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Review Article

Liposomal Nanocarriers for Targeted Antitubercular Drug Delivery: Recent Developments, Therapeutic Applications and Formulation Challenges

Sakshi Jagtap[1*], Pratiksha Ravankole[2], Sampat Navle[3]

[1] *Final Year Bachelor of Pharmacy Student, Dr. Babasaheb Ambedkar Technological University, Pune, Maharashtra, India-412216.*
[2] *Assistant Professor, Department of Pharmaceutical Chemistry, Delight College of Pharmacy, Koregaon Bhima, Pune, Maharashtra, India- 412216.*
[3] *Principal of Delight College of Pharmacy, Koregaon Bhima, Pune, Maharashtra, India, 412216.*

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ABSTRACT

Tuberculosis (TB), caused predominantly by Mycobacterium tuberculosis, remains a major global infectious disease and requires combination antimicrobial therapy. Drug exposure within infected macrophages and heterogeneous pulmonary lesions may differ from plasma exposure, creating a rationale for investigating targeted delivery systems. Liposomes are vesicular carriers composed of phospholipid bilayers that enclose an aqueous compartment; this architecture permits association of hydrophilic compounds with the internal aqueous phase and lipophilic compounds with the bilayer. This review evaluates published evidence on liposomal antitubercular delivery, with emphasis on isoniazid, rifampicin, macrophage targeting, pulmonary administration, formulation development and translational barriers. Foundational animal studies reported altered tissue distribution and sustained exposure after administration of liposome-encapsulated drugs. More recent investigations have explored mannosylated and transferrin-functionalised liposomes for intracellular delivery of drug combinations. However, encapsulation and release can differ substantially between drugs, and macrophage uptake does not guarantee uniform penetration into caseous or necrotic lesion regions. Formulation stability, reproducible manufacturing, sterile processing, aerosol performance, safety and clinical validation remain unresolved requirements. The available literature supports liposomes as investigational platforms for antitubercular delivery; it does not yet establish shorter treatment duration or improved clinical outcomes in humans.

***Corresponding Author:** Sakshi Jagtap
Address: Final Year Bachelor of Pharmacy Student, Dr. Babasaheb Ambedkar Technological University, Pune, Maharashtra, India-412216.
Email ✉: sakshijagtap8151@gmail.com

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Future studies should link critical quality attributes with lesion pharmacokinetics, microbiological response and patient-relevant outcomes.

INTRODUCTION

Tuberculosis is an infectious disease caused mainly by M. tuberculosis and continues to impose a substantial health burden worldwide. The World Health Organization's 2025 global report documents the continuing scale of TB and the need to strengthen prevention, diagnosis and treatment [1]. Drug-susceptible pulmonary TB is generally treated with combinations of first-line medicines, while regimen selection and duration depend on disease status, drug susceptibility and current clinical guidance [2].

A major delivery challenge is the biological distribution of M. tuberculosis. Following inhalation, bacilli reach the lung and interact with alveolar macrophages. The pathogen can survive within host cells and may also occupy lesion microenvironments with distinct vascularity, oxygen tension, pH and tissue architecture. Consequently, plasma drug concentration alone may not represent exposure at all infected sites [12,17,18].

Nanocarrier-based delivery has been investigated to modify drug distribution, improve intracellular exposure or sustain release. Liposomes are of particular interest because their lipid bilayer and aqueous core can accommodate drugs with different physicochemical properties. Experimental work has evaluated liposomal isoniazid and rifampicin, including lung-associated, stealth and ligand-modified formulations [3-10]. The purpose of this review is to critically discuss the formulation science and evidence base, distinguishing conventional liposomes from other lipid-based or polymeric carriers.

2. REVIEW APPROACH

This narrative critical review synthesises selected peer-reviewed original research articles, review papers and authoritative TB guidance relevant to liposome architecture, preparation, drug loading, macrophage-associated delivery, pulmonary administration and preclinical evaluation. Foundational antitubercular liposome studies were considered alongside more recent work on ligand-functionalised vesicles and broader nanocarrier approaches. The review is not a systematic review or meta-analysis; no pooled effect estimate or formal risk-of-bias assessment was performed. Evidence from conventional liposomes is identified separately from findings involving polymeric microparticles, solid lipid nanoparticles, nanostructured lipid carriers or glucan-lipid particles.

