification or functionalization [22].

That brings us to the second reason why we need new anti-TB drugs. Drug resistance has emerged as a phantom from the dark, threatening today every corner of the world. Often RIF-resistance correlates to the MDR category (resistant to INH and RIF). XDR is an MDR M. tuberculosis strains resistant to any fluoroquinolone also and at least one injectable agent. The prognosis is less favorable for harboring XDR-bacilli patients compared to patients with MDR, with a five times higher risk of death, therefore the XDR patients need to be hospitalized or requires longer treatment times. However, it has been shown that within an aggressive treatment, XDR-TB patients have been successfully cured by 60%. The treatment of M/XDR-TB usually takes more than 2 years, and requires the use of more toxic, less effective, and more expensive drugs [15].

Pulmonary tuberculosis is the most ubiquitous form of the disease, and the respiratory path represents the means of delivering a unique ATD’s directly to the lungs. The reduction of toxicity and accomplishing higher systemic drug concentration at the chief site of infection are the promising advantages of the direct delivery of the drug to the lungs. Inhalable nanoparticles possess an enhanced ability of mucosal adherence, particle delivery, and net drug delivery to the lungs [23].

Anti-TB drug carriers are classified: synthetic or natural origin. They allow the flexibility of selecting the route of drug delivery, Depending on the drug formulation. Not only the smaller size but also the ability of higher drug encapsulation and enhancement of the orally administered-drug bioavailability is the key difference between the nanoparticles and microparticles. poly-dl-lactide-co-glycolide (PLG)-A nanoparticles are commonly used in preparation for emulsification or evaporation [15].

Nanomedicine approach significantly prolonged provided a mean residence time, and elimination half-life of the drugs in comparison to the conventional orally administered formulations and resulted in an enhanced relative bioavailability for the nanoparticle-preparations (rifampicin, pyrazinamide, and isoniazid). The nebulization of the nano-encapsulated drug led to an absence of Mycobacterium tuberculosis in the lungs [17].

Drug resistance tuberculosis is an important health issue in progress made in TB care and control programs worldwide. Drug resistance arises due to pathogen inappropriate use of medicines in the treatment of drug-susceptible tuberculosis patients. This improper use may be due to the administration of improper treatment regimens and the failure of noncompliance of the patients to complete the course of therapy [17].

The treatment of tuberculosis has become a challenge for the physicians because of the emerging threat of drug-resistant strains of the pathogen. The M. tuberculosis responsible for the disease can overcome the cellular defense mechanisms, infecting the cells and turning them into reservoirs. The drawbacks of conventional tuberculosis drug formulation are the inability to kill the intracellular pathogens because of reviewing their limited bioavailability and limited penetration power in the targeted pathogens to produce a therapeutic effect [17].

Nanomedicine has the potential to challenge such limitations and improve the therapeutic efficacy of such drugs. Nanovesicles formulation of gentamicin, vancomycin amikacin, kanamycin, streptomycin, present enhanced in vitro and in vivo efficacy. Reviewing these formulations successfully reduced the viable bacteria counts of M. tuberculosis. However, in some cases, the pulmonary availability of the drugs was small or absent roommates can overcome by the development of localized particles targeted for delivery by inhalation or by targeting the pulmonary area [17].
5 Nanoparticle for diagnose tuberculosis

Diagnose tuberculosis with detection of mycobacterium DNA in clinical samples using nanoparticles has been developed, and it is a great futuristic vision. Nanocrystalline silicon photodetector with suitable software can detecting tuberculosis for diagnose tuberculosis and it could be to lessen the human error in diagnose tuberculosis. Recently, a convenient and low-cost biosensing platform was presented to detect Mycobacterium tuberculosis [24].

Exploited of scanobased, fluoremetric, colorimetric, surface-enhanced Raman scattering and electrochemical methodologies as a ultrasensitive techniques can developed to detect gold nanoparticles in clinical sputum samples, which that engineered with thiol-modified oligonucleotides to make the detection efficient, simplified, and relatively cheaper. Mycobacterium tuberculosis can be easily differentiated from other members of Mycobacterium species with the help of these nanoparticles. Fluorescent semiconductor quantum dots and magnetic beads are also used to detect DNA of Mycobacterium species without prior PCR. Even the probe consisting of superparamagnetic ironoxide nanoparticles has been designed and this probe is specific for diagnosing the extrapulmonary TB [24].

