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SPRAY-DRIED INHALABLE MICROPARTICLES OF RIFAMPICIN FOR PULMONARY TUBERCULOSIS THERAPY

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1. INTRODUCTION

Tuberculosis still kills more people each year than any other single infectious agent, and the burden has proved stubborn despite effective drugs. The World Health Organization estimated that about 10.6 million people developed the disease in 2021, with around 1.4 million deaths among people without HIV [1]. Standard treatment for drug-susceptible disease lasts six months, with rifampicin, isoniazid, pyrazinamide and ethambutol given for the first two months and rifampicin with isoniazid for the remaining four [1, 2]. The regimen cures most patients who finish it. Completion is the weak point, because the

Abstract

Tuberculosis treatment depends on rifampicin, yet long oral courses, variable absorption and dose-related toxicity undermine completion. Delivering the drug directly to the lung as an inhalable powder is an attractive alternative. This narrative review summarises published work on spray-dried rifampicin microparticles, covering the biology that justifies pulmonary delivery, the principles of particle formation, polymer, sugar and amino acid excipients, and the methods used to judge aerosol performance, release and efficacy. It reports no new experimental data. The literature supports the concept in animal models, but studies are small, methods differ and human data are almost absent, so robust conclusions on dose, safety and clinical benefit are not yet possible.

long duration, the daily pill burden and frequent adverse effects lead many people to stop early, and every interrupted course risks relapse and acquired resistance. These facts explain the continuing search for ways to deliver the same drugs more efficiently to the site of infection.

Inhalation is one such route. Because *Mycobacterium tuberculosis* infects the lung in most patients and is harboured largely inside alveolar macrophages, a powder deposited in the deep airways can place drug directly where the organism lives [3, 4]. Dry powder inhalers avoid the need for nebulisers, electricity and sterile solutions, which suits settings with limited infrastructure [5, 6]. Rifampicin is an obvious candidate, since it is the most important sterilising drug in the regimen. This review examines spray-dried inhalable microparticles of rifampicin: why the lung is a rational target, how spray drying shapes particles, which excipients have been used, how such powders are characterised, and where the evidence stops. It reports no new experimental data and no new measurements of any formulation.

The literature on this topic is spread across several disciplines, including aerosol physics, polymer science, microbiology and clinical pharmacology. Papers differ in the drug load, carrier, device and animal model they use, so direct comparison is rarely possible. Where findings from other antitubercular drugs or from non-tuberculosis inhalation products illustrate a principle, they are included and flagged as such [7, 8, 9]. Published work on quality by design and on rifampicin degradation supplies the framework against which any such powder would eventually be judged [10, 11]. The aim is to give a readable account of what has been established, what is plausible but unproven, and what a development team would still need to show before a rifampicin powder reached patients.

Two motivations recur in the papers. The first is local targeting, meaning a high concentration in the airways and lung tissue with a smaller systemic exposure than a comparable oral dose would give. The second is the possibility of less frequent dosing, if particles release drug slowly after being taken up by macrophages [12, 13]. Neither is guaranteed. Particle behaviour in a diseased lung, with its cavities, mucus and fibrosis, is harder to predict than in healthy airways, and most published efficacy data come from small animals. Those cautions run through the rest of this article, and they explain why the field has produced many promising formulations

but very few clinical trials.

Interest in inhaled antitubercular therapy goes back decades, and it returned with the rise of multidrug-resistant disease and with advances in powder engineering [3, 5]. Early attempts used nebulised solutions, which are bulky and depend on power and clean water. Modern work aims at small, passive devices and at powders that remain stable in hot, humid climates, which are the conditions in many high-burden countries. The change in emphasis from the drug to the delivery system reflects both the cost of discovering new antitubercular agents and the realisation that existing drugs may be under-used at the very site where they matter most.

2. RIFAMPICIN AND THE LUNG

Rifampicin is a semisynthetic rifamycin that inhibits the β subunit of bacterial DNA-dependent RNA polymerase. Its value lies in sterilising activity against slowly dividing bacilli, and its introduction allowed treatment to be shortened from regimens lasting a year or more to six months [14, 15]. The drug is lipophilic, highly protein-bound and extensively metabolised in the liver by deacetylation. It is also a potent inducer of cytochrome P450 3A4 (CYP3A4) and of P-glycoprotein (P-gp), which accounts for its long list of drug interactions, including those with antiretrovirals, hormonal contraceptives and anticoagulants [15]. These properties matter for inhalation because any fraction absorbed systemically from the lung would carry the same interaction potential, although at a lower total exposure than a full oral dose.

