REVIEW ARTICLE

Direct Lungs Targeting: An Alternative Treatment Approach for Pulmonary Tuberculosis

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Abstract

In the present review, authors are tried to analyze existing and advanced formulation with novel drug delivery and potential treatment approach with an aim to determine current knowledge gaps to control pulmonary tuberculosis (TB). Currently, in the market single as well as in fixed-dose combination tablet dosage forms are available. However, the conventional route of administrations, the oral route has drawbacks. Direct targeting of drug to the lungs is not achievable. Due to high dose of anti-TB drugs and shorter half life, the dosing frequency is more, resulting into hepato-toxicity and other side effects associated with them. One more challenge in TB treatment is lengthy treatment protocol. So there is a need of the novel treatment approach than the conventional, which is able to target the site of infection, where *Mycobacterium* resides. For pulmonary infections where direct drug administration to the lungs is desirable, the inhalation mode of drug delivery is the most advantageous. By taking advantages of the pulmonary route as well as the novel drug delivery system, we might be able to resolve the above challenges. Direct lungs targeting with inhalable microparticulate and nanoparticulate systems could potentially reduce dose, dosing frequency and to target the pulmonary site. Novel drug delivery systems such as Niosomes, Liposomes, Dendrimers, Microencapsulated particles, Microspheres, and Hydrogels have been identified as new antitubercular drug delivery strategies. These drug delivery systems may emerged as a promising solution to overcoming the limitations of traditional formulations and treating drug resistance, indicating that new advances in this field are possible.

Key words: Direct lung targeting, inhalable, novel approach, pulmonary tuberculosis

INTRODUCTION

Tuberculosis (TB) is a granulomatous airborne infectious disease predominantly occurred due to *Mycobacterium TB* (MTB), considered among the leading causes of mortality in India. It is spread when you inhale the bacteria in droplets containing *Mycobacterium*, if an infected person talks, coughs, or breaths.[1-3] Humans and bovins are the main vectors of infection, with human infection almost exclusively occurring by inhalation of aerosols and intake of bacillus-containing milk.[4] It often influences the pulmonary system; named as pulmonary TB (PTB), and extrapulmonary TB is the TB affecting the organ excluding pulmonary system, but together with lymph node, larynx, brain, kidney, pleura, or bones and joints.[5,6] Miliary TB emerges as tubercle bacilli invade the bloodstream and spread to all areas of the body. It is most prominent in babies and children under the age of five. TB meningitis is the TB in the tissue surroundings the brain or spinal cord.[7]

Microbiology

The *Mycobacterium* is <5 microns in size and has a generation time of 18–24 h.[8] Because of the low replication rate and capacity to adapt in a latent state, long-term drug therapy is needed to prevent TB infection.[9-12] It is multiplied

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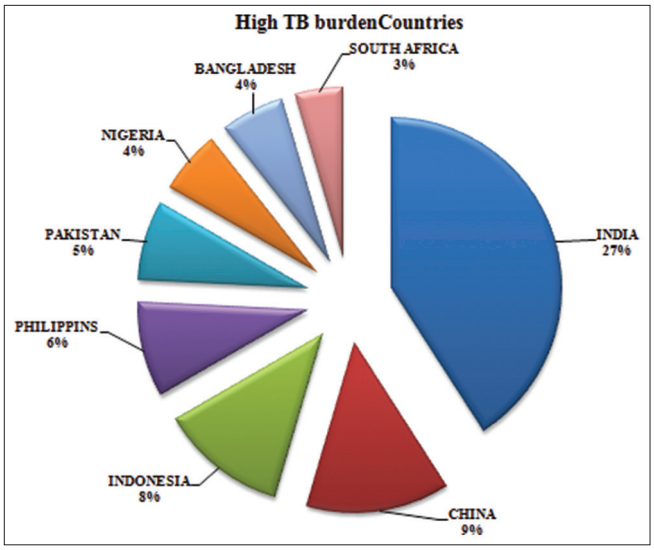

Figure 1: Current scenario of high TB burden countries

in macrophages and inside massive cystic tubercles, resulting in the formation of liquefied tissue surrounded by infected macrophages.[9] It remains airborne up to 6 h. As can be seen in graphical abstract, the symptoms of TB are bad cough with blood or sputum which is more than 2–3 weeks, fever, chest pain, loss of appetite, night sweat.

