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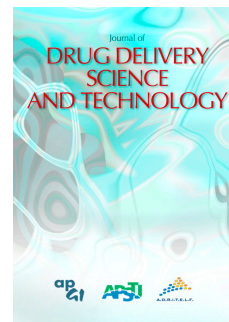
Please cite this article as: N. Verma, V. Arora, R. Awasthi, Y. Chan, N.K. Jha, K. Thapa, T. Jawaid, M. Kamal, G. Gupta, G. Liu, K.R. Paudel, P.M. Hansbro, B.G. George Oliver, S.K. Singh, D.K. Chellappan, H. Dureja, K. Dua, Recent developments, challenges and future prospects in advanced drug delivery systems in the management of tuberculosis, *Journal of Drug Delivery Science and Technology* (2022), doi: https://doi.org/10.1016/j.jddst.2022.103690.

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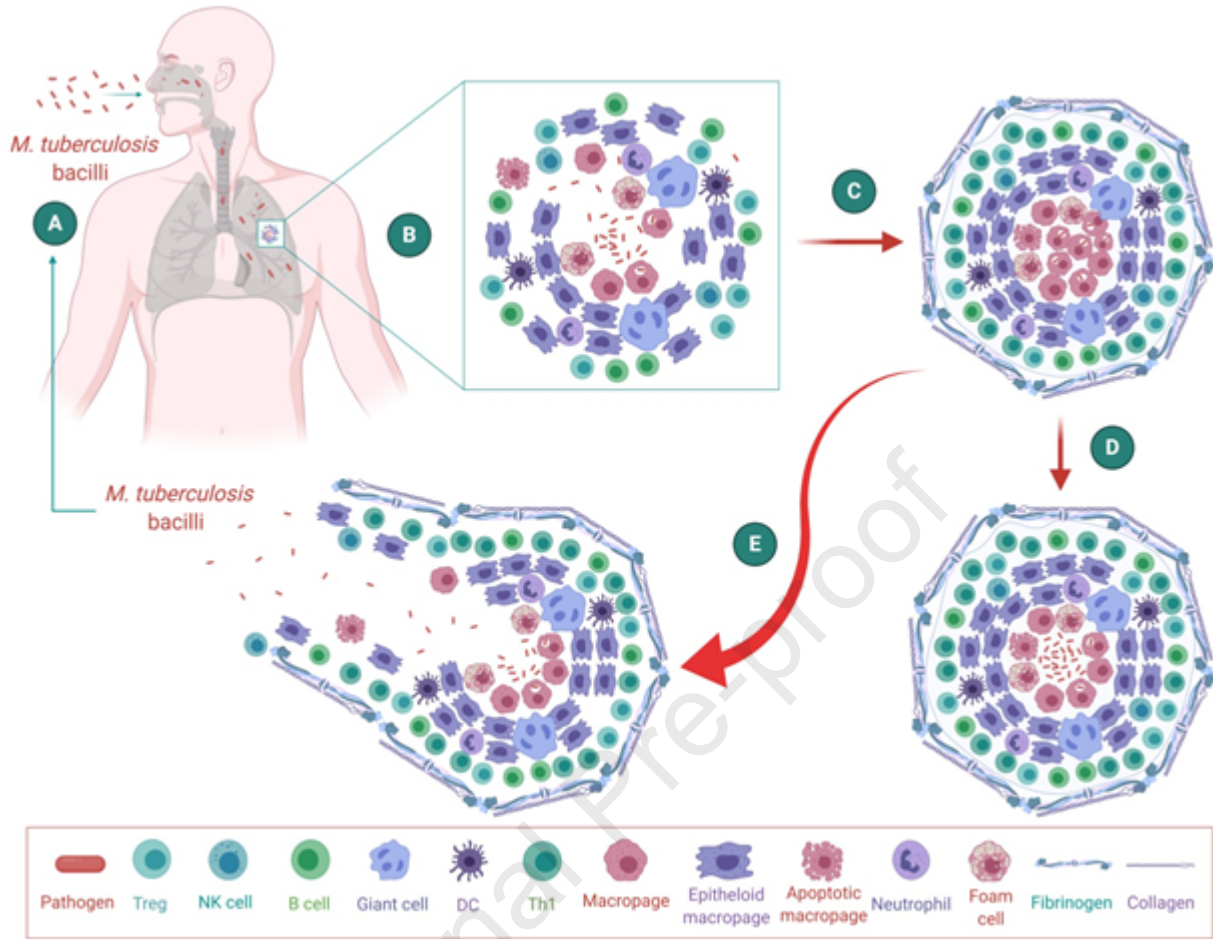
Recent developments, challenges and future prospects in advanced drug delivery systems in the management of tuberculosis

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ABSTRACT

Tuberculosis (TB) is reported as one of the most prevailing life-threatening health problems, affecting almost one third of the population globally. It is one of a major reason of death with an imposing amplified socio-economic impact. Tuberculosis patients have infrequent endocrine and metabolic derangements, but they are important when they occur. Multiple drug regimen, poor patient compliance, and stiff administration schedule are factors that are answerable for the development of and extensive drug resistance (XDR) and multi drug resistance (MDR) instances in TB along with poor drug targeting effects. The emerging resistance strains and high transmittance rate of the disease have prompted the need for studies in advanced drug delivery, particularly nanotechnology for the management of TB. Nanocarriers offer unique physicochemical properties that provide beneficial outcomes such as targeted effects and better patient compliance as drug delivery, thereby presenting as a promising solution to the constraints linked with conventional treatment strategy for TB. Both *in vitro* and *in vivo* studies have been reported to access release behavior of antitubercular agents with a view to being interpreted in clinical practice in the future. The present review highlights contemporary trends and advancements in drug delivery systems employed for the effective management of TB. This communication will be useful to the researchers working in the field of drug delivery systems for effective management of TB.

1. INTRODUCTION

Tuberculosis (TB) is a serious transmissible disease caused by *Mycobacterium tuberculosis* (MTb), a rod-shaped bacterium, that not only causes pulmonary TB in the lungs but can also affect other organs regarded as extra pulmonary TB [1, 2]. The highest number of deaths worldwide are caused by TB rather than human immunodeficiency virus (HIV) induced AIDS [3]. One-third of the population worldwide is contagion with MTb as reported by WHO. MTb resistance has made it extremely difficult to treat TB due to very low cure rates and high death rates [3-5]. The infection is transmitted by a diseased person in the form of droplets in the air during speaking, coughing, and sneezing (Figure 1). Pulmonary TB consist of 80% of overall cases of TB infection [6]. After inhalation of MTb through the droplet, they reach bronchioles and alveoli (Figure 1A). The bacteria initially provoke polymorph nuclear leukocyte reaction followed by their phagocytosis by pulmonary macrophages (Figure 1B). Bacteria likely proliferate inside macrophages if they are virulent or if inhaled in a large population. The resulting inflammatory cascade/ lesion may exacerbate due to infiltration of more monocytes/ macrophages, NK cells, neutrophils, dendritic cells (DC), and lymphocytes from the systemic circulation. In this condition, an immune reaction is primarily mediated by tissue-damaging delayed hypersensitivity response that kills MTb-laden macrophages and generates a solid caseating centre containing extracellular MTb. These immune cells form a spherical structure with the outermost layer of collagen and fibrinogen (Figure 1C). The nature of lesion depends on quality and intensity of cell-mediated immunity leading to granuloma formation. In a latent/asymptomatic state, MTb can survive inside the granuloma (Figure 1D). If only poor cell-mediated immune response develops, the granuloma disintegrates and the bacilli escapes from the periphery of the caseating center. This results in an active disease state (symptomatic disease) and can spread to other individuals (Figure 1E) [7].

