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MINI-REVIEW

Nano *vs* Resistant Tuberculosis: Taking the Lung Route

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Abstract

Tuberculosis (TB) is among the top 10 infectious diseases worldwide. It is categorized among the leading killer diseases that are the reason for the death of millions of people globally. Although a standardized treatment regimen is available, non-adherence to treatment has increased multi-drug resistance (MDR) and extensive drug-resistant (XDR) TB development. Another challenge is targeting the death of TB reservoirs in the alveoli via conventional treatment. TB Drug resistance may emerge as a futuristic restraint of TB with the scarcity of effective Anti-tubercular drugs. The paradigm change towards nano-targeted drug delivery systems is mostly due to the absence of effective therapy and increased TB infection recurrent episodes with MDR. The emerging field of nanotechnology gave an admirable opportunity to combat MDR and XDR via accurate diagnosis with effective treatment. The new strategies targeting the lung via the pulmonary route may overcome the new incidence of MDR and enhance patient compliance. Therefore, this review highlights the importance and recent research on pulmonary drug delivery with nanotechnology along with prevalence, the need for the development of nanotechnology, beneficial aspects of nanomedicine, safety concerns of nanocarriers, and clinical studies.

Keywords extensive drug-resistant (XDR) · multi-drug resistance (MDR) · nanocarrier · nanomedicine · tuberculosis

Introduction

Mycobacterium tuberculosis (MTB) causes the terrible and contagious disease known as tuberculosis (TB). It has affected individuals for a very long time and resulted in a high mortality rate. According to theories, the prevalence of mycobacteria in humans began to rise in Africa 70,000 years ago due to the migration of humans [1, 2]. Egyptian mummies were found to have this bacterium. This illness has historically had an impact on people's physical, economic, and social well-being. MTB is still a serious issue for world health. The disease of pulmonary TB is significant for public health [3, 4].

Globally, a projected 10.6 million persons contacted TB in 2021, up 4.5% from 10.1 million in 2020 as reported by WHO 2023 report [5]. According to the WHO's estimation of 1.6 million persons, TB is the main cause of death worldwide. The overall 933,381 persons notified of TB infection during 2021 was as opposed to 1,628,161 in 2020, a 19% rise from the year of patient reporting for TB in 2020 [6, 7]. According to "Centres for Disease Control and Prevention," the number of TB incidences reported in the USA is 8300 in 2022 showing an increment from previous years. It may be due to late diagnosis or missed TB and association with various factors of the COVID-19 pandemic [8].

Lung TB is one of the top 10 fatalities caused by infectious diseases in humans worldwide. The common symptoms of TB include persistent cough, mild fever, weight loss, tiredness, and fatigue. Drug-resistant tuberculosis

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(DR-TB)-infected patients are tracked and treated under the National Tuberculosis Eradication Programme (NTEP). In India, there is a directly observed therapy (DOT) treatment plan available. Focused on preventing tuberculosis in vulnerable groups, the National Strategic Plan for Elimination of Tuberculosis (NSP 2017-25) was created. One of India's four key pillars (Detect-Treat-Prevent-Build) of its TB elimination strategy is "Prevent." In the case of drug-sensitive TB (DS-TB), an injection-free treatment plan was successfully adopted across the nation under the NTEP. Patient noncompliance is caused by multiple dose intervals, protracted therapy, liver damage, and significant medication resistance [9–11].

To ensure successful therapy and to prevent the development of resistance, a range of medications have been used in combination to treat MTB. WHO 2021 " List of Essential Medicine" includes isoniazid, rifampin, pyrazinamide, streptomycin, and ethambutol in fixed dose or in combination as the first line of defense in the conventional and modified formulation [12, 13]. WHO also added rifapentine and moxifloxacin for the treatment of drug-susceptible TB in pediatric patients. Additionally, bedaquiline and delamanid were included for treating MDR TB. Furthermore, some TB medications were removed from the essential drug list, which provide comprehensive details about a drug used for preventive, MDR, and drug-susceptible TB [13].

The stringent regimen required for conventional TB treatment results in low patient compliance. The development of DR-TB and granulomas, the complexity of mycobacterial cells, and changes in gene expression are limitations to the use of conventional treatment [14]. Additionally, the majority of medications have poor water solubility, low bioavailability, poor penetration, low therapeutic effectiveness, and lower metabolic stability. This emphasizes the need for more sophisticated drug delivery methods to set back the mentioned issues [15, 16]. This review is mainly focused on the recent update on nanocarriers for MDR TB administered through the pulmonary route along with barriers of the pulmonary route, causes of MDR, and possible toxicity of nanocarriers given through the pulmonary route.

Drug Therapy for TB and Associated Drawbacks

A combined regimen of antibiotics is commonly used for the treatment of TB with the objective of efficiently targeting the MTB bacteria and lowering the likelihood of developing resistance to drugs. The most effective drugs are isoniazid, rifampin, pyrazinamide, ethambutol, streptomycin and aminoglycosides, fluoroquinolones (e.g., levofloxacin, moxifloxacin), and some newer drugs (bedaquiline and delamanid) [17]. The major problems with these anti-tubercular drugs are their severe side effects; viz., hepatotoxicity and development of resistance are commonly associated with isoniazid, rifampin, and pyrazinamide [18]. In addition, peripheral neuropathy is observed in the patients treated with isoniazid. Optic neuritis, inflammation of the optic nerve is common for ethambutol [19], while nephrotoxicity and ototoxicity are associated with streptomycin and aminoglycosides [20]. In addition, streptomycin and aminoglycosides are available in injectables which make it convenient for patients to administer [21]. Tendonitis and tendon rupture have been observed in the patients on fluoroquinolone antibiotics [22]. Furthermore, prolongation of QT, hyperlactatemia, and rashes on the skin had been observed in patients with bedaquiline therapy [23].

Barriers to Pulmonary Drug Delivery for TB

The systemic adverse effects and low bioavailability are the main constraints of conventional oral routes of drug administration [24, 25]. Therefore, site-specific drug delivery via the pulmonary route has emerged as an effective and alternative drug delivery route to treat TB [26, 27]. The pulmonary route enhances the treatment efficacy by increasing drug concentration at the site of action and reducing the off-target accumulation, beside drug particles reached to internal part of lungs and deposit on luminal surface of the epithelial membrane [28, 29]. The first barrier is coughing while using inhaled remedies can cause insufficient inhaling of the drug as well as increased upper airway accumulation or exhale of the aerosol that's in movement while inhaling. After inhaling the drug, coughing might not physiologically prevent the administration of inhalation drugs, but it might make it harder for patients to follow their treatments [30]. Two different types of sensory nerves—the extrapulmonary Widdicombe cough receptor sensitive towards pH as well as the intrapulmonary bronchopulmonary C-fibers responsive towards environmental allergies—may be stimulated through specific inhaled medications, which can result in a coughing episode. Additionally, the extremely high local osmolarity of the respiratory surface liquid near dissolving breathed-in particles might trigger these afferent neurons, causing a cough reflex [31]. The second barrier is the specific targeting of inhaled particles in the respiratory tract which comprises of oropharyngeal, trachea-bronchial, and alveolar area. Around twenty-three divergent and asymmetrical splits exist between the trachea and the alveoli. Several airborne particles are eliminated by inertial impaction at bronchial splits as the breathed air moves through the intricate respiratory tract [32]. The direction of the airflow changes at the last point of inhalation. Following inhalation, particulates that remain in the air are forced out of the lungs, where certain quantities of particles settle on the lining of the airways. Consequently, while using breathed air to deliver medications to the lung is a rational strategy,

focusing only on the trachea-bronchial or pulmonary areas is quite challenging [32]. By decreasing the rate of inhalation flow and aerosol particulate size (for example, to 1–3 m), as well as by holding one's breath to enhance accumulation through sedimentation, one can improve the localization of inhaled medication deposition to the alveolar areas. Additionally, the active ingredient should be absorbed before it degrades or clears off from the lumen. The effectivity of the designed formulation is based on the ability of the drug molecule to cross the biological barrier that consists of the epithelial layer, mucus, endothelium, etc. [33]. The air-blood barrier and surfactant layer are the next biological barrier in the alveolar region. The drug should solubilize and stabilize in a surfactant layer if intended to be absorbed in systemic circulation [34, 35]. Sometimes, the surfactant may enhance the solubility of drug molecules but still, it acts as a barrier. Additionally, mucus and cilia present in the airways may lead to clearance of the drug. Incorporation of permeation enhancers may reduce the drug loss due to ciliary action. Moreover, drugs from the surfactant layer of the alveolus can be cleared by the action of macrophages [29, 36, 37].