Current scenario of TB

About 1/3rd of worldwide people are affected due to TB. It kills 3 million people every year, mainly in developing countries, in which it kills 1 in every 5 adults. WHO reported that TB infected ten million people and there were 1.5 million TB deaths (including 251,000 among people with HIV) in 2018, made it most infectious killer worldwide.[7,13-16] Figure 1 depicts 60% of global epidemic burden of TB contributed by eight countries. Here authors are tried to focus on novel approach for the treatment of PTB exclusively, so let's have look at what is PTB and what are the worldwide treatment strategies including India.

PULMONARY TB

When mycobacteria enter the pulmonary alveoli, they infect and replicate inside alveolar macrophages, causing TB. Alveolar macrophages phagocytise inhaled mycobacteria, which associate with T lymphocytes, causing macrophages to differentiate into epithelioid histocytes. Granulomas are formed when epithelioid histocytes and lymphocytes assemble into small clusters.[17] Cluster of differentiation (CD)4 T-lymphocytes (effector T cells) secrete cytokines like interferon-gamma in the granuloma that stimulate macrophages to kill the bacteria they are infected with. CD8 T lymphocytes (cytotoxic T lymphocytes) may destroy infected cells directly.[21] Importantly, bacteria do not always get rid of themselves from the granuloma; they may go dormant and cause a latent infection.[17] *Mycobacterium* is able to survive within macrophages of host. This would result in occurrence of chronic infection which requires long-term treatment.[18] Many antibacterial agents do not penetrate mycobacterium's cell wall, and some mycobacteria live within macrophages, creating another protective layer that successful agents must overcome.[19]

WORLDWIDE TREATMENT AND CONTROLS MEASURES FOR TB INCLUDING INDIA

Perhaps one of the difficulties of treating latent as well as active TB is the duration of treatment regimens.[65] After independence, India was one of the first countries to invest in TB prevention, and the national TB program has been in operation since 1962, resulting in the establishment of district TB centers and TB clinics throughout the world.[20] Sometimes, failures and flaws are discussed by experts of National TB Programme (NTP) and Revised National TB Control Programme (RNTCP). All feedback from different stakeholders has been incorporated into the recently established National Scholarship Portal.[21] RNTCP is being implemented in-line with NTP.[22] Action plan tribal action plan for the tribal patients,[23] developed comprehensive guidelines for diagnosis and treatment of pulmonary TB. To monitor it National Informatics Centre has created, a web-based, case-based monitoring program called NIKSHAY.[24] Figure 2 depicted the India's efforts along with WHO to combat TB.

Although there are three distinct regimens, each of which is prescribed for a specific group of people.[25]

- Directly Observed Therapy Short-course (DOTS) has been one of the major strategies to combat the epidemic of TB globally. Patients are issued medications under the supervision of health professionals in DOTS.[26,27] This close monitoring by health care professionals ensures that the patient follows the treatment plan
- Long-term chemotherapy, that lasts for a year
- Retreatment regimen.