Oral rifampicin is not an easy drug to formulate or to absorb consistently. Solubility is low at intestinal pH and higher in acid, and the drug is unstable in acidic gastric fluid in the presence of isoniazid, a reaction implicated in poor bioavailability from some fixed-dose combinations [16]. Biopharmaceutical classification of the drug varies between analyses, and it is generally treated as having low solubility, with permeability that depends on the criteria applied [16, 17]. Reported exposures differ widely between patients, and the standard dose of about 10 mg/kg sits on the steep part of the dose-response curve. In trials of higher

doses, exposure rose more than proportionally, the drug was tolerated, and some studies reported faster early bacterial clearance [18, 19].

The pathology of tuberculosis complicates drug delivery. Bacilli are taken up by alveolar macrophages and may persist inside granulomas, where a necrotic and poorly vascularised centre known as caseum limits what circulating drugs can reach [2, 20]. Mass spectrometry imaging of resected lung lesions showed that drug distribution differs by compound and by lesion type, and that penetration into necrotic regions can be limited even for drugs with good plasma exposure [20]. An oral dose must be large enough that the fraction reaching these sites is effective, and that requirement is part of what drives high systemic doses and their toxicity. Inhalation does not solve the problem of necrotic lesions, but it favours deposition in ventilated regions and in the macrophages that line them [4].

Resistance gives the pharmacological argument extra urgency. Resistance to rifampicin arises mainly through mutations in the *rpoB* gene, and disease resistant to both rifampicin and isoniazid is far harder to treat, needing longer courses of less effective and more toxic drugs [1, 2]. Low or erratic drug exposure is widely regarded as one route by which resistance is selected, because bacilli surviving at sub-inhibitory concentrations can be enriched over weeks of therapy [15]. An inhaled powder cannot reverse established high-level resistance, and it would not be expected to. Its more modest promise is to secure adequate local concentrations in patients with drug-susceptible disease and to reduce the opportunity for resistance to emerge, an argument that remains to be tested in any clinical programme.

Targeting alveolar macrophages offers a second rationale. These cells phagocytose particles within a size window, and microspheres of a few micrometres are taken up efficiently while very small or very large particles are handled less well [21]. Rifampicin-loaded PLGA microspheres were shown to be ingested by alveolar macrophages, and the conditions that favoured uptake included particle size,

surface properties and the culture conditions used [21]. Particles that reach the deep lung are therefore engineered for two jobs at once: to deposit in the alveoli, which depends on aerodynamic behaviour, and to be taken up by macrophages, which depends on geometry and surface chemistry [4, 22]. The two requirements overlap but are not identical.

Lung physiology sets practical limits. Mucociliary clearance sweeps particles deposited in the conducting airways towards the throat within hours, whereas particles reaching the alveoli are cleared mainly by macrophages over days or longer [23]. Disease changes this picture. Cavities, bronchiectasis and mucus plugging alter airflow and deposition, so powders that perform well in healthy volunteers or healthy animals may distribute unevenly in a patient with advanced disease [3, 23]. Inspiratory effort also falls in weak, malnourished patients, which is a real consideration in tuberculosis and one that argues for powders that disperse easily at low flow.

3. SPRAY-DRYING PRINCIPLES

Spray drying converts a solution, suspension or emulsion into a dry powder in a single step. The feed is atomised into fine droplets in a stream of hot gas, the solvent evaporates within seconds, and the resulting particles are separated in a cyclone and collected. The process is continuous, scalable and already familiar to the industry, which is why it features so heavily in inhalation research [24, 25]. Control comes from a modest number of variables: feed concentration, solvent composition, atomising conditions, inlet and outlet temperature, and drying gas flow. Each influences droplet size and the rate at which the droplet surface recedes, and in combination they decide whether the final particle is dense, hollow or wrinkled [26].

Particle formation is described reasonably well by the balance between evaporation and diffusion. When a droplet dries quickly, solutes with low diffusivity cannot redistribute fast enough and accumulate at the receding surface to form a shell, whereas slow drying lets solutes stay uniform and leaves a solid particle [26, 27]. The ratio of the two rates is expressed as the Péclet

number. In practical terms, a formulator can steer morphology with the choice of excipients and drying conditions instead of relying on trial and error alone. A surface-active component such as leucine concentrates at the droplet surface early, and a hollow, low-density particle with a corrugated shell is the common result [27, 28].