The next barrier is the epithelial cell membrane, which shows transepithelial electrical resistance at the alveolar region due to the formation of pneumocytes. The particles have a size of 100 nm or less and can penetrate the epithelial cell membrane barrier freely. The epithelial membrane of other regions of airways consists of pseudostratified columnar cells with tight junctions [38, 39]. To penetrate through these tight junctions, the particle should be small enough for passive diffusion or transport via the paracellular pathway. The next barrier is capillary endothelium and basement membrane, which is not significant for lung targeting; however, it should be considered for systemic delivery through the pulmonary route [40, 41]. Figure 1 highlights all the biological barriers via pulmonary routes.

Causes and Mechanism of Multi-drug Resistance

The effective course of treatment must last at least 6 months and include a fixed dose combination of antibiotics. It is reported in various literatures and research papers that the poor efficacy, increased hepatotoxicity, lengthened duration, and patient non-compliance cause the emergence of MDR and XRD TB; however, present therapeutics for MDR and XDR TB are limited [42–46].

This biological phenomenon was first observed when many patients were administered streptomycin for 18 months and showed clear sputum from *Mycobacterium*. However, further continuation of the same antibiotic showed the presence of bacilli in sputum that is streptomycin resistant.

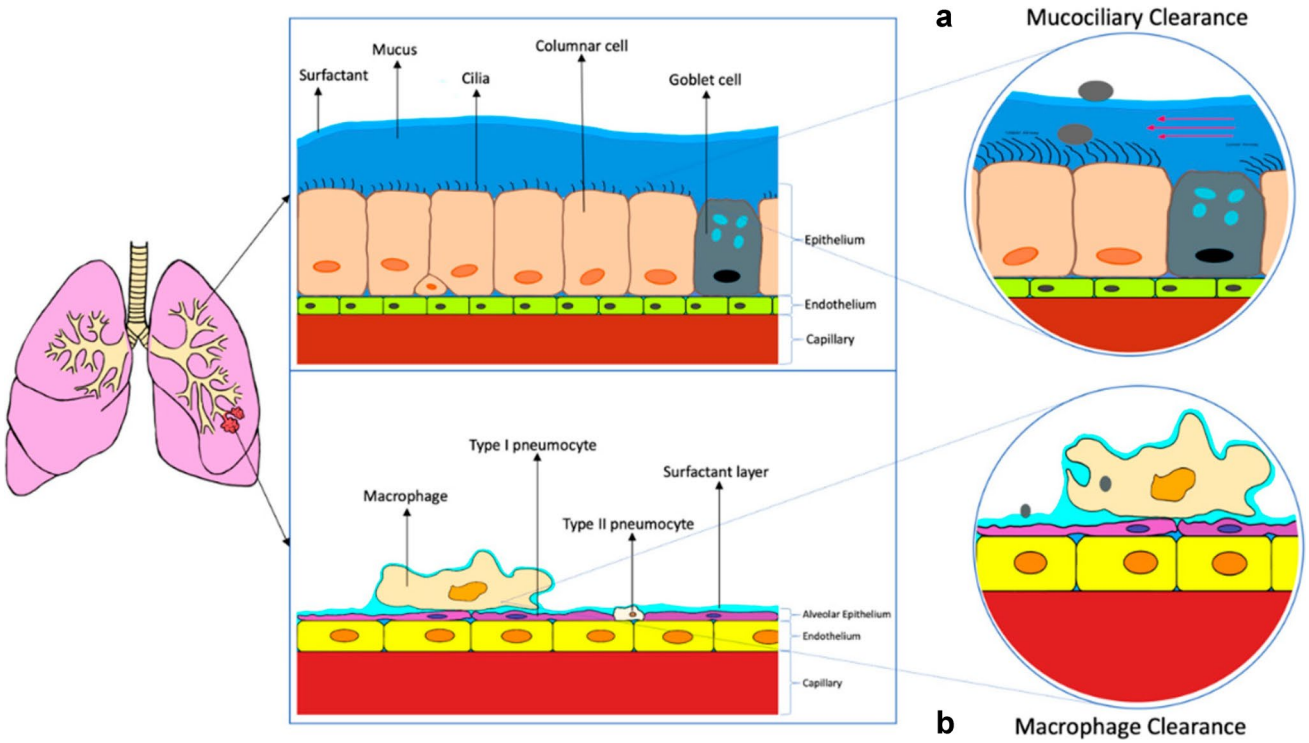

Fig. 1 Biological barriers to lung delivery via the pulmonary route. **a** Mucociliary clearance of the drug by cilia present on pseudostratified columnar cells, **b** macrophage clearance in the surfactant layer of the alveolus. Figure taken with permission from Tan *et al.* [41]

Streptomycin and rifampicin were administered as part of combination therapy to avert the problem. It also reduces the duration of therapy. Later on, the combination of rifampicin and isoniazid emerged as a shorter TB therapy and was adopted as the standard therapy by DOTS (directly observed treatment, short-course) to control TB since 1993 [47, 48].

MDR bacteria are resistant to at least one antibiotic in three or more different classes of antibiotics. As a result, it is harder to properly treat MDR bacteria since they have become resistant to a wide variety of antibiotics. MDR refers to the strain's resistance to at least rifampicin and isoniazid, which are regarded as the cornerstone drugs for treating TB. In comparison to MDR bacteria, XDR bacteria are considerably more resistant [49]. The bacteria that cause XDR-TB are even more resilient, exhibiting resistance to at least one fluoroquinolone and one of the three commonly used second-line injectable medications (amikacin, kanamycin, or capreomycin) in addition to being resistant to isoniazid and rifampin. XDR develops as a result of M. tuberculosis strains that meet the criteria for MDR/RR (rifampicin resistance)-TB as said by Seung and co-workers [49, 50]. Despite effective therapy, an outbreak of resistance was observed worldwide. The possible reasons were chaotic treatment—countries were not following the standard TB regimen, no free treatment, low adherence to medications, non-availability of medication, and structural weakness of health care system. Drug resistance patterns were also intensified because of repeated DOTS course of the TB regimen [48, 51]. Another observation revealed that many patients do not gradually acquire resistance to drug; in fact, they were initially infected with the MDR-TB strain. Furthermore, nosocomial transmission in hospitals is another drive for the epidemic, exclusively in the area of HIV prevalence [52, 53]. So further research has been focused on nanomedicine and nanocarrier to combat MDR-TB.