Drugs used in TB treatment

First-line oral anti-TB drugs such as Isoniazid, Pyrazinamide, Ethambutol and Rifampicin, and injectable anti-TB drugs such as streptomycin, Amikacin, Kanamycin, Capreomycin, Vincomycin, newer second-line anti-TB drugs such as Nevofloxacin, Ceprofloxacin, Oflaxacin, Moxifloxacin, Gatifloxacin, oral second-line anti-TB drugs such as Thioacetazone, P-amino salicylic acid, Ethionamid, and Cycloserine are used to treat TB.[28-32] Third-line anti-TB drugs are needed for the treatment of extensively drug-resistant TB, however, these drugs get more side effects than

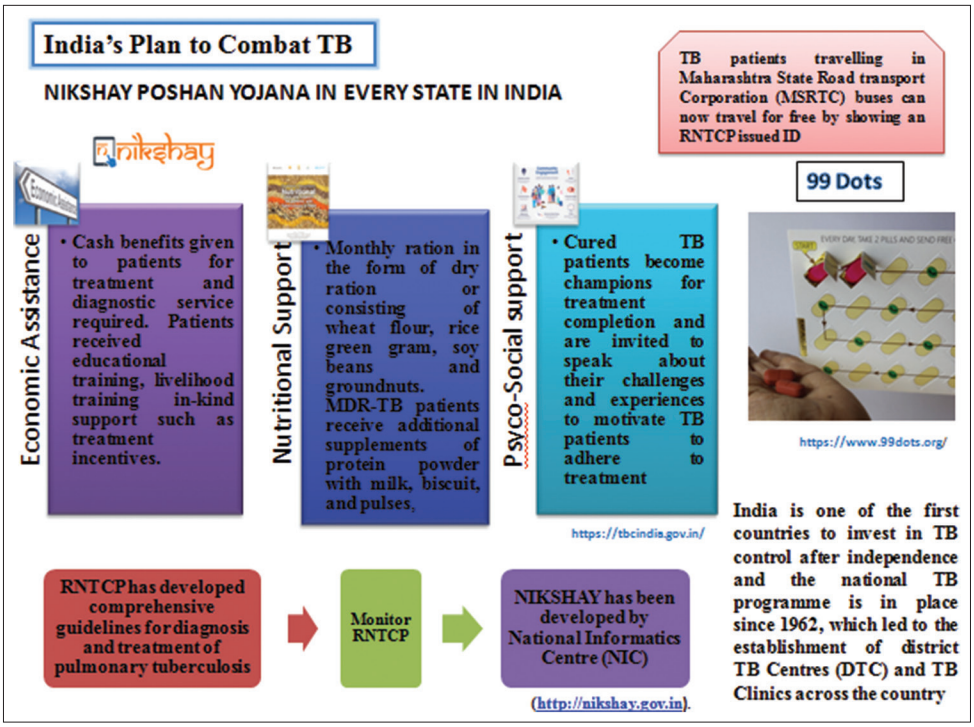

Figure 2: India's efforts along with WHO to combat tuberculosis

first- or second-line TB drugs.[27,33,34] Multi drug-resistant TB treatment is costly, takes a long time (18–24 months), and is complicated (requiring at least five medications, including some injectables), as well as having a higher rate of side effects.[32,35] Delaminid and Bedaquiline are the recently approved drugs.[36,37] Non-antibiotic medicines are now being studied as a means of eradicating TB infection. Vitamin C, A, D singly as well as in combination with first-line drugs is also used, that demonstrate the importance of trace elements in the success of anti-TB drugs.[38]

Market scenario

Currently, in market AKT-2, AKT-4, AKT-FD tablets, streptomycin injection is available. Immediate, reliable diagnosis and treatment of TB needed for optimal patient care, but they are also critical components of the public health response to TB and the backbone of any TB control initiative.[39] If we look at the comparative treatment strategies in between single drug formulation and fixed-dose combination (FDC), in today's situation this FDC is most relevant. According to Blomberg *et al*. (2001), to cure TB patients and avoid the selection of drug-resistant mutants that may occur during treatment, multidrug therapy is needed. FDC reduced probability of monotherapy and can reduce the likelihood of the occurrence of drug-resistant bacteria TB, despite the fact that this claim has yet to be proven.[40] But still for the treatment of TB needs the alternative treatment strategies.

DISADVANTAGES OF CURRENT TREATMENT (FOCUSING ON PTB)

- Drug targeting to lung not achieved
- Drugs are exposed to first pass effect which increases the chances of hepato-toxicity
- Due to short half-life drugs eliminated from the body
- And due to that dosing frequency is more, which affects patient compliance.