3. TUBERCULOSIS BIOLOGY AND ANTITUBERCULAR DRUGS

3.1 Intracellular infection and lesion heterogeneity

Alveolar macrophages are among the first host cells to encounter inhaled M. tuberculosis. The interaction between the bacillus and host immunity influences whether infection is contained, progresses to active disease or persists in a latent state. Macrophage targeting is therefore a rational delivery objective, but it should not be equated with complete lesion targeting. TB lesions may contain cellular, fibrotic, necrotic and caseous regions, and drug penetration can vary across these compartments [12,17,18].

3.2 Principal first-line agents

Isoniazid is a prodrug activated by the mycobacterial catalase-peroxidase KatG. Its activated species interfere with InhA-dependent mycolic-acid synthesis, an essential process in mycobacterial cell-envelope formation [18]. Rifampicin binds the β-subunit of bacterial DNA-dependent RNA polymerase and inhibits transcription [19]. Pyrazinamide and ethambutol contribute complementary activity through different bacterial targets. The different solubility, ionisation, stability and lipid affinity of these agents mean that a combination formulation must be assessed drug by drug [2,13].

Table 1: First-line Antitubercular Drugs and Formulation Considerations. Compiled from TB Guidance and Pharmacological Literature [2,18,19].

Drug	Principal action	Formulation consideration
Isoniazid	KatG-activated inhibition of InhA and mycolic-acid synthesis	Relatively hydrophilic; aqueous-phase loading may be feasible, but retention and leakage require assessment.
Rifampicin	Inhibition of DNA-dependent RNA polymerase	Drug association with the lipid phase and chemical stability must be evaluated.
Pyrazinamide	Prodrug converted to pyrazinoic acid; activity depends on mycobacterial physiology	Compatibility, loading and release should be measured in the complete formulation.
Ethambutol	Interferes with arabinogalactan biosynthesis	Drug-specific loading and release data are required before co-formulation.

4. LIPOSOMES: STRUCTURE, COMPOSITION AND TYPES

Liposomes are closed vesicles formed by one or more phospholipid bilayers enclosing an aqueous compartment. Amphiphilic phospholipids orient their hydrophilic head groups toward the surrounding aqueous medium and their hydrophobic chains toward the bilayer interior. Hydrophilic drugs may be entrapped in the aqueous compartment, whereas lipophilic drugs may partition into the bilayer. Cholesterol is commonly incorporated to influence bilayer packing, permeability and physical stability [20-27].

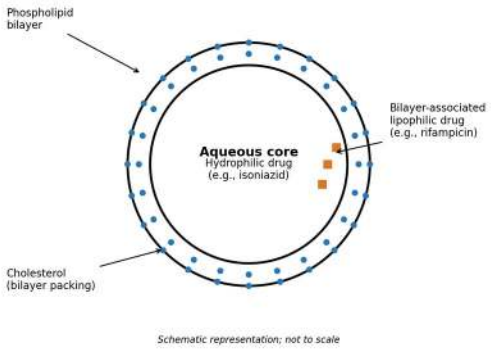

Figure 1: Schematic Structure of a Drug-Loaded Liposome. the Drawing Is Original and Conceptual; the Structural Principles Are Based on Published Liposome Literature [20-27].

Table 2: Structural Classes of Liposomes and Potential Formulation Relevance [20-27].

Liposome category	Structural feature	Potential relevance
Multilamellar vesicles (MLV)	Several concentric bilayers	May provide multiple bilayer compartments but can show heterogeneous size and loading.
Small unilamellar vesicles (SUV)	One relatively small bilayer vesicle	Useful when smaller vesicles and defined size distribution are required.
Large unilamellar vesicles (LUV)	One bilayer surrounding a larger aqueous volume	Can provide greater aqueous volume per vesicle than smaller unilamellar systems.
PEGylated/stealth liposomes	Hydrophilic polymer associated with the surface	May reduce rapid recognition by the mononuclear phagocyte system, depending on composition.

