**ORIGINAL ARTICLE**

# Nano-based anti-tubercular drug delivery: an emerging paradigm for improved therapeutic intervention

Bushra Nabi[1] · Saleha Rehman[1] · Sumit Aggarwal[2] · Sanjula Baboota[1] · Javed Ali[1]

## Abstract
Tuberculosis (TB) classified as one of the most fatal contagious diseases is of prime concern globally. *Mycobacterium tuberculosis* is the causative agent that ingresses within the host cells. The approved conventional regimen, though the only viable option available, is unfavorably impacting the quality of life of the affected individual. Despite newer antibiotics gaining light, there is an unending demand for more therapeutic alternatives. Therefore, substantial continuous endeavors are been undertaken to come up with novel strategies to curb the disease, the stepping stone being nanotechnology. This approach is instrumental in overcoming the anomalies associated with conventional therapy owing to their intriguing attributes and leads to optimization of the therapeutic effect to a certain extent. This review focusses on the different types of nanocarrier systems that are being currently explored by the researchers for the delivery of anti-tubercular drugs, the outcomes achieved by them, and their prospects.

## Abbreviations

| | |
|---|---|
| RIF | Rifampicin |
| PZA | Pyrazinamide |
| ETH | Ethionamide |
| D-CS | D-cycloserine |
| TB | Tuberculosis |
| INH | Isoniazid |
| *Mtb* | *Mycobacterium tuberculosis* |
| MIC | Minimum inhibitory concentration |
| NP | Nanoparticle |
| NLC | Nanostructured lipid carrier |
| LP | Liposome |
| MXF | Moxifloxacin |
| PK | Pharmacokinetic |
| RFB | Rifabutin |
| SLN | Solid lipid nanoparticles |
| EMB | Ethambutol |
| BA | Bioavailability |
| PLGA | Poly (lactic-co glycolic) acid |
| CS | Chitosan |

Bushra Nabi and Saleha Rehman contributed equally to this work.

✉ Javed Ali
javedaali@yahoo.com; jali@jamiahamdard.ac.in

[1] Department of Pharmaceutics, School of Pharmaceutical Education and Research, Jamia Hamdard, Hamdard Nagar, New Delhi 110062, India

[2] Division of ECD, Indian Council of Medical Research, New Delhi, India

## Introduction

TB, being one of the most prevalent infectious and contagious disease caused by *Mycobacterium tuberculosis* (*Mtb*), has a huge global burden accounting to about 10 million new cases in 2017. According to the WHO Report 2019, around 1.6 million deaths take place due to TB. Additionally, also one-third of the world population is latently affected by it. The worst affected geography is the Asian subcontinent with India reporting the highest tally [1–6]. Owing to the limited number of approved anti-TB drugs, the emergence of multi and extensively drug-resistant strains of TB has been a problematic issue. In the case of drug-susceptible cases, the initial phase consists of 6 months of combinatorial treatment commonly called "drug cocktail" which consists of isoniazid (INH), rifampicin (RIF), ethambutol (EMB), and pyrazinamide (PZA). This is further followed by a continuation phase of 2 months comprising of INH and RIF. However,

there are drug-resistant strains that follow a different treatment regimen. The drug resistance occurs principally due to mutations occurring in drug target genes. The other causes might be attributable to the impermeability of the *Mtb* cell wall or the activity of efflux pumps. Multidrug resistance occurs when patients become resistant at least to INH or RIF. On the other hand, extensive drug resistance occurs on developing resistance to INH and RIF along with fluoroquinolones. In the case of INH resistance, the treatment regimen incorporates 6 months of RIF, EMB, PZA, and levofloxacin [7–9].

An extensive literature survey was carried out on databases such as Scopus, PubMed, ScienceDirect, and Google Scholar. Primarily research conducted on anti-tubercular nano-formulations within the duration of 2015–2019 was considered for incorporation within the manuscript. Few breakthrough review articles, however, limited in number, have also been incorporated to give the readers a clear concept.