To reduce dose, dosing frequency, and to target the pulmonary site, there is a need of sustained release treatment and site-specific drug delivery. Direct targeting to lungs with novel drug delivery approaches it could possible to achieve it.

ALTERNATIVE DRUG DELIVERY STRATEGIES FOR THE TREATMENT OF PTB

Direct targeting to the lung

Physiology of human and animal body system suggests that lungs are complex organs, which having following advantages such as

- Contains near about 300 million of alveoli[41]
- Having surface area of 70–160 m^2
- Thin epithelial barrier, high blood flow, non-invasive[42]
- Hepatic first-pass metabolism is avoided and

- Allows therapeutic agents to be targeted to the site of infection
- Inhaled delivery can also minimize the amount of medication needed and the side effects that come with it.[43]

Half of all pharmaceuticals are not soluble in water but are soluble in lipid. Since the lung can absorb both water and oil into the tissue, it does not make limitation to lung delivery.[44] A rational therapeutic strategy for treating or preventing TB is to administer pharmacological agents directly to the respiratory system, following the normal route of infection.[43] Basically, the drug deposition into the lungs is particle size dependent. Inertial impaction, sedimentation, and diffusion are three processes involved in the deposition of inhaled particles in the respiratory track. The impaction mechanism deposits particles larger than 5 μm in the mouth and upper airways, while the inertial impaction and sedimentation mechanism deposits particles 1–5 um in the lungs. Particle smaller than 1um diffuses and settle into the pulmonary alveoli, while larger than 500 nm are phagocytized by alveolar microphages.[41] Figure 3 depicts the deposition of particles into the lungs according to its size.

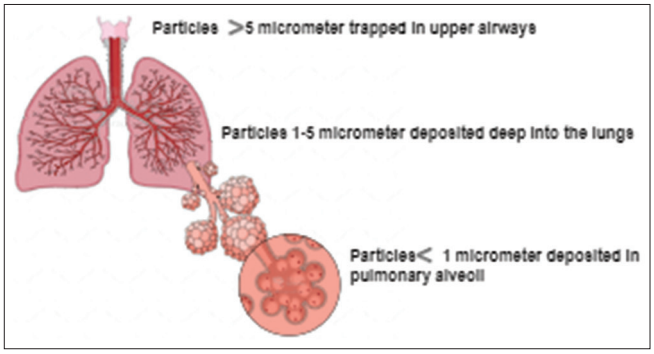

Figure 3: Deposition of drug particles into the lungs according its size

NOVEL DRUG DELIVERY SYSTEM

Target action in pulmonary TB can be achieved by nanoparticulate and microparticulate drug delivery approaches by the routes other than oral such as inhalation, which could help in reducing the side effects that come with these anti-TB drugs. Novel drug delivery systems such as Niosomes, Liposomes, Dendrimers, Microencapsulated particle, Microspheres, and Hydrogels have been identified as new antitubercular drug delivery strategies.[45] Figure 4 depicts the conventional and novel treatment approaches for the treatment of Pulmonary Tuberculosis.

Here authors have tried to quote couple of interesting examples of pulmonary drug delivery for the treatment of PTB. Researchers nowadays are focusing their efforts on the nanoparticulate system, which has a wide surface area and a small size, allowing it to interact with targets on cell surfaces as well as internally, and helps in increasing the bioavailability of drug. Donnellan and Giardiell (2019), explained the phenomenon of the "enhanced permeability and retention" effect, further they revealed that targeting NPs to specific sites (size dependent) improves permeation by directing drug away from sites with tight epithelial junctions in the healthy vasculature and toward areas where fenestrations occur

