REVIEW ARTICLE

Nanocarriers for Multidrug Resistant Tuberculosis (MDR TB) Therapy: A State-of-the-Art Review

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Abstract

Background: Multidrug Resistant tuberculosis is a significant global health problem because of low drug efficacy, low bioavailability and high side effect of the traditional therapy. Nanocarrier mediated drug delivery systems have been reported to an effective approach for improving therapeutic effects by enhancing the solubility of drugs, targeted delivery and minimizing systemic toxicity.

Objective: This review provides a current overview of recent developments in nanocarriers for MDR TB treatment, emphasizing their ability to bypass drug resistance mechanisms, improve pharmacokinetics & increase patient compliance.

Methodology: An extensive literature search was made via PubMed, Scopus and Web of Science, on studies (2010–2025) on polymeric nanoparticles, lipid carriers, inorganic nanoparticles, and hybrid systems for the treatment of MDR-TB. Critical parameters like drug loading efficiency, release rate, in vitro/in vivo efficacy, and toxicity profiles were evaluated.

Results: Nanocarriers like liposomes, solid lipid nanoparticles, polymeric micelles and mesoporous silica nanoparticles have enhanced drug stability, controlled release and better targeting towards infected macrophages. Ligand conjugated nanocarriers enhance cellular uptake and minimize off targeting. Preclinical evidence indicates dramatic reductions in bacterial load and treatment duration when compared to free drugs. Some issues still remain regarding scalability, regulatory clearance, and long-term safety.

Conclusion: Nanocarrier derived delivery systems have immense potential to transform the management of MDR TB by overcoming pharmacokinetic barriers and resistance mechanisms. Areas to target in the future should be clinical translation, combination therapy, and smart stimulus responsive systems for efficient TB management.

Keywords: MDR-TB, Nanocarriers, Targeted drug delivery, Liposomes, Polymeric nanoparticles, Drug resistance.
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Introduction

TB is caused by the bacterium Mycobacterium tuberculosis, which is still among the top ten causes of death worldwide and which over ranks even HIV/AIDS as the leading cause of death from a single infectious agent. It is basically a lung disease that can sometimes affect other body systems, wherein it becomes extrapulmonary TB. The World Health Organization estimates that, about 10 million people fall sick with TB each year and about 1.5 million deaths were recorded. In spite of effective treatments for the drug susceptible TB, the development and rapid spread of the multidrug resistant tuberculosis have made the control efforts grossly complicated. MDR TB refers to TB resulting from the strains of Mtb which are found to be resistant to Isoniazid and Rifampicin, the two strongest first line anti TB drugs. It is mostly caused by wrong or lack of treatment, non-compliance to therapy and lack of healthcare facilities. The MDR-TB occurs in about 450,000 people annually in the world and its management imposes many clinical, economic and logistical challenges. MDR TB is then more aggravated by the rise of the extensively drug-resistant TB (XDR-TB) that is characterized by resistance to the second line agents such as fluoroquinolones and injection agents. These types of TB are hard to cure, necessitating longer treatment, more harmful, and less effective regimes, frequently with poor treatment results. Success rate of MDR TB treatment is around 50-60 %, it is significantly lower compared to 85-90% for drug sensitive TB. Combating MDR TB involves novel approaches in the effectiveness of treatment, minimization of toxicity, and increased patients' compliance, and requires advanced drug delivery, e.g. nanocarriers [1]. Early and correct prognosis of TB is a cornerstone of powerful disorder manage. Diagnostic delays now not handiest make scientific control greater complicated in patients however additionally location them susceptible to population transmission. studies have validated in investigations that each untreated patient of TB infects about 10 to 15 individuals in keeping with yr and reinitiating the cycle of contamination. besides, postpone in analysis also reasons past due development of the disorder, ensuing in higher mortality and healthcare prices. behind schedule prognosis in drug-resistant TB can accelerate resistance patterns, making remedy greater difficult and at higher cost. accurate prognosis is likewise essential to offer suitable remedy without time wastage [2].

Challenges in Conventional MDR-TB Therapy

Typically, MDR-TB treatment regimen is the standard therapy of multiple second line anti-TB drugs for a long duration of time ranging between 18-24 months and longer. Such a long and complicated treatment leads to a number of difficulties. First of all, the drugs administered in MDR-TB regimens are harmful in terms of high adverse effects such as ototoxicity, nephrotoxicity, hepatotoxicity, and gastrointestinal disturbances. Such side effects lead to poor adherence, interruptions of the treatment, and enhancement of the risk of treatment failure or additional resistance development. Second, as for many of the second-line drugs, there are suboptimal pharmacokinetic properties such as poor solubility, low bioavailability, and limited ability to penetrate the tissue [3]. Consequently, attaining levels of therapeutic drugs at the infection site, particularly intracellular and granulomatous situations, becomes difficult. Mtb can be found in macrophages and in the form of granulomas, the structures that prevent the drug from penetrating deep into the site and which maintain the hypoxic and acidic microenvironment, which also reduces the effectiveness of the drug. Thirdly, the pill burden and the necessity of daily dosing exacerbate the patient's fatigue and non-compliance. In the resource-limited settings, these challenges are made worse by the poor or intermittent access to the healthcare facilities, poor drug stocks, lack of monitoring and socio-economic challenges. High rates of defaulting treatment lead to continuous transmission and development of drug-resistant strains. Further, the pipeline of the new anti-TB drugs is in a slow and underfunded mode, thus call for new methods that can enhance the efficacy of the existing drugs. The same goes for traditional delivery mechanisms that are not able to protect drugs from premature degradation or maintain its sustained release, thereby reducing its general therapeutic potential. These constraints highlight a pressing need to develop advanced drug delivery platforms that also dismiss biological barriers and efficiently direct drugs as well as impart therapeutic effects in the treatment of MDR-TB [4].