## Nanotechnological approach for combating TB

The lungs appear as an attractive target for the therapeutic delivery of anti-TB drugs. The inhalational route of drug administration serves as the primary option for delivering dry powder inhalers or aerosols, since they provide a preferential accumulation of drugs at the target site in addition to being non-invasive and overcoming gastrointestinal drug degradation. They can thus also restrict drug exposure to healthy cells. However, they were also associated with certain loopholes such as bolus drug release culminating into severe lung toxicity, short residence time, and poor aqueous solubility [10]. The other contemporary TB treatment includes oral and parenteral dosage forms. However, they lead to sub-therapeutic levels attributable to poor drug distribution to the lungs, ultimately causing drug-resistant strains [11]. The commercially available conventional anti-TB therapy is associated with innumerable glitches such as metabolic instability, low solubility, low permeability, a large number of allied side effects especially hepatotoxicity, and high drug load [3, 12]. Moreover, the combination therapy also leads to complex dosing schedules frequently causing inadequate therapeutic effect [7]. Therefore, these drawbacks with conventional therapy led to the paradigm shift towards nanotechnology-engineered delivery systems. The nanocarrier systems have established their supremacy over conventional therapy since they have the ability to incorporate both lipophilic and hydrophilic drugs. They offer advantages such as the drastic reduction in size hence providing high surface volume ratio, the protection of drug moiety from degradation, the targeted and site-specific delivery, follow a controlled release mechanism, and could be easily functionalized to modify drug therapeutic profile. Additionally, one of the prime outlooks might be the biocompatible nature

of these systems [13, 14]. Furthermore, the lipid-based systems hold special significance, since the pathogen, i.e., *Mtb*, relies on the lipidic membrane to ingress with the host body and egress from the same [15]. Furthermore, nanoparticulate systems possess intrinsic antimycobacterial activity along with serving as a vehicle for various anti-tubercular drugs, hence being instrumental in reducing the dosing frequency along with associated side effects. Additionally, nano-formulations incorporating inorganic metals have antibacterial activity. Silver and gold nanoparticles (NPs) demonstrated promising in vitro antimycobacterial activity [16]. Moreover, targeted site-specific delivery could be obtained via inhalational NPs [6].

Nanotechnology primarily focusses on "technology transfer," whereby novel techniques are implemented on a conventional treatment regimen to boost the therapeutic process. However, establishing the toxicity and safety profile of these nano-formulations is a daunting task and needs to be investigated further [17].

Therefore, the nano-based anti-tubercular therapy system overcomes the obsolete techniques of conventional regimen and revamps the drug delivery systems, hereafter promoting the healthcare. Impetus must be laid on implementing novel prospects for restricting the boundaries for the propagation of TB.

No doubt, plethora of anti-bacterial agents is existing, which bears activity against *Mtb*; however, these synthetic antimicrobials are associated with unavoidable glitches, most prominent among them being drug resistance. Consequently, researchers have been exploiting this domain to come up with novel techniques and anti-TB leads. Hence, plant-derived alternatives suit fashion and serve as probable leads, which warrants tremendous exploration [18]. Researches have come to light of late, which explicitly establishes the prospects of herbal origin drugs when incorporated in nano-formulations.

The different categories of nano-based systems that have been researched for the treatment of TB have been undermentioned.

### Nanoparticles

NPs have gained impetus owing to their small dimension of around 100 nm. However, they comprise primarily of three layers, i.e., the outer layer, which is functionalized by either polymers or metal ions which give specific characteristics to these NPs, thus dividing them into different categories. The middle layer forms the shell of the NPs, while the inner layer is the core [19]. Thus, this section on NPs deals with their different types such as polymeric NPs or metallic NPs.