Nanoparticles are versatile and diverse with respect to their properties and structural, which enables them to be used for clinical diagnosis and effective drug delivery purpose in a unique and more reliable manner. Owing to their wide range of distribution manner and functional modes, nanoparticles can be used for multiple applications. The main reason behind this is the excellent geometric control of structures by arresting their formation during different stages of their synthesis. Better and more effective disease treatment protocols can be achieved with the use of systems like programmable nanorobots that can be employed for site-specific drug delivery [24].

Dendrimers has a layer, outer core on dendrimers there has hydrophilic characteristic and on an inside core on dendrimers has hydrophobic characteristic, so possible to deliver material component (as shown in Figs. 15.6 and 15.7). This arrangement forms the basic formulation

FIGURE 15.7 Different nanotechnology-based approaches [8].
Nanotechnology approach in conquering anti-TB resistance

for dendrimers in drug delivery systems. Mycobacterium is a Gram-negative bacterium. Its cell-wall composition (a rich layer of mycolic acid) renders it difficult for potential anti-TB medicinal preparations to enter into the infected cells. With the use of dendrimers, the conformation of the carried medicinal formulation is biochemically altered in a way that favors its entry into the specific target cells [24].

Nanoparticles have also been explored for the coencapsulation of tuberculosis drugs. Respiratory delivery developed because nanocarriers loaded with RIF, INH, and PYR. Data demonstrated that the inhalable nanotechnological platform allowed improving the pharmacotherapy regimen in Mycobacterium tuberculosis infected. Nanoparticles were investigated to encapsulate these tuberculosis drugs. Polymeric micelles (PMs) have become well-investigated nanovehicles. They are composed by amphiphilic biocompatible polymers that can self-assemble into nanostructures when the polymers concentration is above their critical micellar concentration. The pharmacotherapy of tuberculosis: this strategy has not been explored as LPs and NPs. The selection of the biomaterials and the pharmaceutical additives allowed developing different dosage forms (Figs. 15.8 and 15.9) [8].

Nanosuspension can make more efficient absorption and better biodistribution of drug molecules. During the formulation of a nanosuspension, the crystalline particles of the drug are converted into amorphous form. The conversion to amorphous forms can be achieved using X-ray diffraction. Various parameters such as particle size, charge distribution, and drug dissolution celerity also can be more effectively and easily monitored as well as suitably modified to suit a particular kind of drug delivery mechanism. Nanoemulsions represent a stable thermodynamic mixture. The use of rifampicin-based nanoemulsions for TB pharmacotherapy: they have elaborated the critical design features such as viscosity, solubility, and chemical interaction ability for nanoemulsion design to become optimized drug delivery vehicles. It has been successfully used for the killing of Mycobacterium tuberculosis germs at low dosage, and there is hardly any risk of toxicity or side effects (Fig. 15.10) [24].

There is a significant improvement from anti-TB drugs with nanoparticle than free anti-TB drugs. Relativity, bioavailability and mean residence time of encapsulated drugs more significant. Five aerosolized doses of PLG nanoparticles coencapsulating rifampicin, isoniazid, and pyrazinamide revealed undetectable cfu in the lungs. Comparison with microparticles: first, the decrease of lung cfu was better, and second, coadministration of three anti-TB drug encapsulations was possible in nanoparticles delivery system. As detection of Mycobacterium tuberculosis nanotechnology more expendable and efficient, especially high sensitivity so diagnose of tuberculosis more effective and efficient because nanoparticles can be tagged with suitable ligands and can be functionalized with various lectins to make more effective PLG nanoparticle uptake [15].
FIGURE 15.9 Nanomedicine in tuberculosis [8].

FIGURE 15.10 Mechanism of both natural and synthetic drug carriers by nanoparticle [14].
References


Index

Note: Page numbers followed by “f” indicate figures.

A
Adaptive immunity, 21
Adjuvanted subunit TB vaccine, 78
Advanced TB vaccine delivery systems
cationic nanoparticle-based TB vaccine delivery, 83
chitosan-based nanoparticle TB vaccine delivery, 83
dendrimer-based TB vaccine delivery system, 85
formulation and their delivery, 87
immune stimulating complexes (ISCOMs) as a TB vaccine delivery system, 86
liposome-based TB vaccine delivery, 85
nanoparticles-based TB vaccine delivery systems, 82
polymeric/polyester-based nanoparticle TB vaccine delivery system, 84
virosomes-based TB vaccine delivery system, 87
virus-like particles (VLPs)-based TB vaccine delivery system, 86
liposome-based TB vaccine delivery, 85
nanoparticles-based TB vaccine delivery systems, 82
polymeric/polyester-based nanoparticle TB vaccine delivery system, 84
virosomes-based TB vaccine delivery system, 87
virus-like particles (VLPs)-based TB vaccine delivery system, 86
Aerosol-based transmissible disease, 161
Airborne particles of M. tuberculosis, 2
Albumin-based carriers, 128
Alginate-based ATD-nanomedicine, 150
Alginate-based carriers, 126
Antigenic target, 10
Antitubercular drug delivery systems, 144
Antituberculosis drug (ATB) delivery, inhalable polymeric dry powders for clinical trials, 100
drug carriers for pulmonary delivery, 96
dry powder inhalers formulations for, 96
inhalation delivery devices for, 99
feasibility of lung as a portal for delivery of, 93
hybrid nano-in-microparticles, 98
liposomes, 98
microparticles, 99
polymeric nanoparticles, 96
polymeric powder-based drug development for TB, 101
pulmonary drug delivery, 92
solid-lipid nano particles, 98
therapies, 92
ATD-nanomedicine, 155

