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Polymeric Nanoparticle-Based Pulmonary Delivery of Isoniazid: Advances in Formulation Design, Controlled Release, and Tuberculosis Therapy

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ABSTRACT

Background: Tuberculosis remains the world's leading infectious cause of death, with an estimated 10.8 million people falling ill and about 1.25 million dying in 2023. Isoniazid has anchored first-line therapy for seventy years, yet it is given orally for months, distributes throughout the body, and reaches the infected lung only after a long detour through the gut and liver.

Objective: This review examines whether biodegradable polymeric nanoparticles delivered directly to the lung can improve the therapeutic index of isoniazid, and sets out what the formulation, aerosol and preclinical evidence actually supports.

Methods: Published work on pulmonary barriers, isoniazid pharmacology, polymer selection, nanoparticle fabrication, aerosol engineering, controlled release, characterization and preclinical testing was surveyed from PubMed, ScienceDirect, Scopus and Google Scholar, then synthesized into comparative tables.

Key Findings: PLGA, PLA, chitosan, alginate, gelatin and albumin have all been used to encapsulate isoniazid, though its high water solubility keeps encapsulation efficiency low in hydrophobic polyesters and pushes formulators toward polyelectrolyte systems or modified emulsion methods. Nanoparticles alone aerosolize poorly; nanoparticle-in-microparticle powders solve the aerodynamic problem while preserving nanoscale behaviour after deposition. Animal studies report prolonged lung and plasma drug levels and reduced dosing frequency, but most used drug combinations rather than isoniazid alone, and none has reached clinical trial.

Conclusion: Inhaled polymeric isoniazid nanoparticles are pharmaceutically feasible and preclinically promising. Translation now depends on raising drug loading, controlling burst release, proving aerosol and storage stability, and generating long-term pulmonary safety data.

Keywords: Isoniazid; Tuberculosis; Polymeric nanoparticles; Pulmonary drug delivery; PLGA; Chitosan; Dry powder inhaler; Alveolar macrophages; Controlled release

1. INTRODUCTION

1.1 Tuberculosis Burden and Current Pharmacological Approaches

The World Health Organization estimated 10.8 million new cases of tuberculosis and roughly 1.25 million deaths in 2023, keeping the disease above every other single infectious cause of death; notifications reached a record 8.2 million, about 400,000 people developed multidrug- or rifampicin-resistant disease, and treatment success falls from near 88% in drug-susceptible disease to roughly 68% in the resistant form [34]. Standard therapy gives isoniazid, rifampicin, pyrazinamide and ethambutol for two months then isoniazid with rifampicin for four more, a four-month rifapentine regimen is a non-inferior alternative, and resistant disease demands longer, more toxic bedaquiline-based regimens [34]. What unites them is the route: oral, systemic and prolonged.

1.2 Limitations of Oral Therapy and Rationale for Pulmonary Delivery

Oral therapy works when taken, but months of daily dosing produce loss to follow-up, irregular intake drives acquired resistance [7], and hepatotoxicity commonly interrupts treatment [28]. Pharmacokinetics compounds this, since oral isoniazid is largely acetylated on first pass and distributed to every tissue to treat a disease localized mainly in the



lung, leaving granuloma and intramacrophage concentrations marginal [7][24][28]. Inhaled delivery promises higher local concentration, lower systemic and hepatic exposure, direct access to infected alveolar macrophages and less frequent dosing from a depot, and the lung suits it, with an enormous thin-walled surface and low enzymatic activity [27]. Because extrapulmonary foci would go untreated, the realistic positioning is adjunctive [10].

1.3 Biodegradable Polymeric Nanoparticles: Role, Scope and Objectives

Inhaling a plain drug solution achieves little, since deposited drug is cleared quickly, whereas encapsulation in a biodegradable polymer slows release, resists clearance and places particles in the size range taken up by alveolar macrophages, exactly where the organism resides [6][18]. PLGA and its relatives are the most studied carriers, with parenteral regulatory precedent and degradation tunable through copolymer ratio and molecular weight [1][9], while chitosan, alginate and gelatin offer mucoadhesion, mild aqueous processing and, for chitosan, a positive charge favouring uptake [22][35]. This review follows the path from drug to deposited dose and closes with the barriers that have kept these systems out of the clinic.

2. PULMONARY ANATOMY AND PHYSIOLOGICAL BARRIERS TO DRUG DELIVERY

2.1 Anatomy of the Respiratory Tract and the Alveolar Region

The tract divides into conducting and respiratory zones across roughly twenty-three generations of branching; diameter falls at each generation while total cross-sectional area rises, so velocity drops sharply in the deep lung, and that gradient governs deposition, impaction dominating the fast upper airways, sedimentation the small airways and alveoli, diffusion only the smallest particles [5][14]. The respiratory zone ends in some 300 million alveoli giving 70-140 m², lined by flat type I and surfactant-secreting type II pneumocytes [27]. Three features matter: an air-blood barrier often under a micrometre, blood flow equal to the cardiac output, and no mucociliary escalator, so clearance rests on macrophages, dissolution and absorption [14]. Figure 1 maps the regions against their deposition mechanisms.

Region	Dominant mechanism	Aerodynamic size	Consequence
Extrathoracic (mouth, pharynx, larynx)	Inertial impaction	Above 5 µm	Swallowed; no therapeutic benefit
Conducting airways (trachea → bronchioles)	Impaction and sedimentation	About 3–5 µm	Cleared by the mucociliary escalator within about 24 h
Alveolar region (respiratory bronchioles, alveoli)	Sedimentation	About 1–3 µm	Target zone: macrophage uptake and long retention
Largely exhaled	Insufficient settling	About 0.1–1 µm	Follows the airstream; deposition minimum near 0.5 µm

Figure 1. *Regions of the respiratory tract and the particle deposition mechanisms operating in each, with the aerodynamic size ranges that favour them.[5]*

2.2 Mucociliary Clearance, Pulmonary Defence and Alveolar Macrophages

Ciliated conducting airways carry mucus that moves toward the pharynx at 4-10 mm per minute, clearing deposited particles within about 24 hours, while the mucin mesh traps or retards nanoparticles by size and surface chemistry; with cough, tight junctions and antimicrobial peptides this region is a formidable gauntlet, one more reason to aim deeper [27]. Alveolar macrophages phagocytose deposited matter within hours to days [14], a loss pathway for most medicines but an opportunity here, since the macrophage is the organism's principal niche, so a phagocytosed carrier delivers drug to the compartment sheltering the pathogen [7][18]. Low-micrometre particles are taken up most readily, those well below 200 nm less avidly and by other routes [6].