TB is generally classified as latent or active TB [8]. The three types of pathogenic strains of TB are drug susceptible, MDR, and XDR strain. The drug-susceptible TB strain is treated by first-line drugs namely ethambutol (EMB), isoniazid (INH), pyrazinamide (PZA), and rifampicin (RIF). MDR-TB strain resistant to the INH and RIF is difficult to manage [9]. XDR-TB develops when the microbial strain is resistant to first-line drugs (INH and RIF) and second line drugs like some fluoroquinolones. Resistance in XDR strain possesses a major challenge in the treatment of TB [10].

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In this review, we first recapitulated recent global statistics and burden of TB and limitations of existing anti-TB drug delivery systems. Second, we discussed an overview of new anti-TB drugs and vaccines. Finally, we outlined novel drug delivery systems investigated and ongoing or completed clinical trials for the effective management of tuberculosis.
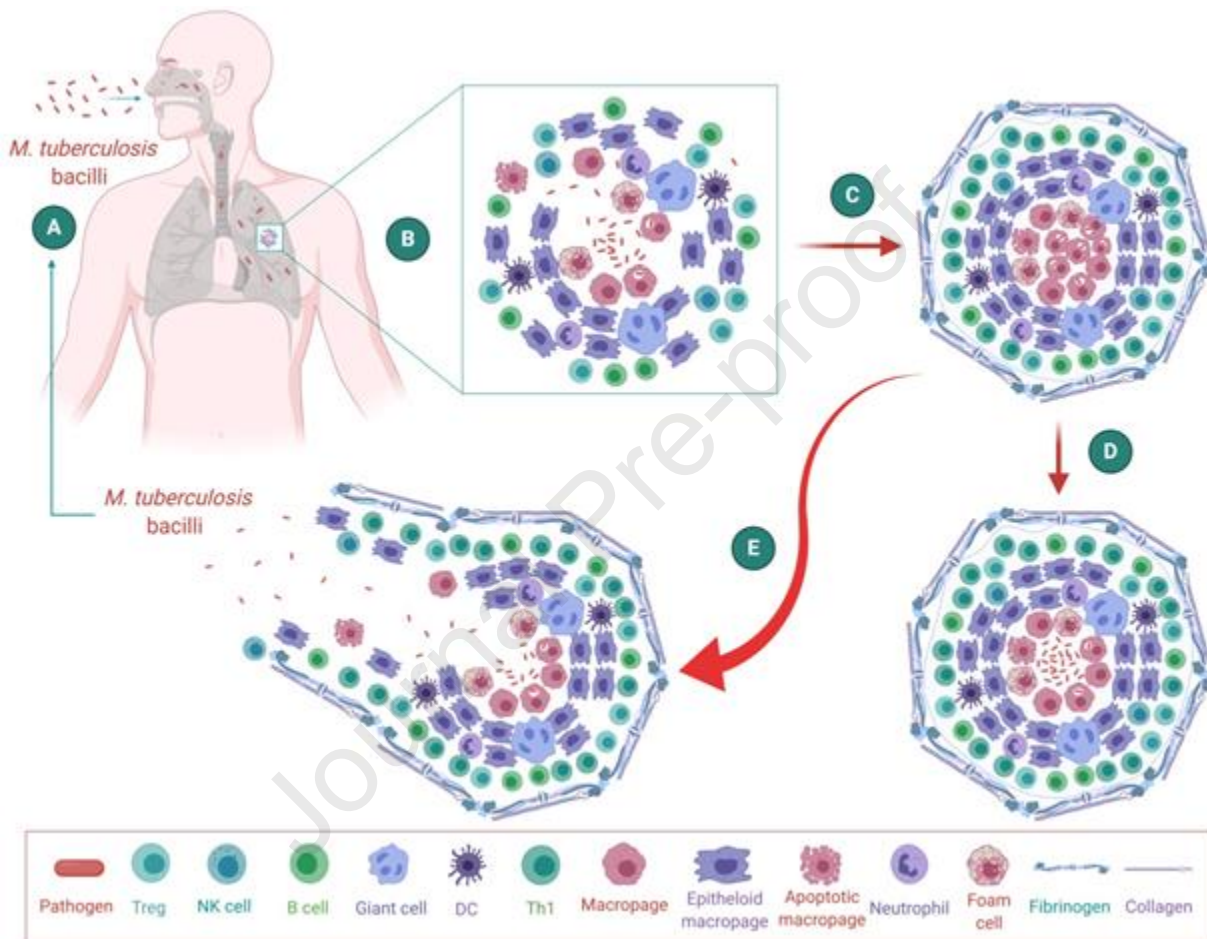

Figure 1 Schematic presentation of basic mechanism of infection of *Mycobacterium tuberculosis*. (A) *M. tuberculosis*-containing aerosols are inhaled. These bacilli may bypass goblet cells and move to the lungs. (B) Macrophage recognition and bacterial engulfment trigger innate immune cascades (provoking a host immune response), which leads to recruitment of other immune cells (more macrophages, NK cells, monocytes, neutrophils, dendritic cells (DC), lymphocytes, *etc*.) to the infection site. (C) Immune cells organize in a spherical structure, surrounded by collagen and fibrinogen. This in turn leads to granuloma formation. (D) Bacteria can survive inside the granuloma in a latent state (asymptomatic disease state) and (E) Due to genetic or environmental factors (malnutrition, HIV, *etc*.), the granuloma disintegrates, allowing the bacilli to spread and

form more lesions, resulting in an active disease state (symptomatic disease) in which the disease can spread to other individuals.

1.1. Global statistics and burden

The World Health Organization (WHO) has reported 1.5 million deaths from TB in 2020 (including 214000 deaths with HIV). According to the recent TB statistics report of WHO, HIV/TB is the 13th leading cause of death and the second leading infectious killer after COVID-19. In 2020, an estimated 10 million people globally diagnosed with 1.1 million children, TB. 5.6 million males, and 3.3 million females. TB has affected all age group peoples globally. Approximately 86% of all estimated cases worldwide were accounted from the 30 high TB burden countries. Eight countries account for 2/3rd of the total TB cases, with India leading the count (26%), followed China (8.5%), Indonesia (8.4%), the Philippines (6%), Pakistan (5.7%), Nigeria (4.4%), Bangladesh (3.6%), and South Africa (3.6%). Drug-resistance is the main cause of death in TB and nearly more than 2 million deaths occur annually. Life of about 66 million people was saved between 2000 and 2020 through timely diagnosis and treatment of TB. United Nations Sustainable Development Goals have targeted the year 2030 for ending TB epidemic [11]. In terms of TB occurrence, Southeast Asia has been reported for 39% of the global burden and 3.4 million new cases of TB have been estimated to occur each year in Bangladesh, India, Indonesia, Thailand, and Myanmar [11]. TB is a social disease. Various social factors involved in the transmission of TB are poor housing, poor quality of life, population explosion, overcrowding, under-nutrition, alcohol abuse, smoking, lack of awareness regarding cause, and lack of education [12]. Tuberculous meningitis or disseminated diseases are responsible for childhood death [13].