Genetic changes in the MTB, rendering it less vulnerable to or entirely immune to the effects of anti-TB medications, are the main cause of drug resistance in TB. Since MTB replicates slowly contrasted to other bacteria that replicate more quickly, spontaneous mutations are less common. However, the bacterial genome can develop mutations gradually. A drug may become resistant to treatment if a gene that it targets for treatment undergoes a mutation [54]. Through a mechanism known as the horizontal transfer of genes, MTB is capable of exchanging gene material from other mycobacterial organisms, even non-pathogenic ones. This may impart drug resistance by transferring resistance-associated genes from species that are not pathogenic [55]. Drug resistance is largely caused by poor or insufficient treatment for TB. Patients who fail to adhere to their recommended antibiotic regimen or who receive inadequate care may foster conditions that encourage the growth of resistant microorganisms [56].

Inhalable TB Therapy: Traditional Drugs and Modern Therapy

As discussed above the drugs used for TB therapy, rifampicin, isoniazid, pyrazinamide, and ethambutol are often the combination of four first-line medications used to treat TB orally. Typically, a course of treatment lasts between 6 and 9 months, with a 1- to 2-year recovery period after. Hepatic impairment and nephrotoxicity yet may occur because of the persistent use of drugs. Several therapeutic approaches have been suggested for dealing with this, such as administering medications directly to the infected location, like via the pulmonary pathway. Moreover, compared to medication taken orally, drug delivery to the lungs bypasses hepatic metabolism and therefore is believed to boost the bioavailability of drugs and may possibly shorten the expenses and length of therapy.

While treating TB, the following pulmonary medication delivery methods and strategies are employed, viz., dry powder inhalers, nebulizers, pressurized metered-dose inhalers, and inhalable aerosolized antibiotics. These formulations are made to be breathed and eventually accumulate in the lung's alveoli. A brief description of these techniques along with advantages and drawbacks is given in Table I. Since the pulmonary system is the main location of MTB infection, inhaled treatments for TB have the benefit of delivering substantial localized medication concentrations there. To increase therapeutic efficacy and more quickly clear the airway to avoid transmission, inhaled TB medicines may be utilized in addition to traditional oral medication [57]. Inhalable drug particles, which are macro- or micro in range, may suffer from the setbacks like lung deposition variability, lung irritation, variations in drug release rates, and particle aggregation. These problems can be overcome with the help of nanotechnology [58].

Nanotechnology can be utilized to improve the drawbacks of microparticulate inhalable formulations for the treatment of tuberculosis. To better target MTB in the lungs, nanoparticles can be manufactured. Anti-TB medications can be encapsulated and released more easily at the site of infection. The reasons behind the preference for nanocarriers are enhanced targeting and bioavailability, reduced systemic toxicity, improved drug stability, and potential for drug resistance mitigation [59].

Nanocarrier-Based Pulmonary Drug Delivery for TB: a Step Towards Hope

Inhalable formulations have dominated the market for the treatment of various types of respiratory disorders because of their local effect and reduced systemic

Table I Compilation of Inhalable Techniques for TB Therapy

S. no	Technique for pulmonary delivery	Advantages	Disadvantages	References
1	Dry powder inhalers	Convenient, portable, do not require propellants	Proper inhalation technique is crucial; not be suitable for very young children or elderly patients; Not all TB drugs are available in this form	Dry powder inhalers of antitubercular drugs
2	Nebulizers		Take longer time to administer; require an electrical power source or a portable battery-operated unit	Treatment of patients with extensive TB and concomitant bronchial lesions with some anti-TB drugs delivered via nebulizer
3	Pressurized metered-dose inhalers	Compact, easy to use, and deliver a precise dose of medication	Coordinating inhalation with actuation can be challenging	Testing Inhaled Drug Therapies for Treating Tuberculosis In: Hickey AJ, editor. Delivery systems for tuberculosis prevention and treatment (Advances in Pharmaceutical Technology): John Wiley and Sons, Ltd; 2016
5	Inhalable aerosolized antibiotics	Targeted delivery, reduce systemic exposure, lower antibiotic dosing	Limited drug selection, excessive use of aerosolized antibiotics can contribute to antibiotic resistance, risk of bronchospasm	Inhalable microparticle platform based on a novel shell-forming lipid excipient and its feasibility for respirable delivery of biologics

exposure to drugs [60]. Nanocarriers with relatively very high surface area enable drug protection, increase their ability to interact with tissues and cells, and frequently enable precise targeting and/or controlled drug release [61, 62]. Studies reported that targeting antitubercular drugs in nano forms via the pulmonary route is able to reduce systemic toxicity and duration of therapy and is beneficial to limit MDR [50, 63–65]. To produce quality product, now researcher is adopting quality by design which starts with a quality target product profile (QTPP). QTPP consist of quality attributes to certify the safety and efficacy of formulation and process parameters. Particle size (less than 5 μm), particle size distribution (≤ 0.5), and entrapment efficiency (60–80%) are the major formulation criteria and characterization parameters for pulmonary drug delivery, which will assure efficacy and a superior therapeutic outcome. As discussed earlier in the barrier section, particle size and particle size distribution play a major role in pulmonary targeting and mainly characterized by the laser diffraction method using Malvern Instruments. The entrapment efficiency of nano pulmonary delivery is estimated by measuring the concentration of the drug in the supernatant after separating the nanocarrier. Additionally, QTPP also considered the physical stability parameters of aerosol which include interparticle interactions (aggregation), surface characteristics, particle density, pH, and viscosity. Usually, SEM is used to determine the surface characteristics which affect flowability; furthermore, bulk density and tap density of prepared formulation also indicate the flow property of the formulation. Structural analysis of prepared nano formulation is done by X-ray diffraction method, thermoanalytical analysis, etc. *In vitro* dissolution and diffusion test is also a key parameter to identify the local delivery of the drug and its sustainability. Moreover, aerodynamic measurements by cascade impactor will also improve the efficacy of the formulation. The main preparative methods of a nanocarrier are selected on the basis of the material used, route of delivery, expected particle size and loading amount, etc. The commonly used methods can be categorized into physical, chemical, and biological [66, 67].

This section is focused on the current research of pulmonary delivery for MDR-TB and different improvement strategies to combat the limitations of traditional medication such as solubility, permeability, off-target release, and systemic side effects.

Numerous medicines used in the treatment of tuberculosis have poor solubility and toxicity profile that could be managed successfully with nanotherapeutics. The solubility enhancement can be done by nano size, addition of permeation enhancer, and use of derivatives of polymers. The recently developed nitroimidazopyrazinone derivative pretomanid and MCC7433, two prospective antitubercular drugs from

the bicyclic nitroimidazole family, are expected to be effective against tuberculosis. Although both have excellent cell permeation, these substances have a low ability to dissolve in water, necessitating the use of specific preparations to make them orally accessible. Researchers explored the application of mesoporous silica nanoparticles (MCM-41) as carriers for medications to overcome this constraint. Sol-gel synthesis was used to create MCM-41 nanoparticles, and then amine and phosphonate units were introduced to the surface to customize it. Substantial entrapment efficiency was achieved using an easy rotating evaporation technique to integrate the chosen drugs into the nanoparticles. As pretomanid and MCC7433 were evaluated by *in vitro* testing against MTB utilizing developed nanocarriers, an altogether substantial enhancement in solubility was also seen, and the pharmacological action was largely unaffected. Amino group–based surface modification of MCM-41 nanoparticles has been shown to increase the total systemic presentation of MCC7433 in mice models as compared to MCC7433 monotherapy [68].

