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Formulation of Nano-Liposomal Drug Delivery Systems for Targeted Therapy of Multi-Drug-Resistant Tuberculosis (MDR-TB)

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Abstract

Multidrug-resistant tuberculosis (MDR-TB) continues to challenge global health due to prolonged, toxic, and poorly effective conventional regimens that fail to achieve sustained therapeutic concentrations at the primary infection site within alveolar macrophages. This review comprehensively examines the formulation, design, and translational potential of nano-liposomal drug delivery systems as a targeted pulmonary platform for MDR-TB therapy. Liposomes, composed of saturated phospholipids and cholesterol, enable simultaneous encapsulation of both hydrophilic and lipophilic anti-TB agents while providing excellent biocompatibility and tunable release kinetics. Optimized particle sizes (100–200 nm) facilitate deep-lung deposition and efficient macrophage phagocytosis, while surface functionalization with mannose or fucose ligands enables active receptor-mediated targeting to CD206 and DC-SIGN receptors overexpressed on infected macrophages. Advanced manufacturing using microfluidics ensures monodisperse, high-encapsulation-efficiency vesicles, and spray-drying with force-control agents produces stable dry-powder inhaler formulations with ideal mass median aerodynamic diameters (1–5 μm). Stimuli-responsive designs incorporating pH-sensitive malachite green or enzyme-cleavable polyphosphate coatings trigger rapid intracellular drug release within the acidic phagolysosome. Clinical evidence from the Phase 3 CONVERT trial of amikacin liposome inhalation suspension (ALIS) demonstrated significantly higher culture conversion rates (29% vs 8.9%) with acceptable safety, while preclinical fucosylated bedaquiline liposomes achieved 6-fold higher lung bioavailability and markedly reduced systemic metabolite exposure. Nano-liposomal systems therefore offer a versatile, macrophage-targeted strategy capable of overcoming intracellular persistence, shortening treatment duration, minimizing toxicity, and combating MDR-TB resistance.

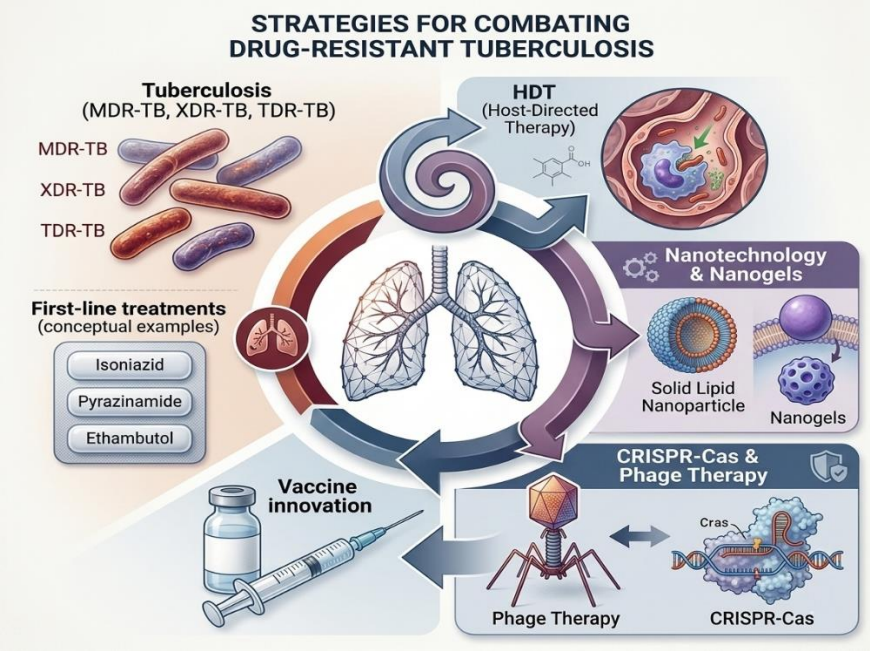
Keywords: MDR-TB, Nano-liposomes, Pulmonary Drug Delivery, Macrophage Targeting, Stimuli-Responsive Release, Dry Powder Inhaler, ALIS, Bedaquiline, Microfluidics, Amikacin, Targeted Therapy, Intracellular Drug Delivery

