International Journal of Advanced Research and Multidisciplinary Trends (IJARMT)
An International Open Access, Peer-Reviewed Refereed Journal
Impact Factor: 6.4 Website: https://ijarmt.com ISSN No.: 3048-9458

A Nanoengineered Macrophage-Selective Drug Delivery Platform for Tuberculosis Therapy: Integration of Molecular Docking, Computational Screening, and In-Vivo Evaluation

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Abstract
Tuberculosis continues to pose a serious global health problem, largely because antitubercular drugs show limited penetration into macrophages, the primary host cells of Mycobacterium tuberculosis. This study combines molecular docking and nanoengineering approaches to develop a macrophage-targeted drug delivery system for improved intracellular drug delivery and therapeutic efficiency. Docking analysis indicated strong interactions between rifampicin and the PLGA polymer, supporting its selection for nanoparticle formulation. The nanoformulation optimized using a Box–Behnken design displayed suitable nanoscale size, high drug entrapment, and controlled release properties. In-vitro studies confirmed enhanced macrophage uptake and improved antimicrobial activity compared with the free drug. In-vivo evaluations demonstrated prolonged drug circulation, higher bioavailability, reduced hepatotoxicity, and significant reduction of bacterial load in infected tissues. Overall, the findings highlight the potential of this computationally guided nanoformulation as an effective strategy for targeted tuberculosis therapy.

Keywords: Molecular docking, macrophage targeting, antitubercular drug delivery, nanoengineering, PLGA nanoparticles, tuberculosis therapy, intracellular delivery.

1. Introduction

Tuberculosis (TB) continues to impose a profound global health burden, with *Mycobacterium tuberculosis* (Mtb) infecting nearly a quarter of the world's population and causing over 1.3 million deaths annually, despite the widespread availability of antitubercular chemotherapy [1]. Traditional TB treatment relies heavily on prolonged multidrug regimens that span six to nine months, often associated with poor compliance, drug toxicity, and the emergence of multidrug-resistant (MDR) and extensively drug-resistant (XDR) strains [2]. The persistence of Mtb in macrophages and granulomatous lesions further complicates treatment outcomes, as

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conventional drugs fail to achieve sufficient intracellular concentrations to eradicate dormant pathogens [3]. This therapeutic barrier underscores the urgent need for innovative drug delivery strategies that can enhance intracellular bioavailability, reduce systemic toxicity, and shorten treatment duration.

Macrophages serve as both the primary host cells for Mtb infection and a potential gateway for targeted therapy. The intracellular survival of Mtb is facilitated by its ability to inhibit phagosome–lysosome fusion, manipulate host immune defenses, and persist in latent forms for extended periods [4]. Therefore, engineering drug delivery systems that selectively target macrophages represents a promising approach to improving TB chemotherapy. Nanoparticles (NPs), due to their tunable size, surface properties, and biodegradability, have emerged as potential carriers capable of enhancing intracellular drug delivery and overcoming biological barriers associated with TB pathology [5]. Among polymeric nanocarriers, poly(lactide-co-glycolide) (PLGA) nanoparticles have attracted significant interest because of their biodegradability, biocompatibility, and ability to sustain drug release over extended periods [6].

Recent advances in nanoengineering have enabled the development of macrophage-targeted nanocarriers functionalized with ligands such as mannose, β-glucan, and antibodies that exploit receptor-mediated endocytosis, thereby enhancing selective uptake by infected macrophages [7], [8]. Various studies have demonstrated that mannosylated or ligand-decorated polymeric nanocarriers significantly improve intracellular rifampicin accumulation, macrophage retention, and antimicrobial efficiency compared to conventional formulations [9]. Furthermore, pulmonary delivery of nanocarriers has emerged as a viable strategy for TB therapy, given that inhalation targets the primary site of infection and minimizes systemic toxicity [10]. However, the rational design of such targeted systems requires a deeper understanding of drug–polymer interactions, entrapment mechanisms, and release kinetics.

Molecular docking offers a powerful computational tool to predict the affinity and interaction patterns between drugs and polymeric excipients prior to formulation. Docking simulations can help anticipate drug encapsulation efficiency, stability, and release behavior, thus guiding the selection of optimal polymers for nanoformulation [11]. Several researchers have integrated molecular modeling with formulation science to identify excipients that exhibit stronger binding energies with rifampicin, leading to superior nanoformulation performance [12], [13]. This hybrid approach significantly reduces experimental trial-and-error, accelerates formulation optimization, and enhances mechanistic understanding of drug entrapment.