Role of Nanotechnology in Drug Delivery

It provides the perfect solution to majority of the predicaments with the conventional management of MDR-TB. The engineered traditional materials, the nanocarriers in the range of 1 -1000 nanometers, are applied for encapsulation activities, preservation from destruction, targeted and advantageous release. Some carriers are as follows; liposomes, polymeric nanoparticles, dendrimers, solid lipid nanoparticles, metallic nanoparticles and nanomicelles etc. Due to their peculiar physicochemical form, the nanocarriers are able to change the nature of pharmacokinetics and pharmacodynamics of the anti-tubercular drugs. The highest benefit of using the nanocarriers is the enhancement of drug solubility and bioavailability [5]. With the resource of growing novel drug shipping architectures that allow molecular level infection manipulation, nanotechnology has extensively extra suitable the treatments field. it's far a ways viable to enhance treatment efficacy even as lowering dangerous remedy reactions and manipulate frequency with the useful resource of utilizing nanotechnology for focused remedy. ultimately, this technique effects in expanded adherence fees and higher affected character compliance. in addition to liposomes, polymeric nanoparticles, nanocrystals, nano suspensions, nano gels, dendrimers, and niosomes, nanocarriers are vital for the centered transport of TB medication [6]. Poorly soluble drugs such as rifampicin and isoniazid, which pose a low dissolution and systemic absorption, can be successfully encapsulated in nanocarriers and hence optimized in dissolution and absorption. In addition, nanocarriers are able to pass through biological barriers and reach the site of the infection with delivering drugs. For example, surface functionalisation of nanocarriers with targeting ligands, including mannose or folate, enables selective uptake of Alveolar macrophages, the major host cells of Mtb [7]. This specific delivery leads to greater intracellular concentrations of the drug and a lower level of systemic toxicity. One of the main features of the nanocarrier systems is controlled and sustained drug release. Nanocarrier formulations are capable of providing therapeutic drug levels for long periods of time through slow release mechanisms. This makes the dosage less frequent, increases compliance of patients, and limits the development of resistance in case of the missed doses [8]. Engineering nanocarriers to respond to a specific stimulus such as pH, temperature or enzymatic activity helps guarantee that the release only occurs in a spot where the infection occurs within the affected cells or tissues. Moreover, nanocarriers provide the possibility of co-delivery of several drugs, which is especially useful for the regimes of MDR-TB treatment, which include combination therapy [9]. Through packaging different drugs on a single nanocarrier, synergistic effects are possible and drug interactions more well regulated. Treatment regimens are also made easier when using this approach as pill burden is reduced and adherence enhanced [10].

Mechanisms Of Multidrug Resistance In Tb

MDR-TB is one of the pressing global health issues that is based on resistance to at least two front line anti-TB drugs, INH and RIF. The development of MDR-TB is a result of genetic mutations in Mycobacterium tuberculosis, as well as sub-optimal treatment adherence and poor drug delivery and poor concentration over a prolonged period [11]. Knowledge of the mechanisms of drug resistance is important in the formulation of effective therapeutic strategy including sophisticated nanocarrier the based drug delivery systems [12].

Genetic Mutations and Resistance Mechanisms

Developement of multidrug-resistant form of tuberculosis is primarily due to spontaneous chromosomal mutation in Mycobacterium tuberculosis that alters the drug targets or

drug-activating enzymes. These are the genetic changes that aid survival of bacteria against the stresses during therapy leading to treatment failure [13]. This is among the best described resistance mechanisms involving isoniazid, a first-line drug for TB requiring activation by bacterial catalase peroxidase enzyme KathG. Mutations related to the katG gene, particularly 315 S substitution, significantly impair isoniazid activation, while inhA promoter region mutations lead to its overexpression of the drug target enoyl ACP reductase that adds to resistance. Similarly, resistance to rifampicin results primarily from rpoB gene mutations that code for RNA polymerase β subunit. Mutations such as S531L, H526Y, and D516V alter the architecture of the drug binding pocket in proteins rendering rifampicin effectively inhibitory [14]. Resistance to pyrazinamide is the usual linked to mutations within pncA, where the gene encoding for pyrazinamidase, a critical enzyme required for the activation of pyrazinamide to the active form pyrazinoic acid [9]. Ethambutol resistance is also usually due to mutations in the embB gene, particularly the M306V substitution, which disrupts arabinosyl transferases that play a role in cell wall biosynthesis. Apart from first line drugs, resistance to second line drugs complicates the MDR TB treatment further [15]. The fluoroquinolones (levofloxacin, moxifloxacin) act on DNA gyrase but mutations in gyrA, gyrB decrease their affinity. Aminoglycoside resistance is often due to overexpression of the eis promoter whereas alterations in rplC and rrl are related to linezolid resistance. Also, the non-genetic mechanism of survival for Mycobacterium tuberculosis involves biofilm formation and intracellular persistence in macrophages that result in phenotypic resistance. Such intricate resistance mechanisms indicate the challenges in stabilizing effective MDR TB therapy and the need to discover new means of treatment that will be able to bypass such adaptive pathways [16].

Limitations of Current Treatment Regimens

However, the current standard of MDR-TB care is overwhelmed with difficulties, which hamper successful patient outcomes. Treatment regimens will usually extend for between 18 months and 24 months and will consist of a complex conglomeration of second-line drugs, including injectable aminoglycosides, fluoroquinolones and oral bacteriostatic agents such as linezolid and clofazimine. The long duration and heavy pill load lead to poor patient adherence, thereby increasing the risk of treatment failure, relapse as well as development of the extensively drug-resistant strains (XDR) [17]. Over time, coating technology have developed from conventional sugar coatings to extra state of the art tactics, together with movie and enteric coatings, designed to regulate drug release and beautify patient compliance. Coating serves various features, which includes shielding the lively pharmaceutical factor (API) from environmental elements, masking ugly tastes or odors, and ensuring targeted drug delivery to particular regions of the gastrointestinal tract (GIT) [18]. Worsening the case are the high negative effects that come along with second-line cures. Aminoglycosides are associated with irreversible ototoxicity and nephrotoxicity quite often, while bedaquiline and clofazimine are known to cause QT prolongation and cardiac arrhythmias. Moreover, linezolid and ethionamide tend to trigger peripheral neuropathy and hepato toxicity is frequently of concern with pyrazinamide and isoniazid. These toxicities often call for the reduction or completion. The situation further adds to the growing resistance [19]. Controlled drug shipping technology is one of the maximum hastily advancing fields, addressing the limitations of traditional dosage bureaucracy whilst improving critical elements which include centered drug transport to specific organ softissues and regulating the rate of drug launch at the target site.developing an oral controlled launch system poses giant formulation challenges because of its problem in keeping localization within particular regions of the gastro intestinal tune [20]. Another glaring limitation is the low bioavailability and low penetration of drugs into mycobacterial sanctuaries. A lot of anti-TB drugs are characterized by low solubility and low permeability, thereby resulting in sub-therapeutic levels at the site of infection. That Mtb is able to live in phagocytes and granulomas is what forms these protective niches where diffusion of drugs is difficult at its core. Furthermore, the thick cell wall of the bacterium is rich in lipid, and it forms a stringent barrier against permeability, decreasing intracellular drug accumulation [21]. There are further difficulties because of drug-drug interactions, especially with regards to the MDR-TB patients with HIV co-infection. For example, rifampicin induces CYP3A4 metabolism that can impair the antiretroviral therapy (ART). Lastly, the unaffordability of newer TB drugs such as bedaquiline and delamanid and the lack of rapid diagnostic tools prolongs the treatment initiation and sustains the global MDR-TB crisis. These common challenges highlight the much needed necessity for improved, tolerable and readily available interventions strategies to counter this growing threat to public health [22].