2.3 Particle Deposition, Lung Retention and Barriers to Nanoparticle Transport

Deposition follows aerodynamic diameter, breathing pattern and airway geometry; aerodynamic diameter folds in density and shape, so a large porous particle can behave like a small dense one, and slow deep inhalation favours the periphery [5][11]. Retention is separate, set by dissolution, mucociliary transport, macrophage uptake and absorption, and isoniazid dissolves and absorbs rapidly, precisely what a carrier must prevent [14][27]. Nanoparticles meet barriers in sequence: aerosol generation, regional deposition, mucus and surfactant, cellular uptake or epithelial transit. Surfactant forms a corona altering aggregation, uptake and release, so buffer data may not predict lung behaviour, and

particles evading macrophages may translocate into the circulation [14][27]. Figure 2 summarizes these barriers and the usual responses.

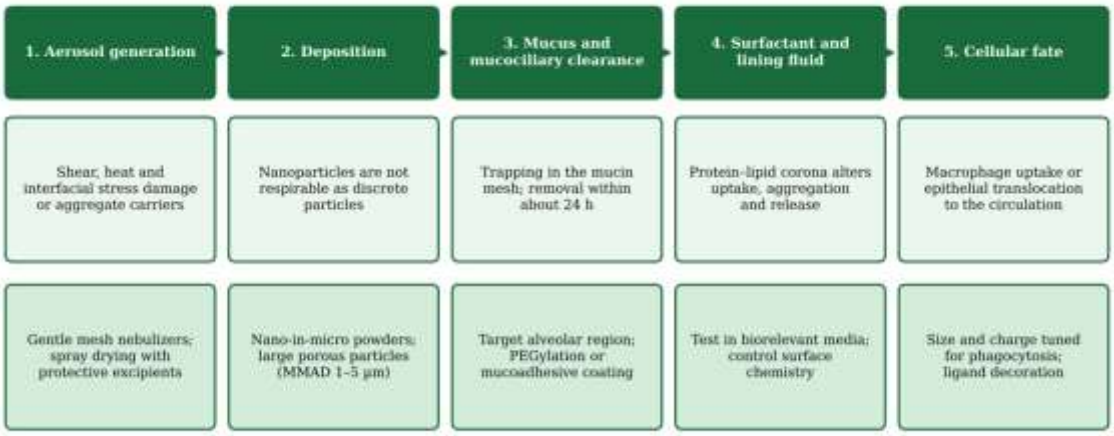


Figure 2. *Sequential barriers encountered by an inhaled polymeric nanoparticle, with the formulation responses commonly used to address each.[14][27]*

3. ISONIAZID: PHARMACOLOGICAL AND BIOPHARMACEUTICAL PROFILE

3.1 Physicochemical Properties and Mechanism of Action

Isoniazid, isonicotinic acid hydrazide, is a small crystalline solid of molecular weight 137.14 g/mol melting near 171-173 °C, freely soluble in water at about 125-140 mg/mL, poorly soluble in polymer solvents, with log P near -0.7 and largely unionized across the physiological range [24]. High solubility with high permeability places it in BCS Class I: excellent for oral absorption, awkward for encapsulation, as Section 3.3 explains. It is a prodrug activated by mycobacterial KatG, and the NAD adduct inhibits InhA, halting mycolic acid synthesis and killing dividing but not dormant organisms, part of why therapy is long and combined [7][24]. Table 1 collects these properties with their formulation consequences.

Table 1. Physicochemical and Pharmacological Profile of Isoniazid and Its Relevance to Nanoparticle Formulation

Property	Reported value	Relevance to pulmonary nanoparticle delivery
Chemical name	Isonicotinic acid hydrazide ($C_6H_7N_3O$) [24]	Small, simple hydrazide; chemically stable as a dry solid
Molecular weight	137.14 g/mol [24]	Low mass allows high molar loading per unit polymer, if entrapment can be achieved
Appearance and melting point	White crystalline powder; melts at about 171–173 °C [24]	Withstands spray drying inlet temperatures; crystallinity must be checked after processing
Aqueous solubility	Freely soluble; about 125–140 mg/mL at 25 °C [24]	Partitions into the aqueous phase during fabrication, lowering encapsulation efficiency and raising burst release
Lipophilicity (log P)	About −0.7 (hydrophilic) [24]	Poor affinity for hydrophobic polyesters such as PLGA and PLA; favours hydrophilic polyelectrolyte matrices
Ionization	Weakly basic hydrazide and pyridine nitrogen; largely unionized at physiological pH [24]	Limited scope for pH-driven partitioning control; ion pairing requires added counter-ions
BCS class	Class I (high solubility, high permeability)	Rapidly absorbed from the alveolar surface once free, so sustained effect depends entirely on the carrier
Mechanism of action	Prodrug activated by KatG; the NAD adduct inhibits InhA and blocks mycolic acid synthesis [7]	Requires intracellular access to replicating organisms, supporting macrophage-directed delivery
Metabolism	N-acetylation by NAT2; fast, intermediate and slow acetylator phenotypes [24]	Pulmonary delivery bypasses first-pass acetylation and may reduce phenotype-driven variability
Half-life	About 1 h (fast acetylators) to 3–4 h (slow acetylators) [24]	Short systemic half-life is the main argument for a sustained-release pulmonary depot
Conventional dose	5 mg/kg daily, to a maximum of 300 mg in adults [34]	Exceeds the mass deliverable by inhalation, so inhaled therapy is best positioned as adjunctive
Principal toxicity	Hepatotoxicity; peripheral neuropathy [28]	Reduced systemic exposure after pulmonary dosing is



Property	Reported value	Relevance to pulmonary nanoparticle delivery
		a key potential safety benefit

3.2 Pharmacokinetics, Conventional Dosage Forms and Therapeutic Limitations

Oral isoniazid is absorbed rapidly and almost completely, peaking within one to two hours, with low protein binding and wide distribution including cerebrospinal fluid and caseous material [24]. N-acetyltransferase 2 dominates metabolism, its polymorphism giving fast, intermediate and slow acetylators with half-lives from about one hour to four, while acetylisoniazid and hydrazine are implicated in hepatotoxicity [24][28]. Marketed at 5 mg/kg daily to a 300 mg maximum, usually in fixed-dose combinations that aid adherence but limit adjustment [34], its limitations belong to the regimen: long duration, systemic exposure far beyond what the lesion needs, hepatotoxicity, neuropathy requiring pyridoxine, and the adherence problem following from all of it [28].

3.3 Solubility and Implications for Nanoparticle Encapsulation

Here is the central formulation problem of this review. The solubility that helps oral bioavailability works against encapsulation in hydrophobic polyesters: in single emulsions or nanoprecipitation the drug partitions into the aqueous phase as polymer precipitates, so reported encapsulation efficiencies in PLGA are modest and loading lower still [15][32]. Responses include double water-in-oil-in-water emulsions, saturating the external phase with drug, pH adjustment, hydrophobic ion pairing, and polyelectrolyte systems such as chitosan-tripolyphosphate, where a hydrophilic matrix forms in water [23][26]. Burst release is the companion problem, since surface drug dissolves on contact with lung fluid [13].