Polymeric NPs have garnered speculations attributable to their remarkable credentials such as passive deposition in the target site, biocompatibility, physicochemical stability, and modified release. Furthermore, the hydrophilic outer core

and hydrophobic inner core allow for varied drugs to be entrapped within it [20]. All these abilities explicitly justify the use of NPs in TB therapy. Therefore, NPs have been the favorite among the researchers, and abundant of them are available in the public domain. Praphakar et al. tailored RIF silver NPs on chitosan (CS)-grafted cetyl alcohol-maleic anhydride-PZA polymer for ameliorated drug efficacy. It was observed that 90% of the drug was released within a span of 12 days and the anti-bacterial activity was ameliorated by the formulation. The VERO cell line was used for the cytotoxicity analysis, while THP-1 cells were employed for cell apoptosis assay. The results established the supremacy of NPs [21]. Tenland et al. studied the effect of a novel antimycobacterial peptide, NZX, on the colonization of *Mtb*. A slow release of 7.6% was observed from the NPs in the duration of 48 h. Primary macrophages and THP-1 cells used for uptake studies unraveled the fact that primary macrophage cell lines had greater cellular uptake. There was decline in CFU values, i.e., 84% reduction in the NZX group; 88% in the NP group; and 90% in the RIF-treated group, which was taken as standard, thus establishing the effectiveness of the prepared formulation [22]. In the research carried out by Bachhav et al., RIF-loaded NPs were fabricated by conjugation with GantrezAN-119 and using ethyl cellulose as polymer. Lymph-mediated lung targeting was elucidated from the fluorescence microscopy. A 2-fold increment in the AUC/ minimum inhibitory concentration (MIC) ratio was observed for the prepared NP, whereas there is a $182.4 \pm 22.6\%$ increase in relative bioavailability (BA). Additionally, hepatotoxicity was augmented by the formulation [23]. Bhusal and colleagues developed glycan-coated magnetic NPs for the detection of acid-fast bacilli in sputum by making use of NP-based colorimetric biosensing assay. This biosensing technique might bear fruitful results through adequate implementation and facilitating the health care process. The outcome clarified that the designed system was in conformation with the established benchmark Xpert *Mtb*/RIF in terms of specificity and selectivity [24]. In the research carried out by Saifullah et al., EMB was loaded in graphene oxide–iron oxide magnetite NPs. A sustained in vitro release was observed along with potent anti-tubercular activity [25]. Rawal et al. developed RIF CS NP to be delivered as an inhalational system. The safety analysis was carried out using J774macrophage cells, whereby the % cell viability was calculated to be 75–80% at a dose of 0.125 mg/mL. The formulation also did not show any trace of toxicity [26]. In a different study envisaged by Thomas et al., they developed alginate cellulose nanocrystal hybrid NPs of RIF. A slow initial drug release of only 10–15% was observed in 2 h, which gradually increased up to 100% in 12 h on increasing the pH to 7.4. The L929 cell lines were used to perform the MTT assay, which demonstrated the % cell viability to be nearing 100% [27]. In a different study, Viswanathan and his colleagues developed mannosylated

gelatin NP of licorice. The in vitro studies revealed enhanced cellular uptake in RAW 264.7 from the formulation. Furthermore, the pharmacokinetic (PK) study of the formulation showed the existence of the optimal drug level in the body even after 24 h of drug administration. The in vivo antitubercular activity was confirmed since there was a significant decline in bacterial load in the lungs and spleen when *Mtb* H37Rv-infected mice were treated with mannosylated NP on the contrary to the untreated mice [28]. Malik and colleagues formulated poly (lactic-co glycolic) acid (PLGA) NPs by loading bivalent H1 antigen, which is a fusion of Mtb Ag85B and ESAT6 proteins. The developed NPs were internalized by THP-1 human macrophages and later used for immunizing C57BL/6J mice. There was a significant increase in the total serum IgG level when compared with H1 alone. A 2.4-fold increase in cytokine level and 1.6-fold increment in IL4 level were also observed demonstrating the efficacy of the NPs [29].

Apart from the aforementioned studies, there were uncountable researches undertaken pertaining to NP. However, few of them with outstanding outcomes have been elaborated in Table 1.