Nanocarriers: Types And Characteristics

Nanocarriers have disrupted the treatment scene for multidrug-resistant tuberculosis (MDR-TB) by overcoming some fundamental pharmacological issues of traditional anti-TB drugs. These advanced delivery systems which usually measure between 10-1000 nm can offer many benefits which include improved solubility of drugs, increased bioavailability of drugs, reduced systemic toxicity and focusing on delivery of drugs to those infected macrophages where Mycobacterium tuberculosis is mostly found [23]. There are lots of various nanocarrier as given in fig.no.01 with the encapsulation of therapeutic agents in protective nanostructure, nanocarriers prevent premature drug degradation, prolong the circulation time and enable drugs to converge at sites of infection through passive drug targeting, as well as, active drug delivery [24]. Polymers play a important role in drug shipping structures with the aid of

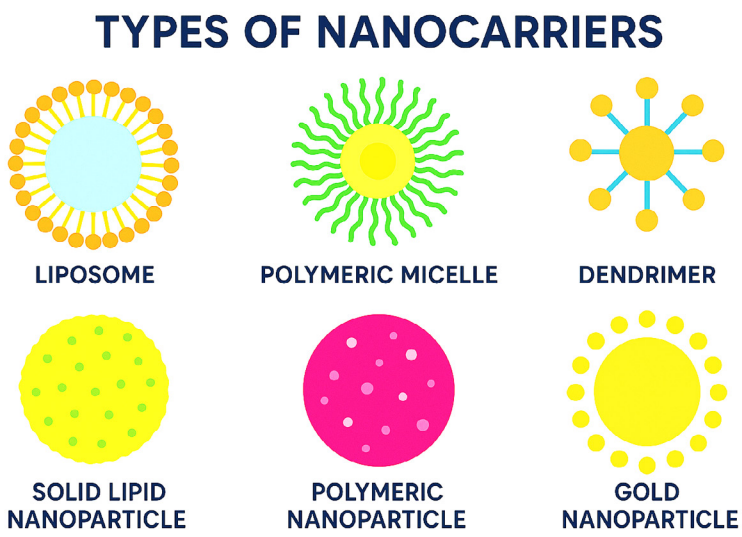

Figure 1: Types of Nanocarriers

improving the effectiveness, safety, and concentrated on of healing sellers. Their particular homes permit for managed and sustained release of drugs, enhancing bioavailability, lowering side outcomes, and growing patient compliance [25]. The adaptability of the nanocarrier systems provides co-delivery of various drugs, which is very beneficial for defeating the MDR-TB strains that are resistant to certain drugs. There are many kinds of nanocarriers that have been widely studied for TB therapy, each having different physicochemical characteristics, drug loading capacities, and release patterns which can be adjusted for optimization of treatment efficacy at the expense of minimum side effects [26]. Lipid nanocarriers represent sizable advancement in trans dermal delivery. stable lipid nanoparticles (SLNs) offer enhanced drug balance and managed release houses even as improving skin penetration [27]. Nano established lipid vendors (NLCs) conquer sure limitations of SLNs through incorporating liquid lipids, presenting multiplied drug loading potential and stepped forward pores and skin permeation. Transfersomes and ethosomes, characterized by using their deformability, facilitate superior drug penetration through limited skin channels [28].

Liposomes

Liposomes are one of the longest standing and most studied nanocarriers for MDR-TB treatment. These spherical vesicles composed of one or more shell of lipid bilayers with an aqueous core inside can entrap hydrophilic drugs in the internal aqueous core, and hydrophobic drugs in the lipid bilayer system [29]. Due to their biocompatibility and biodegradability as well as their structural resemblance to biological membranes, liposomes provide an efficient cellular uptake and intracellular drug release [30]. For TB therapy, liposomes have the special benefit of the passive targeting of macrophages by the enhanced permeability and retention effect and active targeting upon decoration with macrophage targeting ligands, mannose, folate and tuftsin. Many preclinical studies have shown the higher efficacy of liposomal formulation over free drug delivery [31]. Liposomal formulations of the first-line anti-TB drugs such as rifampicin, isoniazid, and pyrazinamide have demonstrated markedly better pharmacokinetic (PK) profiles, particularly lung tissue and alveolar macrophages, the main site of Mtb infection. In addition, it has been shown that liposomal formulations cause significant decrease in drug-induced hepatotoxicity and other systemic side effects, which are the primary drawbacks of existing TB treatment regimens [32]. By conjugating with polyethylene glycol to the surfaces of polymeric micelles liposomes, liposomes modified with PEG have been developed that further enhanced their therapeutic potential by prolonging systemic circulation time and reducing recognition and clearance by the reticuloendothelial system. These long-circulating liposomes exhibit improved biodistribution and can achieve higher drug concentrations at infection sites with less frequent dosing, potentially addressing compliance issues that plague current MDR-TB treatment protocols [33].

Recent technological improvements in liposome technology have also made it possible to formulate multifunctional formulations that are both drug carriers and diagnostic tools. For example, theranostic liposomes with both anti-TB medication and contrast agents enable concurrent treatment and tracking of disease advancement [34]. Also being developed is stimulus-responsive liposomes that deliver their load in response to particular stimuli within the TB microenvironment. To provide more specific, on-demand drug delivery, the latter are under investigation. Although liposomal formulations hold immense promise, issues pertaining to large-scale production, stability over prolonged periods, and sterilization techniques must be overcome to allow them to scale up clinically and become broadly used in MDR-TB therapeutic programs [35].

Polymeric Nanoparticles

Polymeric nanoparticles have also been identified to be another highly promising category of nanocarriers for MDR-TB treatment with the clear advantages of controlled release of drugs, shielding of therapeutic agents, and site-specific targeting [36]. Polymeric nanoparticles are generally made up of biocompatible and biodegradable polymers, chitosan, alginate, which can be designed to deliver desired release patterns of the drug from days to weeks. The advantage of polymeric nanoparticles is that they can encapsulate a broad range of anti-TB drugs, hydrophobic as well as hydrophilic drugs, without degrading them in the extreme biological environment [37].

PLGA nanoparticles have received particular attention for TB therapy due to their FDA approved status that excellent safety profile and well characterized degradation kinetics. These nanoparticles degrade through hydrolysis of their ester linkages, releasing encapsulated drugs in a sustained manner that can be precisely controlled by the adjusting the polymer molecular weight and lactide to glycolide ratio [38]. Studie have demonstrated that PLGA nanoparticles loaded with anti TB drugs like as rifampicin, moxifloxacin or bedaquiline exhibit significant enhance intracellular accumulation in macrophages compared to free drugs, leading to improved bactericidal activity against both drug sensitive and resistant Mtb strains [39]. The sustained release characteristic of polymeric nanoparticles are especially valuable for the TB treatment as they can maintain therapeutic drug concentrations for extended periods, potentially reducing dosing frequency from the daily to weekly or even monthly administration [23].