Size matters for lung deposition in well-known ways. Particles with aerodynamic diameters of about 1 to 5 μm are the ones most likely to pass the oropharynx and reach the lower airways, with larger particles lost by impaction in the throat and very small ones largely exhaled [22, 23]. Aerodynamic diameter depends on both geometric size and density, so a particle of 8 μm that is highly porous and of low density can behave aerodynamically like a much smaller one. Large porous particles were promoted originally because they could escape rapid macrophage uptake, a property that sits uneasily with macrophage targeting [7]. For rifampicin, which is needed in milligram quantities, design has to balance deposition efficiency against how much powder a patient can inhale in one or two breaths [6, 7].

Heat is a concern for any drug sensitive to temperature, and rifampicin is no exception. The drug is susceptible to oxidation to rifampicin quinone and to hydrolysis, and exposure to light, moisture and acidic conditions speeds loss of potency [16]. Spray drying exposes droplets to high gas temperatures, but evaporative cooling keeps the particle temperature well below the inlet value while the droplet still contains solvent, and residence time is short [26]. Even so, the outlet temperature, the solvent chosen and the residual moisture in the powder all deserve attention, and stability studies under the conditions recommended by international guidance are needed before any claim of chemical integrity can be made [11, 16].

Organic solvents are often needed because rifampicin dissolves poorly in water at neutral pH. Methanol, ethanol and mixtures with water are common choices in published work, and the residual solvent in the dried powder must be controlled and justified against pharmacopoeial limits [24, 29]. Aqueous

suspensions of micronised drug, or emulsions in which a polymer such as PLGA is dissolved in an organic phase, are alternatives, each with its own consequences for encapsulation and release [29, 30]. A four-fluid nozzle spray dryer has been used to prepare rifampicin-PLGA nanoparticles within mannitol microspheres in one step, the sugar matrix being expected to break up on contact with fluid and release the nanoparticles [30]. The choice of solvent system is thus a formulation decision, not merely a processing one.

Laboratory-scale equipment shapes what is reported. Small spray dryers recover a modest fraction of the powder, because the finest particles pass through the cyclone and deposit on the glass walls, so yields below fifty per cent are common in published work and say little about industrial performance [24, 25]. Inlet temperature mainly affects drying rate and residual moisture, feed rate and atomising gas flow influence droplet size, and feed concentration sets the final particle size for a given droplet [26]. Changing one variable usually moves several responses together, which is why factorial or response surface studies are more informative than single-factor experiments. Few rifampicin papers have used such designs, and most simply report the settings that worked for the batch described.

Scale-up deserves a mention even in a review of laboratory work. Results from small laboratory spray dryers do not transfer directly to production equipment, because droplet size, drying time and residence time change with the geometry and gas flow. Quality by design offers a way to manage that transfer by identifying critical process parameters early and defining a design space [10]. Few of the published rifampicin powders describe more than one batch size, so evidence of reproducibility is thin. For a product intended for health systems that are sensitive to price, cost per dose will also matter, which favours simple, solvent-light processes over elaborate ones [24, 25].

4. FORMULATION STRATEGIES

Published formulations fall into a few families, summarised in table 1, and the

distribution of entries by family is shown in fig. 1. The simplest is a neat, micronised or spray-dried drug powder, sometimes with a dispersibility enhancer. Others rely on a biodegradable polymer matrix, most often poly(lactic-co-glycolic acid) (PLGA), to sustain release and to target macrophages. Sugar-based carriers such as mannitol and lactose provide bulk and a degree of moisture protection, while lipid and nanoparticle systems offer a way to raise the drug load or to alter the release profile [29, 30, 31]. Combination powders, including rifampicin with isoniazid and pyrazinamide, have been explored because the first-line regimen relies on several drugs given together [32]. Each approach trades something away in return for its advantage.