Liposome category	Structural feature	Potential relevance
Ligand-functionalised liposomes	Surface ligand such as mannose or transferrin	May promote receptor-associated interaction with selected cell populations.

These categories describe structure or surface design and do not, by themselves, establish therapeutic superiority. Vesicle size, polydispersity, lamellarity, surface charge, lipid composition and drug retention must be measured in the final product [21,22,25].

5. FORMULATION DEVELOPMENT AND PREPARATION

5.1 Selection of formulation components

The lipid composition should be selected according to drug solubility, intended route, desired release profile and storage conditions. Phosphatidylcholine-containing lipids are widely used as structural components, while cholesterol can reduce bilayer permeability and alter membrane order. Charged lipids or surface modifiers may be included to modify colloidal behaviour or biological interactions. However, changing lipid composition can also affect encapsulation, release, toxicity and manufacturing reproducibility [20,23,25,26].

5.2 Drug-loading strategies

Drug incorporation may occur during vesicle formation (passive loading) or after formation through an appropriate loading gradient or other active-loading approach. The choice depends on the drug's ionisation, solubility, membrane permeability and chemical stability. In dual-drug formulations, encapsulation efficiency, drug recovery and release should be quantified independently for each agent. A single combined loading value can conceal unequal incorporation, as illustrated by reported differences in rifampicin and isoniazid entrapment in mannosylated liposomes [9].

5.3 Preparation methods

Thin-film hydration involves dissolving lipid components in a suitable organic solvent, removing the solvent to produce a thin film, and hydrating the film with an aqueous phase. The resulting multilamellar vesicles may be reduced in size by extrusion, sonication or homogenisation. Reverse-phase evaporation forms a water-in-oil emulsion before solvent removal and can support aqueous drug entrapment. Solvent injection and microfluidic mixing provide alternative routes in which mixing conditions influence vesicle formation and size distribution [21-24]. The selected process must be followed by purification and testing for residual solvent, free drug and product consistency.

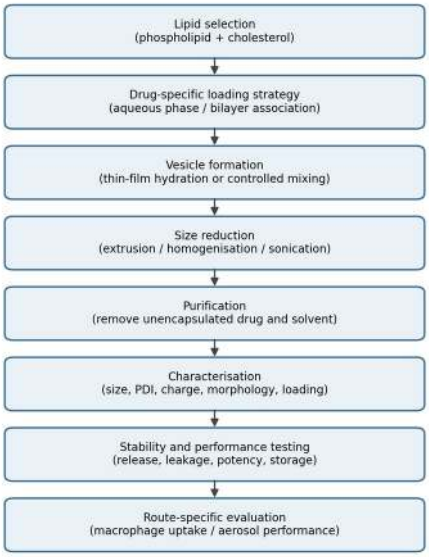

Figure 2: Proposed Workflow for Development of an Antitubercular Liposomal Formulation. This Original Process Schematic Summarises Established Preparation and Evaluation Steps [21-24].

5.4 Formulation-specific design considerations

For isoniazid, the aqueous compartment is a logical loading environment because of its hydrophilic character; however, high initial entrapment does not guarantee adequate retention during storage or dilution. Rifampicin has different physicochemical behaviour and may associate with the lipid bilayer, but chemical stability and drug-to-lipid ratio must be optimised. In a combination product, the formulation should preserve a therapeutically appropriate ratio during manufacture, storage, administration and release. The mannosylated dual-drug study by Shrivastava et al. is important because it directly measured the two drugs separately and demonstrated that entrapment was not equivalent for isoniazid and rifampicin [9].