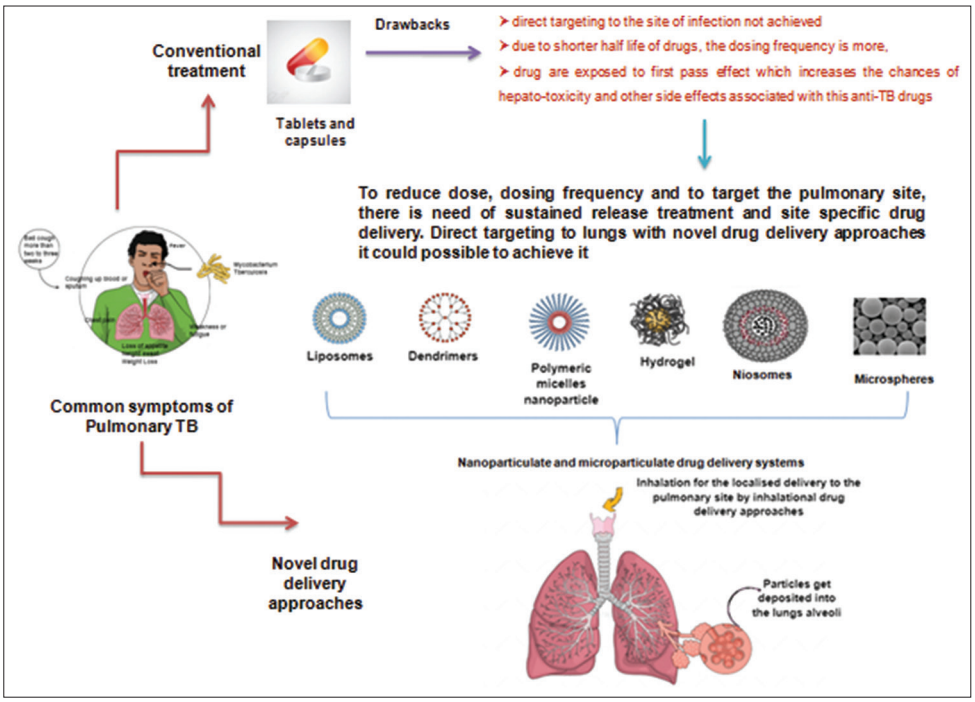

Figure 4: Conventional and novel drug delivery approaches for the treatment of Pulmonary Tuberculosis

Table 1: Drug, excipients, and formulations of some antitubercular drugs

Drug	Excipients	Formulation and method of preparation	Outcome of the research	Ref
Pyrazinamide	Eudragit RS-100, poloxamer/polyvinyl alcoholw	Polymeric NPs by simultaneous double-emulsion (W/O/W) solvent evaporation/ diffusion method	Via fluorescent micrograph, *in vivo* and *ex vivo* studies revealed substantial absorption of the NPs by alveolar macrophages and sustained drug release, resulting in reduced dosage, toxicity, and improved patient compliance	[54]
Q203, bedaquiline, and superparamagnetic iron oxides	Poly (D, L-lactide-co-glycolide) (PDLG)	NP aggregates by single emulsion technique	The study found that encapsulated NPs can reduce the number of bacteria of the organism BCG and are viable against A549 epithelial cells. Furthermore, in-silico computational fluid dynamics simulations showed that 100% of the NPs were transported into pulmonary	[55]
Rifampicin	Here, aqueous solution of Rifampicin was used for spray drying	Inhalable powder by spray drying method	Interfacial properties of Rifampicin contribute to early crust formation upon drying of the droplets, which gradually decoupled from the liquid core and formed strongly collapsed, low apparent density powders with excellent aerosol properties, according to acoustic levitator and surface tension experiments	[56]
Isoniazid	Polylactide	Microspheres Spray drying (solid in oil)) method	For up to 4 weeks after microsphere administration to rats, pulmonary drug concentrations remained relatively constant	[57]
Isoniazid and Lamivudine	Ethyl cellulose, Eudragit RS 100	Polymeric microsphere by oil in oil emulsion solvent evaporation method	*In vitro* drug release displayed a biphasic release pattern with up to 12 h of sustained release	[58]
Rifampicin		Floating microsphere by solvent evaporation technique	Entrapment efficiency was found to be 86.34%. The % buoyancy after 8 h was found to be 61.06%	[59]
Rifabutin	Ethylcellulose, chitosan	Complex microspheres by spray drying	Pulmonary drug concentration in rats after administrating the complex microspheres were maintained on a therapeutic level for at least 24 days	[60]
Rifampicin and Rifabutin	Chitosan	Microsphere by ionic gelation method followed by spray drying	*In-vitro* Lung disposition studies were done using Andersons cascade impactor followed by *in-vitro* uptake study in U937 human macrophages cell line	[61]
Rifapentine and Linezolid	PLGA	Microsphere by o/w emulsion solvent evaporation method	*In vitro* drug release and bronchial mucosal retention study were done. The drug loading of Rifapentin and linezolide was 18.51±0.26% and 8.24±0.24% respectively	[62]

