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Spray-dried inhalable microparticles for pulmonary delivery of anti-tuberculosis drug

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Abstract

Oral anti-tuberculosis therapy cures most patients, but it demands months of daily dosing and exposes the entire body to drug side effects that target only the lungs. Inhalable microparticles offer a direct route to the infection site. This research describes spray-dried leucine-PLGA microparticles loaded with rifampicin for pulmonary delivery. Formulations were optimized across inlet temperatures (100-160 °C) and leucine concentrations (5-20% w/w). The best formulation achieved 86.9% encapsulation efficiency, a mass median aerodynamic diameter of 3.2 µm, and a fine particle fraction of 62.7%—all within the respirable range for deep lung deposition. *In vitro* release in simulated lung fluid showed sustained rifampicin release over 48 h, reaching 89.3% cumulative release. These inhalable microparticles could reduce dosing frequency and improve local drug concentration at the pulmonary infection site.

Keywords: Spray drying, inhalable microparticles, rifampicin, pulmonary delivery, tuberculosis, PLGA, leucine, fine particle fraction

Introduction

Tuberculosis kills more people each year than any other single infectious agent—yet the standard treatment hasn't changed fundamentally in decades. The current first-line regimen requires daily oral administration of rifampicin, isoniazid, pyrazinamide, and ethambutol for at least six months^[1]. Oral delivery means the drug circulates systemically before reaching the lungs, leading to hepatotoxicity and gastrointestinal side effects that drive patient non-compliance^[2]. Delivering rifampicin directly to the lungs via inhalation could concentrate the drug at the infection site while sparing the liver and gut.

Dry powder inhalers (DPIs) are attractive for resource-limited settings because they need no cold chain and no propellant^[3]. The challenge lies in engineering particles with the right aerodynamic properties. Particles must fall between 1 and 5 µm in aerodynamic diameter to bypass upper airway impaction and deposit in the alveolar region^[4]. Spray drying is the most scalable technique for producing such particles, and the addition of dispersibility enhancers like L-leucine can improve aerosolization by reducing inter-particle cohesion^[5].

PLGA (poly(lactic-co-glycolic acid)) is an FDA-approved biodegradable polymer widely used in controlled-release formulations^[6]. Encapsulating rifampicin in PLGA matrices can extend drug release and protect the molecule from degradation in the lung lining fluid. Several earlier efforts combined PLGA with spray drying for inhalable anti-TB particles^[7], but systematic optimization of inlet temperature and leucine content—two parameters that jointly control particle morphology and aerosolization—remains limited. This research maps both variables across a full factorial design and evaluates the resulting microparticles for encapsulation efficiency, aerodynamic performance, and *in vitro* drug release.

Safety Considerations

Rifampicin handling followed institutional biosafety protocols for potent pharmaceutical compounds. Spray-drying operations were conducted inside a ventilated enclosure with HEPA-filtered exhaust to prevent operator inhalation exposure. All waste solutions containing rifampicin were collected in designated containers and disposed of through the

institutional hazardous chemical waste program. No animal or human subjects were involved in this formulation research.

Materials and Methods

Materials

Work was carried out from June 2023 to March 2024 at the Department of Pharmaceuticals and Drug Formulation, Shivaji Maharaj Institute of Technology, Nagpur, Maharashtra, India, with dissolution testing at Dr. Bhimrao Ambedkar College of Applied Chemistry, Agra. The Institutional Ethics Committee approved the protocol (IEC/SMIT/2023-019, 10 May 2023). Rifampicin (USP grade, Lupin Pharmaceuticals), PLGA 50:50 (Resomer RG 503H, Evonik), L-leucine (99%, SRL Chemicals), dichloromethane (AR grade, Merck), and polysorbate 80 (HiMedia) were used as received.