6. TARGETED DELIVERY TO MACROPHAGES

Macrophage-associated delivery may occur through nonspecific phagocytic uptake or through interactions between a surface ligand and a cell receptor. Mannose-functionalised liposomes have been investigated to engage mannose-recognising receptors, while transferrin-functionalised nanoliposomes have been explored as a strategy for intracellular delivery of antitubercular bioactives [9,10,17]. The actual extent of uptake depends on ligand density, vesicle size, surface charge, protein adsorption and the biological state of the target cell.

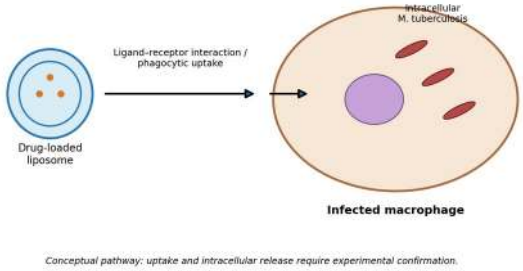

Figure 3: Conceptual Illustration of Ligand-Associated Liposome Uptake by an Infected Macrophage and Intracellular Drug Release. the Figure Is Original and Does Not Imply That All Vesicles Reach Every TB Lesion Compartment [9,10,12,17].

Cellular uptake is an intermediate endpoint, not a surrogate for cure. A formulation that accumulates in macrophages may still show limited access to extracellular bacilli or poorly vascularised caseous lesion cores. Accordingly, studies should assess intracellular drug concentration, bacterial viability, lesion distribution and relevant pharmacokinetic/pharmacodynamic relationships [12,15-17].

7. RESEARCH EVIDENCE FOR LIPOSOMAL ANTITUBERCULAR DELIVERY

7.1 Foundational liposome studies

Deol and colleagues evaluated lung-specific stealth liposomes containing isoniazid and rifampicin in experimental murine TB. The work reported improved antitubercular performance for selected liposome-encapsulated regimens compared with free drugs under the study conditions [3,4]. These findings provided an early preclinical rationale for modifying drug distribution, but animal results cannot establish efficacy or an appropriate dosing schedule in humans.

Dutt and Khuller compared liposomes with poly (lactide-co-glycolide) microparticles as sustained-release carriers for isoniazid and rifampicin. Liposomal preparations showed sustained in-vitro release and altered tissue disposition, while the microparticle platform showed different release behaviour. These results should be attributed to the individual carrier systems rather than generalised across nanocarriers [5]. Labana et al. subsequently investigated once-weekly administration of liposome-encapsulated isoniazid and

rifampicin in a murine TB model, reporting prolonged drug presence in plasma and selected organs [6].

7.2 Pulmonary delivery and macrophage localisation

Vyas et al. designed rifampicin-containing liposomal aerosols to improve delivery to alveolar macrophages. The study illustrates the importance of considering aerosol characteristics and pulmonary deposition in addition to vesicle size [8]. Pandey et al. further investigated lung-specific stealth liposomes in guinea pigs, extending preclinical evaluation beyond murine models [7]. These studies remain preclinical and do not demonstrate clinical effectiveness or replacement of standard multidrug therapy.

7.3 Ligand-functionalised and dual-drug systems

Shrivastava et al. developed mannosylated and non-mannosylated liposomes containing isoniazid and rifampicin. The study reported different entrapment efficiencies for the two agents and evaluated macrophage-associated delivery and antitubercular activity in experimental models [9]. In a later study, transferrin-functionalised small unilamellar vesicles were investigated for intracellular delivery of rifampicin-associated bioactive material and isoniazid in infected macrophages [10]. These studies support continued investigation of surface functionalisation, while the evidence remains preclinical.

Nongkhlaw et al. reported drug-loaded liposomes evaluated for macrophage targeting and infection models [11]. Glucan-lipid particles have also been investigated for targeted antitubercular delivery, but these particles are not conventional liposomes and should be treated as an adjacent lipid-based platform rather than direct evidence for liposome performance [14].

Table 3: Selected Original Studies Relevant to Antitubercular Liposomal or Related Lipid-Carrier Delivery [3-11,14].