B
Bacilli Calmette-Guérin (BCG), 130
Bacterial metabolic pathway, modulation of, 10
BCG. See Bacilli Calmette-Guérin (BCG)
Bedaquiline, 231
Biodegradable synthetic polymer-based nanoparticles, 138

C
Calcineurin pathway, 8
Capsule, mycobacterium tuberculosis cellular structure of, 12
host-pathogen interaction from, 12
pharmaceutical methodology to target, 14
Carbonaceous nanomaterials-based DNA biosensors
carbon nanotubes, 211
graphene derivatives, 208
Carbon nanotubes (CNTBs), 45, 211
Cationic nanoparticle-based TB vaccine delivery, 83
Cerebral TB, 118, 153
Chitosan-base carriers, 124
nanoparticle TB vaccine delivery, 83
CNTBs. See carbon nanotubes (CNTBs)
Cold homogenization method emulsification-ultrasonication method, 195
film-ultrasonication method, 195
microemulsion technique, 195
solvent diffusion method, 195
solvent emulsification evaporation method, 195
supercritical fluid (SCF) technology, 195
Combination chemotherapy, 117
Conducting airways, mechanical defense of, 15, 16f
Cord factor, 6
CS. See Cycloserine (CS)
Cycloserine (CS), 32
Cytokines, role of, 10

D
Delamanid, 235
dendrimers, 43
based drug delivery systems for tuberculosis treatment Melamine, PEHAM, and PEA dendrimers, 168
PAMAM dendrimers, 164
PPI dendrimers, 166
based TB vaccine delivery system, 85
Directly observed therapy, 38. See also First line drugs
DNA structure, 206
DNA TB vaccine, 78
DPI. See dry powder inhalers (DPI)
Drug carriers, for pulmonary delivery, 96
Drug regimens, for treatment of tuberculosis, 28
Drug resistance, mechanisms of, 32
Drug-resistant TB, 153

267
Drug-resistant tuberculosis, 55  
Dry particle deposition, in lungs, 95f  
Dry powder inhalers (DPI) formulations for, 96  
   inhalation delivery devices for, 99  

E  
Emulsification-ultrasonication method, 195  
Emulsion-based systems  
   microemulsion, 42  
   nanoemulsions, 42  
Ethambutol, first line drugs for tuberculosis, 30, 162  
Exocytosis, 7  
Extensively drug-resistant tuberculosis (XDR TB), 108  

F  
Feasibility of lung, as portal for delivery of ATB, 93  
Film-ultrasonication method, 195  
First line drugs, for tuberculosis  
   ethambutol, 30  
   isoniazid, 29  
   pyrazinamide, 30  
   rifampin, 30  
   streptomycin, 31  
Formulation and their delivery, 87  

G  
Gelatin-based carriers, 127  
Generic sec-dependent secretion pathway, 10  
Genomics, 64  
Granuloma formation, 22  
Graphene derivatives, 208  
Guar gum-based carriers, 127  

H  
Host-directed therapies, 238  
Host-directed therapy, for tuberculosis, 61  
Hot homogenization method, 194  
Hybrid nano-in-microparticles, 98  