1. Introduction

The global burden of tuberculosis (TB) remains one of the most significant challenges to modern public health, characterized by high morbidity and mortality rates that persist despite the existence of effective antibiotic regimens for over half a century (Chakaya et al., 2021). Annual data indicates that approximately 10 million individuals contract the disease, resulting in roughly 1.33 million deaths (Glaziou et al., 2018). The crisis is most acute in low- and middle-income countries,

particularly across Asia and Africa, which together account for a vast majority of the global disease burden (Kola et al., 2021). A defining factor in the failure to eradicate this airborne infection is the emergence and proliferation of drug-resistant strains, primarily multidrug-resistant tuberculosis (MDR-TB), which is defined by resistance to the foundational first-line agents isoniazid and rifampicin (Anim-Ayeko et al., 2021).

Figure 1: Comprehensive Strategies and Emerging Therapeutic Modalities for Combating Drug-Resistant *Mycobacterium tuberculosis*.



The clinical management of MDR-TB is notoriously difficult, requiring prolonged treatment durations often extending to 20 months or more. These regimens utilize second-line drugs that are typically more toxic, less effective, and significantly more expensive than standard first-line therapy (Nabi et al., 2020). The evolution of the pathogen has progressed further with the identification of extensively drug-resistant (XDR-TB) and totally drug-resistant (TDR) strains, for which virtually no effective pharmaceutical interventions exist (Hameed et al., 2018). The rise of these resistant phenotypes is driven by a complex interplay of genetic adaptability in Mycobacterium tuberculosis (Mtb) and systemic failures in treatment adherence, often caused by the heavy pill burden and severe side effects associated with conventional oral dosing (Saravanan et al., 2018).

Table 1. Comparison of Tuberculosis Strain Resistance Patterns and Treatment Outcomes

Strain Type	Resistance Definition	Typical Treatment Duration	Clinical Outcomes
Drug-Susceptible (DS-TB)	Sensitive to all first-line agents	6 Months	High success rate (over 85%) (Hussain et al., 2025)
Multidrug-Resistant (MDR-TB)	Resistant to Isoniazid and Rifampicin	9 - 20 Months	60% success rate; high toxicity (Hussain et al., 2025)

Extensively Drug-Resistant (XDR-TB)	MDR-TB plus resistance to Fluoroquinolones and injectables	20+ Months	Poor prognosis; limited options (Hussain et al., 2025)
Rifampicin-Resistant (RR-TB)	Resistance to Rifampicin detected by molecular tests	Variable	Treated similarly to MDR-TB (Hussain et al., 2025)

The inability of standard oral therapies to provide sustained, targeted concentrations of antibiotics at the primary site of infection the lungs leads to sub-therapeutic drug levels. This promotes the selection of resistant mutants and allows the pathogen to persist within its intracellular reservoir, the alveolar macrophage (Allard et al., 2018). Consequently, there is an urgent need for innovative delivery platforms that can enhance drug bioavailability and specifically target the intracellular niches of Mtb (Omoteso et al., 2025).

2. Pathophysiology of Mycobacterium tuberculosis and Intracellular Survival

The persistence of Mtb within the host is facilitated by its unique structural components and sophisticated immune evasion strategies. The hallmark of the mycobacterial cell envelope is an exceptionally thick and lipid-rich wall, which serves as a formidable physical barrier against host immune responses and antibiotic penetration (Chandra et al., 2022). This structure is primarily composed of three interconnected layers: a basal peptidoglycan layer, a branched arabinogalactan layer, and an outer layer of long-chain mycolic acids (Chai et al., 2020). This hydrophobic architecture restricts the entry of many hydrophilic drugs, contributing to the intrinsic resistance of the organism (Falanga et al., 2024).