TB has become an all-time challenge for researchers due to its long-term treatment and drug resistance. Despite extensive research, in past 2-3 decades, no promising outcome is available yet for the effective management of this deadly disease and its prevalence [14]. In case of first-line and second-line treatment, drug resistance is the typically evolving issue in the management of TB. Drug resistance or the ability of strains to survive for a longer duration in the host cell or its dissemination to other surrounding cells makes it more vulnerable and challenging for health professionals to combat the disease [15,16]. Poor drug targeting and high dose of drugs lead to dose-dependent toxicity. Undoubtedly, with the advancement of healthcare system along with the

oral administration, various new routes of drug administration such as parenteral, nasal, and implants have been investigated [17].

1.2. Limitations of current anti-TB drug delivery systems

Pharmacokinetic and pharmacodynamic characteristics of a drug have presented reasonable approach for the development of an optimal drug delivery system [18]. A more efficacious and better drug delivery system may offer opportunities to the pharmaceutical companies for the treatment of disease [19–22]. Conventional dosage forms are not competent to target drugs at specific sites, but the novel drug delivery systems (NDDS) are much efficient to maintain drug concentration to the site of action for an extended period of action [23, 24]. Treatment of TB with a conventional therapeutic system has an increased risk of multi-drug resistant-TB (MDR-TB). Drug resistance result in poor patient compliance due to the drug-related side effects from high doses, dosing frequency, and lengthy treatment [25].

Moreover, the drawbacks like inefficient efficacy, poor tolerability of second-line anti-TB drugs (ATDs) leads to the withdrawal from treatment. This may result in further resistance like extremely drug-resistant TB (XDR-TB) which leads to an increased death rate [26]. This indicates the need for new drug delivery technology such as the use of novel controlled release nanoparticulate systems containing existing ATDs. These nanocarriers will overcome the limitations of conventional drug delivery system in the treatment of MDR-TB [27]. Nanocarrier systems can be exercised to distribute drugs through the parenteral, oral, nasal, and pulmonary routes. Moreover, pulmonary drug delivery of ATD loaded nanocarriers increases drug deposition at target site and reduces systemic side effects. [28]. ATDs loaded nanocarriers together with site-specific targeting holds the potential to treat intermittent therapy of drug susceptible and resistant TB. An advanced drug delivery systems can effectively overcome patient noncompliance and avoid limitations of current conventional chemotherapy [29].

2. OVERVIEW OF NEW ANTI-TB DRUGS

2.1. Bedaquiline

Bedaquiline, marketed under the name Sirturo, received approval by the FDA for treating MDR-TB [30]. Bedaquiline, associated with the diarylquinolines group of chemical compounds, is a

newly emerging class of anti-TB drugs [31]. The implication of bedaquiline against MDR-TB is cost-effective. Contrasting with other anti-TB drugs, Bedaquiline aims at targeting the energy metabolism of mycobacterium [32]. Nevertheless, mycobacterium may thrive in stress conditions such as hypoxia. ATP production is necessary for continued existence of all kinds of mycobacterium either extracellular or intracellular, replicating, or non-replicating, active or dormant, and fermenting or non-fermenting [33,34]. The most common side effects of bedaquiline are arthralgia, anorexia, chest pain, hemoptysis, headache, and nausea [35].

Mechanism of action of bedaquiline

Bedaquiline hampers the enzyme responsible for the synthesis of ATP by ATP synthase that transforms ADP to ATP by employing the transmembrane electrochemical ion (H+ or Na^+) [36]. ATP synthase has sites for the binding ions at c-subunit which produce power for ATP synthesis by carrying ions across the membrane. Bedaquiline inhibits these ion-binding sites resulting in diminishing intracellular ATP concentrations [37]. Besides c subunit, bedaquiline also aims to target the ε subunit of F-ATP synthase by binding with Trp16 residue. ATP synthase generates ATP through oxidative phosphorylation and is significantly preserved in both prokaryotes and eukaryotes [37, 38].

2.2. Delamanid

Delamanid is a drug of group nitroimidazole that is employed for the treatment of MDR-TB [39]. Delamanid demonstrates least minimum inhibitory concentration as compared to other TB drugs and acts against resistant *M. tuberculosis* strains. The drug also hinders the replication process [40, 41]. However, it is not advisable to use Delamanid and Bedaquiline due to their cardiotoxic effect [49]. Delamanid has oral bioavailability of 35%-60%, which increases with food containing high fat [35].

Mechanism of action of delamanid

Delamanid acts by blocking the production of keto mycolic and methoxy mycolic acid (main elements of mycolic acids). The activity of delamanid is specific against mycobacteria as the cell wall is made up of mycolic acids, it disrupts the cell wall promoting enhanced drug penetration [42- 45].

2.3. Pretomanid

Pretomanid is a nitroimidazole category of drugs and is powerful against *M. tuberculosis* in comparison to Delamanid [46, 47]. Pretomanid is a prodrug that goes through bioreductive activation through Ddn enzyme; generating several metabolites that secretes nitric oxide, which destroys cell wall lipids, intracellular proteins, and other macromolecules, which in turn create it bactericidal for anaerobic bacteria [48]. Pretomanid is readily absorbed, well tolerated, and shows good bioavailability. Pretomanid prescribed as a single daily dose as it has a long half-life of 16-20 h [49]. Studies have revealed that the main mechanism of action of pretomanid is cell wall disruption that in turn reduces ketomycolates and builds hydroxymycolate [50].

2.4. Linezolid

Linezolid (an oxazolidinone class drug) is approved for treating infections induced by Gram-positive bacteria such as vancomycin-resistant Enterococcus and methicillin-resistant Staphylococcus [51]. However, now it is not recommended due to safety matters, particularly hepatotoxicity. Soon after 1990, the oxazolidinones were developed with better safety profiles [52]. The drug is proficient against Gram-positive bacteria with improved antimycobacterial activity [53]. Linezolid exhibits bacteriostatic activity against *Mycobacterium tuberculosis*, extensively drug-resistant (XDR) and including multidrug-resistant (MDR) strains (MIC < 1 µg/mL) [54, 55]. WHO has recommended a daily dose of 600 mg for drug-resistant tuberculosis patients. The toxicity of linezolid is due to structural homology between 16S rRNA in human mitochondria and target 23S rRNA in *Mycobacterium tuberculosis* [56]. It shows a very high oral bioavailability of approximately 100% and therefore its oral and injectable dosage is the same. The most common side effects of linezolid are myelosuppression, peripheral neuropathy, thrombocytopenia, gastrointestinal disorders, and optic neuritis [49].