Table 1: Published inhalable formulation approaches for rifampicin and related antitubercular drugs

Formulation approach	Reported feature	Ref.
Rifampicin PLGA microspheres Respirable size	Evaluated in an infectious disease model after pulmonary delivery.	[12]
Rifampicin PLGA microspheres Sustained release	In vitro release prolonged over days from inhalable particles.	[33]
PLGA microspheres Macrophage uptake	Phagocytosis by alveolar macrophages depended on size and surface properties.	[21]
Drug-combination microparticles Rifampicin, isoniazid, pyrazinamide	Designed to reach alveolar macrophages with the first-line drugs together.	[32]
Rifampicin microspheres Guinea pig dosing	Dosing at intervals of days was compared with conventional therapy.	[13]
Nanoparticles in mannitol microspheres Four-fluid nozzle	One-step spray drying; sugar matrix intended to release nanoparticles on contact with fluid.	[30]
Self-assembled rifampicin nanoparticles	Pulmonary pharmacokinetics measured in animals.	[34]
Large porous particles	Low density gives small aerodynamic diameter despite large geometric size.	[7]
Leucine and amino acid excipients	Surface enrichment improved morphology and dispersibility of spray-dried powders.	[28, 35]

Formulation approach	Reported feature	Ref.
Capreomycin large porous particles	Reduced bacterial counts in infected guinea pigs.	[8]
Clofazimine microparticles	Efficacious in experimental infection in mice.	[9]

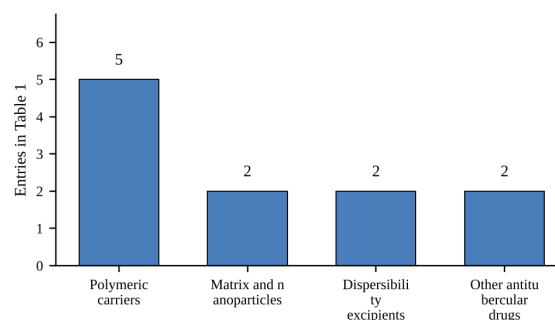


Fig. 1: Number of entries in table 1 by formulation family

PLGA microspheres dominate the early literature. Respirable rifampicin–PLGA microspheres were tested in an infectious disease model soon after the turn of the century, and in vitro work by other groups later described sustained release over days from particles sized for inhalation [12, 33]. The polymer degrades by hydrolysis, so release is governed by diffusion through the matrix and by erosion. Drug loading is usually limited to tens of per cent by mass, which means that a therapeutic dose requires a sizeable quantity of powder, and acidic degradation products may in principle affect both the polymer and a pH-sensitive drug [29, 33]. Those practical limits have kept polymeric systems largely at the research stage.

Combination microparticles aim to put all the first-line drugs into the same macrophage. Microparticles carrying rifampicin, isoniazid and pyrazinamide were reported to target alveolar macrophages, a rational design since a single drug in the lung would invite resistance [32]. The difficulty lies in the differing physicochemical properties of the drugs. Isoniazid and pyrazinamide are small, polar and water-soluble, while rifampicin is large and lipophilic, so one particle may not retain them in the right ratio, and rifampicin and isoniazid can interact chemically in the presence of moisture [16, 32]. Ratios have to be maintained during storage, delivery and

dissolution in the lung, which is a harder standard than any individual drug requires.

Sugar carriers bring their own complications in warm, humid climates. Mannitol can crystallise in different polymorphic forms depending on drying conditions, lactose is hygroscopic in its amorphous state, and trehalose forms a stable glass that protects some sensitive molecules [29, 31]. When a sugar sits around rifampicin particles it may shield the drug from oxygen and light to some extent, which is helpful given the instability of the drug [16, 30]. If the sugar picks up moisture on storage, however, particles can fuse, aerosol performance falls and chemical degradation may speed up. Packaging in moisture-tight blisters or capsules is therefore part of the formulation, not an afterthought, and should be considered at the same time as the choice of carrier.

Dispersibility excipients deserve attention because they often decide whether an otherwise sound powder works. Leucine and other hydrophobic amino acids enrich at the droplet surface, lower cohesion and raise the fine particle fraction of spray-dried powders, as shown in several non-tuberculosis systems [28, 35]. Corrugated particles have fewer points of contact than smooth spheres and therefore stick less to one another [36]. Carrier-free powders avoid the need for lactose and the detachment step that carrier-based blends require, although they place greater demands on particle engineering [31, 37]. These findings come mainly from other drugs and model compounds, and the rifampicin literature has drawn on them more than it has tested them.

Evidence from other antitubercular drugs adds weight to the approach. Large porous particles of capreomycin, given by insufflation to guinea pigs, reduced bacterial counts in infected animals, and inhaled clofazimine microparticles were efficacious in experimental infection in mice [8, 9]. Studies in guinea pigs with respirable rifampicin microspheres examined whether dosing at intervals of days, rather than daily, could produce an effect comparable to oral therapy, an idea of obvious interest for supervised treatment [13]. Animal models are imperfect, since guinea pigs form lesions

closer to the human pattern than mice do but differ in dose scaling and breathing. These findings support the concept without proving that a rifampicin powder will work in people.