3.4 Rationale for Localized Delivery, Resistance and Combination Therapy

A pulmonary formulation seeks a different exposure profile rather than a different drug: sustained concentrations in lung tissue and macrophages, lower peak plasma and hepatic exposure, dosing intervals in days [7]. Inhalable microparticles of isoniazid with rifabutin achieved intramacrophage concentrations and altered biodistribution relative to oral dosing, though clinical benefit is unproven [33]. Resistance arises mainly through katG and inhA promoter mutations, and isoniazid mono-resistance is the commonest worldwide [7][34]. Combination therapy is therefore not optional, so any inhaled product must sit within a multi-drug regimen; co-encapsulation is one answer, and carriers holding isoniazid with rifampicin or rifabutin have been prepared [25][34]. Sub-inhibitory lung levels are themselves a resistance risk.

4. NANOPARTICLES FOR PULMONARY DRUG DELIVERY

4.1 Classification of Nanocarriers and the Case for Polymeric Nanoparticles

Pharmaceutical nanoparticles are solid colloidal carriers of roughly 10-1000 nm, divided into matrix nanospheres and core-shell nanocapsules [21][32]. Liposomes have been dried into inhalable antitubercular powders and lipid nanoparticles offer tolerability and easy scale-up [7], but polymeric nanoparticles are mechanically robust, allow wider release control through polymer chemistry and better tolerate drying and aerosolization [9][21]. Their case rests on sustained release, payload protection, tunable surfaces and engineerable degradation; their limitations are modest loading of hydrophilic drugs, burst release, residual solvents, aggregation on storage, and a nanoscale size that is the wrong size for an aerosol [13]. Table 2 compares the main biodegradable polymers available.

4.2 Nanoparticles versus Microparticles: Size and Surface Properties

Microparticles of 1-5 µm deposit efficiently in the deep lung and are phagocytosed well, which is why most successful animal formulations have been microparticulate [18][25]. Nanoparticles offer surface area, dissolution advantage, longer retention and intracellular access but aerosolize poorly alone, so the resolution, developed in Section 7, is to assemble them into micron-sized carriers that disperse after deposition [16][31]. Size governs deposition, phagocytic uptake, mucus penetration and epithelial translocation [5][6], while cationic chitosan particles adhere to the airway surface and enter cells readily, whereas poly(ethylene glycol) coatings reduce opsonization and may aid mucus transport [22][27].

4.3 Nanoscale Particle Size versus Inhalable Aerodynamic Size

This distinction causes persistent confusion. A 200 nm particle delivered in isolation has an aerodynamic diameter far below 1 µm, follows the airstream and is largely exhaled, deposition reaching a minimum near 0.5 µm [5]; a nanoparticle is therefore not automatically respirable because it is small. What matters is the mass median aerodynamic diameter of the aerosol generated, not the hydrodynamic diameter measured in a vial, so an effective inhaled nanomedicine must present 1-5 µm at inhalation while behaving as nanoparticles after it lands [11][31].



Table 2. Comparison of Biodegradable Polymers Used in Pulmonary Drug Delivery

Polymer	Nature and degradation	Advantages	Limitations for inhaled isoniazid
PLGA	Synthetic polyester; bulk hydrolysis to lactic and glycolic acid [1]	Release tunable from weeks to months via copolymer ratio and molecular weight; extensive parenteral regulatory precedent [9]	Hydrophobic, so entrapment of isoniazid is low; acidic degradation products; no chronic inhalation precedent [4][15]
PLA	Synthetic polyester; slower hydrolysis than PLGA [1]	Very prolonged release; high mechanical strength	More hydrophobic and more crystalline than PLGA, worsening the loading problem; slow clearance from lung
Chitosan	Cationic polysaccharide; enzymatic degradation, chiefly by lysozyme [22]	Aqueous, solvent-free ionic gelation; mucoadhesive; positive charge aids cell uptake; compatible with respiratory epithelium [3]	Batch variability in molecular weight and deacetylation; poor solubility near neutral pH; limited long-term lung safety data [22]
Alginate	Anionic polysaccharide; ionotropic gelation with calcium [35]	Mild aqueous processing suited to hydrophilic drugs; used in inhalable antitubercular nanoparticles [35]	Weaker release control than polyesters; sensitive to ionic strength; source-dependent composition
Gelatin	Protein; prepared by desolvation, enzymatically degraded	Biocompatible; readily functionalized, including mannosylation for macrophage targeting	Animal origin and associated variability; chemical crosslinkers raise toxicity concerns
Albumin	Protein; desolvation or thermal crosslinking	Defined composition; abundant functional groups for conjugation; good tolerability	Cost; crosslinking chemistry; limited inhalation data
Hyaluronic acid	Anionic glycosaminoglycan; endogenous, enzymatically degraded	CD44-mediated macrophage targeting; used with mannosylated chitosan for isoniazid nano-powders [23]	Highly water-soluble, so rarely used alone; usually a complexing partner
PEGylated copolymers	Hydrophilic block grafted to a degradable backbone [27]	Reduced protein adsorption; improved mucus transport and colloidal stability	Adds synthetic complexity; may reduce the macrophage uptake that is desirable here

5. BIODEGRADABLE POLYMERS FOR ISONIAZID NANOPARTICLE FORMULATION

5.1 Synthetic Polyesters: PLGA and PLA

These polymers fall into synthetic polyesters, natural polysaccharides and proteins, differing in degradation chemistry, local pH effects, processing needs and inhalation precedent, which for most is thin [21]. PLGA hydrolyses to monomers cleared by normal metabolism [1], and its advantage is tunability, since glycolide fraction and molecular weight set degradation from weeks to months, backed by parenteral safety data [9]. Two cautions apply to inhalation: acidic degradation products lower local pH [13], and hydrophobicity poorly matched to isoniazid gives low encapsulation [15]; nor is there any precedent for chronic pulmonary administration in humans [4]. PLA degrades more slowly, useful for multi-week release but worse for a hydrophilic drug, so blends are a common compromise [1].

5.2 Chitosan, Proteins, Alginate and Polymer Blends

Chitosan is a cationic polysaccharide whose amino groups, protonated below about pH 6.5, provide mucoadhesion and membrane interaction [22], and for isoniazid it has a decisive advantage: nanoparticles form spontaneously by ionic gelation with tripolyphosphate in water at room temperature, entrapping a dissolved hydrophilic drug as the network forms [3]. Spray-dried chitosan nanoparticle powders have been made specifically for pulmonary isoniazid [26], and mannose-functionalized chitosan with hyaluronic acid gave isoniazid nano-powders taken up by cells without significant cytotoxicity [23]; batch variability and scarce long-term lung safety data remain limitations [22]. Mannosylated gelatin has carried isoniazid to macrophages and calcium-crosslinked alginate has given inhalable nanoparticles with prolonged drug levels [7][35]. Blends add what single polymers lack: chitosan-coated PLGA, PEGylation for mucus transport [27], and polyelectrolyte complexes tuned by mixing ratio.