Table 2. Molecular Targets and Genetic Mechanisms of Acquired Drug Resistance in Mtb

Targeted Drug	Relevant Gene	Mechanism of Resistance	Genetic Locus Detail
Isoniazid	katG	Failure of prodrug activation by catalase-peroxidase	S315T mutation (Trajman et al., 2025)
Isoniazid	inhA	Overexpression or alteration of enoyl-ACP reductase	Promoter mutations (C-15T) (Trajman et al., 2025)
Rifampicin	rpoB	Altered binding to beta-subunit of RNA polymerase	95% mutations in 81-bp region (Trajman et al., 2025)
Fluoroquinolones	gyrA / gyrB	Reduced drug affinity for DNA gyrase	Mutations at Ala90 and Asp94 (Trajman et al., 2025)
Ethambutol	embB	Interference with arabinosyltransferase activity	Disruption of cell wall synthesis (Trajman et al., 2025)

The Macrophage as a Pathogenic Reservoir

Upon inhalation, Mtb is phagocytosed by alveolar macrophages. While these cells are equipped with antimicrobial mechanisms, Mtb has evolved ways to subvert these processes. The pathogen secretes effectors like the protein tyrosine phosphatase A (PtpA), which binds to the H subunit of the host's v-ATPase pump, effectively blocking the acidification of the phagosome (Truszkowska et al., 2025). Additionally, effectors such as PtpB are secreted to inhibit host pyroptosis by dephosphorylating plasma membrane phosphoinositides, such as PI4P and PI(4,5)P2. This

prevents the membrane localization of the N-terminal cleavage fragment of gasdermin D (GSDMD-N), thereby obstructing the release of inflammatory mediators and promoting intracellular survival (Chai et al., 2022).

3. Structural and Functional Characteristics of Nano-Liposomes

Liposomes are among the most established and versatile nanotherapeutic platforms, consisting of one or more lipid bilayers surrounding an internal aqueous core. Their unique amphiphilic structure allows for the simultaneous encapsulation of lipophilic drugs within the hydrophobic bilayer and hydrophilic agents within the aqueous interior (Nsairat et al., 2022). This dual-loading capability is particularly advantageous for the treatment of MDR-TB, which requires complex combinations of drugs with varying physicochemical properties (Al Badri et al., 2023).

Phospholipid Composition and Bilayer Stability

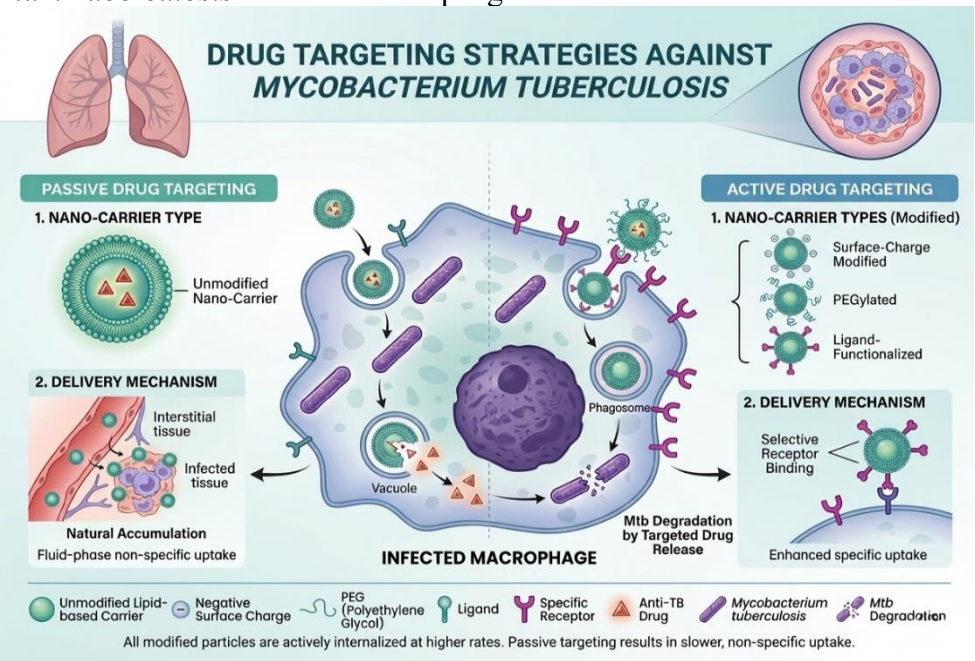
The choice of lipids significantly influences the stability and drug release profile of the liposomal formulation. Commonly utilized phospholipids include 1,2-dimyristoyl-sn-glycero-3-phosphocholine (DMPC) and 1,2-dimyristoyl-sn-glycero-3-phospho-rac-glycerol (DMPG) (Marwitz et al., 2024). Acyl saturation is a critical design lever; replacing fluid, oxidizable chains with saturated species (such as C16:0 or C18:0) suppresses lipid peroxidation and raises the gel-to-liquid-crystalline transition temperature (Tm), preventing molecular slippage and fusion (Talo, 2025).