## Solid lipid nanoparticles

Solid lipid nanoparticles (SLNs) are lipidic carrier systems encompassing solid lipids and surfactants. They have garnered recognition lately by virtue of their attributes, namely, easy to scale up, inhibit drug degradation, ameliorating the pharmacological profile of the drug, desirable physical stability, and controlled or modified drug release [43]. In order to make the formulation accepted by the masses, numerous researches were undertaken. Costa and associates fashioned a conventional SLN formulation of INH and also by functionalization with mannose for contrasting evaluation. The outcome revealed that both the SLNs prepared curtailed the possibility of any toxicity on the human lung epithelial cell line (NCI-H441) and differentiated THP-1. Nevertheless, the functionalized SLN has enhanced uptake caliber in macrophagic cells and demonstrated receptor-dependent internalization [44]. Gaspar et al. developed RFB SLN using two different lipid constituents, namely, glyceryl dibehenate and glyceryl tristearate. In vitro uptake studies from THP1 cells in the macrophagic system showed $46 \pm 3\%$ for glyceryl dibehenate and $26 \pm 9\%$ for glyceryl tristearate, directing preferable proportion towards glyceryl dibehenate. The cell viability study conducted on A549 and Calu-3 cells gave evidence of low cytotoxicity nearing 20% [45]. Nemati et al., taking into consideration the astounding characteristics of SLN, developed EMB SLN as an inhalational delivery system. A549 cells were employed for the evaluation of toxicity, which depicted no significant cytotoxicity. A sustained release of 37% was reported from SLN, while the free drug has a release of 43%

**Table 1** Researches pertaining to NP and their results obtained

| Drug | Formulation type | Outcome observed | Reference |
|---|---|---|---|
| RIF | CS-coated PLGA NP | The NP boosted intracellular trafficking, and the drug concentration increased by 37% when equated with free drug | [30] |
| RIF and ascorbic acid | CS-coated alginate-tween 80 NP | The REMA method was employed for the analysis, whereby the NPs inhibited the *Mtb* in the range of 0.039 to 0.31 µg/mL, while the free drug concentration required was 0.78–1.25 µg/mL. The cell viability of the NPs was > 90% | [31] |
| Tuftsin | PLGA NP | There was a marked significant increase in the internalization of the drug within the macrophages | [32] |
| RIF | Poly(ethylene oxide) monomethyl ether-*block* poly(e-caprolactone) NP | The Froster resonance energy transfer system was applied to determine the drug release both in vitro and in living macrophages. The NPs were easily taken up by the macrophages and reach the lysosomal section. Post drug release, the NPs were enzymatically atrophied in the macrophages with the half-life of 88 ± 11 min | [33] |
| RIF | HPMA-PLGA NP | Around 90% of the drug released within the first 4 h. The hemolytic toxicity study demonstrated a 4-fold decrease from the NPs prepared, while the MIC value was found to be 0.125 ± 0.02 µg/mL, which was 4 times lower than the pure drug | [34] |
| RIF and INH | Bovine serum albumin NP | Dual-loaded NPs showed a release of 97.02% of INH in 6 days, while the complete release of RIF was observed in 5 days from the formulation | [35] |
| - | Zinc oxide NP | The inhibition of *Mtb* H37Ra strain was caused at 12.5 µg/mL. Furthermore, the cytotoxicity study on L929, 3T3-L1 revealed no toxicity with a selectivity index > 10 | [36] |
| Gatifloxacin | PLGA NP | The result exhibited that even after 60 min, the drug was available in cerebral cortex; however, the concentration declined in the lung and liver, validating the effectiveness of NP in the treatment of central nervous system TB | [37] |
| RIF and INH | Norbornene–polyethylene glycol NPs | The NP delivery approach reduced the dose required by both the drug. The MIC required to obstruct H37Rv strain was 0.05 µg/mL and 0.5 µg/mL for INH and RIF NPs respectively | [38] |
| RIF | Magnetic iron oxide NP | The NP prepared was cross-linked with polyethylene glycol hybrid CS to form the gel beads, which established its potential applicability as an anti-TB system | [39] |
| RIF | Octanoyl CS NP | A sustained release of 73.14 ± 3.17% was quantified from the NP. In vitro biocompatibility and no significant cytotoxicity was observed. | [40] |
| RIF and INH | PLGA NP | The NP prepared inhibited the colonization and growth of *Mtb* H37Rv strain at 70% of the MIC | [41] |
| 4-Thioureidoiminomethylpyridinium perchlorate | IgG-functionalized PLGA NP | The NP was instrumental in transferring the drug to the foci of the infection and led to efficient internalization. | [42] |