Mechanism of action of linezolid

Linezolid inhibits protein production in bacterial ribosomes (small (30S) and a large (50S) subunits). Each subunit is formed of ribosomal RNA (rRNA) and numerous amino acids function mutually to generate proteins for the cell [52, 53, 57-60].

2.5. Sutezolid

Sutezolid is a promising drug belonging to the oxazolidinone class. It is active against *M. tuberculosis*. Sutezolid displays favorable pharmacokinetics, well-tolerated and safer in humans and rat models of TB. Sutezolid has an improved safety profile than Linezolid and has effective antimycobacterial activity [61-64]. Half-life of sutezolid is approximately 4 h [49].

Mechanism of action of Sutezolid

Sutezolid possesses similar mechanism as that of Linezolid. It acts on 23S rRNA of 50S ribosomal subunit and inhibits protein production. Sutezolid is transformed into an active Sulfoxide (an active metabolite of Sutezolid) that has a relatively short plasma half-life. Sutezolid can act against drug-resistant TB, and it has shown additive effects with other new TB drugs [65-71].

2.6. Fluoroquinolones

Fluoroquinolones are the broad-spectrum antimicrobial agents prescribed for the treatment of TB [67]. In the United States, Fluoroquinolone ranks top in antibiotic expenditure with one-fourth of the $10 billion market of antibiotics [68]. Nalidixic acid is the first quinolone licensed for the treatment of human urinary tract infection [69]. At present, fluoroquinolones such as ofloxacin, levofloxacin, and ciprofloxacin are recommended drugs for second-line treatment of TB whereas moxifloxacin and gatifloxacin are under investigation for anti-TB action [70, 71]. Apart from the better efficacy, moxifloxacin shows cardiovascular risks [72, 73]. Gatifloxacin causes hypoglycemia/ hyperglycemia [49].

2.7. Moxifloxacin

Moxifloxacin is an antibiotic of fluoroquinolone class prescribed for treating MDR-TB [74]. Currently, the drug is being evaluated in combination with pretomanid, bedaquiline, and rifapentine or pyrazinamide. Moxifloxacin is used in the patients who are resistant to isoniazid or first-line TB drugs. Moxifloxacin displays different pharmacokinetic profiles in different individuals. Also, it has bactericidal action against bacterial strains both Gram positive and negative [75, 76]. Besides its efficacy, moxifloxacin shows cardiovascular risks [49].

Mechanism of action of moxifloxacin

Moxifloxacin act by DNA gyrase inhibition that ultimately inhibits replication of bacterial DNA [77, 78]. Moxifloxacin combines with enzyme-DNA complex formed by DNA gyrase during replication process and forms stabilized drug-enzyme-DNA complex [79, 80].

2.8. Clofazimine

Clofazimine is an antibiotic of class riminophenazine employed for treating MDR-TB. Clofazimine displayed remarkable *in vitro* antimycobacterial action. However, it was terminated because its side-effects like mental disturbances and discoloration of skin [81]. WHO has recommended clofazimine for multidrug-resistant leprosy treatment. The increasing incidence of drug resistant-TB has again drawn special attention on clofazimine that is a key element of newer TB treatment options owing to its anti-inflammatory properties [82]. Clofazimine is a highly lipophilic drug. Irrespective of its poor aqueous solubility, clofazimine is orally bioavailable. It has a large volume of distribution and an extremely long half-life (~70 days). Thus, it needs to formulate as an oil-wax base microcrystalline suspension for better absorption. Highly lipophilic nature leads to its accumulation in fat tissue-rich organs and caused its most common side effect *i.e*. skin discoloration starts. However, once the drug administration is discontinued, this side-effect disappears [49].

Mechanism of action of clofazimine

Clofazimine hampers respiratory chain of bacteria by generating an excess ROS as it first goes via reduction of type 2 NADH-quinone oxidoreductase (NDH-2) and generates reactive oxygen species when gets reoxidized (ROS) [81]. Clofazimine compete for electrons with menaquinone (the substrate for type NDH-2) which is the initial event in the mycobacterial respiratory chain [81]. The buildup of excess ROS radicals destroys the bacteria by damaging lipids, proteins, nucleic acids, and other biomolecules [83].

2.9. SQ109

SQ109 (1, 2-ethylenediamine) is at present in clinical phase II for drug resistant-TB [84]. SQ109 structural design is derived from ethambutol, a recognized drug of first-line treatment of TB [85]. SQ109 is active against both XDR-TB and MDR-TB [79]. Due to the presence of diamine groups

and hydrophobic nature, SQ109 has a high volume of distribution. However, it has low bioavailability [49].

Mechanism of action of SQ109

SQ109 displayed combined effects with rifampicin and isoniazid and cumulative effects with streptomycin and ethambutol [86]. This drug mainly works by cell wall targeting [87].

2.10. PBTZ169

PBTZ169 is a drug of class benzothiazinone (BTZ) and presently is under phase II study [88]. BTZ043 (the lead compound of BTZ) is utilized for the development of PBTZ169 [89]. PBTZ169 is stable among other BTZ against nitroreductase attack due to the presence of cyclohexyl group [90]. BTZ043 and PBTZ169 showed noteworthy bactericidal action against strains MDR-TB strains [91].

Mode of action of PBTZ169

Irreversible covalent adducts are formed by PBTZ169 with DprE1 [91, 92]. Inhibition of DprE1 hampers decaprenyl phosphoryl arabinose synthesis, which is the main component for mycobacterium cell wall synthesis [93].

2.11. Q203

Q203 is an imidazopyridine amide which is presently in clinical phase II. The drug is vigorous against strains of *M. tuberculosis* such as XDR and MDR and it has displayed potential effect in mice induced with TB [94]. The bioavailability of Q203 is 90%. It has a moderate volume of distribution with a terminal half-life of 23.4 h. It has a low systemic clearance [49].