Cholesterol is frequently incorporated into the lipid bilayer as a structural stabilizer. It wedges between adjacent phospholipid molecules, filling free-volume pockets that would otherwise be susceptible to water penetration and subsequent hydrolysis, thereby extending the shelf life of the liposomal suspension (Kumarage et al., 2023).

4. Precision Targeting Mechanisms in Pulmonary Delivery

Targeted drug delivery aims to increase the therapeutic index of anti-tubercular drugs by maximizing their concentration at the site of infection while minimizing systemic exposure (Nabi et al., 2020).

Figure 2: Comparative Mechanisms of Passive and Active Nanocarrier Targeting in *Mycobacterium Tuberculosis*-Infected Macrophages.



Passive Lung Targeting and the Influence of Particle Size

Passive targeting relies on the natural clearance of inhaled particles by the alveolar macrophages. When liposomes are administered via inhalation, they are deposited in the alveolar regions and subsequently internalized through phagocytosis. The efficiency of this uptake is highly dependent on the particle size (Sarkar et al., 2022).

Table 3. Impact of Particle Size on Internalization Pathways and Cellular Destination

Particle Size Range	Primary Internalization Pathway	Cellular Outcome
< 120 nm	Clathrin/Caveolin-mediated endocytosis	Leads to endosomes/caveosomes (Hussain et al., 2025)
250 nm - 1 micrometer	Phagocytosis	Direct delivery to phagosomes (ideal for Mtb) (Hussain et al., 2025)

Research indicates that liposomes with a diameter around 100-200 nm are optimal for deep lung deposition while still facilitating macrophage uptake (Mazlan et al., 2021).

Active Targeting via Receptor-Ligand Interactions

Active targeting involves functionalizing the liposome surface with ligands that have a high affinity for receptors overexpressed on infected macrophages, such as mannose receptors (CD206). Functionalizing nanocarriers with fucose or mannose residues has been shown to significantly enhance uptake (Paul et al., 2021). For example, bedaquiline-loaded liposomes modified with fucose residues target the macrophage mannose receptor and DC-SIGN, providing localized antibiotic delivery directly to the Mtb habitat (Huck et al., 2022).

5. Formulation Technologies for Nano-Liposomal Systems

Transitioning liposomal formulations to industrial production requires robust manufacturing technologies (Basak et al., 2025).

Traditional Synthesis vs. Microfluidic Innovation

While thin-film hydration is a common laboratory technique, it often results in heterogeneous size distributions. In contrast, microfluidics enables the synthesis of monodisperse liposomes with high encapsulation efficiency in a continuous process. Microfluidic devices manipulate fluids in sub-millimeter channels where flow is laminar (Jaradat et al., 2021). By controlling the Total Fluid Flow Rate (TFR) and Flow Rate Ratio (FRR), the precipitation of lipids can be precisely managed (Akar et al., 2024). Advanced micromixer geometries, such as staggered herringbone designs, induce chaotic advection, which enhances mixing efficiency even at low flow rates (Re less than 10) and produces vesicles with a narrow polydispersity index (PDI) (Osouli-Bostanabad et al., 2022).

Particle Engineering for Dry Powder Inhalers (DPIs)

For pulmonary administration, converting liquid liposomes into dry powders is often necessary to improve stability. Spray drying is widely used for this purpose. Optimal deep lung deposition requires a Mass Median Aerodynamic Diameter (MMAD) between 1 and 5 micrometers. To achieve this, force control agents like L-leucine or magnesium stearate are added to reduce inter-particulate cohesion (Sibum et al., 2018).