(Contd..)

Table 1: *(Continued)*

Drug	Excipients	Formulation and method of preparation	Outcome of the research	Ref
Rifampicin and Isoniazide	Sodium alginate	Microsphere by Ionic gelation method followed by spray drying	*In vivo* lung deposition studies, and pharmacokinetic and bio-distribution studies were done	[63]
Pyrazinamide	DPPC, DSPE-PEG2K and leucine	Inhalable powder by spray drying	–	[63]
Rifampicin, Isoniazid and pyrazinamide	Alginate and chitosan	Microspheres by ionic gelation technique followed by spray drying	Encapsulation efficiency 65–85% with loading of 220–280 mg of drug per gram microsphere	[64]
Amikacin sulfate	Hydrogenated soybean phosphatidylcholine, cholesterol saturated soybean phosphatidylglycerol or stearylamine and lactose carrier	Inhalable Dry powder by freeze dying	Liposomal formulation. Addition of lactose carrier was crucial to enhance the flowability of liposome powder	[43]
Vaccine				
Bacillus Calmette-Guérin (BCG)	Leucine	Inhalable dry powder by spray drying and freeze drying	Bacteria in a matrix of Leucine. Spray drying superior to freeze drying due to former reduced loss of viable bacteria	[43]
Respirable protein and peptides				
D-LAK120-HP13 (antimicrobial peptide)	Mannitol	Dry powder inhalers by spray drying	Corrugated surfaces particles and 6.35. Microparticles showed satisfactory FPF of 62% without losing structural features of peptide	[51]
D-LAK120-A (antimicrobial peptide)	Mannitol	Dry powder inhalers by spray drying	Smooth surfaces particles and 7.38. Microparticles showed satisfactory FPF of 44% without losing structural features of peptide	[51]
Cutinase	Lipokel and TLR2 (ligand moiety)	Dry powder inhalers by spray drying	Pulmonary immunization with protein-lipokel complexes showed satisfactory protective responses in the lung against aerosol Mtb challenge test	[38]

NPs: Nanoparticle

following new, irregular tissue development.[46] Andrade *et al*. (2013) reviewed about nanomaterials-based drug delivery systems have emerged as a promising solution to overcoming the limitations of traditional formulations and treating drug resistance, indicating that new advances in this field are possible.[47] Swindells *et al*. (2018) studied the use of long-acting injections, which are given once a month, can improve patient compliance and treatment outcomes.[48]

Along with particle size, formulation design and inhalation device have significant function in determining the aerosol performance.[49,50] Inhaler ought to convey exact and steady portions to a focused on area in the lungs and keep up the soundness of the conveyed drugs. Dry powder inhalers (DPIs) are turning out to be increasingly well known as a result of their usability and the powder steadiness. Pressurized metered-dose inhaler are as yet confronting difficulties from the detailing and the plan perspective. Nebulizers are being renovated to expand their pertinence. Truly, there is no device that satisfies the bunch of prerequisites to convey drugs with various physicochemical properties.[50] Parumasivam *et al*. (2016) focused on the powder formulation approach, and new advances in inhalable dry powder formulations of drug and vaccine delivery for TB are highlighted, with the idea that it

may be an attractive medium for TB drug delivery.[43] Mehta *et al*. (2018) have explained, repurposing drugs is a viable choice in the treatment of PTB because it allows for faster, less expensive, and less dangerous product growth, even though the effectiveness and safety of the medication when administered through a new delivery route must still be decided.[51]