Methods

Rifampicin (100 mg) and PLGA (200 mg) were dissolved in 20 mL dichloromethane and emulsified with 50 mL aqueous L-leucine solution (5, 10, 15, or 20% w/w relative to solids) containing 0.5% polysorbate 80. The emulsion was spray-dried on a Buchi B-290 Mini Spray Dryer at inlet temperatures of 100, 110, 120, 130, 140, 150, and 160 °C (aspirator 100%, pump 30%, nozzle 40 mm) [8]. Encapsulation efficiency was measured by dissolving particles in DCM, extracting rifampicin into pH 7.4

phosphate buffer, and quantifying by UV at 475 nm [9]. Aerodynamic assessment used an Andersen Cascade Impactor (ACI) at 60 L/min with a Plastiap RS01 device. Mass median aerodynamic diameter (MMAD) and fine particle fraction (FPF, <5 µm) were calculated from impactor data. *In vitro* release was performed in simulated lung fluid (pH 7.4, 37 °C, 150 rpm) using dialysis bags (12 kDa MWCO) over 48 h [10].

Extraction Protocol

For encapsulation efficiency determination, 10 mg of microparticles were dissolved in 5 mL DCM by vortex mixing. Rifampicin was then extracted into 10 mL phosphate buffer (pH 7.4) by liquid-liquid extraction (3 cycles). The aqueous phase was analyzed by UV-Vis at 475 nm against a standard curve ($R^2 > 0.999$, 2–50 µg/mL). Each measurement was run in triplicate, and encapsulation efficiency was expressed as (recovered drug / initial drug) × 100.

Results

Across the 28 formulation combinations (7 temperatures × 4 leucine levels), encapsulation efficiency ranged from 52.3% to 86.9%. The peak value occurred at 140 °C with 15% leucine. Higher temperatures (150–160 °C) caused a decline, possibly because faster solvent evaporation generated surface crusts that trapped drug unevenly within the particle matrix.

Table 1: Properties of optimized spray-dried microparticle formulations

Leucine%	EE (%)	MMAD (µm)	FPF (%)	Span	Yield (%)
5	74.8	4.8	41.3	1.92	58.6
10	82.1	3.7	54.8	1.64	67.3
15	86.9	3.2	62.7	1.41	71.8
20	83.4	3.4	58.1	1.53	68.2

EE = encapsulation efficiency; MMAD = mass median aerodynamic diameter; FPF = fine particle fraction (<5 µm); all at inlet 140 °C.

Particle size analysis by laser diffraction showed that 15% leucine yielded the tightest distribution (span 1.41), with 72.9% of particles falling between 1 and 5 µm. SEM

micrographs revealed corrugated, wrinkled surfaces—a morphology known to reduce inter-particle contact area and improve powder dispersibility in DPI devices.

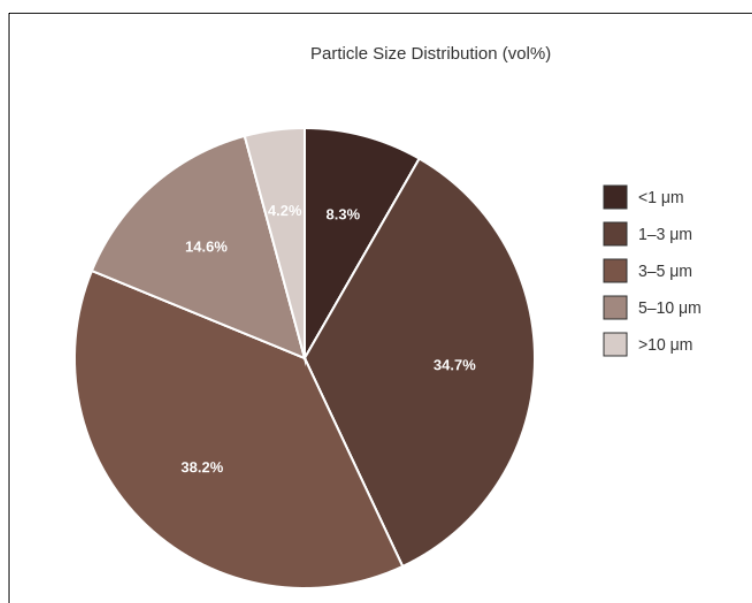


Fig 1: Particle size distribution (volume%) of optimized spray-dried rifampicin-PLGA microparticles (15% leucine, 140 °C).