Surface modification of polymeric nanoparticles with targeting ligands has further enhanced their therapeutic potential for MDR TB treatment. Conjugation of macrophage specific molecules like mannose, tuftsin or antibodies against macrophage surface receptors enables active targeting to infected cells increase drug concentrations at the site of infection while minimizing exposure to healthy tissues [40]. Additionally the development of "smart" polymeric nanoparticles that respond to specific stimuli in the TB granuloma microenvironment allows for triggered drug release precisely where needed. Recent innovations include the design of dual-drug loaded nanoparticles that combine first- and second-line anti-TB agents in optimal ratios to combat drug resistance, as well as nanoparticles incorporating resistance-modifying agents to potentiate the effects of conventional antibiotics [41]. Despite their considerable promise with polymeric nanoparticles face several challenges that must be addressed before clinical implementation. These include optimizing drug loading efficiency, ensuring batch to batch reproducibility during scale up production and addressing potential polymer related inflammatory responses with chronic use [42]. Furthermore, the cost of good manufacturing practice grade biodegradable polymers may present economic challenges for widespread use in resource limited settings where TB is most prevalent. Ongoing research is focused on developing cost effective natural polymers and simplifying fabrication processes to overcome these barriers and bring polymeric nanoparticles based TB therapies closer to clinical reality [43].

Solid Lipid Nanoparticles (SLNs)

Solid lipid nanoparticles represent an innovative in class of nanocarriers that combine the advantages of polymeric nanoparticles and liposomes while overcoming some of their limitations. Composed of solid lipid matrix stabilized by surfactants where SLNs offers superior stability compared to liposomes and reduced toxicity relative to polymeric system. The solid lipid core that typically made from the physiologically tolerated lipids like glyceryl monostearate, stearic acid, or cetyl palmitate the remain solid at body temperature, preventing premature drug leakage while allowing controlled release. This unique structure makes SLNs particularly suitable for delivering both hydrophobic anti-TB drugs and hydrophilic compounds through various loading strategies including homogeneous dispersion, drug-lipid conjugate formation or nanostructured lipid matrices [44].

The macrophage targeting capability of SLNs is one of their most valuable features for TB therapy. Due to their lipidic nature and optimal size range where SLNs are readily recognized and internalized by alveolar macrophages through phagocytic pathways. This natural tropism for macrophages, the primary host cells for Mtb, enables targeted drug delivery without requiring complex surface modifications. Studies have demonstrated that SLN formulations of rifampicin achieve 5 to 8 time higher intracellular concentrations in macrophages compared to free drug, with corresponding improvements in bactericidal activity against both drug-sensitive and resistant strains. The sustained release properties of SLNs (ranging from several days to weeks) could potentially reduce dosing frequency in MDR-TB regimens, addressing one of the major compliance challenges in current treatment protocols [45].

Manufacturing advantages further enhance the translational potential of SLNs for TB therapy. Unlike liposomes that require specialized handling to the maintain structural integrity where SLNs demonstrate excellent physical and chemical stability during storage. They can produced using scalable techniques like high pressure homogenization or microemulsion methods that are amenable to industrial-scale production. Recent advances have led to the development of freeze dried SLN formulations that maintain stability under tropical climate conditions a critical factor for TB-endemic regions. However, challenges remain regarding drug loading capacity (particularly for highly hydrophobic drugs) and potential lipid polymorphism during storage that might affect release characteristics. Ongoing research is exploring hybrid approaches combining SLNs with other nanocarrier technologies to create next-generation systems with enhanced performance for MDR-TB treatment [46].

Nanostructured Lipid Carriers (NLCs)

Nanostructured lipid carriers represent advanced evolution of SLN technology that designed to address the drug loading and stability limitations of traditional solid lipid nanoparticles. By incorporating a mixture of solid and liquid lipids, NLCs create a less ordered, more imperfect crystalline matrix that provides higher drug loading capacity and minimizes the drug expulsion during storage. The liquid lipid component forms nano compartments within the solid matrix that can accommodate drug molecules, while the overall structure remain solid at the body temperature. This innovative architecture makes NLCs particularly effective for delivering challenging anti-TB compounds as bedaquiline, delamanid and clofazimine that have poor aqueous solubility and tend to crystallize in conventional formulations. For MDR-TB therapy, NLCs offer several distinct advantages over first-generation lipid nanoparticles. Their enhanced drug loading capacity (typically 2-5 times higher than SLNs for lipophilic drugs) allows for more compact dosage forms, which is particularly important for combination therapy requiring multiple drugs. The imperfect crystalline structure not only improves drug incorporation but also creates multiple release pathways, enabling tailored release profiles from burst release to sustained delivery over weeks. Importantly, NLCs have demonstrated superior ability to overcome bacterial efflux pumps - a key resistance mechanism in MDR-TB - by bypassing microbial drug efflux systems through lipid fusion mechanisms [47].

Recent preclinical studies highlight the potential of NLC in TB treatment. NLC formulations co-encapsulating rifampicin and isoniazid has shown synergistic effects against MDR-TB strains, with lung drug concentrations 10 to15 times higher than oral administration of free drugs. The incorporation of absorption enhancers like sodium taurocholate in NLC formulations has further improved pulmonary bioavailability through both inhalation and oral routes. Moreover, surface modified NLCs demonstrate selective targeting to infected macrophages, reducing systemic exposure and associated toxicities. While NLC technology shows tremendous promise, challenges related to long term stability of certain liquid lipid components and scale-up manufacturing need to be addressed. Current research is focusing on developing temperature stable NLC formulations and optimizing lyophilization processes to enhance their suitability for global TB treatment programs [48].

Dendrimers

It represents a unique class of synthetic nanocarrier with highly branched with monodisperse and precisely controllable architectures that offer unprecedented opportunities for MDR TB treatment. These tree like macromolecule are built from a central core with successive layers of branching units that creating a globular structure with numerous surface functional groups available for drug conjugation or encapsulation. Poly like amidoamine and dendrimers have been most extensively studied for TB applications due to their well defined synthesis where water solubility and ability to penetrate biological barriers including the mycobacterial cell wall and biofilms. The multivalent surface of dendrimer enable simultaneous the conjugation of multiple anti-TB drugs along with targeting ligands, creating combinatorial therapeutic systems in a single nanostructure. For instance, a single generations that can carry 16-32 drug molecules through covalent conjugation or ionic interactions, plus several targeting moieties like mannose or antibodies for macrophage specific delivery. This high payload capacity is particularly valuable for MDR-TB therapy where drug combinations are essential. Dendrimer drug conjugates have demonstrated the ability to reduce minimum inhibitory concentrations by 10 to 100 fold against resistant strains that likely due to enhanced cellular uptake and avoidance of efflux pumps [49].