Mechanism of action of Q203

Q203 hampers *M. tuberculosis* energy metabolism by inhibiting respiratory b-subunit of cytochrome bcc complex that is important in the respiratory chain as it catalyzes transport of electrons from ubiquinol to Cytochrome C [95, 96]. Hence, Q203 displays a bacteriostatic effect. The mode of actions of all above discussed drugs is illustrated in Figure 2.
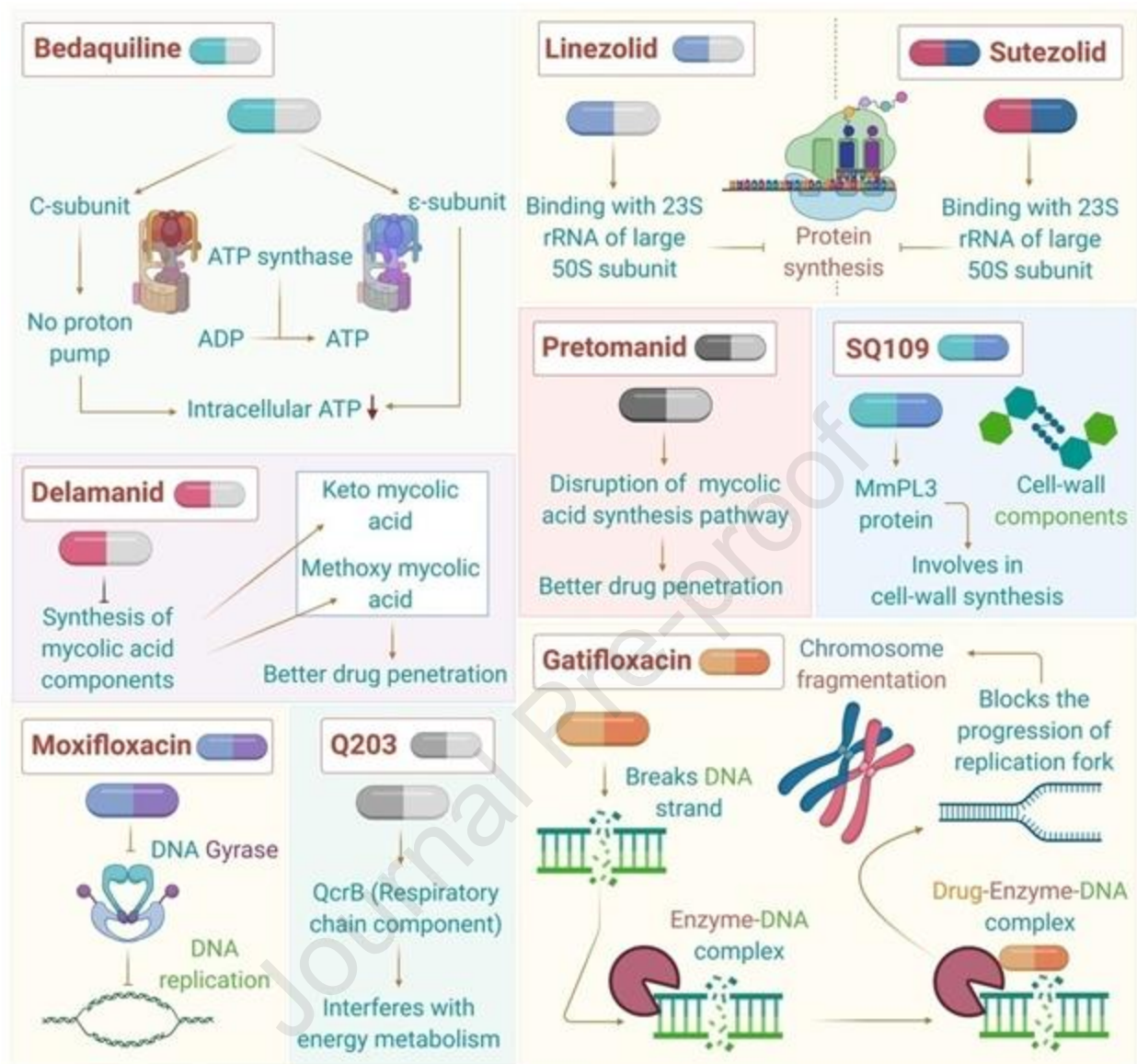
Figure 2. Schematic presentation showing possible mechanisms of new anti-TB drugs.

3. OVERVIEW OF NEW ANTI-TB VACCINES

Various strategies such as preventive pre-exposure, preventive post-exposure, and therapeutic have been reported for vaccine delivery [97]. Pre-exposure vaccines focus on an inducing protective immune response than BCG against disease [98] whereas; post-exposure vaccine stimulates a long-lasting response to eradicate TB.

3.1. Live Attenuated Vaccines

Live attenuated vaccines are composed of either containing whole MTb either in its weaker or changed form [99]. MTBVAC (live attenuated vaccine) has been developed for BCG replacement is currently undergoing phase 3 clinical trials (NCT03767946; NCT03152903) [99, 100]. MTBVAC is a clinical isolate of *M. tuberculosis* Mt103 developed after removal of two virulence-related genes phoP and fadD26. Safety studies revealed that MTBVAC is more attenuated form of vaccine than BCG and have been tested in mice with severe combined immunodeficiency (SCID) [101]. Further study has demonstrated that MTBVAC-L2 and MTBVAC-L3 provided considerable protection as compared to BCG in immunocompetent mice, treated with these three representative strains. MTBVAC has also been utilized as a vector for TB-HIV vaccine known as MTBVAC.HIVA2auxo [102]. TB-HIV vaccine offered similar effects as provided by parenteral strain against MTb challenge in mice. In addition, MTBVAC.HIVA2auxo has increased safety profile in comparison with BCG and MTBVAC showing a ray of hope for individuals who are immunocompromised and are at risk of serious infection [103, 104].

3.2. Inactivated Vaccines

Inactivated vaccines do not carry infectious particles, therefore, are safer than live vaccines. However, they have weak immunogenicity as compared to live vaccines therefore multiple doses are required [105, 106]. RUTI is the inactivated vaccine containing liposomes with detoxified and are fragmented *M. tuberculosis* cells. In phase 2b, RUTI showed considerable humoral and cellular immune responses against bacilli [107]. It has efficiently managed latent TB in animal models and being in use for treating active TB in patients with reduced treatment duration [107, 108]. A study showed that RUTI reduced mycobacterial counts with a considerable shift towards Ly6C- and Ly6C+ monocyte phenotype in the spleens of immunized mice. Ly6C- monocytes have an anti-inflammatory role [109], whereas Ly6C+ monocytes have proinflammatory effects [110].

3.3. Subunit/Adjuvanted Vaccines

Subunit vaccines are reliable as they contain a specific pathogen that brings less robust immune response [111]. For inducing a protective immune response, adjuvants are commonly used for the administration of vaccines. Frequently used subunit vaccine includes MPT64, ESAT6, Ag85A, and Ag85B [112]. H56: CAF01 vaccine induces both adaptive and innate immunity in mice [113]. Despite of humoral response, aluminum-based adjuvants are not protective against MTb because

of their intracellular pathogenic property [114]. Thus, novel adjuvants need to be developed to stimulate protective Th1 responses [115]. Recent adjuvants used in MTb vaccines include IC31, GLA-SE, AS01E, QS21, CFA01, and DPC [116]. The efficacy of subunit vaccine H4: IC31 has been evaluated in high-risk TB individuals at reduced *M. tuberculosis*-specific immune response. The results showed a negative response for *M. tuberculosis*-specific immune response as determined by using Quanti FERON-TB Gold In-tube assay (QFT) that determined the concentration of IFN-γ [117]. Further, in the phase 2b clinical trial study, the subunit vaccine M72/AS01E prohibited pulmonary TB in MTb infected adults with an efficacy of 54% [118]. M72/AS01E stimulated higher memory Th1-cytokine expressing CD4+ T-cell memory responses, thereby demonstrated itself as the best vaccine giving protective immunity in TB [119, 120].