5.3 Degradation, Biocompatibility and Polymer Selection Criteria

Polyesters degrade by bulk hydrolysis, water cleaving ester bonds throughout before mass loss, so release combines surface burst, pore diffusion and finally erosion [1][13]. Ionically crosslinked chitosan releases through swelling, ion exchange and network dissociation and degrades enzymatically by lysozyme [22]; for the lung, biocompatibility must be judged over repeated exposure, since chronic therapy means chronic polymer deposition [4]. A defensible selection would weigh compatibility with a very soluble drug, achievable loading, release over the dosing interval, degradation products, low-solvent processing, aerosolization behaviour, reproducibility and inhalation precedent [9][22]. Hydrophilic polyelectrolytes lead on the first criterion, PLGA on release control and regulatory familiarity, and hybrids attempt both.



Table 3. Preparation Methods for Polymeric Nanoparticles, with Advantages and Limitations

Method	Principle	Suited to	Advantages	Limitations
Nanoprecipitation (solvent displacement)	Polymer precipitates as a water-miscible organic solvent diffuses into an aqueous phase [12]	PLGA, PLA; lipophilic drugs	Simple, reproducible, low energy; narrow size distribution	Very low entrapment of water-soluble drugs such as isoniazid; dilute suspensions [15]
Single emulsion–solvent evaporation	Oil-in-water emulsion of polymer solution, hardened by solvent removal [32]	Polyesters; lipophilic drugs	Well established; scalable with homogenization	Chlorinated solvent residues; high energy input; poor for hydrophilic drugs
Double emulsion (w/o/w)	Inner aqueous drug phase emulsified in polymer solution, then in outer aqueous phase [32]	Polyesters with hydrophilic drugs	Markedly better entrapment of water-soluble drugs than single emulsion	Drug leakage across the organic phase; complex, multi-step; broader size distribution
Ionic gelation	Electrostatic crosslinking of a polyelectrolyte with a multivalent counter-ion [3]	Chitosan–TPP; alginate–calcium	No organic solvent, heat or high shear; well suited to hydrophilic drugs [23][26]	Soft particles with limited mechanical strength; faster release; narrow pH window
Desolvation	Protein precipitated by a desolvating agent, then crosslinked [32]	Gelatin, albumin	Mild aqueous conditions; good control through two-step protocols	Residual crosslinker toxicity; protein batch variability
Salting-out	Phase separation induced by a saturated electrolyte solution [32]	Polyesters	Avoids chlorinated solvents and high temperature	Extensive washing needed to remove salts; not suited to electrolyte-sensitive drugs
Emulsification–diffusion	Partially water-soluble solvent diffuses out after emulsification [32]	Polyesters	High encapsulation for lipophilic drugs; narrow distribution; scalable	Large water volumes; drug loss to the external phase
Supercritical fluid methods	Rapid expansion or anti-solvent precipitation using supercritical CO_2 [32]	Thermolabile drugs	Solvent-free product; single-step particle formation	High capital cost; limited polymer solubility in CO_2

6. FORMULATION AND FABRICATION OF ISONIAZID-LOADED POLYMERIC NANOPARTICLES

6.1 Excipient Selection, Nanoprecipitation and Emulsion-Solvent Evaporation

A formulation also needs a stabilizer, usually poly(vinyl alcohol), a poloxamer or a polysorbate, and residual stabilizer is hard to remove and affects surface properties and tolerability [32]; crosslinkers, cryoprotectants such as mannitol or trehalose and buffers complete the list [3], while inhalation narrows the choice to the few excipients with established pulmonary safety [19]. Nanoprecipitation, described by Fessi and colleagues, adds a water-miscible organic solution of polymer and drug to water, precipitating nanoparticles simply and reproducibly, but a freely soluble drug follows the solvent out, so isoniazid entrapment is low [12][15]. For hydrophilic drugs the double water-in-oil-in-water emulsion retains drug in an inner compartment and improves encapsulation, though interfacial leakage limits efficiency and residual solvent must meet ICH Q3C [32].

6.2 Ionic Gelation and Other Polymer-Specific Methods

Ionic gelation crosslinks a polyelectrolyte with a multivalent counter-ion: tripolyphosphate bridges protonated chitosan amino groups, and calcium gels alginate analogously [3][35]. For isoniazid the attraction is obvious, with no organic solvent, heat or high shear and an aqueous environment that accommodates a soluble drug. Desolvation serves gelatin and albumin, precipitating protein with acetone or ethanol before crosslinking, while supercritical fluid methods, salting-out, dialysis and emulsification-diffusion complete the repertoire [32]. Table 3 sets out the main methods with their advantages and limitations.

6.3 Particle Size, Drug Loading and Encapsulation Efficiency

Size responds to polymer concentration and molecular weight, phase ratio, stabilizer, emulsification energy, solvent removal rate, temperature and, for ionic gelation, crosslinker ratio and pH [3][32]; polydispersity deserves equal attention, with values below about 0.3 generally acceptable [2][9]. Encapsulation efficiency is the fraction of drug ending up in particles, loading the drug mass per unit particle mass, and good efficiency can coexist with poor loading [32]. Loading matters enormously for inhalation, because perhaps only a few tens of milligrams of powder can be delivered per administration [19]. A 300 mg adult dose cannot be given this way, which is the strongest argument for treating inhaled isoniazid as an adjunct rather than a systemic replacement.

6.4 Process Optimization, Reproducibility and Scale-Up

Factorial, Box-Behnken and central composite designs now routinely map formulation and process variables onto size, polydispersity, zeta potential and encapsulation efficiency, while batch-to-batch reproducibility is harder than any single optimized batch and hinges on raw material control, especially for natural polymers [21][22]. Laboratory batches are made in beakers with probe sonicators. Neither scales. Industrial production uses high-pressure



homogenization, microfluidic mixing or continuous precipitation, each altering particle formation and therefore the product [32]. Sterility is a genuine obstacle, since heat destroys most polymeric nanoparticles, irradiation degrades polymer and drug, and 0.22 µm filtration suits only small, non-aggregated particles [32].