I  
Immune stimulating complexes (ISCOMs) as TB vaccine delivery system, 86  
Immunology  
   adaptive immunity, 21  
   granuloma formation, 22  


inflammatory responses, 20  
innate immune system  
   bacterial factors that evade these innate immune responses, 18  
   effector functions of macrophages against engulfed mycobacterium tuberculosis, 20  
   mechanisms of recognition of MTB by innate immune system, 19  
   mycobacterial cell wall, 17  
   recognition of mycobacterium tuberculosis of tuberculosis, 15  
   Inflammatory responses, 20  
Injectable ATD-nanomedicine, 149  
Innate immune system  
   bacterial factors evade innate immune responses, 18  
   effector functions of macrophages against engulfed mycobacterium tuberculosis, 20  
   mechanisms of recognition of MTB by innate immune system, 19  
   mycobacterial cell wall, 17  
   recognition of mycobacterium tuberculosis, 17  
   Intradermal route of administration, 81  
   Intramuscular route of administration, 81  
   Intranasal (mucosal, sublingual) route of administration, 81  
   ISCOMs. See immune stimulating complexes (ISCOMs)  
   Isoniazid, first line drugs for tuberculosis, 29, 162  
Liposomes (LPS), 42, 98  
   based drug delivery systems, 151  
   based TB vaccine delivery, 85  
   pulmonary TB and the importance of liposomal drugs, 112  
   Si-RNA liposomes, 113  
   targeting of, 114  
   types and uses of, 111  
Lipospheres (LIPs), 43  
LIPS. See lipospheres (LIPs)  
LPS. See liposomes (LPS)  

M  
Macrophage apoptosis, 20  
   stages of, 9f  
Magnetic beads (MBs), 221  
MBs. See magnetic beads (MBs)  
MDR TB. See multidrug resistant tuberculosis (MDR TB)  
ME. See microemulsion (ME)  
Melamine dendrimers, for tuberculosis treatment, 168  
Metabolomics, 66  
Metal oxide nanoparticles, 220  
Microemulsion (ME), 42  
   as potential ATD delivery systems, 152  
   technique, 195  
Microparticles, 99  
Microspheres, 43  
MTB. See Mycobacterium tuberculosis (MTB)  
Multidrug-resistant tuberculosis (MDR-TB), 108  
   bedaquiline, 231  
   delamanid, 235  
   host-directed therapies, 238  
   pretomanid, 235  
Mycobacterial glycolipids, role of, 10  
Mycobacterium tuberculosis (MTB) capsule  
   cellular structure of, 12  
   host-pathogen interaction from, 12  
   pharmaceutical methodology to target, 14  
   drug regimens, 109  
   factors responsible for transmission bacteriological factors, 4  
   patient-related risk factor, 3
immunology
adaptive immunity, 21
granuloma formation, 22
inflammatory responses, 20
innate immune system, 16
of tuberculosis, 15

Nanosomedicine

liposomes
pulmonary delivery of nanoparticle
polypeptide and protein-based carriers, 127
polysaccharide-based carriers, 124
based on synthetic polymers
PLGA-based nanocarriers, 128
types of, 110

Nanodelivery systems
nanocarriers, types of, 110
nanotechnology-based delivery system, 110
Nanoemulsions (NE), 42

Nanomedicine

Nanomicelles (NMCs), 46
Nanoparticles (NPs)
based delivery systems for
vaccination against tuberculosis
adjuvants, 135
tuberculosis vaccines, 130
vaccine delivery systems, 136
based-DNA biosensors
magnetic beads, 221
metal oxide nanoparticles, 220
noble metal nanoparticles, 213
quantum dots, 222
based TB vaccine delivery systems, 82
miscellaneous
carbon nanotubes, 46
dendrimers, 43
microspheres, 43
nannomicelles, 46
nano/micro particles, 43
nanosuspension, 46
polymersomes, 47

Nanostructured lipid carriers, 197
Nanosuspension (NSP), 46

Nanotechnology approach
alginate-based ATD-nanomedicine, 150
antitubercular drug delivery systems, 144
ATD-nanomedicine, 155
cerebral TB, drug-resistant TB, and latent TB, 153
in conquering anti-TB resistance
antituberculosis and mechanism of antituberculosis resistant, 251
nanoparticle and its use, 256
pathogenesis and its problem in resistant, 249
injectable ATD-nanomedicine, 149
ligand-appended oral ATD-nanomedicine, 148
lipid-based ATD-nanomedicine
liposome-based drug delivery systems, 151
microemulsions as potential ATD delivery systems, 152
niosomes-based ATD delivery system, 152
solid lipid nanoparticles-based ATD-nanomedicine, 153
nanomedicine, 146
oral ATD-nanomedicine, 147
potential toxicity of ATD-nanomedicine, 154

Nanotechnology-based systems, and administration of drugs against tuberculosis
emulsion-based systems
microemulsion, 42
nanoemulsions, 42
nanoparticles, miscellaneous
carbon nanotubes, 45
dendrimers, 43
microspheres, 43
nannomicelles, 46
nano/micro particles, 43
nanosuspension, 46
polymersomes, 47
solid-lipid forms
nanostructured lipid carrier, 42
solid-lipid microparticles, 40
solid-lipid nanoparticles, 40
vesicular drug-delivery systems
liposomes, 42
lipospheres, 43
niosomes, 43