3.4. Recombinant Vaccines

The preparation of recombinant vaccines is done through engineering techniques by inserting DNA encoded with MTb antigen into an appropriate vector [121]. The recombinant vaccines are categorized based on the kind of organism expressing MTb antigens. For the preparation of live mycobacterial vaccines, BCG, *Mycobacterium vaccae* and *Mycobacterium smegmatis* are used as a vector. Out of these BCG is cost-effective, stable, and it stimulates non-specific immune [122]. *Lactococcus lactis* is used as a vector for Pnz8149-ag85a/NZ3900 which is another bacterial recombinant that induced antibody responses in mucosal immunized mice [123]. Currently, the only approved vaccine is BCG which is works based on preventative pre-exposure strategy. Some vaccines have exceptional methods of administration to boost immune response [124, 125]. Presently, vaccine development mainly focuses on live inactivated or attenuated and recombinant vaccines. MVA85A is currently under phase 2a clinical evaluation [126].

4. NOVEL DRUG DELIVERY SYSTEMS FOR THE MANAGEMENT OF TUBERCULOSIS

Successful treatment of TB is all-time challenging area for the formulation scientists [127]. In the recent few decades, extensive research has been made for the effective management of this deadly disease and its prevalence across the globe. However, still no promising outcome is achieved in overcoming the limitations of available treatment options. When we talk about the first-line and second-line treatments for the management of TB, the typically evolving issue is drug resistance

which can be further considered as multidrug and extensive drug resistance [128]. Drug resistance or the ability of strains to survive for a longer duration in host cell or its dissemination to other surrounding cells makes it more vulnerable and challenging for health professionals to combat TB [127]. A high dose of standard drugs lead to dose-dependent toxicity due to the poor drug targeting. Table 1 highlights the limitations of conventional delivery system for the treatment of TB. Undoubtedly with the advancement of drug delivery technologies, various novel formulations and administration routes other than the oral route have been investigated.

Applications of nanotechnological advancements in the delivery of anti-tubercular drugs have contributed significant outcomes encompassing effective delivery, better drug distribution and availability, and hence better patient compliance [129]. Nanotechnology has several advantages in the treatment of tuberculosis like targeted delivery, reduced dose, better penetration, increased bioavailability, better distribution, lesser side effects, and better patient compliance. This simply reveals that this transformation from conventional to novel technology can be a promising solution to overcome limitations of conventional therapeutics in the management of TB [130–133]. Various vesicular and non-vesicular nanocarriers have been discussed below:

Table 1: Limitations of conventional delivery system for the treatment of tuberculosis [129].

Route of drug administration	Limitations/challenges
Oral	Sub-therapeutic levels and poor distribution
Parenteral	High dosing load and poor patient compliance
Inhalants	Critical delivery and narrow window for drug selection
Implants	Need of surgical procedures

4.1 Vesicular Carrier Systems: Liposomes and Niosomes

The nano-particles size range and the vesicular structure of liposomes demonstrated their efficacy in effective management of TB. Liposomes and niosomes have advantages like high drug loading efficacy, ease of administration, and cost-effectiveness [134]. The nanocarriers have flexibility of utilization of alternative routes of administration, achieving the high concentration of drugs in the target cell and/or the microbial flora (Mycobacterium), which significantly proves its efficacy at

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lower drug concentrations and shorter drug regimen frequency, as compared to that of the conventional drug delivery approaches [135]. Liposomes have merits like biodegradability, biocompatibility, and tailored formulation designing using phospholipids. These advantages of vesicular nanocarriers make them versatile and prove them the suitable drug carrier for exhaustive research in the effective management of TB [136,137]. Various liposomal approaches for efficacious delivery of drug candidates are summarized in Table 2.

Table 2: Studies related to liposomal drug delivery for the treatment of tuberculosis.

Type of nanocarrier	Drug incorporated	Advantage	Ref.
Thermo-responsive hydrogel	Isoniazid	Target site delivery with least systemic exposure; used for bone tuberculosis.	[138]
Spray dried nano liposomes	Moxifloxacin	Improved drug uptake by alveolar macrophages; biphasic drug release mechanism.	[139]
Inhalation liposomes	Licorice	*In vivo* lung deposition studies in mice revealed that 46% of the drug reaches the lungs.	[140]
pH dependent liposomes	Isoniazid	pH dependent drug release; 100% release at pH 4.4.	[141]
Natural polysaccharide-based liposomes	Isoniazid	Pulmonary and macrophage-targeted delivery of anti-TB drugs.	[142]

4.2. Solid lipid nanoparticles for delivery of ATDs

Solid lipid nanoparticles (SLNs) are surfactants and solid lipids based nanocarriers used for controlled release and site-specific drug delivery. The key characteristics of SLNs are inhibition of drug degradation, improved pharmacokinetic profile of drugs, improved physical stability of drugs, and modified drug release [143]. Various successful investigations have been made in the

field of design and development of SLNs, representing their promising results in efficacious drug delivery system. SLNs investigated to deliver ATDs are presented in Table 3.

Table 3: Studies related to solid lipid nanoparticles drug delivery for the therapy of tuberculosis.

Type of nanocarrier	Incorporated drug	Advantages	Ref.
Mannose functionalized SLNs	Isoniazid	Reduced toxicity in human lung epithelial cell line (NCI-H441) and differentiated THP-1.	[144]
Glyceryl dibehenate and glyceryl tri-stearate SLNs	Rifabutin	*In vitro* studies using THP1 cells showed an uptake of $46 \pm 3\%$ for glyceryl dibehenate and $26 \pm 9\%$ for glyceryl tristearatein the macrophagic system.	[145]
Ocular SLNs	Isoniazid	Reported 1.6 times increased corneal permeability and about 4.6-fold higher ocular bioavailability.	[146]
Inhalation SLNs	Ethambutol hydrochloride	Insignificant cytotoxicity in A549 cells with 37% sustained release.	[147]
Double drug SLN	Rifampicin & Isoniazid	*In-vitro* studies revealed sustained release and *in-vivo* studies demonstrated 7.5 times higher bioavailability as compared to drug suspension.	[148]
Stearic acid and compritol SLNs	Rifampicin, Isoniazid and Pyrazinamide	SLNs (3.125% solution) at a concentration of RIF (2.16 μg/mL), INH (2.55 μg/mL) and PYZ (5.04 μg/mL) effectively inhibited the growth of *M. marinum*. *In vitro* studies using RAW264.7 cells showed RIF, INH and PYZ were not cytotoxic at a concentration of 12.5 μg/mL, 50 μg/mL and 100 μg/mL, respectively.	[149]

4.3. Nano-structured lipid carriers

The drawbacks of SLNs are overcome by nanostructured lipid carriers (NLCs), which are the combination product of solid lipid and liquid lipid. Thus, possessing a reduction in crystallinity with a loosely packed matrix. These characteristics of NLCs lead to the overall increased capability of drug entrapment and better stability [150]. Successful research studies have been carried out so far demonstrating the potential of NLCs as the most promising nano-carrier (Table 4).

Table 4: Research studies related to nano-structure lipid carriers.