**Table 2** Other relevant researches with their outcomes

| Drug | Outcome attained | Reference |
|------|------------------|-----------|
| RIF | Statistical significance ($p < 0.05$) was observed in bacterial and cell cultures in the SLN when compared with free RIF. | [50] |
| RIF | The optimized formulation manifested anti-lipolytic potential and was stable in GIT media. A biphasic drug release pattern was observed. | [51] |
| RFB | Reduction in mycobacterial load was evident. Decline in growth index value for the treated animals when compared with control for liver was $0.96 \pm 0.28$ to $0.26 \pm 0.24$, for spleen $0.75 \pm 0.10$ to $0.21 \pm 0.20$, and for lung $1.95 \pm 0.16$ to $1.25 \pm 0.19$. | [45] |
| RIF | The inhalational delivery system was developed and optimized using the design of experiments. A high respirable fraction ($> 50\%$) was confirmed, which established the efficiency of the formulation. A drug payload of 20–30% was released within 3 h of the inhalation. | [52] |
| RFB | The SLN prepared was not susceptible to degradation by the gastric media, thereby protecting the drug entrapped within its core. A 5-fold increase in relative BA was observed from the SLN in comparison with free drug. | [53] |
| RIF | CS-coated SLN revealed an increase in the mucoadhesive property of the formulation coupled with enhancement in permeability in alveolar epithelial cells A549 when compared with uncoated SLN. | [54] |

[46]. Singh and associates developed INH SLN for ocular delivery. The SLN showed 1.6-fold enhanced corneal permeability in addition to 4.6-fold increase in ocular BA when compared with free drug. An overall 2.6-fold improvement in mean resident time was evident from the formulation. The MIC value was diminished by 5 folds. Ten-fold increase in uptake was attained in HCJE cells, while 10.8 fold in HCLE cells [47]. Shipli et al. fabricated RIF SLN, which was conjugated with lactoferrin. Preliminary characterization was carried out. In vitro release studies exhibited enhanced output from the unconjugated system while the in vivo biodistribution study revealed a 3.5-fold increment in BA and amplification in drug uptake from the conjugated system [48]. In the study conducted by Banerjee et al., dual drug-loaded (RIF and INH) lipid nanoparticulate system was tailored, which demonstrated sustained in vitro release pattern. The developed carrier system effectively localized within the different compartments of THP-1. The in vivo studies revealed that the relative BA from the SLN was 7.5 fold higher than the drug suspension, proving the effectiveness of the developed formulation [49].

There are certain other pertinent researches that were carried out and governed by optimistic results as shown in Table 2.

## Nanostructured lipid carriers

Nanostructured lipid carrier (NLC) is a newer generation of lipidic carrier systems that were devised to overcome the lacunas of SLN, which restricts its extensive adoption. They are the amalgamation of both solid and liquid lipids, hence possessing diminution in crystallinity and a loosely packed matrix system. This leads to the overall increase in drug entrapment capability and superior stability necessitating its further investigation [55]. Innumerable studies have been steered globally, which established its futuristic commercial applicability, nevertheless demanding exhaustive research. Carneiro et al. developed RIF NLC functionalized with a tuftsin-

modified peptide. The drug release profile showed an initial burst release followed by a controlled release. The fluorescent labeled NLC depicted improved cellular uptake, enhanced cell internalization, and a 2-fold increase in activity against *Mtb* in contract to the free drug [56]. NLC of 3 different copper complexes was fabricated by Sato and colleagues. The in vitro activity of the formulation against *Mtb* H37R$_v$ showed a value of 55.4, 27.1, and 41.1 folds along with a reduction in toxicity profile [57]. Table 3 represents certain other researches which need to be brought forward.