Another strategy to improve targetability is to optimize the diameter and surface chemistry of antimicrobial drug-loaded nanocarriers that leads to macrophage targeting. Pinheiro and his team revealed that macrophages play a crucial part in the active as well as passive targeting of nanocarriers. They explained that liposomes with adequate size are capable of accessing the alveolar region and easily phagocyte by macrophages due to their smaller sizes. This targeting is possible due to the natural phenomenon of macrophages to phagocyte particles less than 5 μm [69]. Another strategy is to formulate stimuli-sensitive (pH and temperature) nanocarriers that can differentiate between healthy and cancer cells. Hwang and co-workers reported that encapsulated medication in the nanoparticles may be released due to the variations in pH (acidosis) and temperature (hyperthermia) difference between healthy tissues and pathogenic cells (infected with MTB) [70]. Furthermore, specific ligands conjugated to the drug bind to the respective receptors expressed by cells at the targeted site is another strategy to improve the targetability and efficacy of drug delivery. Active targeting relies on molecular recognition to deliver drugs to these specific tissues [69–72]. These delivery methods enhance bioavailability and biodistribution by lowering the dosing frequency and intensity of concomitant side effects. The more focused distribution also serves as a foundation for reducing the occurrence of antimicrobial resistance, a significant contemporary objective in antibiotic therapy. One of the biggest issues with public health has been antibiotic resistance for a long time. Since their discovery, these compounds have been misused more and more, which has led to the cellular systems in bacteria becoming increasingly resistant. This has repeatedly presented a fresh challenge for the management of infectious diseases [73, 74].

Nanotechnology, medicine, and engineering should collaborate to achieve ground-breaking development and also ensure the clinical efficacy of the nanocarrier given by the pulmonary administration. It is also evident that the co-delivery of hydrophilic as well as hydrophobic drugs using lipid-based nanocarriers can reduce MRD among TB patients and also increase patient compliance [75, 76].

Nanoparticles that are multi-functionalized, ligand-anchored, polymeric, metallic, lipoidal, nano-embedded, and produced through phytotechnology are currently the subject of research [77]. An aerodynamic diameter of particles should be less than 5 μm which can be inhaled as aerosols and settle in the lungs depending on their composition and physicochemical qualities. Nanocarriers have a number of benefits, including the prevention of a compound's breakdown, controlled medication release, enhanced bioavailability, and non-toxicity [78, 79].

Novel Nano Approaches for Pulmonary Drug Delivery to Treat MDR TB: Recent Research Updates

In the history of pharmaceutical technology, there have been many justifications for the necessity for drug formulation, ranging from the straightforward protection of pharmaceuticals to the more intricate targeting of cells or tissues [80]. Nevertheless, nano-based targeted pulmonary delivery has grown in prominence recently, because it is non-invasive, and more evidence has been shown of its ability to provide systemic activity in addition to local therapy. The properties of these carriers can be extremely advantageous for lung delivery [81, 82]. As discussed earlier, novel approaches are required to improve the efficacy of existing drugs against MDR TB. This section is focused on the research conducted on the pulmonary delivery of antitubercular drugs in nano formulation to treat MDR TB.

To improve drug delivery to the site of infection and reduce systemic adverse effects, nanoparticles can be created to facilitate passive as well as active targeting in TB therapy.

Passive Targeting in TB Therapy

In the context of TB, passive targeting usually refers to the biological accumulation of anti-TB medications in the impacted lung tissues and areas, where MTB predominately resides. The physiological and pathological aspects of TB infection as well as the characteristics of the drugs that are administered are utilized in passive targeting. A few strategies of passive targeting in TB are tailoring of size, delivery of drug via the inhalation route, and enhanced permeability and retention (EPR) effect in inflamed TB tissues.

Acinetobacter baumannii, an antibiotic-resistant pathogen, is reported to cause hospital-acquired pneumonia in critically ill patients [83]. Rifampicin is frequently used via intravenous route to treat this infection; however, its effectivity is limited for pulmonary infection [84]. So, in this regard, Tewes *et al.* prepared complexes of rifampicin with cyclodextrin and aimed at lung nebulization to enhance the efficiency of treatment for lung infections and to overcome MDR gram-negative bacteria apparition. The use of hydroxypropyl-β-cyclodextrin (HPβCD) and methylated beta-cyclodextrin (RAMED) was supposed to permit the high dose of rifampicin into the lungs via improving the apparent solubility of rifampicin without affecting lung absorption which improves the pharmacodynamic profile of the drug. The results of the solubility curve indicate the 7.6- and 22-fold increase in rifampicin solubility in RAMED and HPβCD complexes respectively. Additionally, complexes are able to generate aerosolized droplets with acceptable MMAD for pulmonary delivery. The resultant complexes of RAMEB or HPβCD also showed similar or better bacteriostatic activity towards *A. Baumannii* compared to free drugs. Permeation of rifampicin was not altered by complex as indicated by a study on the Calu-3 epithelial cell model but acted as a reservoir for it. However, further details in the investigation of the pharmacokinetic profile are required for clinical implications [85].

Instead of using first-line anti-TB drugs, MDR TB therapy may require second-line drugs such as capreomycin, a polypeptide antibiotic. However, the main impediment with capreomycin is its frequent injections along with ototoxicity and nephrotoxicity which may cause heavy load in the elderly patient or with renal impairment. So, Shao *et al.* used a spray drying technique to create an inhalable dry powder of capreomycin aimed at lung targeting. A total sixteen formulation were developed and evaluated. The formulation containing 25%w/w capreomycin, spray-dried at 90°C if inlet temperature, is considered best among 16 formulations with mass median aerodynamic diameter of less than 5 µm and fine particle fraction of around 65%. *In vivo* study on mice revealed that the drug concentration in the lungs was roughly eightfold greater than the required MIC (1.25 to 2.5 µg/mL) and maintained at this level for almost 24 h. Inhaled capreomycin had a considerably greater area under the curve, longer mean residence time, and slower clearance at plasma and lungs for MDR TB compared to intravenous injection. It may reduce the dosing frequency and systemic side effects; however, detailed *in vivo* investigations are required for antimicrobial efficiency in the lungs [86]. It was discovered that capreomycin changed mycobacterium smegmatis's metabolism and transformed the cell envelope, making the cell wall stiffer and more resistant to antibiotics. So, Shao *et al.* further investigated capreomycin's effectiveness *in vitro* by incorporating D-LAK120-A or D-LAK120-HP13 an antimicrobial peptide, which altered the surface characteristics of mycobacteria and reduced the remodelling caused by the drug. The resultant was formulated as an inhalable dry powder which was prepared using spray drying technique. A total of 16 formulations with varying degrees of drug-to-peptide ratios were created. In most formulations, an adequate production yield of more than 60% (w/w) was obtained. The spherical shape, smooth surface, and less than 2% residual moisture were observed in co-spray dried particles. D-LAK peptides and capreomycin and were both found at the particle's surface. Overall, this investigation demonstrated the feasibility of generating a spray-dried form of capreomycin and peptides that are antimicrobial for MDR TB pulmonary administration. Further, pharmacokinetic and pharmacodynamic studies are needed to investigate the potential of D-LAK peptides and capreomycin for site-specific delivery [87]. Similarly, Verma *et al.* had chosen a second-generation anti-TB drug for the effective treatment of MDR TB. Dry powder inhalation powder was prepared with drug (sutezolid) and PLGA. After ensuring the *in vitro* characteristics, the efficacy of formulation was estimated on a mouse model infected with MTB. The mice were treated via the oral route with a dose of 100 mg/kg/day and the pulmonary route with a reduced dose of 0.25–0.5 mg/kg/day for 28 days, and the goal was to reduce microbial load on the lungs. Additionally, the same pulmonary dose with a reduced oral dose (50 mg/kg/day) was also effective in irradicating Mtb. The data showed that inhaled adjunct therapy with a second-line drug has the capacity to reduce the oral dose and is effective for MDR TB treatment [88].