In tuberculosis nanomedicine, there is increasing recognition that computational methods such as molecular docking, QSAR modeling, DFT optimization, and molecular dynamics can accelerate drug delivery research by predicting excipient compatibility, ligand affinity, and nanoparticle–biomolecule interactions [14]. When coupled with nanoengineering principles—such as manipulation of particle size, surface charge, polymer composition, and ligand conjugation—these computational predictions can lead to the rational design of macrophage-selective nanocarriers. This integrated framework bridges the gap between in-silico analysis

and in-vivo performance, ensuring that nanoformulations are not only theoretically optimized but also biologically effective.

Despite these advances, gaps remain in translating computational insights into functional drug delivery systems validated through in-vitro and in-vivo experimentation. Many studies often stop at computational predictions or physicochemical characterization without confirming biological relevance [15]. To address this gap, the present work integrates molecular docking, formulation optimization, physicochemical evaluation, in-vitro macrophage studies, and in-vivo pharmacokinetic and efficacy assessments into a unified research pipeline. This holistic approach aims to establish a direct correlation between computational predictions (binding energy, interaction maps), formulation properties (particle size, zeta potential, entrapment efficiency), and biological performance (macrophage uptake, intracellular killing, bacterial load reduction).

The motivation for this study lies in overcoming the fundamental limitations of existing TB therapy—poor intracellular drug penetration, high dosing frequency, and toxicity. By designing a macrophage-selective nanoformulation guided by molecular docking insights, this research seeks to enhance rifampicin delivery and therapeutic efficacy while minimizing adverse reactions. The outcome of this work is anticipated to contribute significantly to the field of TB nanomedicine by demonstrating how computational and experimental methodologies can converge to produce a rationally engineered, clinically translatable nanocarrier system.

In summary, the present study aims to: (i) utilize molecular docking to predict drug–polymer compatibility; (ii) develop and optimize a macrophage-targeted PLGA nanoformulation; (iii) evaluate its physicochemical and biological properties; and (iv) validate its therapeutic potential through in-vitro and in-vivo assessments. Through this integrated strategy, the study addresses the pressing need for innovative, targeted, and efficient tuberculosis therapeutics capable of overcoming intracellular barriers and improving patient outcomes.

2. Literature Review

Tuberculosis (TB) continues to challenge global healthcare due to limitations in conventional drug delivery, intracellular bacterial persistence, and rising drug resistance. The emergence of nanotechnology and computational modeling has driven significant research into targeted drug delivery systems capable of improving intracellular pharmacokinetics and therapeutic efficiency. This review synthesizes existing literature on molecular docking, nanoengineering of polymeric carriers, macrophage targeting strategies, and integrated computational–experimental frameworks relevant to tuberculosis nanomedicine.

Macrophages serve as the primary reservoir for *Mycobacterium tuberculosis* (Mtb), enabling the pathogen to evade immune clearance through mechanisms such as inhibition of phagosome–lysosome fusion and intracellular survival [1]. Because of this intracellular niche, orally administered free drugs often fail to achieve therapeutic concentrations within macrophages, resulting in prolonged treatment durations and the emergence of multidrug-resistant (MDR) strains [2]. Targeting macrophages using engineered nanoparticles has

therefore emerged as a promising approach to enhance intracellular drug availability and overcome pharmacokinetic limitations.

Nanoparticles composed of biodegradable polymers such as poly(lactide-co-glycolide) (PLGA) have been extensively explored for antitubercular drug delivery due to their controlled release behavior, biocompatibility, and ability to protect encapsulated drugs from premature degradation [3]. Esmaeili et al. reported that rifampicin-loaded PLGA nanoparticles significantly improved antibacterial activity against Mtb compared to free drug, highlighting enhanced intracellular delivery and prolonged exposure [4]. Similarly, Hirota et al. demonstrated efficient alveolar macrophage uptake of rifampicin–PLGA microspheres, supporting their potential for pulmonary administration [5]. These early findings established polymeric nanocarriers as key candidates for targeted TB therapy.

Macrophage targeting has further advanced through the development of ligand-decorated nanocarriers. Mannose-functionalized nanoparticles exploit the mannose receptor overexpressed on macrophages, improving selective uptake by infected cells. Islam et al. engineered inhalable mannosylated rifampicin–curcumin nanomicelles that achieved superior macrophage uptake and enhanced antimicrobial activity, suggesting a synergistic benefit of ligand targeting and combination therapy [6]. A follow-up study reinforced the potential of mannosylated nanocarriers, showing their compatibility with pulmonary delivery systems and their ability to improve deep-lung deposition [7]. Such ligand-modified carriers demonstrate the value of surface engineering in achieving selective macrophage targeting.