N
Nanocarriers
based on natural polymers
immunology
adaptive immunity, 21
granuloma formation, 22
inflammatory responses, 20
innate immune system, 16
of tuberculosis, 15

Nanosomedicine

liposomes
pulmonary delivery of nanoparticle
polypeptide and protein-based carriers, 127
polysaccharide-based carriers, 124
based on synthetic polymers
PLGA-based nanocarriers, 128
types of, 110

Nanodelivery systems
nanocarriers, types of, 110
nanotechnology-based delivery system, 110
Nanoemulsions (NE), 42

Nanomedicine

Nanomicelles (NMCs), 46
Nanoparticles (NPs)
based delivery systems for
vaccination against tuberculosis
adjuvants, 135
tuberculosis vaccines, 130
vaccine delivery systems, 136
based-DNA biosensors
magnetic beads, 221
metal oxide nanoparticles, 220
noble metal nanoparticles, 213
quantum dots, 222
based TB vaccine delivery systems, 82
miscellaneous
carbon nanotubes, 46
dendrimers, 43
microspheres, 43
nannomicelles, 46
nano/micro particles, 43
nanosuspension, 46
polymersomes, 47

Nanostructured lipid carriers, 197
Nanosuspension (NSP), 46

Nanotechnology approach
alginate-based ATD-nanomedicine, 150
antitubercular drug delivery systems, 144
ATD-nanomedicine, 155
cerebral TB, drug-resistant TB, and latent TB, 153
in conquering anti-TB resistance
antituberculosis and mechanism of antituberculosis resistant, 251
nanoparticle and its use, 256
pathogenesis and its problem in resistant, 249
injectable ATD-nanomedicine, 149
ligand-appended oral ATD-nanomedicine, 148
lipid-based ATD-nanomedicine
liposome-based drug delivery systems, 151
microemulsions as potential ATD delivery systems, 152
niosomes-based ATD delivery system, 152
solid lipid nanoparticles-based ATD-nanomedicine, 153
nanomedicine, 146
oral ATD-nanomedicine, 147
potential toxicity of ATD-nanomedicine, 154

Nanotechnology-based systems, and administration of drugs against tuberculosis
emulsion-based systems
microemulsion, 42
nanoemulsions, 42
nanoparticles, miscellaneous
carbon nanotubes, 45
dendrimers, 43
microspheres, 43
nannomicelles, 46
nano/micro particles, 43
nanosuspension, 46
polymersomes, 47
solid-lipid forms
nanostructured lipid carrier, 42
solid-lipid microparticles, 40
solid-lipid nanoparticles, 40
vesicular drug-delivery systems
liposomes, 42
lipospheres, 43
niosomes, 43