Patil *et al*. (2019) focused on various assessment criteria during process development, release specifications, and stability studies suggested by the Centre for Drug Evaluation and Research of the US Food and Drug Administration, European, US, British, and Indian pharmacopeias were summarised.[41] One of patent which is for short-course treatment was a stabilized oral powder or granule mixture having at least two different antimicrobial TB drugs such as Rifampicin, Isoniazid, Ethambutol, and Pyrazinamide, where they have mentioned the guidelines for consuming the powder can be consumed by mixing in a glass of water or juice and assures that each of the various drugs is in fact consumed by the TB patient.[52]

Tan Z.M. et al (2020), have critically reviewed the novel treatment approaches for the PTB. In which they have described the DPI, which could be the promising approache for the treatment of PTB [53]. Recently Chogale *et al*. (2021), have studied critically on triple combination "nano" DPI for TB, where they have analyzed the *in vitro* and *in vivo* pulmonary characterization. *In vitro* drug release showed that the released of formulations were sustained. *In vivo* investigations revealed a longer deposition in the lung at higher dosages than the conventional route.[66] In Table 1 authors are compiled the formulation of some antitubercular drugs, respirable protein and peptides, and vaccines along with the drug, and excipients. Using this one may get an idea about the recent research on the pulmonary route for the treatment of PTB as well as it would be easier to understand that for pulmonary infections where direct drug administration to the lungs is desirable, the inhalation mode of drug delivery is the most advantageous.

CONCLUSION

TB is deadly killer communicable disease caused due to MTB, spread when you inhale the bacteria in droplets expelled if an infected person talks or coughs. Along with the WHO, India also implementing some schemes such as RNTCP, an on-going centrally sponsored scheme, being implemented under the umbrella of the National Health Mission (NHM).[22] The NHM of India starts "Nikshay Poshan Yojana" under Extended Gram Swaraj Abhiyaan for the nutritional and financial support to TB patients.[22] Currently, available dosage form is tablets of Isoniazid, pyrazinamide, and ethambutol and capsules of Rifampicin in single as well as in combination of all in the form of FDC and its mode of administration is oral, but the dose of this anti-TB drugs are high, also due to shorter half life of drugs, the dosing frequency is more, resulting into hepato-toxicity and other side effects associated with this anti-TB drugs. One more challenge in this TB treatment takes a long time to complete, so there is a need of the alternative route of treatment as well as drug delivery approach than the conventional. With the advantages of inhalable route such as lungs having larger surface area, non-invasive, allows therapeutic agents to be targeted to the site of infection, by pass the hepatic first-pass metabolism, and drug delivery through inhalable route can also minimize the dose. Because of all these beneficial aspects of inhalable route, it would be the alternative route for the treatment of PTB. Now move towards the drug delivery approach, which is also a key element in the treatment strategy. Actually drug delivery to the lungs is particle size-dependent. Nanoparticulate and microparticulate drug delivery approach which considered as novel drug delivery system has wide surface area and small size, allowing it to interact with targets on cell surface as well as internally, and helps increasing the bioavailability of drug. So inhalable microparticulate and nanoparticulate systems could used to target pulmonary alveoli, reduce the dosing frequency and duration of drug treatment by sustaining it. In this perspective, there is a need of thinking about formulation aspects, new drug synthesis, patient compliance, and socio-economic aspects for the betterment of TB patients.

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AUTHORS' DISCLOSURE STATEMENT

Authors have no conflict of interest to disclose.

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