Pyrazinamide (PZ), a pyrazine family member, is a highly effective antimycobacterial drug utilized in primary and secondary line treatments. The introduction of PZ-resistant strains is a major public health concern because this medicine has the potential to shorten tuberculosis treatment from 9 to 12 months to a 6-month period. To increase the efficacy of pyrazinamide, Ali *et al.* created ferrous, copper, cobalt, ferric, and manganese complexes of pyrazinamide (PZ), and efficacy was tested against five MDR strains of mycobacterium TB. The BACTEC MGIT 960 system was employed to investigate the *in vitro* anti-TB activity of compounds. This research was conducted over a 6-week period. The growth of these strains was examined to determine resistance to the synthesized metal complexes of PZ. The most powerful against all resistant strains was the Co (II)-PZ complex. Ni (II)-PZ showed efficacies for all strains till the fourth week, later resistant towards only two strains. Among all the complexes studied, the cobalt and manganese complexes were found to be the most effective again [89].

By combining information from observational studies, Khan *et al.* evaluated the efficacy and safety of standardized, shorter MDR-TB regimens. Individual patient data

(IPD) meta-regression is used to determine risk factors for unsuccessful treatment in patients. These patients were gone through 9- to 12-month MDR-TB regimens that include gatifloxacin/moxifloxacin, clofazimine, prothionamide, isoniazid, pyrazinamide, and ethambutol. The therapeutic outcome was estimated by aggregate data meta-analyses. A total of 796 out of 1279 (62.2%) patients with no prior exposure to second-line medications and confirmed with MDR-TB (98.4%) or rifampin-resistant TB (1.6%) were recruited for five studies. Successful treatment was received by 669 patients (83%, 95% CI 71.9–90.3%) out of 796. Fluoroquinolone resistance (crude OR 46, 95% CI 8–273) and pyrazinamide resistance (OR 8, 95% CI 2–38) were linked with failure/relapse. No culture conversion by month 2 of therapy (OR 7, 95% CI 3–202) in an IPD meta-regression (three studies, $n=497$). Medication resistance was reported in two subjects and 55 out of 304 participants (18.1%) in four studies had adverse events of grade 3 or 4 [63].

Another cohort produced silver nanoparticles (AgNPs) using the naturally derived biopolymer alginate as a stabilizer and isoniazid and rifampin as active pharmaceutical ingredients. This enhanced the biocompatibility of the developed formulation with the use of ecofriendly excipients. Drug susceptibility testing of the developed formulation revealed that both drug-resistant and dormant MTB strains are affected. The formulation's anti-mycobacterial effect is accomplished by a rise in cell-wall permeability, according to the results of a bacterial cell-wall permeability assay. Furthermore, the antimycobacterial potential of the formulation was evaluated in the zebrafish model and rodent TB model, which was found to be significant. Several therapeutic benefits can be achieved from the developed formulation, viz., increased drug's therapeutic effect duration, enhanced drug-loading, lesser side effects, and good compliance [90].

Another research that highlights the use of nanocarrier-based drug delivery systems increasing local drug levels at points of infection while minimizing systemic toxicity is the development of amorphous nanoparticles containing bedaquiline (BDQ) and BTZ (1,3-benzothiazin-4-one 043) via solvent-antisolvent approach. The drug load in the nanoparticles was found to be very high, viz., 69% for BDQ and more than 99% for BTZ. The developed nanosuspensions were stable for many weeks. Experiments conducted *in vitro* and *in vivo* using susceptible C3HeB/FeJ mice and MTB-infected macrophages demonstrate an intriguing effect that surpasses traditional BDQ/BTZ solutions with up to 50% greater efficacy following pulmonary administration. The developed nanoparticles revealed *in vitro* that they can penetrate multiple barriers located in biological systems to get to the intracellular mycobacterium. In preclinical studies, a higher concentration of nanoparticles was found in lung granulomas while tiny amounts were spotted in the liver and spleen [91].

To improve medication delivery effectiveness and get rid of resistance to drugs *in vitro*, fluoxetine and isoniazid were conjugated in a multi-walled carbon nanotube nanofluid. On MTB, the developed nanofluid was examined. Real-time PCR was used to find out how much inhA and katG mRNAs were expressed. Cytokines, viz., TNF-α and IL-6 secretion levels from infectious macrophages managed with the nanoformulations, were measured using ELISA. The outcomes demonstrated that these nanoformulations for fluoxetine are efficient at far lower concentrations than for free medications. Many clinical forms of MTB infection can be treated effectively by concurrently using fluoxetine and isoniazid in the delivery system. Fluoxetine and isoniazid have synergistic effects. It has been established that both the free and coupled forms of these two drugs have a synergistic effect on one another, increasing their antibacterial efficacy against all strains [92].

Likewise, using the same drug, i.e., rifampicin, nanoparticulate pulmonary preparations had been developed using an emerging hydrophobic chitosan derivative, octanoyl chitosan, which claims to enhance the drug's organic solubility. Nanoparticles were developed using a double emulsion solvent evaporation technique. With a mean particle size of 253 nm and entrapment efficiency of 64.86%, the optimized nanoformulation showed a smooth and spherical shape. On A549 cell lines, initial cytotoxicity tests of octanoyl chitosan had no impact on cell survival after 24 h. After nanoparticles from a jet nebulizer were aerosolized for pulmonary deposition tests, the fine particle fraction was 43.27%. Rifampicin was released constantly from the nanoparticles throughout a 72-h period, as determined by *in vitro* release testing, with nanoparticles retaining their physical resilience for 2 months [93].

Similarly, another cohort also developed a lipoidal nanoparticulate system of ethambutol for TB treatment and delivered via dry powder inhalers. Two different techniques were used for the solid-lipid nanoparticles, viz., hot homogenization and ultrasonication which were further spray-dried with and without mannitol. The resulting particles had an entrapment effectiveness of more than 98% and a particle size of less than 100 nm. The biological compatibility and non-toxic properties of the ethambutol-loaded SLNs were determined by toxicity research using the MTT test which demonstrated no cellular toxicity. The efficacy of the manufactured powders was validated by the evaluation of the flowability, i.e., Carr's index and Hausner's ratio and aerodynamic characteristics via next-generation impactor analysis of the developed DPI powder [94]. In another research, researchers explored an intriguing approach to improve therapeutic outcomes by enhancing drug concentration at the infection site with a reduction in systemic exposure. They have prepared amorphous NPs to entrap bedaquiline via solvent and anti-solvent methods. The prepared NPs were exhibited nanosize (60 nm) with high drug loading efficiency (69%). NP suspension was found to

be stable for several weeks. *In vivo*, a study on M.tb.-infected macrophages and susceptible C3HeB/FeJ mice showed 50% more efficiency of the drug via the pulmonary route. The results also indicate the ability of NPs to cross the biological barriers; however, major concentration was reported in the lungs. This indicates the site-specific effectivity of antitubercular drugs for the treatment of MDR TB [91].

Active Targeting in TB Therapy

The human immunological response to infection with MTB, which is caused by macrophages, is critical. However, TB bacteria can manipulate and endure within macrophages, aiding in the development of the illness. Utilizing specific ligands or molecules to actively direct drug-loaded nanoparticles or drug carriers to the site of TB infection or target cells within the body is known as active targeting in tuberculosis (TB) therapy. This strategy seeks to increase the concentration of drugs in the macrophages, boost drug delivery efficiency, and minimize exposure to healthy tissues. A few important components of active targeting in TB treatment are ligand-functionalization of nanoparticles, alteration in the surface properties such as charge and hydrophobicity, pH, and enzyme-responsive nanoparticles [95].