Recent advances in the dendrimer technology have addressed earlier concerns about potential toxicity. Strategie that like surface modification with PEG, acetylation of terminal amines, or use of biocompatible cores have significantly reduced cytotoxicity while maintaining therapeutic efficacy. Innovative "self-assembling" dendrimer nanocarriers that respond to TB-specific stimuli show particular promise for targeted drug release. However, challenges remain in large-scale synthesis with perfect monodispersity and comprehensive long-term toxicity evaluation. Current research is exploring hybrid dendrimer systems combined with other nanocarriers (like liposomes or SLNs) to create next-generation delivery platforms for MDR-TB therapy [50].

Metallic Nanoparticles

Metallic nanoparticles offers the unique dual function approach to MDR-TB therapy by combining intrinsic antimicrobial propertie with the drug delivery capabilities. Gold, iron and silver oxide nanoparticles have been most extensive investigated where each offering distinct advantages for TB treatment. Silver nanoparticle exhibit potent direct antimycobacterial activity through multiple mechanisms including cell wall disruption, oxidative stress induction & interference with bacterial electron transport systems. Studies have shown silver nanoparticle alone can inhibit MDR TB strain at concentrations significant below cytotoxic level for mammalian cell and their combination with the conventional anti TB drugs often show synergistic effect [51]. Gold nanoparticles serve as the excellent platforms for targeted drug delivery due to their ease of surface functionalization, biocompatibility, and unique optical properties. Anti-TB drugs can be conjugated to AuNPs through various linker, creating stable complexes with controlled release profile. The surface plasmon resonance properties of AuNPs enable additional the therapeutic modalities like photothermal therapy, where laser irradiation of accumulated nanoparticles generates localized heat to kill mycobacteria. Superparamagnetic iron oxides nanoparticles

offers some unique advantage of magnetic targeting external magnetic field can guide these particles to specific lung regions containing TB lesions that dramatically improving drug localization while reducing systemic exposure [52].

Despite their promise with metallic nanoparticles face significant to translational challenges including potential long term accumulation in organs, batch to batch variability in synthesis, and regulatory hurdles. Recent research has focused on developing biodegradable metallic nanocarriers and improving surface coatings to enhance biocompatibility. Hybrid approaches combining metallic cores with organic are showing particular promise for creating safer with more effective systems for MDR-TB treatment [53].

Other Emerging Nanocarriers

Beyond established nanocarrier platforms, several innovative nanosystems are emerging as potential game changers for MDR-TB treatment. Exosomes naturally occurring nanovesicle secreted by cells offers unparalleled biocompatibility and intrinsic homing capabilities. Engineered exosomes derived from macrophages naturally target TB infection sites and can deliver drug payloads across biological barriers that synthetic nanocarriers cannot penetrate. Carbon based nanomaterials including carbon nanotubes and graphene oxide sheets provide exceptionally high drug loading capacities and unique cellular uptake mechanisms, though their long-term safety profile requires further evaluation [53]. Nanofibers feature as an superior drug shipping gadget that improves cellular healing, together with controlled drug delivery methods and deep tissue penetration capabilities. The latest improvement of twin-drug transport systems, stimuli-responsive nanofibers, and scaffolds composed of nanofibers and smart substances has extended their usage in precision medicine [54]. Mesoporous silica nanoparticles with their tunable pore structures (2-50 nm) enable precise loading of multiple anti-TB drugs with distinct physicochemical properties. Their high surface area more than 1000 m^2/g allows unprecedented drug loading capacities, while surface functionalization enables targeted delivery and stimuli responsive release. Recent developments in "nanomotors" self-propelled nanoparticles that can actively navigate through lung mucus and granuloma tissues - represent another frontier in TB drug delivery. While these emerging technologies show remarkable potential, most remain in early preclinical development. Key challenges include scalable manufacturing, long term stability & comprehensive safety evaluation. The next decade will likely see convergence of multiple nanocarrier technologies into hybrid systems that combine the best features of different platforms, potentially revolutionizing MDR-TB treatment through smarter, more effective targeted therapies [55].

Mechanisms Of Drug Delivery Using Nanocarriers

Nanocarriers have emerged as revolutionary approaches to the treatment of multidrug resistant tuberculosis due to the their abilities to enhance drug bioavailability, reduce systemic toxicity & improve therapeutic efficacy. These carriers which include liposomes, polymeric nanoparticles, solid lipid nanoparticles and dendrimers that employs sophisticated mechanisms to deliver anti TB drugs precisely to infected site while overcoming biological barrier. The key mechanisms by which nanocarriers improve MDR-TB therapy include targeted delivery to infected site, controlled and sustained release of drugs, and overcoming drug resistance mechanisms employed by Mycobacterium tuberculosis [56].

Targeted Delivery to Infected Sites

One of the most significant advantage of nanocarrier in MDR TB therapy is the abilitie to deliver drug specifically to

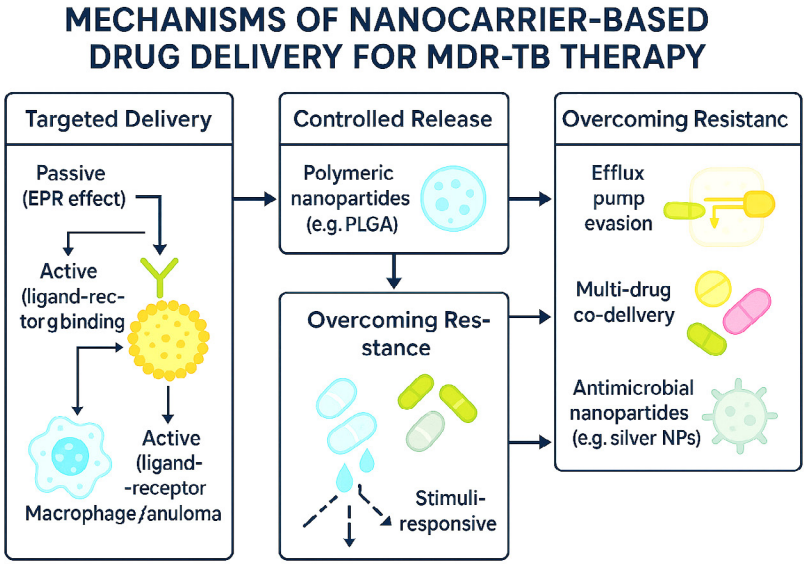

Figure 2: Flow Diagram for Mechanism of nanocarrier based drug delivery for MDR TB therapy