Study	Carrier / drug approach	Main contribution and evidence boundary
Deol et al. [3,4]	Lung-specific stealth liposomes with isoniazid and rifampicin	Foundational mouse studies; altered distribution and preclinical therapeutic activity.
Dutt & Khuller [5]	Liposomes and PLG microparticles	Sustained-release comparison; findings are carrier-specific.
Labana et al. [6]	Once-weekly liposomal isoniazid and rifampicin	Murine study of prolonged tissue exposure and activity.
Pandey et al. [7]	Lung-specific stealth liposomes	Preclinical pharmacokinetic/chemotherapeutic evaluation in guinea pigs.
Vyas et al. [8]	Rifampicin liposomal aerosols	Pulmonary delivery and alveolar macrophage localisation.
Shrivastava et al. [9]	Mannosylated dual-drug liposomes	Characterisation and ex-vivo/in-vivo evaluation; unequal drug entrapment.
Shrivastava et al. [10]	Transferrin-functionalised nanoliposomes	Intracellular delivery study in infected macrophage models.
Nongkhlaw et al. [11]	Drug-loaded liposomes	Recent macrophage infection-model investigation.
Jaecklein et al. [14]	Glucan-lipid particles	Related lipid platform; not conventional liposomes.

8. CHARACTERISATION AND QUALITY ATTRIBUTES

A robust characterisation programme should connect formulation composition and process variables with critical quality attributes. Dynamic light scattering is commonly used to estimate hydrodynamic diameter and polydispersity index (PDI); electrophoretic light scattering can be used to estimate zeta potential under specified conditions. Transmission or scanning electron microscopy can provide information on

morphology, while validated chromatographic or spectrophotometric assays are required for drug quantification. Free and vesicle-associated drug should be separated using a validated method before calculating encapsulation efficiency [21,22,24,25].

Table 4: Suggested Quality Attributes and Analytical Approaches for Antitubercular Liposomes [21,22,24,25].

Attribute	Common approach	Interpretation / reporting need
Particle size and PDI	Dynamic light scattering	Report mean, distribution, dilution medium, temperature and replicate number.
Zeta potential	Electrophoretic light scattering	Interpret with pH, ionic strength and measurement conditions.
Morphology	TEM / cryo-TEM / SEM	Assess vesicle shape, lamellarity where possible and aggregation.
Encapsulation efficiency	Validated separation plus drug assay	Report separately for every drug and include recovery.
Drug loading	Drug mass relative to lipid or formulation mass	State calculation basis clearly.
In-vitro release	Dialysis or separation-based method	Validate sink conditions and distinguish membrane transport from vesicle release.
Stability	Physical, chemical and microbiological testing	Monitor size, PDI, leakage, lipid degradation, potency and sterility as applicable.

9. THERAPEUTIC APPLICATIONS AND FORMULATION CHALLENGES

9.1 Potential therapeutic applications

The principal proposed applications are intracellular delivery to macrophages, pulmonary administration, sustained drug release and co-delivery of multiple antitubercular agents. These approaches may alter exposure at selected biological sites and potentially reduce dosing frequency, but each proposed advantage requires direct experimental confirmation. For inhaled products, aerosol aerodynamic diameter, emitted dose, fine-particle fraction, device compatibility, lung deposition and pulmonary tolerability are distinct from the nanometre-scale diameter of the liposomes themselves [8,12,13,15].

9.2 Key formulation and translational challenges

A central challenge is the unequal encapsulation and release of combination drugs. If isoniazid and rifampicin leave the carrier at different rates, the local drug ratio may diverge from the intended regimen. Other concerns include leakage during storage or dilution, phospholipid oxidation or hydrolysis, vesicle aggregation, residual solvent, sterilisation-related changes and batch-to-batch variability. Scale-up from laboratory hydration or extrusion procedures to reproducible manufacturing requires control of mixing, temperature, shear, residence time and purification [20-26].

Biological translation is equally complex. Macrophage uptake does not prove adequate distribution to all lesion compartments, and surface ligands may alter protein adsorption, clearance or tolerability. For pulmonary formulations, the carrier must remain stable during aerosol generation and deposition. Before clinical use, studies should establish pharmacokinetics of free and encapsulated drug, lesion penetration, safety, microbiological response and compatibility with the complete recommended regimen [2,12,13,15].