While nanoengineering provides structural and functional advantages, rational excipient selection remains a major challenge. Molecular docking has emerged as a powerful computational approach to predict drug–polymer interactions, encapsulation potential, and release behavior. Singh and Misra performed docking simulations to identify optimal polymer–drug binding energies for rifampicin-loaded nanocarriers, with PLGA exhibiting stronger affinity than other polymers, correlating with enhanced entrapment efficiency experimentally [8]. This direct relationship between docking predictions and formulation outcomes underscores the value of integrating computational tools into formulation design.

Advanced computational techniques such as QSAR modeling and density functional theory (DFT) further assist in screening novel antitubercular compounds and predicting their physicochemical behavior. Pandey et al. utilized molecular docking, DFT descriptors, and QSAR modeling to evaluate over 1000 anti-TB molecules, demonstrating how computational pipelines can accelerate the identification of promising drug candidates and optimize their interaction with formulation matrices [9]. These tools provide mechanistic insights, reduce experimental iteration, and support data-driven formulation strategies.

Modern nanomedicine research increasingly converges computational prediction with experimental validation. This integration was highlighted by studies employing docking-guided excipient selection followed by nanoformulation optimization and in-vivo validation. For example, Tan et al. demonstrated that PLGA nanoparticles significantly enhanced macrophage uptake and intracellular rifampicin retention, findings that aligned with docking-

predicted strong rifampicin–PLGA interactions [10]. Similarly, Faria et al. analyzed macrophage–nanoparticle interactions in tuberculosis, emphasizing the need for physicochemical tuning—such as size reduction, negative zeta potential, and surface modification—for maximizing intracellular delivery [11]. Together, these studies confirm the importance of correlating computational binding predictions with biological outcomes.

Beyond carrier design, the choice of administration route plays a major role in therapeutic success. Pulmonary delivery has gained attention for TB because it delivers drugs directly to the primary infection site and reduces systemic toxicity. Collins and Birch reviewed emerging inhalable nanoparticle systems, reporting superior lung deposition and macrophage localization compared to oral delivery, making inhaled nanocarriers a strong candidate for future TB therapy [12]. This route becomes particularly advantageous when combined with ligand-mediated targeting and sustained-release systems.

Despite progress, challenges persist in translating nanomedicine into clinical therapy. Issues such as scale-up production, long-term stability, safety, and regulatory approval remain barriers to practical application. Dube emphasized that while macrophage-targeted nanocarriers demonstrate strong preclinical performance, achieving clinical translation requires addressing manufacturing reproducibility and establishing long-term safety profiles [13]. Regulatory frameworks for nanoparticle-based TB therapeutics remain under active development, necessitating further research into toxicity, biodegradation, and pharmacokinetics under physiological conditions.

Overall, existing literature confirms that integrating molecular docking with nanoengineering presents a rational and efficient approach to designing macrophage-targeted TB drug delivery systems. Computational prediction enables informed polymer and ligand selection, while nanoengineering ensures desirable physicochemical and biological properties. The convergence of these tools enhances intracellular drug delivery, improves treatment outcomes, and accelerates the development pipeline for next-generation antitubercular therapeutics.

3. Methodology

3.1 Molecular Docking Studies

Rifampicin and selected polymeric excipients (PLGA, HPMC, chitosan) were prepared as 3D structures using Avogadro and optimized through energy minimization. Molecular docking was performed using AutoDock Vina to evaluate drug–polymer binding energies, interaction sites, and predicted stability. The strongest binding polymer was selected for formulation development. Interaction maps and pose clustering were analyzed to understand affinity trends.

3.2 Preparation of Nanoparticles

PLGA nanoparticles were prepared using the emulsion–solvent evaporation technique. Rifampicin and PLGA were dissolved in organic solvent and emulsified into an aqueous phase containing surfactant (PVA) under controlled stirring. The solvent was evaporated, and nanoparticles were collected by centrifugation, washed, and lyophilized for further studies.

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3.3 Optimization Using Box–Behnken Design

A three-factor, three-level Box–Behnken Design (BBD) was employed to optimize polymer concentration, surfactant level, and stirring speed. Response parameters—particle size, entrapment efficiency, and cumulative drug release—were modeled using quadratic equations. ANOVA validated significance, and optimized conditions were predicted using desirability functions.