infected tissue, particularly macrophages and granulomas where M. tuberculosis predominant reside. Conventional drug administration often fail to achieve sufficient drug concentration at these site due to poor tissue penetration and rapid clearance. Nanocarrier however can be engineered to exploit passive and active targeting strategie. Passive targeting relie on the enhanced permeability and retention effect where nanoparticles accumulate in infected tissues due to their leaky vasculature & impaired lymphatic drainage. current antibacterial trial treatments in al-lopathy face several drawbacks that restriction their effectiveness [56]. The overuse and misuse of antibiotics have caused the emergence of re sistant lines, along with MRSA and multidrug-resistant tuberculosis (MDR-TH), rendering trendy troumenis ineffective [57]. Active targeting involves surface modification of nanocarrier with ligands such as mannose antibodies that bind specifically to receptors overexpressed on infected macrophage. Moreover ensuring selective drug delivery to the primary site of TB infection. This targeted approach minimizes off target effect that reduces systemic toxicity and enhance therapeutic efficiency [58].

Controlled and Sustained Release

One of the significant challenges in treatment of MDR TB is to sustain therapeutic drug concentrations for long periods to achieve complete eradication of bacteria while avoiding too frequent dosing. Nanocarrier overcome this problem by offering controlled and sustained delivery of anti TB medication. Drug entrapment in nanoparticle shields the drugs from early degradation and facilitates delayed release over days or weeks. For instance, the polymeric nanoparticle prepared from PLGA degrades slowly under physiological conditions and delivers drugs in a controlled fashion. Such a feature is very useful for the drugs such as rifampicin and isoniazid that have a short half live and must be administered several times a day in regular therapy [59]. Controlled release not only enhances patient compliance by decreasing the frequency of dosing but also provides a continuous exposure of drug to M. tuberculosis, inhibiting bacterial regrowth and lowering the chances of resistance generation. Further, stimuli responsive nanocarriers that release drug upon exposure to particular trigger in TB microenvironment also increases site specific drug delivery and minimize systemic side effect. Sometime pellets are also used as they may be small, loose-flowing, round or semi-round strong debris commonly inside the length variety of zero.five–2 mm. they're designed for oral drug transport and are often used as a multi particulate dosage form in the pharmaceutical enterprise [60]

Overcoming Drug Resistance

Drug resistance in M. tuberculosis is due to several different mechanisms such as efflux pump overexpression, drug inactivation, and alterations in drug-target genes. These resistance mechanisms can be overcome by nanocarriers using several approaches. Firstly, encapsulation of drugs by nanoparticles renders them insensitive to enzymatic degradation and efflux pumps that would otherwise eject them out of bacterial cells. For example, rifampicin nanoformulations have been found to overcome efflux-mediated resistance by directly introducing high intracellular drug concentrations into macrophages. Secondly nanocarriers are capable of co-delivery of multiple drugs at the same time, promoting synergistic effects that break through resistance. Combination therapy by nanoparticles that are pre-loaded with first- and second-line TB drug has shown increased bactericidal activity against MDR strains. Third, certain nanocarriers have intrinsic antibacterial activity or may be functionalized with antimicrobial peptides to enhance efficacy [61]. Silver nanoparticles, for instance, have direct antimycobacterial action and can be added to standard TB drugs to augment their effectiveness. By tackling resistance at more than one level, nanocarriers offer a good solution to the increasing problem of MDR-TB. In summary, nanocarrier provide an advanced and multi-dimensional strategy to MDR-TB treatment by facilitating targeted drug delivery, sustained release, and resistance mechanism evasion. These development have significant promise in reshaping TB treatment, especially when other traditional therapies have been unsuccessful. Clinical translation should be optimized through future research into nanoparticle formulations, their scalability and long-term safety profiles to ultimately maximize their therapeutic potential [62].

Advantages Of Nanocarrier-Based Therapies For Mdr-Tb

Nanocarrier based therapies represent a revolutionary approach in the treatment of Multidrug Resistant Tuberculosis, offering several advantages over conventional drug delivery systems. These benefit stem from the unique physicochemical properties of nanoparticles which allow for targeted drug delivery, controlled release, and improved pharmacokinetics. Below we discuss the key advantages of nanocarrier based therapies for MDR-TB, focusing on improved bioavailability, reduced toxicity & side effects and enhanced patient compliance [63].

Improved Bioavailability

The biggest challenge of MDR TB therapy is the poor bioavailability of anti tuberculosis drugs, particularly drugs with poor aqueous solubility. Hydrophobic drugs can be entrapped by nanocarriers such as liposome, polymeric nanoparticle and solid lipid nanoparticle thus enhance their solubility & stability in biological matrices. By doing that nanocarrier increase drug absorption and systemic availability, enabling therapeutic concentrations to be achieved at the infection site. For instance, rifampicin and isoniazid, both oral first line drug for TB, exhibit irregular oral absorption and rapid metabolism. They are still augmented in their bioavailability with improved circulation time and stability against enzymatic degradation when they are encapsulated in nanocarriers. Nanocarrier are also able

bypass first pass metabolism in the liver, improving drug bioavailability even further. This is especially applicable to second line MDR-TB treatment drugs like delamanid and bedaquiline with low oral bioavailability and where efficacy exists only with escalated dosing. Nanocarriers conserve dosing by achieving utmost efficiency of drug delivery with potency in the case of diminished dosing [64].

Reduced Toxicity and Side Effects

Traditional MDR TB treatment is accompanied by harsh side effects such as hepatotoxicity, nephrotoxicity and gastrointestinal side effects which usually cause discontinuation of therapy. Nanocarriers alleviate these concerns by facilitating targeted drug delivery to infected tissue while sparing healthy cell. For instance, polymeric nanoparticles can be designed to deliver drugs in a pH-dependent mode so that the payload is released mostly in the acidic microenvironment of TB granulomas and not in systemic circulation. This targeted therapy is less likely to induce off-target toxicity and damage to critical organs. In addition, nanocarriers can encapsulate harmful drugs such as aminoglycosides that are notorious for inducing ototoxicity and nephrotoxicity [65]. By regulating drug release kinetic, nanocarriers avoid plasma concentration spikes and subsequently reduce the incidence of adverse effects. An additional benefit is the possibility of co delivery of more than one drug in a single nanocarrier, lowering the pill burden and obviating drug drug interactions that tend to increase toxicity. For example, single nanoparticle formulation with rifampicin and pyrazinamide can decrease hepatic stress relative to different high-dose treatments. In general, nanocarrier-based systems improve the safety profile of MDR-TB therapy, rendering it more acceptable for patients on prolonged treatment [66].