N
Nanocarriers
based on natural polymers
<table>
<thead>
<tr>
<th>Subject</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nasopharyngeal airways</td>
<td>15</td>
</tr>
<tr>
<td>Natural killer cells (NK cells)</td>
<td>20</td>
</tr>
<tr>
<td>Natural polymer-based nanoparticles</td>
<td>137</td>
</tr>
<tr>
<td>NE. See nanoemulsions (NE)</td>
<td></td>
</tr>
<tr>
<td>NIOs. See niosomes (NIOs)</td>
<td></td>
</tr>
<tr>
<td>Niosomes (NIOs)</td>
<td>43</td>
</tr>
<tr>
<td>advantages of</td>
<td>115</td>
</tr>
<tr>
<td>application of</td>
<td>116</td>
</tr>
<tr>
<td>based ATD delivery system</td>
<td>152</td>
</tr>
<tr>
<td>definition</td>
<td>115</td>
</tr>
<tr>
<td>drug delivery system role in cerebral, drug-resistant</td>
<td>118</td>
</tr>
<tr>
<td>treatment of TB</td>
<td>117</td>
</tr>
<tr>
<td>types of</td>
<td>116</td>
</tr>
<tr>
<td>NK cells. See Natural killer cells (NK cells)</td>
<td></td>
</tr>
<tr>
<td>NMCs. See nanomicelles (NMCs)</td>
<td></td>
</tr>
<tr>
<td>NMPs. See nano/micro particles (NMPs)</td>
<td></td>
</tr>
<tr>
<td>Noble metal nanoparticles</td>
<td>213</td>
</tr>
<tr>
<td>Nonbiodegradable synthetic polymers</td>
<td>139</td>
</tr>
<tr>
<td>NPs. See nanoparticles (NPs)</td>
<td></td>
</tr>
<tr>
<td>NSP. See nanosuspension (NSP)</td>
<td></td>
</tr>
<tr>
<td>O</td>
<td></td>
</tr>
<tr>
<td>OMICs of tuberculosis</td>
<td>62</td>
</tr>
<tr>
<td>Oral ATD-nanomedicine</td>
<td>147</td>
</tr>
<tr>
<td>Oxidants impair ciliary function</td>
<td>15</td>
</tr>
<tr>
<td>Phagolyosome</td>
<td>7</td>
</tr>
<tr>
<td>lysosome, inhibition of</td>
<td>8</td>
</tr>
<tr>
<td>PLGA-based nanocarriers</td>
<td>128</td>
</tr>
<tr>
<td>PMDs. See pressurized metered dose inhalers (pMDIs)</td>
<td></td>
</tr>
<tr>
<td>Polymer-based nanoparticles as delivery systems</td>
<td></td>
</tr>
<tr>
<td>nanocarriers based on natural polymers</td>
<td></td>
</tr>
<tr>
<td>polypeptide and protein-based carriers</td>
<td>127</td>
</tr>
<tr>
<td>polysaccharide-based carriers</td>
<td>124</td>
</tr>
<tr>
<td>nanocarriers based on synthetic polymers</td>
<td></td>
</tr>
<tr>
<td>PLGA-based nanocarriers</td>
<td>128</td>
</tr>
<tr>
<td>nanoparticle-based delivery systems for vaccination against tuberculosis</td>
<td></td>
</tr>
<tr>
<td>adjuvants, 135</td>
<td></td>
</tr>
<tr>
<td>tuberculosis vaccines</td>
<td>130</td>
</tr>
<tr>
<td>vaccine delivery systems</td>
<td>136</td>
</tr>
<tr>
<td>Polymeric micelle, based drug delivery systems for tuberculosis</td>
<td></td>
</tr>
<tr>
<td>treatment advances of</td>
<td>182</td>
</tr>
<tr>
<td>amphiphilic block copolymers</td>
<td>177</td>
</tr>
<tr>
<td>bradykinin and permeability of cells</td>
<td>180</td>
</tr>
<tr>
<td>corona of</td>
<td>174</td>
</tr>
<tr>
<td>delivery approaches, 181</td>
<td></td>
</tr>
<tr>
<td>enhanced permeability and retention effect, 178</td>
<td></td>
</tr>
<tr>
<td>free radicals in cell permeability, 180</td>
<td></td>
</tr>
<tr>
<td>permeability and prostaglandin with other factors, 181</td>
<td></td>
</tr>
<tr>
<td>structure of</td>
<td>174</td>
</tr>
<tr>
<td>Polymeric nanoparticles</td>
<td>96</td>
</tr>
<tr>
<td>Polymeric/polyester-based nanonanoplemic TB vaccine delivery system</td>
<td>84</td>
</tr>
<tr>
<td>Polymeric powder-based drug development for TB, 101</td>
<td></td>
</tr>
<tr>
<td>Polymersomes</td>
<td>47</td>
</tr>
<tr>
<td>Polypeptide based carriers</td>
<td></td>
</tr>
<tr>
<td>albumin-based carriers</td>
<td>128</td>
</tr>
<tr>
<td>gelatin-based carriers</td>
<td>127</td>
</tr>
<tr>
<td>Polysaccharide-based carriers</td>
<td></td>
</tr>
<tr>
<td>Alginate-based carriers</td>
<td>126</td>
</tr>
<tr>
<td>Chitosan-based carriers</td>
<td>124</td>
</tr>
<tr>
<td>Guar gum-based carriers</td>
<td>127</td>
</tr>
<tr>
<td>Polysaccharide-conjugate vaccine, 14</td>
<td></td>
</tr>
<tr>
<td>Postexposure vaccines</td>
<td>132</td>
</tr>
<tr>
<td>Potential toxicity of ATD-nanomedicine</td>
<td>154</td>
</tr>
<tr>
<td>PPI dendrimers, for tuberculosis treatment</td>
<td>166</td>
</tr>
<tr>
<td>Preexposure vaccines</td>
<td>131</td>
</tr>
<tr>
<td>Pressurized metered dose inhalers (pMDIs)</td>
<td>119</td>
</tr>
<tr>
<td>Pretomanid, 235</td>
<td></td>
</tr>
<tr>
<td>Programmed cell death</td>
<td>20</td>
</tr>
<tr>
<td>Proteomics</td>
<td>65</td>
</tr>
<tr>
<td>Proximate risk factor, in MTB and socioeconomic status, links between</td>
<td>3</td>
</tr>
<tr>
<td>urbanization, role of</td>
<td>4</td>
</tr>
<tr>
<td>PRRs. See pattern recognition receptors (PRRs)</td>
<td></td>
</tr>
<tr>
<td>Pulmonary drug delivery</td>
<td>92</td>
</tr>
<tr>
<td>drug carriers for</td>
<td>96</td>
</tr>
<tr>
<td>of nanoparticle encapsulated antitubercular drugs</td>
<td>118</td>
</tr>
<tr>
<td>Pulmonary TB disease</td>
<td>2</td>
</tr>
<tr>
<td>Pyrazinamide, first line drugs for tuberculosis</td>
<td>30, 162</td>
</tr>
<tr>
<td>Q</td>
<td></td>
</tr>
<tr>
<td>QDs. See quantum dots (QDs)</td>
<td></td>
</tr>
<tr>
<td>Quantum dots (QDs)</td>
<td>222</td>
</tr>
<tr>
<td>R</td>
<td></td>
</tr>
<tr>
<td>Reactive nitrogen intermediates (RNI)</td>
<td>20</td>
</tr>
<tr>
<td>Reactive oxygen intermediates (ROI)</td>
<td>20</td>
</tr>
<tr>
<td>Rifampin, first line drugs for tuberculosis</td>
<td>30, 162</td>
</tr>
<tr>
<td>RNI. See Reactive nitrogen intermediates (RNI)</td>
<td></td>
</tr>
<tr>
<td>ROI. See Reactive oxygen intermediates (ROI)</td>
<td></td>
</tr>
<tr>
<td>S</td>
<td></td>
</tr>
<tr>
<td>SCF technology. See supercritical fluid (SCF) technology</td>
<td></td>
</tr>
<tr>
<td>Second-line antituberculosis drugs</td>
<td>31</td>
</tr>
<tr>
<td>SLM. See solid-lipid microparticles (SLM)</td>
<td></td>
</tr>
<tr>
<td>Solid-lipid forms</td>
<td></td>
</tr>
<tr>
<td>nanostructured lipid carrier</td>
<td>42</td>
</tr>
<tr>
<td>solid-lipid microparticles</td>
<td>40</td>
</tr>
<tr>
<td>solid-lipid nanoparticles</td>
<td>40</td>
</tr>
<tr>
<td>Solid-lipid microparticles (SLM), 40, 98, 197</td>
<td></td>
</tr>
<tr>
<td>based ATD-nanomedicine</td>
<td>153</td>
</tr>
<tr>
<td>Solvent diffusion method</td>
<td>195</td>
</tr>
<tr>
<td>Solvent emulsification evaporation method</td>
<td>195</td>
</tr>
</tbody>
</table>
Streptomycin, first line drugs for tuberculosis, 31
Subcutaneous route of administration, 81
Supercritical fluid (SCF) technology, 195
Survival mechanisms of mycobacterium tuberculosis
advantages due to presence of lipid at cell wall, 6
after stages of macrophage activation, 9
eukaryotic like protein kinases in mycobacterial cell, role of, 8
inhibition of phagosome-lysosome fusion, 8
intercellular growth, 7
phagocytic cells, function of, 7
seizing of calcineurin pathway, 8
stage of granuloma, 7
uniqueness in cell wall structure, 6