Type of Nanocarrier	Incorporated drug	Advantages	Ref.
Copper complex NLCs	Copper(II)	*In vitro* studies using $H_{37}R_v$ cells showed a remarkable increase in activity.	[151]
Tuftsin modified peptide functionalized NLCs	Rifampicin	Reported initial bulk release, followed by controlled release with an improved cellular intake and activity.	[152]

4.4. Nanoemulsion

Nanoemulsion bears some remarkable attributes like enhanced drug loading, better stability, superior bioavailability, and controlled release. These characteristics make them robust nano-carriers for effective drug delivery. These nanostructures have demonstrated remarkable outcomes when administered orally. Orally administered nanoemulsions led to enhanced solubility of the lipophilic drugs with a prolonged residence time in the GIT and an expanded lymphatic uptake. Thus, nanoemulsions avoiding first-pass metabolism of the drug candidate [153]. Few potential research studies performed in the field of nanoemulsions for the delivery of ATDs are discussed in Table 5.

Table 5: Nanoemulsions investigated for the delivery of anti-tuberculosis drugs.

Type of Nanocarrier	Incorporated drug	Advantages	Ref.

Conventional nanoemulsion	Rifampicin	Significant decrease in drug degradation, leading to better pharmacological profile.	[154]
Intranasal nanoemulsion	Pretomanid	Significant rise in drug concentration in brain.	[155]
CS-folate nanoemulsion	Rifampicin	Better inhalation efficiency and declined cytotoxicity.	[156]

4.5. Micelles

Micelles are commonly preferred choice of delivery system for hydrophobic drug candidates. Micelles have hydrophobic core and hydrophilic outer covering with a particle size of less than 20 nm, which is the characteristic feature that differentiate these carriers from other nanocarriers. Micelles allows better circulation time through escape from renal infiltration. These can be flexibly designed using either lipids or other polymer-based amphiphilic molecules like PEG, methacrylate, poly (amidoamine), poly (L-aspartic acid), and many more [157]. Micelles investigated to deliver ATDs are discussed in Table 6.

Table 6: Research studies related to micelles for delivery of anti-tuberculosis drugs.

Type of nanocarrier	Drug incorporated	Advantage	Ref.
Insulin and vitamin E micelles	Rifampicin	Cytocompatibility on human alveolar macrophages demonstrated a value of more than 60%.	[158]
Pulmonary micelles	Rifampicin	Aerodynamic study demonstrated the suitability of alveolar delivery and *in-vitro* antibacterial study reported 2.5 times higher activity in *Mycobacterium tuberculosis*-infected THP-1 macrophages; as compared to rifampicin solution.	[159]

Polymeric micelles	Rifampicin and Isoniazid	Significant inhibition of *Mycobacterium tuberculosis* H$_{37}$R$_v$ by the formulation.	[160]

4.6 Magnetic Nanoparticle

Lipoamino acid-coated magnetic nanoparticles isoniazid have been accessed for antibacterial activities against *M. tuberculosis* and Gram-positive and Gram-negative non-mycobacterial strains. The effective concentration of the drug against *M. tuberculosis* decreased to 44.8% and 16.7%, respectively in conjugation with naked and surface-modified nanoparticles [161]. Magnetic nanoparticle-based colorimetric bio-sensing assay increased acid-fast bacilli count compared to sputum smear microscopy, improving the grade from "1+" (in SSM) to "2+" [162]. Zhanying *et al* detected *M. tuberculosis* via magnetic nanoparticle combined with polymerase chain reaction technology with the highest capture rate of 71% at OD$_{500}$ value of 0.4. Synthesized nanoparticles were positively charged with a pH value of 2-8. At 900 °C, the thermal weight loss of *M. tuberculosis* was ~85% without addition of magnetic nanoparticles. It was ~45% from magnetic nanoparticle-captured *M. tuberculosis* and 71% from uncaptured *M. tuberculosis*. Polyethyleneimine could enhance the adsorption of magnetic nanoparticles to *M. tuberculosis* [163]. Minero *et al* reported a novel on-chip DNA analysis technique for tuberculosis detection using magnetic nanoparticles [164].

5. Monoclonal antibodies in the treatment of tuberculosis

Monoclonal antibodies can interfere with the natural immunity that may predispose for tuberculosis infection [165]. Human antibody responses to the polysacharide arabinomannan/ glycolipid lipoarabinomannan are heterogenous. However, the information related to the reactivity to specific glycan epitopes at the monoclonal level is limited in individuals controlling *M. tuberculosis* infection. Ishida *et al,* generated human IgG monoclonal antibodies to polysacharide arabinomannan/ glycolipid lipoarabinomannan from B cells of two asymptomatic individuals infected with *M. tuberculosis*. These monoclonal antibodies recognized virulent *M. tuberculosis* and nontuberculous mycobacteria. It can detect detect *M. tuberculosis* and lipoarabinomannan in infected lungs [166]. Anti-TNF-α monoclonal antibodies (adalimumab, infliximab), thalidomide, and soluble TNF-α receptor (etanercept) play an important role in tuberculous meningitis treatment

[167]. Hoel et al, screened antibodies in immunohistochemistry and validated the antibody (anti-MPT64 antibody) in humans. However, the authors could not generated functional monoclonal antibodies. They obtained multiple functional polyclonal antibodies pre-immune sera and antisera samples [168].

6. CLINICAL TRIALS OF NDDS

Despite numerous pre-clinical studies conducted with regards to the use of nanotechnology in the management of TB, there is limited safety and efficacy data of nanotechnology-based drug delivery carriers is available for human use. Pre-clinical studies may provide researchers with basic information regarding the pharmacokinetic profiles of NDDS, however, such studies are not sufficient to explain how these drug carriers will interact and behave within the human biological environment. Hence, clinical trials are crucial in the development of novel therapeutics as these studies may reveal results that deviate drastically from those obtained from animal models and cell lines, attributed to the complex host interactions as well as human metabolic responses [132, 169]. Inhalable nanoparticles have shown promising results in several preliminary laboratory investigations and preclinical trials. However, these have uncertainties regarding their safety profile in the human body. Inhalable nanoparticles are actively underway in clinical trials with an understanding of the efficacy, safety, and toxicity of pulmonary tuberculosis. Arikayce® (Liposomal amikacin) for the treatment of *M. tuberculosis* infection, and Ambisome® (liposomal amphotericin B) for the treatment of various lung diseases are under clinical trials [170]. Inhaled capreomycin has shown well toleration in Phase I clinical trial [171].

An open phase 1 clinical trial was conducted in 2011 (NCT00922363) to evaluate the safety profile of a novel liposomal adjuvant, CAF01, when used with the TB vaccine Ag85B-ESAT-6. The clinical trial disclosed a novel liposome-based adjuvant formulation that is safe for human use. Long-lasting T-cell immunity was induced when Ag85B-ESAT-6 vaccine was adjuvanted with CAF01, suggesting that the liposomal system is relevant for the development of future TB vaccines [172, 173]. Table 7 summarizes a list of anti-TB drugs under the clinical pipeline in various academic institutions and pharmaceutical industries [174].

Table 7: Anti-tuberculosis drugs under clinical pipeline [174].