7. PULMONARY ADMINISTRATION STRATEGIES AND AEROSOL ENGINEERING

7.1 Nebulizers, Dry Powder Inhalers and Metered-Dose Inhalers

Nebulization delivers a suspension as a mist without patient coordination, the usual choice for early animal work, though ultrasonic devices heat and can damage carriers while vibrating-mesh devices are gentler but may clog [8]. Dailey and colleagues showed device technology and particle characteristics jointly determine the aerosol and that nanoparticles can survive nebulization largely intact, but suspensions store poorly and treatment times are long [8]. Dry powder inhalers avoid propellants, store better and deliver in seconds [19][30], the powder usually spray dried with lactose, mannitol, trehalose or leucine forming the respirable carrier [16]. Pourshahab and co-workers spray dried chitosan nanoparticles into inhalable isoniazid powders [26] and Mukhtar and colleagues freeze-dried mannosylated nanoparticles into a nano-powder [23], with flow, moisture uptake and de-aggregation the practical constraints. Metered-dose inhalers suspend polymers poorly in hydrofluoroalkanes, so dry powders dominate [30]. Table 6 compares the three platforms.

7.2 Nanoparticle-in-Microparticle Systems and Aerodynamic Performance

The nano-in-micro strategy turns aggregation into a design feature. Tsapis and colleagues described Trojan particles, large porous microparticles spray dried from nanoparticles, which deposit with microparticle aerodynamics then disperse [31], and Grenha and colleagues microencapsulated chitosan nanoparticles in mannitol [16]; the approach works only if the carrier truly releases its nanoparticles, and verifying redispersion is a frequently skipped step. Figure 3 illustrates the concept. Edwards and colleagues used the dependence of aerodynamic diameter on density to make large porous particles that are geometrically above 5 µm yet respirable and resist phagocytic clearance [5][11]. Two parameters matter practically: mass median aerodynamic diameter, ideally 1-5 µm, and fine particle fraction below 5 µm, both from cascade impaction [30]. A report giving only light-scattering diameter has not demonstrated inhalability, a gap common in this literature.

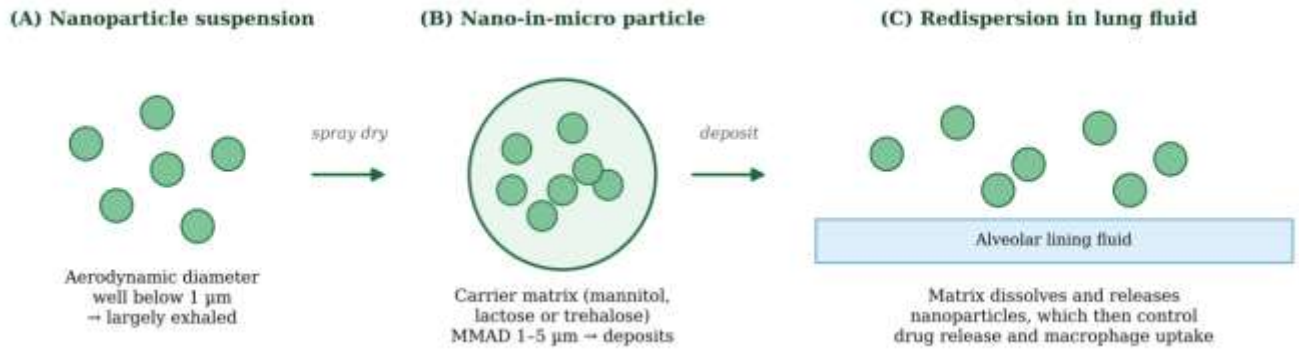


Figure 3. *The nanoparticle-in-microparticle principle: nanoparticles are assembled into respirable microparticles for delivery, then redispersed after deposition in the lung.[16][31]*

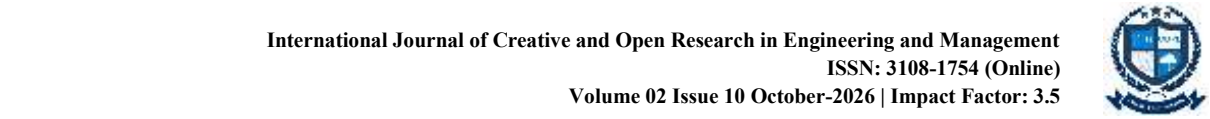
7.3 Aerosol Stability and Regional Deposition

Aerosolization imposes shear, cavitation, air-liquid interfaces and evaporation, under which carriers may aggregate, leak or fracture, so size, polydispersity, drug content and encapsulation efficiency should be measured on the aerosol collected after the device, not only in the vial [8]. Conducting-airway deposits are cleared within a day while alveolar deposits meet macrophages and a far longer residence [14][27]. Alveolar deposition is the objective for tuberculosis and needs roughly 1-3 µm with slow deep inhalation and a breath hold [5][7]. Disease complicates this, as obstruction, cavitation and consolidation redirect airflow away from the most diseased regions.

8. MECHANISMS OF PULMONARY TARGETING AND CONTROLLED DRUG RELEASE

8.1 Deposition, Retention and Release Mechanisms

Retention is the net of competing rates: carrier and drug dissolution, mucociliary transport, phagocytosis and absorption [14][27]. Free isoniazid is absorbed within minutes, which is why unencapsulated inhaled drug gives little local advantage; encapsulation shifts the rate-limiting step from absorption to release. In a slowly degrading matrix drug diffuses through polymer and water-filled pores, the behaviour Higuchi captured as a square-root-of-time relationship [17], while the Korsmeyer-Peppas exponent distinguishes Fickian diffusion near 0.43 for a sphere from anomalous transport above it [20]. Polyesters add bulk hydrolysis, so PLGA release is often triphasic, a surface burst, a diffusion phase, then acceleration as the matrix erodes, and autocatalytic ester hydrolysis makes degradation size-dependent [1][13].



8.2 Drug Release in Pulmonary Fluids

Release is usually studied in phosphate-buffered saline, which bears little resemblance to the lung, where lining fluid amounts to perhaps 10-20 mL in total, is rich in surfactant lipids and proteins and is essentially unstirred, so the sink conditions assumed in a dissolution vessel may not exist [27]. Simulated lung fluids containing surfactant, Transwell systems and air-liquid interface models are more biorelevant, but none is a compendial standard, which is itself part of the regulatory problem for inhaled nanomedicines [27].

8.3 Macrophage Uptake and Targeting of Infected Cells

Phagocytosis begins with opsonin-mediated recognition and proceeds through engulfment into a phagosome that fuses with lysosomes, where a carrier releases its drug, which for tuberculosis is the destination of interest [6]. Hirota and colleagues found rifampicin-loaded PLGA microspheres of about 3 μm most efficiently taken up by alveolar macrophages [18], and cationic particles are taken up more than neutral or anionic ones [22]. Figure 4 summarizes deposition through to intracellular release. Mannose receptor targeting predominates among ligand strategies, hyaluronic acid addresses CD44 [23], and Sharma and colleagues used wheat germ agglutinin-coated PLG nanoparticles to prolong drug levels in guinea pigs [29]. The caveat is that such claims usually rest on cell-culture uptake rather than in vivo selectivity, since macrophages phagocytose indiscriminately and a well-sized plain particle is already substantially targeted [6][14].