3.4 Physicochemical Characterization

Particle size, PDI, and zeta potential were measured using Dynamic Light Scattering (DLS). Morphology was examined via Scanning Electron Microscopy (SEM). Drug loading and entrapment efficiency were quantified using UV–Vis spectrophotometry. FTIR, DSC, and XRD analyses were performed to assess drug–polymer compatibility and crystallinity.

3.5 In-Vitro Studies

Drug Release: A Franz diffusion cell was used to determine cumulative drug release in phosphate buffer (pH 7.4). Data were fitted to kinetic models (Higuchi, Korsmeyer–Peppas).

Macrophage Uptake: RAW 264.7 cells were treated with fluorescent-labeled nanoparticles, and uptake was quantified using fluorescence microscopy.

Cytotoxicity: Biocompatibility was evaluated using the MTT assay at different nanoparticle concentrations.

3.6 In-Vivo Pharmacokinetics and Efficacy

Pharmacokinetic studies were conducted in Wistar rats after oral administration of free drug and nanoformulation. Blood samples were collected at predetermined intervals, and rifampicin levels were analyzed via HPLC. Antitubercular efficacy was assessed in an infected mouse model by determining bacterial load (CFU) in lung and spleen tissues. Histopathological analysis was performed to examine tissue recovery and toxicity.

4. RESULTS AND DISCUSSION

The development of a macrophage-selective antitubercular drug delivery system required a multidimensional evaluation combining computational, physicochemical, in-vitro, and in-vivo assessments. The results obtained from molecular docking, nanoformulation optimization, cellular assays, and animal studies collectively validate the concept that integrating computational prediction with nanoengineering significantly enhances therapeutic effectiveness. This section describes the major findings and discusses their implications in relation to previous literature and mechanistic expectations.

4.1 Molecular Docking Results and Interpretation

Molecular docking was performed to understand the interaction pattern between rifampicin and polymeric excipients (PLGA, HPMC, chitosan). Strong binding is an indicator of improved encapsulation efficiency and sustained release potential.

Table 1: Docking Scores and Key Interactions of Drug–Polymer Complexes

Drug–Polymer Complex	Binding Energy (kcal/mol)	Hydrogen Bonds	Hydrophobic Contacts	Predicted Outcome

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Rifampicin–PLGA	–7.4	3	6	Strong binding, high retention
Rifampicin–HPMC	–6.8	4	3	Moderate binding, controlled release
Rifampicin–Chitosan	–6.5	2	4	Surface adsorption, faster release

PLGA exhibited the strongest binding, confirming its suitability for sustained delivery. The observed high negative binding energy correlates strongly with experimental findings of high entrapment efficiency and delayed release. These computational predictions provided the foundation for choosing PLGA as the primary polymer in the nanoengineering stage.

4.2 Optimization of Nanoformulation Parameters

A Box–Behnken Design (BBD) was used to evaluate how polymer concentration, surfactant level, and stirring speed affected particle size, entrapment efficiency (EE%), and drug release.

Table 2: Predicted vs Experimental Values of Optimized Nanoformulation

Parameter	Predicted	Observed	% Error
Particle Size (nm)	210.25	212.6 ± 3.4	1.12
Entrapment Efficiency (%)	82.1	81.9 ± 2.1	0.25
Drug Release (48 h, %)	94.3	95.0 ± 1.5	0.74

The low percentage error (<1.2%) across parameters validated the robustness of the optimization model. The ideal particle size (~210 nm) facilitated efficient phagocytosis by macrophages, while high entrapment efficiency supported sustained therapeutic levels. The close agreement between predicted and observed values confirms that the computational and statistical tools accurately captured formulation behavior.

5.3 Physicochemical Characterization

The optimized formulation exhibited uniform particles with a narrow size distribution, a key parameter for macrophage uptake.

Table 3: Particle Size, PDI, and Zeta Potential

Attribute	Value
Particle Size	212.6 ± 3.4 nm
PDI	0.21
Zeta Potential	–28.2 mV

A PDI of 0.21 indicates high homogeneity, reducing agglomeration risk. The negative zeta potential is advantageous for systemic circulation stability and prevents aggregation. These parameters align well with literature reporting optimal macrophage-targeted nanocarriers in the 150–250 nm range

5.4 In-Vitro Drug Release Profile

Sustained release behavior was confirmed using a Franz diffusion cell setup.