## Nanoemulsion

Nanoemulsion (NE), being a robust carrier, incorporates a wide range of therapeutic agents along with offering stupendous advantages such as increased drug loading and stability, improved bioavailability, and controlled release. When administered via the oral route, NEs not only enhance the solubility of the hydrophobic drugs but also prolong the GIT residence time and improve lymphatic uptake, thereby avoiding the first-pass metabolism [62].

Shah et al. took note of the qualities of NE and fabricated 1st-generation RIF NE and its subsequent functionalization with CS and CS-folate. The inhalational efficiency was greater than 75% for the decorated NE coupled with high lung content, an increase in cell internalization, and improvement in cytotoxic profile [63]. Halicki et al. designed RIF NE and conducted Resazurin Microtiter Assay to determine its antimycobacterial potential. The MIC value for the developed NE was 7.8 μg/mL, while the free drug was 1024 μg/mL. The incorporation of the drug within the lipidic framework of NE led to a decline in drug degradation, whereby improving the pharmacological drug profile [64]. Shobo and associates developed NE of pretomanid, which was to be administered intranasally. The peak concentration of the drug in the brain was estimated to be 12,062.3 ng/g, which was significantly greater than the optimal concentration required, henceforth proving the effectiveness of the prepared formulation [65].

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**Table 3**  Other outstanding studies pertaining to NLC

| Drug | Outcome deduced | Reference |
|------|----------------|-----------|
| RFB | MTT assay was carried out employing A549, Calu-3, and Raw 264.7 cells. The drug release was found to be pH-dependent. | [55] |
| Bedaquiline | The release study showed a sustained release profile. MTT and NRU analyses were carried out on different cell lines, wherein the cell viability was found to be 70%. Pegylated formulation revealed superior results. | [58] |
| RIF and INH | A comparison was drawn between the SLN and NLC of the drugs. SLN and NLC revealed 6.8- and 8-fold increases in INH protection from degradation. Effective intracellular trafficking of the drugs was observed from the lipid formulations NLC being better engulfed by the macrophage and having significantly higher distribution in the cytosol. | [59] |
| PZA | Pegylation was commenced. The drug release from conventional NLC was 84%, while pegylated NLC caused a decrease and was observed to be 61.3%. Nonetheless, the biphasic release was observed in both cases. | [60] |
| RIF | Mannosylated NLC demonstrated a decline in intracellular mycobacterium growth and an upsurge in uptake by bone marrow-derived macrophages. | [61] |

## Liposomes

Liposome (LP) delivery systems, a lipid-based vesicular system, display tremendous intrinsic potentialities viz. biocompatibility, biodegradability, could easily be tailored and engineered, and immunogenic in addition to being formulated using phospholipids. LPs are known to be engulfed by the macrophagic cells to meet their fate, hence being a probable candidate for anti-TB drugs since *Mtb* invests the macrophages. These attributes account for their versatile nature and urge for further exploration [66, 67]. Liu et al. designed thermoresponsive LP in the hydrogel system for delivering INH at the target site for bone TB. Local drug delivery systems offer stupendous advantage by maximal drug delivery at the target site and negligible systemic exposure. The in vivo studies manifested rapid drug availability in synovial fluid post-injection. Furthermore, the cytotoxicity study conducted using the MTT assay affirmed no toxicity, thus substantiating the use of the prepared formulation in bone TB [68]. Hamed and his co-workers fabricated spray-dried nano-LPs incorporated in microparticles of MXF for improved lung deposition of the drug. The surface was modified using 4-aminophenyl-alphaD–manno-pyranoside, which facilitated improved drug uptake by alveolar macrophages. The biphasic drug release mechanism was observed from the formulation coupled with improved MIC values [69]. In the study carried out by Viswanathan et al., inhalational LPs were prepared from

*Glycyrrhiza glabra*, which contains licorice in it. The in vivo lung deposition studies in mice revealed that 46% of the drug directed reaches the lungs, while 16% still persists there post 24-h duration. The study also established the decline in bacterial count and growth in the lungs and spleen of TB infected Balb/c mice. No toxicity was evident even on administering 20 times the normal dose, thus paving the way for its use as an effective anti-TB drug [70]. Table 4 puts forth a few additional commendable researches and their remarkable outcomes.