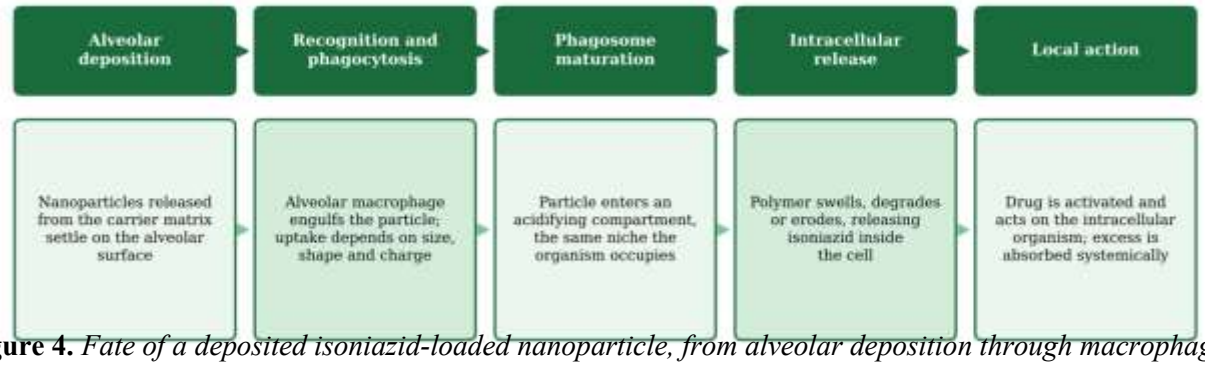


Figure 4. *Fate of a deposited isoniazid-loaded nanoparticle, from alveolar deposition through macrophage uptake to intracellular drug release.[6][18]*

8.4 Local Drug Exposure versus Systemic Absorption

The balance between local retention and systemic escape is set by release rate, particle fate and drug permeability [27]. Slower release holds more drug in the lung but risks sub-inhibitory concentrations; faster release raises local peaks while shortening benefit and increasing systemic exposure. Because isoniazid crosses the alveolar epithelium readily once free, systemic absorption after pulmonary dosing is substantial, and a measurable plasma profile does not by itself prove a lung depot has formed [33].

9. CHARACTERIZATION AND EVALUATION OF POLYMERIC NANOPARTICLES

9.1 Particle Size, Zeta Potential, Morphology and Drug Content

Dynamic light scattering is the routine method for dispersions but assumes spheres, is biased toward larger species and handles multimodal distributions poorly [2]. Zeta potential indicates surface charge and colloidal stability, magnitudes beyond about ±30 mV suggesting good stabilization, and the medium must be reported since pH and ionic strength govern it [2]. Electron microscopy shows shape, texture and aggregation, an essential check on scattering, which cannot distinguish one large particle from an aggregate of small ones [32]. Drug content is assayed by UV spectrophotometry or HPLC after dissolution, with free drug separated by ultracentrifugation, ultrafiltration or dialysis; separation is the main error source, so both encapsulation efficiency and loading should be reported with the method stated [32].

9.2 Solid-State Characterization and In Vitro Release

Infrared spectroscopy detects drug-polymer interaction, differential scanning calorimetry and X-ray powder diffraction show whether the drug stays crystalline or becomes amorphous, which governs dissolution and physical stability, and thermogravimetry gives residual moisture and solvent [23]. Loss of the melting endotherm and characteristic diffraction peaks is the usual evidence of molecular dispersion. Release is measured by dialysis bag, sample-and-separate or flow-through methods, each with artefacts [13], and data are fitted to zero-order, first-order, Higuchi and Korsmeyer-Peppas models [17][20]. Burst release should be quantified explicitly as the fraction released in the first hour or two, since for isoniazid it often dominates the profile.

9.3 Aerosol Performance and Aerodynamic Characterization

Cascade impaction remains the reference method, with the Andersen impactor or Next Generation Impactor operated at a defined flow rate and volume as described in the pharmacopoeial chapters [30]. Reported outputs should include emitted dose, mass median aerodynamic diameter, geometric standard deviation and fine particle fraction; laser



diffraction estimates droplet or particle size more quickly for nebulized products but does not replace impaction [5][30].

9.4 Cell Compatibility, Antimycobacterial Activity and Stability

Cytotoxicity is screened in A549, Calu-3 and macrophage lines by MTT or lactate dehydrogenase assays, with air-liquid interface culture more representative than submerged culture; inflammatory potential matters as much as viability, since biodegradable nanoparticles can trigger cytokine release at non-cytotoxic doses [4], and chitosan nanoparticles have proved compatible with respiratory epithelium [22]. Antimycobacterial activity is measured as broth minimum inhibitory concentration, free versus encapsulated drug, though a slow-release system may appear less potent simply because less drug is free during the assay; intracellular activity in infected macrophage models is the more meaningful test [7][18]. Stability should follow size, charge, assay, encapsulation efficiency, moisture and, for powders, aerosol performance under ICH conditions, with lyophilization usual for suspensions [19][32]. Table 5 collects these methods against the critical quality attributes they address.

Table 5. Characterization Methods and Critical Quality Attributes of Pulmonary Polymeric Nanoparticles

Attribute	Method	Typical target or acceptance basis	Why it matters
Particle size and distribution	Dynamic light scattering; nanoparticle tracking analysis; laser diffraction [2]	Defined mean size; polydispersity index below about 0.3	Governs uptake, release rate, stability and redispersion behavior
Zeta potential	Electrophoretic light scattering, with medium and pH stated	Magnitude above about ±30 mV for electrostatic stabilization	Predicts aggregation and influences cell interaction
Morphology	SEM, TEM, AFM	Discrete, regular particles without fused aggregates	Confirms light-scattering data and reveals aggregation
Drug loading and encapsulation efficiency	HPLC or UV assay after separation of free drug by ultrafiltration, ultracentrifugation or dialysis [32]	Both values reported, with the separation method stated	Determines the powder mass needed per dose, which is limiting for inhalation
Solid-state character	DSC, XRPD, FTIR, TGA	Loss of drug melting endotherm and diffraction peaks; moisture within specification	Indicates molecular dispersion and predicts physical stability
In vitro release	Dialysis, sample-and-separate or flow-through; fitted to Higuchi and Korsmeyer–Peppas models [20]	Burst fraction quantified; profile matched to intended dosing interval	Burst release is the principal obstacle to a sustained-release claim for isoniazid
Aerodynamic performance	Cascade impaction (Andersen or Next Generation Impactor) [30]	MMAD about 1–5 µm; fine particle fraction reported with GSD	Determines whether and where the dose deposits; frequently omitted from formulation reports
Redispersion of nano-in-micro powders	Size measurement after reconstitution or after impactor collection	Recovery of the original nanoparticle size distribution	Confirms that the nano-in-micro design actually delivers nanoparticles
Lung-cell compatibility	MTT or LDH assays in A549, Calu-3 and macrophage lines; air–liquid interface exposure	Viability typically above 80% at relevant doses	Screens tolerability before animal work
Inflammatory potential	Cytokine release; bronchoalveolar lavage cell counts	No significant elevation versus vehicle control	Inflammation can occur at non-cytotoxic doses
Antimycobacterial activity	MIC determination; intracellular activity in infected macrophage models [7]	Activity equal to or better than free drug, interpreted against the release profile	Confirms the encapsulated drug remains active and accessible
Storage stability	ICH conditions, following size, charge, assay, moisture and aerosol performance	Attributes within specification over the proposed shelf life	Aerosol performance often degrades before any chemical change appears