Liposomal and lipid-based carriers have also been proposed for antimycobacterial drugs, and their appeal is the compatibility of lipids with lung surfactant and their uptake by macrophages. Rifampicin's lipophilicity makes it easy to load into lipid bilayers, but stability of the vesicles during drying and storage is a recurring difficulty. Spray drying with a sugar such as lactose or trehalose as a protectant is the usual solution, adding another component that must be justified [29, 31]. At present the evidence on lipid-based rifampicin powders is more preliminary than for polymer microspheres, and head-to-head comparisons between the two families are absent.

5. CHARACTERISATION AND PERFORMANCE

Characterisation begins with the physical attributes that predict aerosol behaviour. Laser diffraction or microscopy gives the geometric size distribution, scanning electron microscopy reveals morphology, and tapped density or helium pycnometry measurements estimate particle density, from which aerodynamic diameter can be calculated [24, 37]. Specific surface area, residual moisture and thermal behaviour by differential scanning calorimetry (DSC) or thermogravimetry complete the basic picture. For a spray-dried drug the question of solid state is particularly important. Rapid drying commonly yields amorphous material, which dissolves faster but is physically unstable and may crystallise on storage in humid air, changing the aerosol performance of the powder over time [25].

The central measure of inhaler performance is the aerodynamic particle size distribution, measured with cascade impactors. The next generation impactor (NGI) was designed for this purpose and has been calibrated across a range of flow rates [38]. Practical guidance on the use and limits of cascade impactors for inhaler aerosols is well documented [39]. From impactor data, the mass median aerodynamic diameter (MMAD), geometric

standard deviation (GSD), emitted dose and fine particle fraction (FPF) are derived. An FPF expressed relative to emitted dose or to nominal dose gives quite different numbers, so comparison across papers needs care. A powder with an MMAD between 1 and 5 μm and a high fine particle fraction would be regarded as promising for deep lung delivery [6, 23].

Device and patient factors share responsibility with the powder. Passive dry powder inhalers rely on the patient's inspiratory effort to disperse particles, and the resistance of the device sets the flow achievable [6, 37]. Powders tested at one flow rate in a laboratory may disperse differently at the lower flows managed by children, older adults or seriously ill patients. Capsule-based single-dose devices are cheap and avoid priming, and they are well suited to a short, supervised course, but capsule piercing, retention in the capsule and wall losses in the device reduce the delivered dose [6]. Development of a rifampicin powder therefore means development of a powder and device pair, with dose per actuation, number of inhalations and cleaning of the device all addressed in advance.

In vitro release testing for inhaled powders is less standardised than dissolution testing for tablets. The usual approaches use modified dissolution apparatus, membrane diffusion cells or dialysis arrangements with simulated lung fluid, and results depend on the method as much as on the product [25, 29]. For polymeric particles, release in simulated lung fluid is typically slower than for the neat drug and often shows an initial burst followed by a sustained phase [33]. The relevance to the macrophage is unclear, because intracellular conditions, including acidic phagolysosomes, are not captured by a buffer. Cell-based tests with macrophage lines and measures of intracellular bacterial killing add biological relevance, although they too are model systems [21, 33].

Chemical characterisation is as important as the physical kind. Drug content, loading efficiency and uniformity are usually measured by a validated chromatographic or spectrophotometric method, with attention to degradation products such as rifampicin

quinone that may form during drying or storage [11, 16]. Residual solvent has to be quantified against accepted limits. Stability studies follow international guidance, which specifies long-term and accelerated conditions of temperature and humidity and a defined testing schedule. For an inhaled product, aerosol performance has to be re-measured at each time point, since a powder can stay chemically intact yet lose its fine particle fraction as particles bond together. Published rifampicin papers rarely report both.

In vivo pharmacokinetic and efficacy work in animals shows what can be achieved. After pulmonary administration of self-assembled rifampicin nanoparticle systems, plasma and lung concentrations were measured in animals, demonstrating that drug could be delivered by this route in a way that can be quantified [34]. Insufflation of rifampicin microspheres and, separately, of other agents in guinea pigs and mice produced reductions in bacterial burden in infected animals in particular models [8, 9, 13]. Studies of this sort are labour-intensive and use small numbers of animals, so confidence intervals are wide and the dose delivered to the lung is often an estimate. Results across laboratories vary with the strain of animal, the route of infection and the dosing schedule.