Table 5: Principal Formulation and Translational Challenges with Suggested Development Priorities [2,12,13,15,20-26].

Challenge	Why it matters	Recommended development response
Unequal co-loading / release	May change the drug ratio at the infection site	Quantify each drug separately during manufacture, storage and release.
Leakage and instability	Can reduce delivered dose and alter exposure	Optimise lipid composition; perform real-time and accelerated stability studies.
Scale-up and batch variability	Can affect size, PDI, loading and reproducibility	Define process parameters and critical quality attributes early.
Sterilisation and sterility assurance	Heat or filtration may alter vesicles or fail to remove contaminants	Validate a compatible sterile manufacturing strategy.
Lesion penetration	Macrophage uptake may not reach caseous/necrotic regions	Measure drug levels in distinct lesion compartments.
Pulmonary delivery	Aerosol generation and deposition affect delivered dose	Evaluate aerodynamic performance, device compatibility and lung tolerability.
Limited clinical evidence	Preclinical efficacy does not establish patient benefit	Conduct appropriately designed clinical pharmacology and outcome studies.

10. FUTURE PERSPECTIVES

Future research should move beyond demonstrating cellular uptake or high encapsulation efficiency. Formulations should be designed around clinically meaningful questions: whether they improve exposure in relevant lesion compartments, maintain appropriate combination-drug ratios, reduce systemic toxicity, or simplify treatment without compromising microbiological efficacy. Comparative studies should include free-drug controls, clinically relevant multidrug regimens and appropriate carrier controls. Reporting should include complete composition, preparation parameters, drug recovery, release conditions, stability and biological model limitations.

Translation will also require manufacturability, scalable production, validated analytical methods, acceptable cost and a clear regulatory strategy. For inhaled systems, device performance and patient usability must be assessed alongside formulation properties. Clinical studies are required before claims of reduced dosing frequency, shorter treatment, improved adherence or higher cure rates can be made.

DISCUSSION

The literature demonstrates a consistent scientific rationale for liposomal antitubercular delivery: liposomes can carry hydrophilic and lipophilic compounds, interact with phagocytic cells and modify drug disposition. The strongest direct evidence consists of preclinical studies involving isoniazid and rifampicin, including lung-specific stealth, aerosolised and ligand-modified formulations [3-10]. More recent targeted systems extend the concept to receptor-associated intracellular delivery [10,11].

Nevertheless, the evidence base is heterogeneous in formulation composition, route, animal model, drug combination and outcome measures. It is therefore inappropriate to compare reported outcomes as though they came from a single standardised platform. Findings from polymeric microparticles or glucan-lipid particles should not be attributed to liposomes [5,14]. Similarly, improved macrophage uptake should not be interpreted as proof of improved lesion-wide exposure. A translationally useful formulation must demonstrate a reproducible relationship between critical quality attributes, pharmacokinetics, lesion distribution, microbiological response and safety.

CONCLUSION

Liposomal nanocarriers represent a promising but investigational platform for targeted antitubercular drug delivery. Their bilayer and aqueous compartments permit the incorporation of drugs with different physicochemical properties, while surface modification may support macrophage-associated uptake.

Preclinical studies involving isoniazid, rifampicin and newer ligand-functionalised formulations provide a rationale for continued development. However, unequal drug loading and release, lesion heterogeneity, stability, scale-up, pulmonary performance and the absence of robust clinical evidence remain major limitations. Liposomal formulations should not currently be regarded as replacements for standard TB treatment. Further work must demonstrate reproducible manufacture and clinically meaningful improvements in drug exposure, safety and treatment outcomes.

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CONFLICT OF INTEREST

The author declares no competing interests. Confirm before submission.

AUTHOR CONTRIBUTION

Sakshi Jagtap: literature collection, synthesis of published evidence and manuscript preparation. Confirm that this statement accurately reflects the author's contribution.

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