Table 4. Critical Manufacturing Parameters for Inhalable Liposomal Formulations

Parameter	Optimal Range	Rationale
Flow Rate Ratio (FRR)	3:1 to 5:1	Higher ratios generally yield smaller liposomes (Beyer, 2025)
MMAD for Inhalation	1 - 5 micrometers	Ideal for deep lung deposition (Nabi et al., 2020)
PDI (Polydispersity)	< 0.2	Indicates a uniform and stable size distribution (Beyer, 2025)

6. Stimuli-Responsive Release and "Smart" Nanocarriers

A significant advancement is the development of stimuli-responsive systems that release their payload in response to specific triggers within the infection microenvironment (Zhang et al., 2023).

pH-Responsive Mechanism and Malachite Green

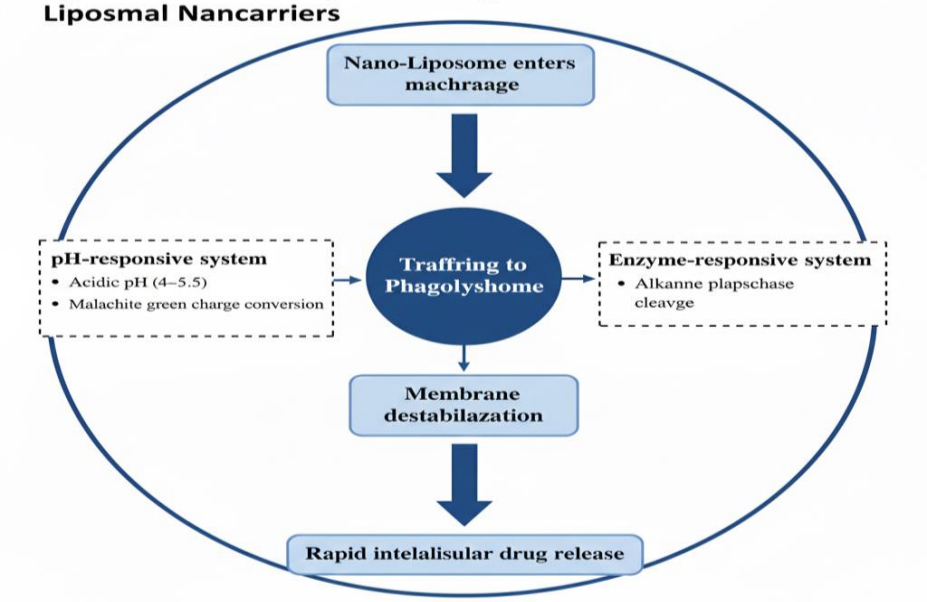
The acidic environment of the phagolysosome (pH 4.0-5.5) serves as a potent endogenous trigger. One innovative approach involves incorporating malachite green carbinol base (MG) into the lipid bilayer (Coradello, 2024). At physiological pH, MG is neutral and resides stably within the bilayer; however, upon entering the acidic lysosome, it transforms into its carbocationic form (MG+). This conversion creates a charge imbalance that leads to the rapid release of encapsulated drugs specifically within the acidic compartments where pathogens reside (Wu et al., 2014).

Enzyme-Triggered Charge Conversion

Intestinal alkaline phosphatase (AP), expressed in the lungs, can trigger charge reversal in polyphosphate-coated liposomes. These liposomes initially possess a negative charge to facilitate penetration through the negatively charged mucus layer (Polidori et al., 2016). Once the liposomes reach the cell surface, AP cleaves the phosphate groups, restoring a positive charge and enhancing electrostatic attraction to the cell membrane for improved cellular uptake (Akkuş-Dağdeviren et al., 2023).

Figure 3 demonstrates the mechanism of stimuli-responsive drug release from nano-liposomes.

Figure 2: Stimuli-Responive Drug Release from Nano-Liposmal Nancarriers



7. Clinical Evidence and Case Studies of Liposomal Anti-Tubercular Drugs

The clinical potential of liposomal delivery has been highlighted by trials involving amikacin and bedaquiline (Marwitz et al., 2024).

Amikacin Liposome Inhalation Suspension (ALIS) and the CONVERT Trial

ALIS was designed to deliver amikacin directly to the lungs via nebulization, achieving high local concentrations while limiting systemic toxicity. The Phase 3 CONVERT study demonstrated a significant improvement in culture conversion rates for patients receiving ALIS plus guideline-based therapy (GBT) compared to GBT alone (Griffith et al., 2018).