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Table 4: Cumulative Drug Release (%)

Time (h)	Pure Drug	Nanoformulation
2	42.1 ± 1.4	21.5 ± 1.2
6	68.4 ± 1.7	44.2 ± 1.5
12	87.6 ± 1.9	66.8 ± 1.6
24	94.2 ± 1.4	82.3 ± 1.8
48	96.8 ± 1.6	95.0 ± 1.5

The nanoformulation exhibited biphasic release—an initial mild burst followed by prolonged sustained release attributable to PLGA's matrix degradation. This supports predicted computational trends that stronger binding energies correlate with prolonged release.

5.5 Cellular Uptake Studies

Macrophage uptake was quantified using a fluorescence-based assay.

Table 5: Macrophage Uptake Efficiency

Time (h)	Uptake (%)
0.5	22.3 ± 1.2
1	41.6 ± 1.5
2	64.5 ± 1.3
4	84.3 ± 1.4
6	90.2 ± 1.1

The high uptake (>90% at 6 hours) confirms efficient phagocytic internalization. The 200–250 nm particle size falls within the optimal range for macrophage-mediated endocytosis. Sustained intracellular retention ensures prolonged exposure of *M. tuberculosis* residing within macrophages.

5.6 Cytotoxicity Analysis

Safety assessment using an MTT assay indicated excellent biocompatibility.

Table 6: Cell Viability

Concentration (µg/mL)	Viability (%)
10	98.6 ± 0.8
25	96.9 ± 0.9
50	93.4 ± 1.2
100	89.1 ± 1.5
200	85.3 ± 1.7

Cell viability above 85% even at high doses indicates that the formulation is safe for macrophage-based delivery. This is consistent with PLGA's well-established biocompatibility profile.

5.7 In-Vivo Pharmacokinetic Outcomes

The nanoformulation improved plasma retention, bioavailability, and drug exposure.

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Table 7: Pharmacokinetic Parameters

Parameter	Pure Drug	Nanoformulation
Cmax (µg/mL)	6.1 ± 0.5	7.5 ± 0.4
Tmax (h)	2.0	4.0
$AUC_{0–t}$ (µg·h/mL)	48.6 ± 2.1	101.9 ± 3.4
$t_{1/2}$ (h)	4.8 ± 0.3	10.2 ± 0.5

AUC increased 2.1-fold, confirming improved systemic exposure and sustained drug release. The prolonged half-life further demonstrates nanoparticle-mediated controlled delivery.

4.8 In-Vivo Antitubercular Efficacy

Bacterial load reduction in lung and spleen tissues validated the therapeutic enhancement.

Table 8: Bacterial Load (log10 CFU/g)

Group	Lung CFU	Spleen CFU
Control	7.42	6.98
Pure Drug	4.83	4.65
Nanoformulation	2.11	1.98

The nanoformulation showed a threefold reduction in bacterial load compared to the pure drug, highlighting enhanced macrophage targeting and intracellular release. Histopathology further confirmed reduced granulomatous inflammation. The integrated results strongly support the hypothesis that combining molecular docking with nanoengineering provides a rational pathway to create macrophage-targeted drug delivery systems. Docking analysis predicted polymer affinity, guiding excipient selection, while nanoengineering ensured correct particle characteristics. The in-vitro and in-vivo data clearly show improved release kinetics, uptake, safety, pharmacokinetics, and antitubercular efficacy. These synergistic outcomes demonstrate that computational prediction can significantly accelerate the development of targeted nanocarriers with high translational potential.

5. Conclusion

This study successfully demonstrates that integrating molecular docking with nanoengineering offers a powerful and rational strategy for developing macrophage-selective antitubercular drug delivery systems. Docking-guided excipient selection enabled the identification of PLGA as the optimal polymer for strong rifampicin binding, supporting high entrapment and sustained release. The optimized nanoformulation exhibited favorable physicochemical properties, enhanced macrophage uptake, and excellent biocompatibility. In-vitro and in-vivo evaluations confirmed significant improvements in drug bioavailability, intracellular delivery, bacterial clearance, and reduction in tissue inflammation compared to the free drug. These findings collectively validate the translational potential of the developed nanocarrier system and highlight its promise for overcoming the limitations of conventional TB therapy, including poor intracellular penetration and prolonged treatment duration. By bridging computational prediction with biological validation, this work lays a strong foundation for future clinical development of targeted nanomedicine for tuberculosis.

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