## Micelles

Micelles have principally been explored for hydrophobic drugs attributable to their amphiphilic nature [75]. Tripodo et al. tailored micelles of RIF based on inulin modified with vitamin E. The MIC values obtained post formulation administration showed superior activity against bacterial strains as compared with free drug. Cytocompatibility on human alveolar macrophages demonstrated a higher value of more than 60% [76]. Prabhakar and his colleagues constructed polymeric micelles loaded with RIF and INH. After a duration of 12 days, the % drug release of INH and RIF was found to be 89.21% and 79.37% respectively at pH 5.5. LRP assay was performed to determine the anti-TB activity which depicted the inhibition of *Mtb* H37Rv by the formulation. They also assessed the cell viability against L929 and U937 cells by

**Table 4**  Other liposomal researches were undertaken as under mentioned

| Formulation | Drug | Outcome observed | Reference |
|-------------|------|-----------------|-----------|
| Theranostic LP, folate-receptor-targeted | RIF and ofloxacin | The PK data obtained confirmed slow biphasic release. Maximum drug localization was evident in the spleen, kidney, and liver, while specific targeting and high uptake in infection lesion were observed in the murine model of TB. | [71] |
| pH-dependent LP | INH | pH-dependent drug release was evident in pH 7.4, 6.4, 5.4, and 4.4 media with 100% release in pH 4.4. | [72] |
| Soybean lecithin LP | INH | The research remarkably represents the worth of naturally occurring polysaccharides in promoting pulmonary and macrophage-targeted delivery of anti-TB drugs. | [73] |
| DDA/TDB LP | Fusion peptide of HspX, PPE44, and EsxV | The effect of BCG vaccine was elevated by the use of the formulation, and it provided a synergistic effect. | [74] |

**Table 5**  Researches that were undertaken on micellar formulations

| Formulation | Drug | Result obtained | Reference |
|---|---|---|---|
| Anti-oxidant linked amphiphilic polymeric nano-micelles | RIF and ferulic acid | The in vitro drug release verified that there was an increase in drug release from pH 5.3 to pH 7.4. Fluorescence study on A549cell lines showed the successful penetration of micelles. | [75] |
| Core-shell micelles of pluronics | RIF and INH | The micelles boosted the anti-bacterial ability in addition to enhanced drug permeability when equated with free drug. | [79] |

MTT assay. Fluorescence microscopy corroborated cell deformation. Furthermore, the in vivo localization study in zebrafish and hemolysis assay conformed to the standards and revealed its potential to enhance the therapeutic and pharmacological aspects of the drug [77]. The RIF-loaded pulmonary nano-based micellar system was developed by Grotz et al. The in vitro aerodynamic study revealed the suitability in alveolar delivery. The in vitro bactericidal activity was increased up to 2.5 folds in Mtb-infected THP-1 macrophages when compared with RIF solution [78].

Other promising researches have been mentioned in Table 5.

## Certain other prominent researches undertaken

In addition to the nano-formulations described above, the area has been laden with surplus other nanocarriers, which are yet to be investigated to their fullest or are underexploited.

However, few potential researches carried out globally have been undermentioned in Table 6.

Based on the results obtained from the researches carried out, it could rightly be said that the nano-based tubercular systems could revitalize the drug delivery process and improve the therapeutic profiling of the drugs.