Safety of inhaled rifampicin has received limited attention. Local effects of a high lung dose could include cough, bronchospasm and irritation, and the red-orange colour of the drug stains secretions and other body fluids, as is well known with oral dosing [15]. Repeated dosing of a polymer carrier into the lung raises questions about accumulation and inflammation that tablets do not. Excipients with a long record in inhalation, such as lactose, mannitol and leucine, are easier to defend than novel polymers, because their local safety is better characterised [29, 31]. Toxicology studies suited to repeated pulmonary dosing would need to be planned from the outset of development.

6. LIMITATIONS AND FUTURE DIRECTIONS

Several limitations temper the optimism. The majority of reported work is preclinical, and

clinical evidence on inhaled rifampicin, including human pharmacokinetics at lung level, is sparse [3, 5]. Animals differ from patients in airway geometry and breathing, and a healthy animal lung says little about a cavitary one. Many papers characterise a single batch, report fine particle fractions by different definitions and use release methods that are not comparable, so reproducibility and cross-study comparison remain weak. There is also a tendency, understandable in exploratory work, to report favourable formulations and leave out those that failed. Reading the evidence honestly means treating performance figures as indicative rather than as design targets.

Safety and interaction questions have to be addressed alongside efficacy. The enzyme-inducing effect of rifampicin persists whatever the route, and lung deposition does not remove systemic absorption, which for particles reaching the alveoli can be rapid [15, 23]. Long-term effects of repeated inhaled doses on the lung, including irritation and any effect on the lung microbiome, are unknown. Patients with tuberculosis commonly also have HIV infection or diabetes, and their lungs may be damaged, so tolerability data would need to cover those groups. Regulatory pathways for a combination of drug and device are not trivial either, and stability, dose uniformity and aerodynamic performance would need to be shown with the final device [10].

Looking ahead, several steps would move the field forward. Standardised reporting of aerosol performance, with fine particle fraction stated against both emitted and nominal dose, would make studies comparable [38, 39]. Platform approaches in which the same excipient system carries several antitubercular drugs could shorten development, as could quality by design studies that map how spray-drying settings affect critical attributes [10, 26]. Early-phase trials measuring lung concentrations in humans are the obvious bridge from animal work. Simple, low-cost devices and heat-stable powders are as important as the formulation itself for use in high-burden countries, and so are cost and supply considerations [3, 5].

Another direction is host-directed and adjunctive therapy. Because alveolar macrophages are both the host cells and a barrier, powders could in principle carry immunomodulators or antimicrobial peptides alongside rifampicin, an idea that has been discussed in the literature but remains speculative. Anything added increases regulatory complexity and the number of interactions to characterise. For now the more realistic ambition is a stable, well-characterised rifampicin powder that performs consistently across devices and flow rates, and that has been shown in a controlled human study to reach the infected lung in useful concentrations [3, 5, 24].

7. CONCLUSION

Spray-dried inhalable rifampicin is a reasonable idea supported by sound pharmaceuticals, and the published work shows steady technical progress. The lung is the principal site of disease, alveolar macrophages harbour the organism, and spray drying can produce particles of suitable aerodynamic size, density and surface character in a scalable step [3, 4, 26]. Excipient work on polymers, sugars and amino acids has produced powders that disperse well in the laboratory, and animal studies of related systems report reductions in bacterial burden [8, 12, 13]. Particle engineering has therefore moved from a curiosity to a practical toolkit for antitubercular powders.

What is missing is clinical proof and consistent methods. Reports use different devices, dose definitions and release tests, most come from a single laboratory, and human data on lung concentration, safety and interaction are scarce [5, 15, 38]. Progress will depend on standardised aerosol reporting, early human studies and powders that tolerate heat and humidity in the settings where tuberculosis is common. Until then the approach should be seen as promising and unproven, not as a replacement for oral therapy, and its future will be decided by trial data that do not yet exist [1].

8. ABBREVIATIONS

CYP3A4-Cytochrome P450 3A4,
DSC-Differential scanning calorimetry, FPF-Fine

particle fraction, GSD-Geometric standard deviation, HIV-Human immunodeficiency virus, MMAD-Mass median aerodynamic diameter, NGI-Next generation impactor, P-gp-P-glycoprotein, PLGA-Poly(lactic-co-glycolic acid), WHO-World Health Organization

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Nil

10. AUTHORS CONTRIBUTIONS

All the authors have contributed equally.

11. CONFLICT OF INTERESTS

Declared none

12. REFERENCES

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