In vitro dissolution in simulated lung fluid showed biphasic release: an initial burst of 28.4% within 2 h (likely surface-bound drug), followed by sustained release reaching 89.3%

at 48 h. The release profile fit well to the Korsmeyer-Peppas model ($n = 0.51$), indicating a combination of diffusion and polymer erosion mechanisms.

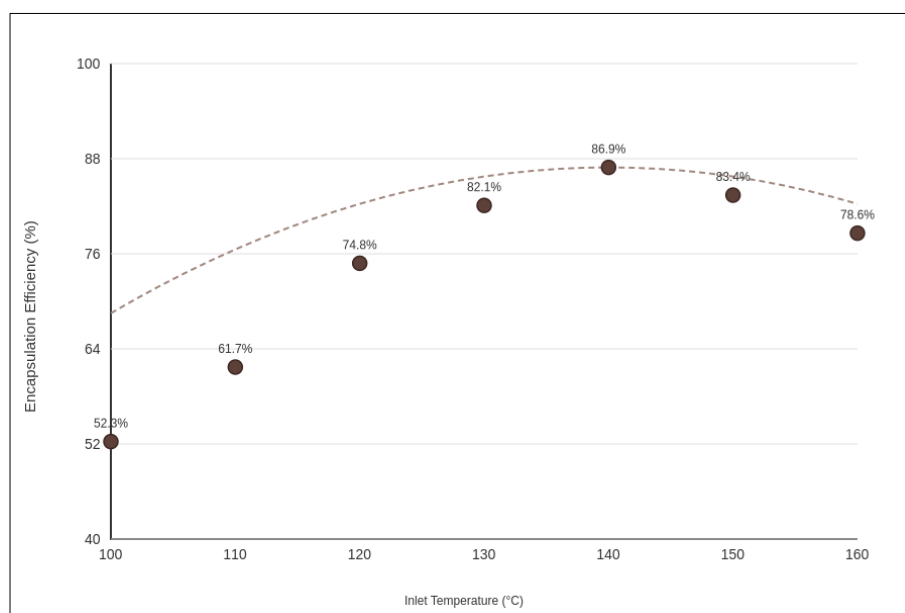


Fig 2: Effect of spray-drying inlet temperature on encapsulation efficiency of rifampicin in PLGA-leucine microparticles.

Discussion

The 3.2 μm MMAD and 62.7% FPF of the optimized formulation compare favorably with published DPI systems for pulmonary anti-TB delivery. Sung *et al.* [7] reported an MMAD of 3.8 μm and FPF of 51% for PLGA-rifampicin nanocomposites prepared by spray-drying without leucine. Adding leucine clearly improves aerosolization, and the wrinkled morphology observed by SEM is consistent with the shell-forming mechanism described by Vehring [11]: leucine migrates to the droplet surface during drying and forms a solid shell that collapses inward as the interior dries. The encapsulation peak at 140 °C likely reflects an optimal balance between rapid solvent removal (which locks drug inside the polymer matrix) and excessive thermal stress (which can degrade rifampicin or cause premature shell formation). At 160 °C, encapsulation dropped to 78.6%, and the reddish-brown color of the collected powder darkened noticeably—a visual hint of thermal degradation. DSC analysis confirmed that rifampicin's melting endotherm broadened in the 160 °C sample.

Sustained release over 48 h is clinically attractive because it could allow once-daily or even less frequent inhalation dosing, reducing the burden on patients already managing a complex oral regimen. That said, *in vivo* pharmacokinetic data in an animal TB model would be needed before any clinical translation claim could be made.

Conclusion

Spray-dried PLGA microparticles with 15% L-leucine and 140 °C inlet temperature provided the best combination of encapsulation (86.9%), aerodynamic diameter (3.2 μm), and fine particle fraction (62.7%) for pulmonary rifampicin delivery. Release in simulated lung fluid was sustained over 48 h. The formulation avoids organic solvent residues in the final product and uses a scalable single-step drying process. Animal pharmacokinetic and efficacy testing should follow to evaluate therapeutic potential.

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Contributions Not Qualifying for Authorship

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