Table 5. Efficacy and Safety Outcomes from the ALIS Phase 3 CONVERT Trial

Trial Metric (CONVERT)	ALIS + GBT Group	GBT Alone Group
Culture Conversion Rate	29.0%	8.9% (Griffith et al., 2018)
Respiratory Adverse Events	87.4%	50.0% (Griffith et al., 2018)
Sputum Culture Conversion (Japan)	26.5%	0.0% (Morimoto et al., 2024)

Bedaquiline-Loaded Liposomes: TargoSphere Platform

Bedaquiline is a cornerstone of MDR-TB treatment, but its extreme lipophilicity leads to cardiac risks related to its metabolite M2. In mouse models, intranasal administration of bedaquiline-loaded liposomes resulted in a significant reduction in lung bacterial burden (Chandra et al., 2022). Importantly, intranasal delivery improved lung bioavailability 6-fold compared to intravenous administration and significantly reduced systemic levels of the M2 metabolite, which is linked to heart rhythm risks in patients (Kumarage et al., 2023).

8. Niche Applications: Female Genital Tuberculosis (FGTB)

FGTB is a significant cause of infertility, affecting up to 48% of women seeking assisted reproduction in high-incidence areas. Lipid-based nanocarriers offer a promising solution by providing targeted delivery directly to reproductive organs, delivering higher drug concentrations to infected sites while minimizing organ damage (Omoteso et al., 2025).

9. Translational Hurdles and Future Outlook

Translating nano-liposomal systems faces challenges regarding manufacturing stability and scalability. Maintaining precise characteristics like size and encapsulation efficiency is difficult during scale-up. Manufacturers implement Quality by Design (QbD) principles to establish a "design space" where manufacturing inputs can vary slightly without impacting critical quality attributes (Falanga et al., 2024).

The future of TB therapy is moving toward host-directed therapies (HDT) that combine antimicrobial action with immune modulation (Al Badri et al., 2023). Liposomes can be used to deliver immune modulators or circular RNAs that enhance the host's natural defenses. Collectively, these advancements signal a pivotal transformation in the fight against MDR-TB (Sarkar et al., 2022).

10. Final Summary of Nano-Liposomal Formulation Parameters and Clinical Impact

Table 6. Summary of Optimized Nano-Liposomal Strategies and Therapeutic Benefits

Formulation Aspect	Optimal Strategy	Clinical/Therapeutic Impact
Lipid Matrix	Saturated Phospholipids + Cholesterol	Reduced drug leakage (BOC Sciences, 2025)

Administration	Dry Powder Inhalation (DPI)	Avoids first-pass effect; lung localization (Nabi et al., 2020)
Particle Size	100 - 200 nm	Optimized for deposition and uptake (Nabi et al., 2020)
Surface Modification	Mannose / Fucose Ligands	Targeted delivery to infected niches (Marwitz et al., 2024)
Release Mechanism	pH or Enzyme-Responsive	Triggered release in phagolysosome (Wu et al., 2014)
Clinical Result	ALIS / TargoSphere Bedaquiline	Higher culture conversion; reduced toxicity (Griffith et al., 2018)

Conclusion

Nano-liposomal drug delivery systems represent a paradigm-shifting advancement in the fight against multidrug-resistant tuberculosis by addressing the fundamental limitations of conventional oral therapy suboptimal lung penetration, poor intracellular delivery, systemic toxicity, and prolonged treatment durations. Through precise engineering of lipid composition, particle size, surface ligands, and stimuli-responsive mechanisms, these nanocarriers achieve high local drug concentrations directly within the alveolar macrophage phagolysosome, the primary niche of Mycobacterium tuberculosis, while dramatically reducing off-target exposure. Clinical translation is already underway, with amikacin liposome inhalation suspension (ALIS) demonstrating superior culture conversion in refractory cases, and promising preclinical data for bedaquiline-loaded fucosylated liposomes showing enhanced lung bioavailability and safety. As manufacturing challenges are progressively overcome through microfluidic scale-up, Quality by Design (QbD) frameworks, and spray-drying technologies, nano-liposomes are poised to become a cornerstone of next-generation TB regimens. Future integration with host-directed therapies and multi-drug co-encapsulation will further accelerate the development of shorter, safer, and more effective treatments. Urgent investment in large-scale clinical trials and regulatory pathways is now essential to translate these innovations into accessible therapies that can finally turn the tide against the global MDR-TB crisis and restore hope for millions of patients worldwide.

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