T
TACO. See tryptophan aspartate containing coat protein (TACO)
Therapeutic vaccines, 133
TLR ligands. See Toll-like receptors (TLR) ligands
Toll-like receptors (TLR) ligands, role of, 10
Transcriptomics, 64
Transmission, factors responsible for bacteriological factors, 4
patient-related risk factor, 3
Tryptophan aspartate containing coat protein (TACO), 8
TST. See tuberculin skin test (TST)
Tuberculin skin test (TST), 4
Tuberculosis (TB). See also Dendrimers; Mycobacterium tuberculosis;
Nanostructured lipid carrier; Polymeric micelle
drug regimens for treatment of, 28
ethambutol, 30
first line drugs for, 29
infectious disease, 28
as infectious disease, 37
isoniazid, 29
mechanisms of drug resistance, 32
nanotechnology-based approaches alginate-based ATD-nanomedicine, 150
antitubercular drug delivery systems, 144
ATD-nanomedicine, 155
cerebral TB, drug-resistant TB, and latent TB, 153
injectable ATD-nanomedicine, 149
ligand-appended oral ATD-nanomedicine, 148
lipid-based ATD-nanomedicine, 151
nanomedicine, 146
oral ATD-nanomedicine, 147
potential toxicity of ATD-nanomedicine, 154
pulmonary delivery of ATD-nanomedicine, 148
nanotechnology-based systems and administration of drugs against emulsion-based systems, 42
factors affecting nanoparticles properties, 48
nanoparticles, 43
solid-lipid forms, 40
vesicular drug-delivery systems, 42
pyrazinamide, 30
rifampin, 30
second-line antituberculosis drugs, 31
streptomycin, 31
translational research for therapy against advance therapy, 55
drugs repurposed for, 58
metabolomics, 66
new drugs for, 56
OMICs of, 62
proteomics, 65
transcriptomics, 64
vaccine delivery systems against adjuvanted subunit TB vaccine, 78
advanced TB vaccine delivery systems, 82
DNA TB vaccine, 78
vaccine administration routes for TB vaccine, 80
whole-cell and live Mycobacteria TB vaccine, 80
V
Vaccine administration routes for TB vaccine
intradermal route of administration, 81
intramuscular route of administration, 81
intranasal (mucosal, sublingual) route of administration, 81
subcutaneous route of administration, 81
Vaccine delivery systems against tuberculosis
adjuvanted subunit TB vaccine, 78
advanced TB vaccine delivery systems
cationic nanoparticle-based TB vaccine delivery, 83
chitosan-based nanoparticle TB vaccine delivery, 83
dendrimer-based TB vaccine delivery system, 85
formulation and their delivery, 87
immune stimulating complexes (ISCOMs) as a TB vaccine delivery system, 86
liposome-based TB vaccine delivery, 85
nanoparticles-based TB vaccine delivery systems, 82
polymeric/polyester-based nanoparticle TB vaccine delivery system, 84
virosomes-based TB vaccine delivery system, 87
virus-like particles (VLPs)-based TB vaccine delivery system, 86
DNA TB vaccine, 78
vaccine administration routes for TB vaccine
intradermal route of administration, 81
intramuscular route of administration, 81
intranasal (mucosal, sublingual) route of administration, 81
subcutaneous route of administration, 81
whole-cell and live Mycobacteria TB vaccine, 80
Vesicular drug-delivery systems
liposomes, 42
lipospheres, 43
niosomes, 43