10. PRECLINICAL EVALUATION AND THERAPEUTIC POTENTIAL

10.1 In Vitro Activity and Macrophage Studies

Screening is against reference strains, usually H37Rv, comparing minimum inhibitory concentrations of free and encapsulated drug, with several reports of comparable or improved activity, although results depend on assay duration because sustained-release carriers release more over longer incubation [7]. Uptake is quantified by flow cytometry or confocal microscopy of labelled carriers and intracellular drug by extraction and chromatography [18][23]. Hirota and colleagues reported efficient macrophage uptake of rifampicin-loaded PLGA microspheres with reduced intracellular organism burden [18], and Mukhtar and colleagues showed uptake of mannosylated chitosan-hyaluronic acid isoniazid nanoparticles without significant cytotoxicity or tolerogenic effect [23].



10.2 Pulmonary Deposition, Distribution and Pharmacokinetics

Distribution is assessed by assaying lung homogenate, lavage, plasma and other organs; Verma and colleagues tracked isoniazid and rifabutin after pulmonary delivery of inhalable microparticles in mice, reporting the intramacrophage time course alongside systemic pharmacokinetics [33]. Cross-study comparison suffers from inconsistent administration, since instillation, insufflation and nose-only exposure deposit very differently. Pandey and colleagues found nebulized PLG nanoparticles of rifampicin, isoniazid and pyrazinamide kept drug detectable in plasma for days and lung for longer, permitting roughly ten-day intervals in guinea pigs [25]; Sharma and colleagues extended this with lectin-functionalized nanoparticles, drug detectable for 13-14 days and present in lung, liver and spleen for 15 days, three fortnightly doses matching 45 daily doses of free drug [29]; and Zahoor and colleagues reported comparable prolongation with alginate nanoparticles [35]. These numbers come from small studies in few laboratories, with methods that could not always separate encapsulated from free drug.

10.3 Animal Models, Pulmonary Safety and Comparison with Oral Therapy

Mice dominate as models, being cheap and well characterized, yet rarely form the necrotic granulomas that create the human drug-penetration problem [34]; guinea pigs do, which is why much inhaled antitubercular work uses them [25], while rabbits and primates are closer still at far greater cost. A formulation succeeding in diffuse murine lesions may not penetrate a human cavity. Safety assessment should cover lung histopathology, lavage cell counts, inflammatory mediators and repeated dosing across a realistic treatment course, the last most frequently omitted [4]; pulmonary responses track surface area, surface chemistry and biopersistence rather than mass dose [14]. Where inhaled formulations have been compared with oral free drug, advantages are prolonged residence, less frequent dosing and often equal or better burden reduction at lower total dose [18][25][29][35], against device dependence, complex manufacture, limited deliverable mass and untreated extrapulmonary disease. Table 4 sets out the published studies.

Table 4. Published Studies on Nanoparticle- and Microparticle-Based Delivery of Isoniazid and Other Antitubercular Drugs

Drug(s)	Carrier system	Route	Evaluation	Key findings	Limitations
Rifampicin, isoniazid, pyrazinamide [25]	PLG nanoparticles	Nebulized, guinea pigs	Encapsulation, release, plasma and tissue drug levels, organism burden	Drug detectable in plasma for days and in tissue for longer; dosing interval extended to about 10 days	Small study; combination only; no aerodynamic characterization
Rifampicin, isoniazid, pyrazinamide [29]	Wheat germ agglutinin-coated PLG nanoparticles, 350–400 nm, 54–66% entrapment	Oral and nebulized, guinea pigs	Pharmacokinetics, tissue distribution, organism burden, tolerability	Isoniazid and pyrazinamide detectable 13–14 days; three fortnightly doses comparable to 45 daily free-drug doses	Lectin immunogenicity; not independently replicated
Rifampicin, isoniazid, pyrazinamide [35]	Alginate nanoparticles	Nebulized, guinea pigs	Encapsulation, pharmacokinetics, therapeutic response	Prolonged drug levels in plasma and organs relative to free drug	Limited release characterization; combination only
Isoniazid [26]	Chitosan nanoparticles spray dried into inhalable powder	Dry powder (*in vitro*)	Size, encapsulation, powder properties, aerosol assessment	Nano-in-micro powder with respirable characteristics obtained for isoniazid	No *in vivo* data
Isoniazid [23]	Mannosylated chitosan–hyaluronic acid nanoparticles by ionic gelation, freeze-dried	Dry powder (*in vitro*)	Characterization, cytotoxicity, haemocompatibility, macrophage uptake, immune markers	Cellular uptake with no significant cytotoxicity; costimulatory markers upregulated; no tolerogenic effect	No *in vivo* efficacy or pharmacokinetic data
Isoniazid, rifabutin [33]	Inhalable microparticles	Pulmonary, mice	Intracellular time course, pharmacokinetics, biodistribution	Drug measurable within alveolar macrophages; altered biodistribution versus oral dosing	Microparticulate rather than nanoparticulate; short study duration
Rifampicin [18]	PLGA microspheres, about 3 µm	Pulmonary, animal model	Phagocytosis, intracellular activity, therapeutic response	Efficient macrophage uptake and reduced intracellular organism burden	Single drug; microparticulate
Capreomycin [10]	Large porous particles (dry powder)	Inhalation, guinea pigs; later phase I in humans	Aerodynamics, pharmacokinetics, efficacy; human tolerability	Effective in animals; single-dose escalation in humans found tolerable	Not a polymeric nanoparticle; different drug class



11. CHALLENGES AND TRANSLATIONAL BARRIERS

11.1 Drug Loading, Burst Release, Scale-Up and Stability

Low loading and premature release are linked and both follow from hydrophilicity: low loading demands a larger powder mass per dose, colliding with device limits, while burst release undermines the rationale for encapsulation [13][15][19]. Remedies include hydrophobic ion pairing, prodrug derivatization, polyelectrolyte matrices and core-shell designs with a diffusion-limiting shell [23]. Manufacture is sensitive to mixing, shear and local supersaturation, none of which scale linearly, and natural polymers add material variability, so continuous and microfluidic routes are more plausible commercially [21][22]. These powders are also cohesive, hygroscopic and prone to irreversible aggregation, and aerosol performance can fall before any assay shifts, so it belongs in the stability protocol [19].