Phase 1	Phase 2	Phase 3
TBAJ-587, Diarylquinoline TB Alliance, ERA4TB (European Regimen Accelerator for Tuberculosis), University of Auckland, Merck & Co., Inc.	**Sudapyridine (WX-081)** Shanghai Jiatan Biotech Ltd., subsidiary of Guangzhou JOYO Pharma Ltd., Shanghai, China	**Bedaquiline** Janssen Research & Development, LLC
GSK-286 GlaxoSmithKline, TB Drug Accelerator, Bill & Melinda Gates Foundation	**Sutezolid** Sequella, Inc, TB Alliance Sutezolid Dose-finding and Combination Evaluation (SUDOCU)	**Delamanid** Otsuka Pharmaceutical Development & Commercialization, Inc.
Macozinone (MCZ, PBTZ-169) iM4TB - Innovative Medicines for Tuberculosis, Bill & Melinda Gates Foundation	**SPR720 (Fobrepodacin)** Spero Therapeutics, LLC, Bill & Melinda Gates Medical Research Institute	**Rifapentine** CDC TBTC, Sanofi
GSK-286 GlaxoSmithKline, TB Drug Accelerator, Bill & Melinda Gates Foundation	**Delpazolid (LCB01-0371)** LegoChem Biosciences, Inc.	**Pretomanid** TB Alliance
TBAJ-876 Diarylquinoline TB Alliance, University of Auckland	**Telacebec (Q203)** Qurient Co., Ltd, Qurient Co. Ltd. / LLC "Infectex", a portfolio firm of Maxwell Biotech Venture Fund	**Clofazimine** Novartis
BVL-GSK098 BioVersys AG, GlaxoSmithKline	**Linezolid** TB Alliance	**Rifampicin** St. George's Hospital University of London

Future Perspectives

22

TB may cause adrenal insufficiency due to the extra-adrenal infection or direct glandular involvement. Thyroid gland is uncommonly involved in TB due to certain intrinsic properties of thyroid gland, high blood-flow with excess bactericidal iodine, the presence of colloid, increased phagocytosis associated with hyperthyroidism, and extensive lymphatic and vascular supply to the thyroid have all been postulated as mechanisms [175]. Regardless of the studies representing the advantages of respiratory administration of the drug, there is a lack of uniform and effective techniques of drug administration in preclinical models resulting in poor translational success. Accurate delivery of dose to the lungs is challenging due to drug loss in the reservoir, delivery accessories, tubing of the aerosol generator, along with the nasopharyngeal region of the animal that may constitute a risk factor for the development of drug resistance. For combating these invasive techniques like intratracheal instillation are considered to attain precise drug dosing to lungs. Encapsulating the drugs may improve the efficacy of antimicrobial drugs by enhancing solubility, preventing rapid clearance with lesser side effects. Nanoparticles exhibit a high loading capacity and minimizes the amount of material administered. Sequential nanoprecipitation and microfluidics techniques lead to high loading capacity [176]. Better encapsulation can be done by chemical conjugation via hydrolysable or responsive chemical bonds [177] or by employing an appropriate system for hydrophilic drugs, such as niosomes, liposomes, or polymeric nanocapsules. Second-line anti-TB drugs cannot effectively penetrate cells leading to affect their efficacy and increased dose. Therefore, encapsulation of second-line anti-TB drugs in nanocarriers may allow selective distribution and uptake of encapsulated drug by target cells. Selective drug delivery can be obtained by the surface modification or surface functionalization of nanoparticles that may improve biocompatibility and stability [178]. Lack of knowledge towards the regulatory guidelines regarding characterization, statistical analyses, and study design corresponds to a common barrier in the clinical translation of nanoformulations. Optimizing the practices may promote the conversion of nanotechnology from experimental achievement into clinical practice.

The effectiveness of a dosage form to treat TB depends on its capacity to provide large local therapeutic dosage to the lungs without exposing the normal cells of the body to the bioactive at a level that leads to the emergence of drug-resistant microorganisms. Targeting alveolar macrophages using inhalable nano-based therapeutics has two basic objectives (i) uptake of particles by macrophages has the potential to activate infected macrophages, and (ii) targeting can

deliver extremely large amounts of the anti-TB drugs to the macrophage cytosol. However, have been very few studies, and those that have been done have mostly dealt with tolerability. Thus, there is an urgent need that provide innovative inhalation formulation available commercially with the regulatory approval. Inhalable nano-based therapeutics are not subjected to the first-pass metabolism.

Conclusions

The current paper presented information related to the most innovative and ground-breaking drug delivery strategies for the treatment of TB with improving therapeutic efficacy and reducing toxic effects of anti-TB drugs. The promising therapeutic effects of novel drug delivery systems in TB, including liposomes, solid lipid nanoparticles, nanostructured lipid carriers, nanoemulsions, and micelles have proven in multiple pre-clinical studies to date. Nonetheless, limited clinical trials have been performed, prompting the need to conduct more clinical studies for elucidating clear, in-depth efficacy and safety profiles of these novel drug delivery systems in humans to pave the path towards successful clinical translation in the future.

List of Abbreviations

ADP	Adenosine diphosphate
ATDs	Anti-tubercular drugs
ATP	Adenosine triphosphate
B Cells	B lymphocytes
BCG	Bacille Calmette-Guerin
DC	Dendritic cells
DNA	Deoxyribonucleic acid
DprE1	Decaprenylphosphoryl-β-D-ribose oxidase
DR-TB	Drug-resistance tuberculosis
DS-TB	Drug-susceptible tuberculosis
F-ATP	F type Adenosine triphosphate/Fo domain
HIV	Human Immunodeficiency Virus
INH	Isoniazid
MDR	Multi drug resistance

MTb	*Mycobacterium tuberculosis*
MTBVAC	First and only live attenuated vaccine based on a human isolate of *Mycobacterium tuberculosis* developed as BCG-replacement strategy
NADH	Nicotinamide adenine dinucleotide
NDDS	Novel drug delivery systems
NDH-2	Type II NADH: quinone oxidoreductase
NK cells	Natural Killer cells
PZA	Pyrazinamide
RIF	Rifampicin
RNA	Ribonucleic acid
ROS	Reactive oxygen species
rRNA	Ribosomal Ribonucleic acid
RUTI	a therapeutic liposomal vaccine containing detoxified fragmented *M. tuberculosis* cells
TB	Tuberculosis
Th1	T helper cells
Treg	Regulatory T cells
Trp16	N-Acetyl-[D-Trp16]-Endothelin 1 fragment 16-21
WHO	World Health Organization
XDR	Extensive drug resistance

Declaration of competing interest

The authors have declared that no conflict of interest exists.

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Recent developments, challenges and future prospects in advanced drug delivery systems in the management of tuberculosis

Highlights

- TB is a life-threatening health issue leading to amplified socio-economic impact
- Conventional therapeutics are not competent to target drugs at specific sites
- Nanocarriers can overcome limitations of conventional systems in treating MDR-TB
- Contemporary trends and advancements for TB management are highlighted

Declaration of interest

The authors have declared that no conflict of interest exists.