U
Upper respiratory track, immunology of, 15
Index

Viral vectored TB vaccines, 78
Virosomes-based TB vaccine delivery system, 87
Virus-like particles (VLPs)-based TB vaccine delivery system, 86

W
WAX D fraction of lipid, 6
Whole-cell and live Mycobacteria TB vaccine, 80

X
XDR TB. See extensively drug-resistant tuberculosis (XDR TB)
Nanotechnology Based Approaches for Tuberculosis Treatment

Edited by
Prashant Kesharwani
Department of Pharmaceutics, School of Pharmaceutical Education and Research, Jamia Hamdard (A Government-aided Deemed University), New Delhi, India

Nanotechnology Based Approaches for Tuberculosis Treatment discusses multiple nanotechnology-based approaches which may help overcome persisting limitations of conventional and traditional treatment of tuberculosis (TB). A quarter of the world’s population is infected with TB, and despite potentially curative pharmacotherapies being available for over 50 years, TB deaths persist, and multidrug-resistant strains of TB are emerging due to prolonged treatment, high pill burden, and low patient compliance. The book summarizes the pathogenesis, biology, immunology, drug regimens and multidrug resistance of tuberculosis followed by various types of nano drugs, their synthesis, formulation, characterization, and applications, along with the most important administration routes. It also explores recent advances and achievements regarding therapeutic efficacy and provides possible future applications in this field. Nanotechnology Based Approaches for Tuberculosis Treatment directly addresses translational aspects and clinical perspectives of tuberculosis nanomedicine from a comprehensive and multidisciplinary perspective. It will be a useful resource for investigators, pharmaceutical researchers, innovators, and scientists working on technology advancement in the areas of designing targeted therapies, nano scale imaging systems and diagnostic modalities in tuberculosis. Nanotechnology Based Approaches for Tuberculosis Treatment will also cater to the basic needs of students and new researchers in the fields of tuberculosis and nanomedicine.

Key Features

- Addresses the gap between nanomedicine late discovery and early development of tuberculosis therapeutics
- Explores tuberculosis nanomedicine standardization and characterization with newly developed treatment, diagnostic and treatment monitoring modalities
- Covers the field thoroughly from pathogenesis of tuberculosis and multi-drug resistant mycobacterium tuberculosis to treatment approaches using nanotechnology and different nanocarriers