Enhanced Patient Compliance

Patient compliance is one of the most significant barriers to MDR-TB therapy because of the long course of treatment usually 18 to 24 month and the high rate of side effect. Nanocarrier based treatment overcome this limitation by decreasing dosing regimens and enhancing compliance. Sustained release nanocarrier including long circulating liposomes or biodegradable polymeric nanoparticle, can provide constant therapeutic levels of drugs for prolonged durations, decreasing the dosing frequency. For instance, a nanocarrier encapsulated anti TB drug might be administered once as a substitute for daily oral doses, making it much more convenient for patient [67]. Moreover, the decreased toxicity linked with nanocarriers increases the willingne of patient to adhere to treatment without stopping. Another feature that increases compliance is the possibility of oral nanocarrier formulations, removing the process of painful injections while still enhancing drug absorption. In addition, nanocarriers can be modified with ligands that specifically target macrophages, the major host cell for Mycobacterium tuberculosis, to deliver drug effectively to the site of infection and prevent the risk of treatment failure. Through the reduction of side effects, ease of administration, and decreased treatment time in certain conditions, nanocarrier-based therapies enhance better compliance and ensure a higher success rate of MDR-TB eradication. Finally, nanocarrier-based treatment present a solution of hope for the shortcoming of traditional MDR-TB treatment. Through enhancing drug bioavailability, minimizing toxicity, and promoting patient compliance, these sophisticated delivery system can revolutionize MDR TB management and enhance clinical outcomes. The future should target the optimization of nanocarrier formulations to allow large scale manufacturing and clinical translation to provide these treatments to patients globally [68].

Challenges and Limitations

The development and implementation of nanocarrier for Multidrug Resistant Tuberculosis therapy present several challenges and limitation. While nanocarrier offers promising advantage such as targeted drug delivery that reduced side effects and enhanced therapeutic efficacy their translation from laboratory research to clinical application faces significant obstacle. These challenge span regulatory and manufacturing hurdle that safety and toxicological concerns as well as cost and accessibility issue. Addressing these limitations is crucial for the successful adoption of nanocarrier based therapie in MDR TB treatment [69].

Regulatory and Manufacturing Hurdles

One of the primary challenge in bringing nanocarrier based therapie for MDR TB for the markets are navigating to the complex which regulatory landscape. Regulatory agencie such as the U.S food & Drug Administration and the European Medicines Agency have stringent requirement for the approval of nano medicine. These requirement include rigorous characterization of nanoparticle size, shape, surface charge and stability with extensive pre clinical and clinical testing to demonstrate safety and efficacy. The lack of standardized protocols for nanocarrier characterization and quality control further complicates the regulatory approval process. Manufacturing nanocarriers at the commercial scale also presents significant challenges. The synthesis of the Nanoparticles with consistent physicochemical properties is difficult to achieve in large batches, leading to variability in drug loading that releases kinetic and therapeutic performance. Additionally the needs for specialized equipments & expertise in nanotechnology increases production costs and limits the scalability of nanocarrier manufacturing. Ensuring reproducibility and compliance with Good Manufacturing Practices are essential but remains a major hurdle for pharmaceutical company developing nanocarrier based MDR TB treatment [70].

Safety and Toxicological Concerns

Although they hold great promise where nanocarrier pose significant safety & toxicology issues that need to be

resolved prior for clinical uses on the large scale. Behavior of nanoparticles in biological systems is multifaceted and not yet complete understand. For example like some nanomaterials can be trigger immune reactions with producing inflammation or hypersensitivity responses. The long-term deposition of nanoparticles in organs like the liver, spleen and kidney are point of concern regarding chronic toxicity and organ damage. Additionally, the biodegradation and clearance rate of nanocarrier that are key to determining their safety [71]. While certain nanoparticle such as lipid and polymer-based particles were engineered to break down into non toxic metabolite, others, such as metallic nanoparticles, will remain in the body for extended periods and produce side effects. Extensive toxicological analyse such as in vitro, in vivo, and chronic exposure analyses, are required to assess the biocompatibility of the nanocarriers. Also, the possibility of off target effect and accidental interactions with biomolecule should be thoroughly examined to guarantee the safety of patient [72].

Cost and Accessibility

The high cost of developing and producing nanocarrier-based therapies poses a significant barrier to their accessibility, particularly in low- and middle income countries there the burden of MDR TB is more The sophisticated technology and specialized materials required for nanoparticle synthesis contribute to elevated production costs. Furthermore the extensive preclinical and clinical testing needed for regulatory approval adds to the financial burden, making nanocarrier based treatment prohibitively expensive for many healthcare systems. Even if the nanocarrier therapies are successfully developed and approved their distribution and administration in resource-limited settings remain challenges. Lot's of LMIC lack the infrastructure for proper storage, handling & delivery of nanomedicines that may require controlled temperature conditions or specialized administration devices. In contrast need for trained healthcare professionals to administer and monitor these advanced therapies further limits their accessibility [73]. Effort to reduce costs through scalable manufacturing processes, the use of affordable materials, and public-private partnerships are essential to ensure that nanocarrier-based MDR-TB treatments reach the populations that need them most. Global health is initiatives and funding support will play a critical role in overcoming these economic and logistical barrier. Although Ascorbic acid is used where it administered intravenously, it bypasses the limitations of oral absorption, main to higher plasma concentrations. This injectable form ensures rapid availability and efficacy, in particular in instances wherein oral supplementation is inadequate or now not feasible [74]

Future Perspectives And Research Directions

The stage of nanocarrier drug delivery in tuberculosis resistant to several drugs is rich with potential; yet, many challenges must be met for labs to see commercial translations. Future work should revolve around the optimization of nanocarriers and targeting efficiencies and consideration of long-term safety of treatment. This may enter the realm of personalized nanodrugs, coupled with diagnostics and multifunctional hybrid nanocarriers. These may bring about the greatest transformation ever in therapies for MDR TB, by improving drug bioavailability and reducing systemic toxicity and mechanisms that resist the drugs [75].

Personalized Nanomedicine in TB

Personalized nanomedicine is one of the avenues by which to optimize the treatment of MDR-TB by tailoring the nanocarriers to individual patient profiles. Disease progression, immune responses, and drug metabolism change in different individuals; therapeutic options must therefore be customized to suit. Developing genomics and proteomics could pave the way for nanocarriers manufactured for the patient that consider genetic polymorphisms affecting drug metabolism (e.g., CYP450 enzymes) or bacterial resistance patterns. Nanoparticles, for example, could be functionalized with biomarkers that react to a patient-specific immune signature to ensure drug release at infectious sites. Alternatively, drug choices may be influenced by pharmacogenomic data and loaded into the nanocarriers to curb adverse effects while promoting efficacy. Instead, personalized nanomedicine might never reach the MDT-TB treatment due to high costs of production and regulatory concerns, environmental infrastructure needs, and others [76].