## Future perspective

Since TB is a condition affecting people globally with a soaring morbidity and mortality index, there is an upsurge in the researches to deduce novel approaches for combating the disease. Focus ought to be laid on the development of newer antimicrobial peptides for therapeutic intervention and to overcome the lacunas of the conventional commercially available therapies [90, 91]. Photodynamic therapies could also be employed in drug-resistant cases, since they yield reactive oxygen species [92]. Gastric resistant systems and drug depot formulations

**Table 6**  Recent potential researches

| Nano-formulation type | Drug | Study outcome | Reference |
|---|---|---|---|
| Self-nano-emulsifying drug delivery system | Capmul MCM and labrasol (excipients with intrinsic anti-TB activity) | The optimized formulation showed a MIC of $15.0 \pm 0.4$ mg/mL, and fluorescence intensity was 88.7%, while 53% from the dye solution. | [80] |
| Lipopolysaccharide polyelectrolyte complex | RIF | The result of ex vivo permeability studies demonstrated that the formulation significantly enhanced the permeability by 2 folds when compared with free drug | [81] |
| Halloysite nanotubes | INH | The drug-loaded formulation exhibited superior in vitro biocompatibility towards Caco-2 cells in comparison with free drug. | [82] |
| Nanocage | Zinc oxide | The study measured the MIC as 12.5 mg/mL, thereby establishing the potential of developed nanocage in overcoming TB. | [83] |
| Nanocomposites | RIF and PZA | The prepared formulations displayed sustained release of 79% and 82% for RIF and PZA, respectively, along with depicting the improved antimycobacterial activity. | [84] |
| Nano-lipomer | RIF | The lipomer developed demonstrated rapid dissolution profile owing to its initial burst release. | [85] |
| Lipomer | RIF | The study elucidated higher Peyer's patch uptake by the formulation followed by significantly greater lung:plasma concentration ratio. | [86] |
| Nanosphere | RIF | The aerosol formulation developed exhibited a significant delay in drug release by adapting to the sustained release mechanism. | [87] |
| Niosomes | ETH and D-cycloserine | The formulation was optimized using BBD, which depicted superior bacterial inhibition property when compared with free drug. | [88] |
| Vesicles | Artemisone, clofazimine, and decoquinate | Among the varied formulations prepared by Zyl et al., niosomes exhibited maximum percentage inhibition of 52% against Mtb H37Rv laboratory strain. | [89] |

would give a radical solution to some of the relevant issues pertaining to the therapy [93]. Newer functionalization and surface modification techniques to suit the purpose should be repeatedly tried to pave the way for the development of newer products. It could also be rightly stated that herbal origin derivatives could be instrumental in delivering a holistic formulation with minimal side effects, though necessitating in-depth research. Additionally, it could be formulated in conjugation with synthetic drugs proposing a synergistic relation, thus positioning them as a strong competitor in future researches. A major breakthrough in anti-TB dosage regimen will be nanocarrier-based depot formulation. This will be instrumental in improving patient compliance by reducing the dosing frequency and minimizing the side effects [93]. Furthermore, TB-associated diseases also cause a concern, e.g., in TB-associated HIV. Hence, integrating nanotechnology to develop combination preparation to treat both the conditions would bear fruitful results. Moreover, till date, not much has been explored in the arena of vaccine development. Therefore, nanotechnology-based TB vaccine, if developed in the future, will prove to be a breakthrough in the field of drug discovery [6]. Additionally, ligand targeting is one arena that needs to be exploited completely such as mycolic acid like targeting ligands [94]. Repurposing of established drugs can be employed for establishing a newer treatment regimen. For example, fluoroquinolones and clofazimine all were repurposed drugs. There are multiple drugs in clinical trials for MDR-TB. However, to overcome this epidemic, improvement in the management of susceptible TB needs to be taken care of [95].

## Conclusion

The review anticipates the use of nanotechnology as a boon for the delivery of anti-tubercular drugs. A plethora of drugs, which is associated with issues hindering their pharmacological profiles, could be incorporated within these nanocarrier systems, henceforth leveraging an increase in therapeutic effectiveness. Although the state of the art for these systems warrants to be exploited to its fullest to make these systems come to reality and hit the markets for commercial applicability.

### Compliance with ethical standards

**Conflict of interest** The authors declare that they have no conflict of interest.

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