Pati *et al.* [96] created a novel anti-TB medication compound with zinc and rifampicin (Zn-RIF) and incorporated it in silver quantum dots conjugated with transferrin (Zn-RIF-Tf-QD) to increase delivery in macrophages. Figure 2 illustrates the fabrication of Zn-RIF-Tf-QD with verification from TEM and UV absorption analysis. A layer was observed in the TEM image of Zn-RIF-Tf-QD compared to Tf-QD which hypothesizes the complex formation of Zn-RIF with Tf-QDs via non-covalent or covalent interaction. In comparison to Zn-RIF, RIF, and Zn, Zn-RIF-Tf-QD displayed ten times higher antibacterial activity against *Mycobacterium bovis and Mycobacterium smegmatis*. Zn-RIF-Tf-QD was found to be efficacious in killing mycobacteria inside macrophages without exerting any cytotoxicity and genotoxicity. Furthermore, conjugates showed stability for up to 48 h, were resided in the late endosomal compartment of macrophages with prolonged release of drug at the target site. Data showed that Zn-RIF-Tf-QDs have a high potential as anti-TB medicines [96].

A similar concept was adopted by Marcianes *et al.* to target alveolar macrophages to combat MDR TB. They developed PLGA microparticles loaded with gatifloxacin along with labrafil (surface modifier) to target macrophages for target release of the drug which was observed through fluorescein-loaded microparticles. The results of cell phagocytosis revealed that the presence of a surface modifier had enhanced the phagocytosis of PLGA nanoparticles by macrophages and their stability inside up to 48, which is why it could be a potential delivery system to treat MDR TB [97].

Scolari *et al.* developed rifampicin (RIF) and ascorbic acid (ASC) inhalable nanocarriers as an interface for pulmonary TB infection therapy. This nanoformulation was made of sodium alginate covered with chitosan and Tween 80. The nanocarrier had a hydrophilic surface, with a mean particle size of 324.0 nm, PDI of 0.226, and zeta potential of 28.52 mV. The nanoformulation was discovered to be substantially more active against nine clinical strains of MTB than the free drug. Additionally, since the freeze-dried nanoformulation powder exhibits outstanding features of dispersibility in water, these RIF/ASC NPs may be promising for the fabrication of inhalable TB treatment delivered via the pulmonary route utilizing dry powder inhalers (DPIs). *In vitro* cytotoxicity was conducted on the Vero cell line by the MTT assay which demonstrated no toxicity to cells [98].

As evident from all the abovementioned studies, novel approaches can help in utilizing the existing treatment for MDR TB (Table II). Further, it will reduce the burden of synthesizing new drugs for resistant strains. However, more research is needed for site-specific delivery of nanocarriers via the pulmonary route to treat MDR TB.

Nano-formulations for TB Therapy: Patents and Innovations

The design and modification of techniques for pulmonary drug delivery have seen an increase in innovation and patent filing in the past few years. The long-term viability of the dosage form and the quantity of medication that enters the lungs will both be improved in the next years by nano-enabled customization of the particles and formulations. In this specific area, patent applications are increasingly being made for both pulmonary drug delivery methods and their combination with obsolete pulmonary-targeted medications with modified compositions.

A South Korean (KR101732744B1) patent granted in May 2017 offered nanocarrier delivery compositions and techniques for immune system cells. The invention delivered nanocarriers with immune-specific surfaces that can activate T cells and/or B cells to produce an immunological response. This innovation offered techniques for creating, utilizing, and developing nanocarriers and therapeutic substances for the treatment of tuberculosis, malaria, respiratory infection, Helicobacter pylori, Staphylococcus infection, or Salmonella infection. Lipoidal, polymeric, and metallic nanoparticles, nanoemulsions, dendrimers, and/or nanoparticles created utilizing a combination of nanomaterials may all be used as nanocarriers. But it is not just restricted to that. This patent has worldwide application in the USA, Russia, Europe, Canada, and Australia [99]. Similarly, the University of California granted with patent (US20220153589A1) to develop a graphene oxide

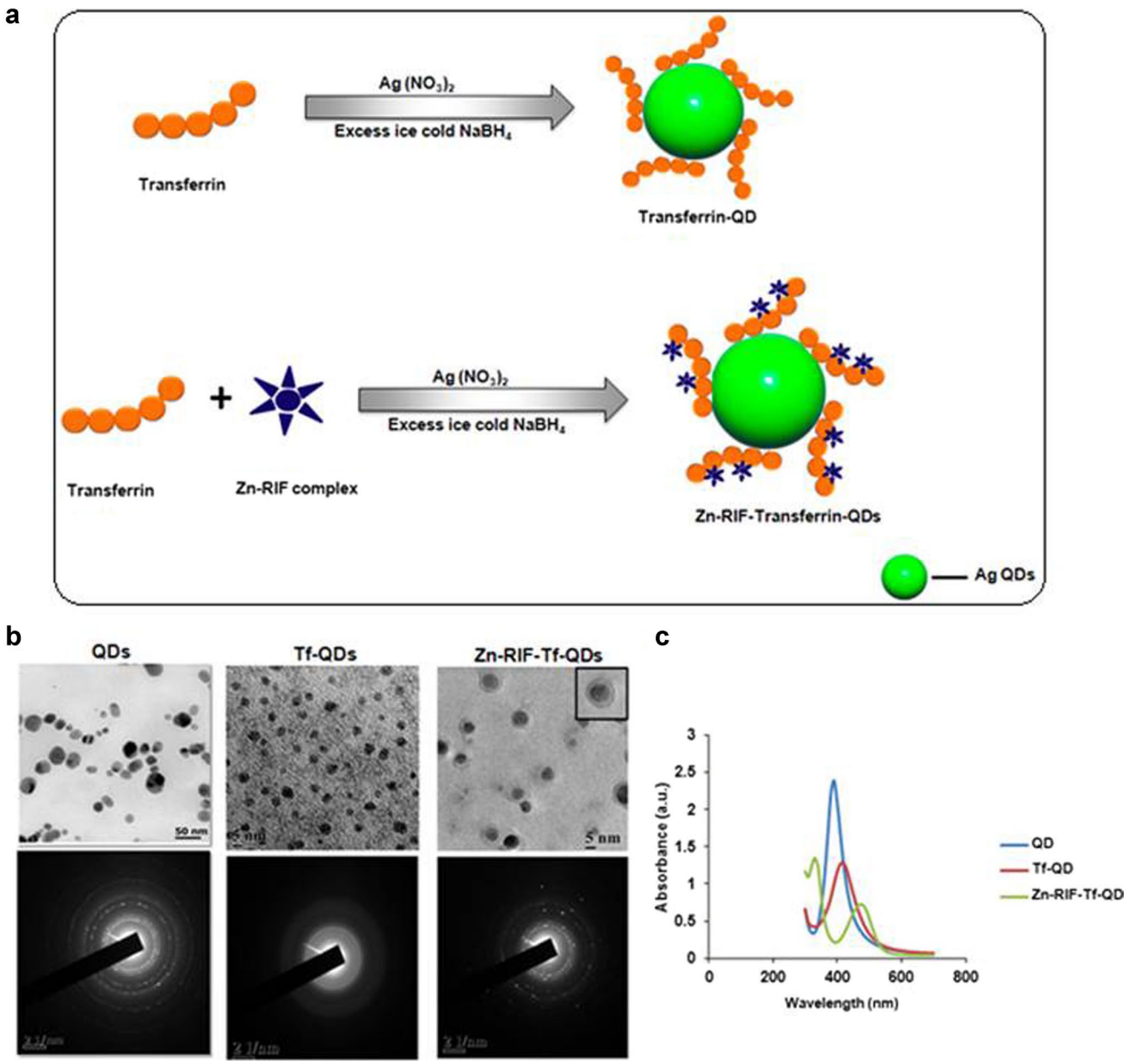

Fig. 2 **a** Schematic illustration of Zn-RIF-Tf-QD fabrication; **b** TEM images of quantum dots (QD), transferrin conjugated QD (Tf-QD), and Zn-rifampicin-loaded Tf-QD. **C** QD, Tf-QD, and Zn-RIF-Tf-QDs absorption spectrum by UV–visible. Figure comes under Creative Commons Attribution 4.0 International License, taken from Pati *et al.* [96]

nanocarrier with surface modification to compact MDR TB and reduce lung inflammation. They have investigated the effect of surface modification on the toxicity profile of nanocarriers used for pulmonary delivery [100].