Integration with Diagnostic Technologies

In concert with the diagnostic technologies, nanocarriers could ensure the real-time monitoring of the treatment response and disease progression to facilitate timely therapeutic interventions. Nanosensors residing in drug-loaded carriers would recognize certain TB-specific biomarkers, such as lipoarabinomannan or IFN-γ, present in biological fluids, thus giving almost immediate feedback about bacterial load or resistance to drugs. Imaging-guided nanocarriers loaded with contrast agents could non-invasively track drug distribution via MRI or fluorescence imaging. Theranostics would then improve the precision of treatment, ensuring drug delivery to infected tissues with minimal unintended side effects to off-target organs. Future studies need to address upscaling of manufacturing techniques and validation of integrated systems in preclinical and clinical settings to be considered reliable and cost-effective [77].

Multi-functional and Hybrid Nanocarriers

The development of multi-functional and hybrid nanocarriers lands at the center of research to meet the challenge of MDR-TB therapies. Such hybrid systems combining polymeric nanoparticles, liposomes, and inorganic materials (e.g., mesoporous silica or gold nanoparticles) offer synergistic

opportunities to increase the drug-loading capacity, stability, and release pattern [32]. Multi-functional nanocarriers would combine immune-modulators (cytokines or checkpoint inhibitors) with antibiotics to reinforce host defenses against Mycobacterium tuberculosis. From the perspective of surface engineering, they may be grafted with target ligands (mannose or folate) for improved macrophage targeting, whereas the coating layer, being stimuli-responsive (pH-sensitive or enzyme-sensitive polymers), ensures drug release at the proper site [78]. Future studies should focus on optimizing the biocompatibility and scalability profiles of these systems, along with their long-term safety, in a bid to make faster headway toward clinical applications [79].

CONCLUSION

Nanocarriers have come with a new generation of therapeutic strategies in the fight against Multidrug-Resistant Tuberculosis, providing solutions to the residual issues of conventional regimens. These delivery systems-from liposomes to polymeric nanoparticles, solid lipid nanoparticles, and dendrimers-have many advantages in comparison to a traditional one. Nanocarriers can be loaded with anti-TB drugs and thus increase the solubility of the drug, protect the therapeutic agents from degradation, and in general, improve bioavailability. These nanocarriers, being small with tunable surface properties, can easily surpass biological barriers to enter intracellular compartments where Mycobacterium Tuberculosis is present [80]. Drug concentration would then be enhanced in key infection sites with the simultaneous reduction of systemic exposure, which will alleviate the potential for severe side effects usually associated with prolonged MDR-TB treatment. This, coupled with the co-delivery of drugs of more than one kind, will aid in keeping a balance toward drug resistance on the complicated scale of drug resistance mechanisms. Nanocarriers are not just used for simple drug delivery, but their versatility extends to innovative targeting strategies that increase the therapeutic efficacy of nanoparticles. Passive targeting is offered by the enhanced permeability and retention (EPR) effect due to leaky vasculature, whereby nanoparticles display preferential accumulation in infected tissues [81]. Active targeting further upgrades the system by using ligands such as mannose, folate, or antibodies that bind to receptors that are overexpressed on infected macrophages. Such a dual-targeting approach should deliver drugs accurately and sparing healthy cells, a major breakthrough in tuberculosis precision medicine. Lastly, the properties of controlled release provide therapeutic drug levels that poise to be delivered over the long term and may therefore decrease dosing intervals, directly influencing patient compliance, which is of essence in MDR-TB treatment that is generally extensive and complicated with respect to drug regimens [82].

Despite these wonderful advantage where there remain challenge for face before nanocarrier based therapies for MDR-TB fully realize their clinical promises. Manufacturing considerations pose major challenges, since nanocarriers must be manufactured under strict controls for particle size, drug loading, and batch-to-batch reproducibility. Maintaining these critical quality attributes during scale-up of a laboratory-scale formulation to industrial production is one of the greatest challenges. Stability issues may further arise during storage or transit if nanoparticles are prone to aggregation or drug leakage, consequently influencing drug efficacy [83]. Safety-wise, while the majority of investigated nanocarriers seem to be biocompatible, further toxicity tests are essential to get insight into their possible implications in the long run, especially taking into account the fact that MDR-TB treatment is a long-term one. Nanocarriers biodegradation pathways and clearance mechanisms need a thorough understanding to confirm that the nanocarriers won't accumulate in vital organs or elicit adverse immune responses. In the meantime, regulatory authorities are faced with the daunting challenge of developing relevant guidelines for this new class of therapeutics, an endeavor that warrants tight collaboration among researchers, manufacturers, and policymakers toward an agreeable consensus on standard evaluation and approval processes [84].

Looking ahead, several attractive avenues could further enhance nanocarrier-based MDR-TB therapies. Development of "smart" or stimuli-responsive nanocarriers that would drop their drug payload in response to triggers in the environment of TB (say, low pH or high enzyme levels) could offer a better punch of targeting. Having a drug delivery system capable of theranostics could quite possibly change the way we monitor treatment, by tracking in real-time when the drug delivery happens and when the patient's response to treatment occurs. New biomaterials that are a whole lot better in biocompatibility and more capable of drug loading may pave the way for highly efficient next-generation nanocarriers. It also will be equally important to ensure that this higher version of therapy does not become prohibitively expensive and thus inaccessible in low-resource settings where MDR-TB continues to have the highest prevalence. This could include looking for inexpensive manufacturing methods and utilizing locally available materials for nanocarrier manufacture [86]. As knowledge on host-pathogen interactions and drug resistance mechanisms matures, nanocarriers can be specifically tailored to overcome challenges unique to MDR-TB treatment, maybe including some immune-modulatory agents or resistance-reversal compounds along with traditional antibiotics [87].

Nanocarrier technology for MDR-TB treatment is a paradigm shift, offering hope in places where conventional therapies have failed. Nanocarriers try to address the limitations inherent in present-day drug delivery systems for better clinical outcomes, shorter treatment duration, and better quality of life for patients. Much work needs to be done yet to tackle various issues, but looking at how fast nanotechnology is progressing, many challenges may be resolved in the

next few years. The extended pathway of transition for nanocarrier-based therapeutics from bench to bedside will call for long-term investment, interdisciplinary working collaboration, and commitment from all stakeholders in the TB research community [88]. Nanocarriers for MDR-TB treatment represent the forefront of this therapeutic revolution wherein cutting-edge science is deployed to tackle one of global development's age-old challenges. The continued existence and broad implementation of these would be able to make way for an active step toward TB's ultimate goal of elimination by saving millions of lives and easing the massive socio-economic expenditure caused by this awful disease [89].

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