11.2 Pulmonary Safety, Cost and Regulatory Requirements

Chronic polymer deposition in the lung is the central unknown, with degradation products, residual solvents, repeated macrophage activation and possible impaired clearance all needing study over therapy-length timescales in a lung already damaged by disease [4][14]. Cost constrains everything, since tuberculosis is concentrated in low- and middle-income countries: six months of first-line oral drugs costs very little, whereas controlled manufacture, protective packaging and a device cost far more, so such a product needs dramatic superiority or a defined niche such as drug-resistant disease [10][34]. Regulation compounds this [21]: there is no compendial dissolution method for inhaled particles, no settled bioequivalence approach, little precedent for these polymers by this route, and attributes that pharmacopoeial methods were not designed to control [30]. The pathway would be largely bespoke.

11.3 Clinical Evidence Gaps and Patient Adherence

No inhaled polymeric nanoparticle formulation of isoniazid has entered clinical trials. The nearest precedent is a dry powder of capreomycin taken into a phase I dose-escalation study and found tolerable, valuable precisely because it shows the pathway is navigable [10]. Adherence also deserves scepticism: less frequent dosing is often presented as an advantage, yet inhalers demand correct technique and adherence to inhaled medicines in chronic respiratory disease is frequently poor, so what is easier in theory may not be easier in practice [19][30]. Table 7 pairs each barrier with the strategies proposed against it.

Table 7. Translational Challenges and Proposed Strategies for Overcoming Them

Challenge	Impact	Proposed strategy
Low encapsulation efficiency of a freely water-soluble drug	Large powder mass per dose, exceeding what an inhaler can deliver	Double emulsion methods, hydrophobic ion pairing, polyelectrolyte matrices, or core–shell hybrids [15]
Burst release	Undermines the sustained-release rationale; risks sub-inhibitory levels later in the interval	Surface drug removal by washing, rate-limiting coatings, crosslinking density control; quantify burst explicitly [13]
Nanoparticles are not respirable as discrete particles	Dose exhaled rather than deposited	Nano-in-micro spray-dried or large porous particles, with redispersion verified after deposition [31]
Aerodynamic performance seldom reported	Inhalability asserted rather than demonstrated	Make cascade impaction (MMAD, FPF, GSD) a routine part of formulation reporting [30]
Aggregation and moisture uptake on storage	Aerosol performance falls before assay values change	Cryoprotectants, moisture-protective packaging, force-control agents; use aerosol performance as a stability-indicating attribute
Scale-up and batch variability	Laboratory results do not transfer to manufacture	Continuous or microfluidic production; QbD design space; tight raw-material specifications for natural polymers [32]
Chronic pulmonary safety unknown	Months of polymer deposition in an already damaged lung	Repeat-dose inhalation toxicology over therapeutically realistic durations, with lavage, histology and inflammatory markers [4]
Monotherapy risk	Inhaled single-agent delivery could promote resistance	Co-encapsulation of two or more agents with matched release profiles, within a standard oral regimen [25]
Cost and accessibility	High-burden settings cannot absorb the cost of complex nanomedicine	Target drug-resistant or refractory disease first; design simple, low-cost, power-independent devices [19]
Regulatory pathway undefined	No compendial dissolution or bioequivalence approach for inhaled nanomedicines	Early engagement with regulators; QbD dossier; define critical quality attributes prospectively
No clinical data	Efficacy in humans entirely unknown	Use the inhaled capreomycin phase I study as a template for first-in-human evaluation [10]



12. FUTURE PERSPECTIVES

12.1 Advanced Polymers, Macrophage Targeting and Nano-in-Micro Architectures

Newer chemistries offer finer control than first-generation polyesters: block copolymers with tunable hydrophilic-hydrophobic balance, stimuli-responsive systems releasing in the acidic phagosome, and lipid-polymer hybrids pairing a polymer core with a lipid shell [9][21]. For a hydrophilic drug, placing a diffusion barrier around a hydrophilic core is among the more logical directions. Mannose and CD44 targeting are encouraging at cell level [23], but whether ligand decoration adds enough over the intrinsic macrophage affinity of a well-sized particle remains open, and a matched untargeted control in vivo would itself be useful. Nano-in-micro formulation is the most mature answer to the aerodynamic problem and should arguably be the default architecture [16][31], with progress resting on routine verification of redispersion and storage robustness.

12.2 Combination Delivery, Quality by Design and Clinical Translation

Since monotherapy is unacceptable, co-encapsulation is a requirement rather than a refinement [25][34]. Combining drugs of differing solubility in one carrier is difficult, blending separate carriers brings uniformity problems, and matching release rates so the lung does not see effective monotherapy late in the interval has had little attention. Quality by design, as set out in ICH Q8(R2), ties material attributes and process parameters to size, zeta potential, loading, release, residual solvent, moisture, aerodynamic performance and redispersibility [21], while deposition and physiologically based pharmacokinetic modelling could reduce animal work [5]. Translation depends as much on the device: a tuberculosis product needs a simple, robust, low-cost, low-resistance inhaler usable by breathless patients without reliable electricity or cold storage [19]. The capreomycin phase I study shows how it can enter clinical evaluation [10], and adjunctive therapy in drug-resistant disease is the most plausible first target.

13. CONCLUSION

The evidence for biodegradable polymeric nanoparticles as pulmonary carriers of isoniazid is real but uneven. On the formulation side, several polymers can be made to carry the drug and the aerodynamic problem has a well-established solution in nano-in-micro powders; on the preclinical side, animal studies have reported prolonged drug residence in lung and plasma, dosing intervals extended from daily to weekly or longer, and organism burden reduced at lower total doses than free drug. The weaknesses are just as clear. Isoniazid's high water solubility limits encapsulation in the polyesters with the best regulatory standing and encourages burst release; much of the influential in vivo work comes from a small number of laboratories, used drug combinations rather than isoniazid alone, and has not been widely replicated; aerodynamic characterization is missing from many formulation papers; chronic pulmonary safety data are scarce; and no such formulation has reached a clinical trial.

Priorities for the next phase of work are therefore fairly specific. Raise drug loading and control burst release through hybrid or polyelectrolyte architectures. Report aerodynamic performance as routinely as particle size. Verify redispersion of nano-in-micro powders after deposition. Generate repeat-dose pulmonary safety data over therapeutically realistic durations. Test co-formulations rather than single drugs, with matched release profiles. And define a clinical position, most plausibly adjunctive therapy in drug-resistant disease, that could justify the cost in the settings where tuberculosis actually occurs. Inhaled isoniazid nanomedicine does not lack good ideas. It lacks the unglamorous confirmatory work that turns them into a product.

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[Mr. Deepak kumar singh]: Critical review of content, interpretation of the literature, and editing of the manuscript.

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