Another patent published in May 2022 develops silica-based nanocarriers with a silica substance and multiple pores suited for holding particles. The phospholipid bilayer on the surface of the nanocarrier is coated with a lipid bilayer that acts as a cargo-trapping agent. Multiple pores are securely sealed by the phospholipid bilayer. A medicine or other desired cargo for the treatment of infections caused by *Escherichia coli* (e.g., UTI), *Staphylococcus aureus* (e.g., blood infection), *Pseudomonas aeruginosa* (e.g., kidney or respiratory infection), *Enterococci* (e.g., blood, UTI, wound), and MTB (e.g., lung) can interact with the cargo-trapping reagent of your choice. This patent also has worldwide applications (JP7068173B2) [101].

Table II Summary of Recent Research on Nanocarriers Against MDR TB via Pulmonary Route

S. no	Objective	Drug	Polymer or complexes	Microorganism	Animal/cell line used	Outcomes	Reference
1.	To develop complexes of rifampicin and cyclodextrin to enhance solubility for lung nebulization	Rifampicin, nebulizer	Hydroxypropyl-β-cyclodextrin (HPβCD)	*Acinetobacter baumannii*	Calu-3 broncho-alveolar cells	Complexation efficiency was pH-dependent The stability constant for the complex was $68.5 \pm 5.2\ M^{-1}$ Solubility increased 7.6 fold which was stable for 2 days Resultant complexes showed similar or better bacteriostatic activity towards *A. Baumannii*	[85]
2.	To improve the efficacy stability and targetability of rifampicin for macrophage	Rifampicin	Zinc, silver quantum dots	*Mycobacterium bovis and Mycobacterium smegmatis*	Mouse macrophages	Transferrin QD were in the range of 5–20 nm Complex showed higher antibacterial activity and was actively endocytosed by macrophages The investigated complex showed huge potential against TB	[96]
3.	To develop a gatifloxacin-loaded PLGA microparticle for macrophage targeting	Gatifloxacin	Librafil, PLGA	-	Mouse macrophage cell line	High encapsulation efficiency ($89.6 \pm 0.2\%$) Enhanced phagocytosis by macrophage	[97]
3.	To develop a dry powder inhaler to target capreomycin at the lung for MDR treatment	Capreomycin	Mannitol	-	BALB/c mice	Particles produced at 90°C inlet temperature in a spray dryer have better properties MMAD od formulation is 3.38 µm Lung concentration is higher than MIC and maintained for 24 h	[86]
4	To investigate inhalable dry powder formulations containing capreomycin and D-LAK peptides combination for MDR TB treatment	Capreomycin and D-LAK peptides	Mannitol	*M. smegmatis mc2 and Mtb Bleupan*	-	60% production yield Spray-dried particles are smooth and spherical No difference was observed in fine particle fraction and emitted fraction	[87]

Table II (continued)

S. no	Objective	Drug	Polymer or complexes	Microorganism	Animal/cell line used	Outcomes	Reference
	To develop inhaled adjunct therapy of a second line anti TB drug for effective treatment of MDR TB	Sutezolid	PLGA	-	Mice	Inhaled adjunct therapy of sutezolid effectively reduces the oral dose of sutezolid to reduce microbial in the lungs	[88]
5	Development of ferric, copper, cobalt, and manganese complexes of anti-tuberculosis medication	Pyrazinamide	Ferric, copper, cobalt, and manganese	*M. tuberculosis*	-	The cobalt and manganese complexes were the most powerful The presence of amide group and carbonyl improves antibacterial activity	[89]
6	To produce silver nanoparticles of isoniazid and rifampin	Isoniazid and rifampin	Silver nitrate	*M. tuberculosis*	*zebrafish and mouse TB animal model*	The developed formulation showed increased bacterial cell permeability	[90]
7	To develop amorphous nanoparticles of highly lipophilic antibiotics	Bedaquiline (BDQ) and BTZ (1,3-benzothiazin-4-one 043)	Amorphous nanoparticles by solvent-antisolvent approach	*M. tuberculosis*	*C3HeB/FeJ mice*	Nanoparticles displayed 50% greater efficacy after pulmonary administration as compared to drug solutions	[91]
8	To develop multi-walled carbon nanotube nanofluid	Isoniazid and fluoxetine	Carbon nanotube	*M. tuberculosis*	-	The coupled forms of both drugs have a synergistic effect on one another, increasing their antibacterial efficacy against all strains	[92]
9	To develop amorphous NPs to entrap bedaquiline for pulmonary delivery	Bedaquiline	Amorphous NPs	*M. tuberculosis*	*M.tb.-infected macrophages and susceptible C3HeB/FeJ mice*	NPs were in 60 nm size with stability in suspension for several weeks. NPs also show the ability to cross biological barriers, however, a major concentration was reported in the lungs	[91]

Safety Concerns of Nanocarrier-based Pulmonary Drug Delivery

Nanocarrier-based pulmonary drug delivery systems offer several advantages, such as improved drug targeting and controlled release. However, like any medical intervention, there are safety concerns associated with their use. A brief description of general safety concerns is mentioned in Table III. The tracheobronchial area, which extends from the larynx to the terminal bronchioles, and the alveolar region, which includes the respiratory bronchioles and alveoli, are the two functioning sections of the lungs. Ahmad and co-workers said that drug delivery methods based on nanocarriers have significant challenges in clinical settings, including increased circulatory clearance, immunological response, and decreased targeting efficacy [102]. Inhaled gases and particles are separated from the blood by the extraordinarily thick and wide alveolar surface of the lungs. It is imperative to address the toxicity of inhaled therapeutic nanocarriers, and studies related to toxicity profile concerning its pulmonary route are much important [103]. Most of the studies were performed to evaluate short-term toxicity by exposing nanomaterial to cells for less than 3 days and evaluating its impact on cell morphology and other parameters. However, long-term toxicity exposure will mimic the realistic scenario, which is why many times, conclusions drawn from short-term toxicity cannot be extrapolated for real scenarios. Keeping this in mind, some researchers explored the pulmonary toxicity of vanadium dioxide NPs. They have performed 1 day of short-term and 20 days of long-term toxicity by exposing NPs to lung cell lines A549. They have observed the different results from both the toxicity. Severe viability was observed in short-term toxicity at 2.5 μg ml^{-1}; however, the viability drop was less than 50% after long-term exposure. Cell membrane leakage, mitochondrial damage, and ROS generation were found as main mechanisms for toxicity. In contrast, long-term toxicity indication indicates ROS generation and cell cycle arrest as main mechanisms for toxicity [104].

The deposition of small particles in lung tissues and extracellular spaces is mainly affected by the size, surface charge, shape, phoretic forces, and density of small particles. The basic principles for deposition are the sedimentation of particles due to gravity, inertial impaction, and Brownian motion. Inertial impaction holds larger particles (> 10 m) in the oropharynx and larynx region, as reported by Cheng. Sudden change in flow direction is the main reason behind the inertial impact deposition of these particles in airways [105]. Morten WB reported that usually, particles between 2 and 10 m in size are deposited in the tracheobronchial area. Gravitational sedimentation causes particles, mostly of tiny size (1–8 μm), to accumulate in the small conducting airways and alveoli [106]. Patton and his team revealed that the alveolar area is the main targeted area for inhaled small particles to get deposited. These particles may get absorbed into the systemic circulation through this area [107]. Due to Brownian diffusion, particles less than 0.5 μm in size are typically not deposited and are ejected during expiration. Hofman and co-workers reported that small aerosol particles (approximately 1 μm) can be expelled up to 80% of the time when breathing depending upon the air velocity, whereas nanoparticles smaller than 100 nm can deposit in the alveolar region in tolerable proportions [27, 108].

Due to an agglomeration process in the lung, drugs in nanocarriers often deposit through sedimentation after being released from the aerosol device. These agglomerated nanoparticles can settle in the tracheobronchial region for extended periods, increasing the biological activity of the medicinal drug that has been given. Pulmonary delivery of dry powder inhalation is challenging because of the restricted aerodynamic size and, in comparison to the oral route, low tolerance of lung tissues. Chaurasia and colleagues said that determining the aerodynamic behavior of the particles is one of the important concerns for researching deposition and analyzing aerosol properties [109].

The main drawback of nanocarriers is that they could be harmful due to their ubiquity in the air. Nanotoxicology has received a lot of interest recently, particularly in the realm of health pollution. To avoid the likelihood of toxicity consequences, the majority of nanocarriers for drug

Table III Compilation of Safety Concerns with Nano-mediated Pulmonary Drug Delivery

Limitations	Description
Inhalation-related adverse effects	Coughing, bronchospasm, or other respiratory symptoms, particularly in individuals with pre-existing lung conditions like asthma or chronic obstructive pulmonary disease (COPD)
Particle aggregation	Aggregate or clumping together, which can affect their aerosolization and dispersion in the lungs
Pulmonary toxicity	Accumulation in lung tissues can lead to inflammation, oxidative stress, and tissue damage
Immunological reactions	May potentially trigger immune responses
Biodegradability and clearance	Non-biodegradable nanoparticles may persist in the lungs, potentially leading to long-term adverse effects
Patient variability	Individual patient factors, such as lung health, age, and genetics, can influence therapeutic effects

administration are, however, typically synthesized with well-tolerated, generally recognized as safe (GRAS) materials. As a result, comprehensive *in vitro* and *in vivo* toxicity studies should be carried out while fabricating these drug-loaded nanocarriers to assure their safety for human health [110, 111].

The scaling up of the preparation process should also be resolved before inhalable nanocarriers are put on the market. The complexity of the nanocarrier creation could be a drawback in this case [112, 113]. After lung deposition, a drug's outcome is heavily influenced by how it interacts with the many elements of the biological environment. The most important ones are lung lining fluids, lung cell populations, and bacterial biofilm [27, 114]. Natural airway mucus can become thicker under certain pathological circumstances, which promotes bacterial growth and impairs the effectiveness of medications [115].

The various cell populations that are present in the lungs are another crucial factor. Alveolar macrophages, for instance, might phagocytose the particles, which could be useful for the treatment of tuberculosis but harmful for the treatment of other types of bacteria. Finally, an important aspect of antibiotic therapy is the dissolving of bacterial biofilms [116]. They are expelled while breathing because of their inadequate aerodynamic flow characteristics due to their particle size. Two basic approaches have been used to get over this restriction: nebulizing nanocarriers as a colloidal suspension or combining the system with smaller carriers. The latter method might be carried out by either embedding the nanosized system into microparticles or by combining nanocarriers with inert carriers [36, 65].

The alveolar clearance of medicines and nanoparticles is significantly slower than in other areas of the body because of low enzymatic activity, making it a non-invasive route as well. Although Wiedmann and his team reported that the cytochrome P450 (CYP) families are the lung's main detoxifying enzymes and act as a first line of defense against ingested or breathed xenobiotics. Additionally, a thin alveolar epithelium with high permeability and significant vascularization, as well as a very broad respiratory surface (about 100 m^2), is an important feature in assisting drug adsorption and targeting [117, 118].

The functional characteristics of surfactants present in the lung lining are either directly or indirectly affected by inhaled nanocarriers or particles, as reported by lipid peroxidation [119, 120], increased oxidative stress [119], increased inflammation [121], and increased degradability of tissues after exposure to inhaled particles [119–122]. Broichsitter and his team revealed that the adverse effects of nanocarriers on various properties of surfactants like hydrophobicity, surface charge, and transference are dose-dependent phenomena; at low administered doses, these properties are not negatively affected [123].

It is critical to emphasize the value of reproducibility in the manufacturing of drug-loaded nanocarriers (drug loading, encapsulation, functionalization effectiveness, physicochemical features), as well as the potential for expanding the process. A major barrier to the clinical implementation of drug-loaded nanocarriers is the lack of appropriate and detailed regulatory requirements addressing characterization, research designs, and statistical analyses. Optimized sharing activities are also necessary to support the transition of nanotechnology from successful research use to clinical use.

Conclusion and Future Perspective

There has been a continuous rise in the cases of antimicrobial drug resistance which resulted in multi-drug resistance and extensive drug resistance. This problem has reduced the efficacy of available treatment for tuberculosis. Nanotechnology has evolved during the past 25 years as an innovative approach to boost drug delivery as well as therapy effectiveness. Nanocarriers present an intriguing prospect for the development of more potent pharmaceuticals due to the enhancement of both the stability and solubility of active ingredients as well as the capacity to target the drug to a particular site. Additionally, nanomedicine also provides added advantages as compared to conventional therapy like reduced side effects, avoidance of first-pass metabolism, and sustained or targeted release. Substantially, the enhanced bioavailability and biodistribution permit lowering the dose and reducing the magnitude of associated adverse effects. In this review, we discussed different aspects of drug resistance against TB and how the application of nanomedicine can improve the efficacy of available treatment. Fortunately, it appears promising; there are currently no products available on shelves that use nanotechnology to treat this disease, and there are significantly fewer patents in this area than there are for nanomedicines that treat cancer. A multifaceted approach with the contribution of nanotechnology, medicine, and engineering needs to be implemented for revolutionary advancement towards rendering the pulmonary delivery of nanoparticles practical for noninvasive clinical trials.

Abbreviations TB: Tuberculosis; MDR: Multi-drug resistance; XDR: Extensive drug-resistant; NTEP: National Tuberculosis Eradication Programme; DOT: Directly observed therapy; HPβCD: Hydroxypropyl-β-cyclodextrin; RAMED: Methylated beta-cyclodextrin; Zn-RIF: Zinc and rifampicin; MIC: Minimum inhibitory concentration; BDQ: Bedaquiline; BTZLF: Labrafac: 1,3-Benzothiazin-4-one 043

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Data Availability The data and materials used during the study are available from the corresponding author upon reasonable request.

Declarations

Ethics Approval and Consent to Participate This is only an observational and theoretical study. No ethical approval is required.

Consent for Publication The authors give their consent for the publication.

Conflict of Interest The authors declare no competing interests.

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