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Review on Pulmonary Drug Delivery Systems for Tuberculosis: Advances in Dry Powder Inhalers and Emerging Nanoparticles Strategies.

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A B S T R A C T

Tuberculosis (TB) is still a serious worldwide health issue, especially the occurrence of multidrug-resistant (MDR-TB) and extensively drug-resistant (XDR-TB) strains. Traditional regimens are constrained by long dosing schedules, systemic toxicity, and patient compliance. Pulmonary drug delivery systems (PDDS), particularly dry powder inhalers (DPIs), have come as a saviour by facilitating targeted lung delivery, the target site for the infection. This method maximizes local drug concentrations, enhances alveolar macrophage uptake, and lowers systemic side effects. The review points to biological barriers in pulmonary delivery, contrasts available routes of administration, and discusses developments in nano/microcarrier-based DPI formulations such as liposomes, polymeric microspheres, and solid lipid nanoparticles. Data from preclinical and initial clinical research to date indicate that DPI formulations of first-line and second-line anti-TB drugs to date can enhance therapeutic efficacy and safety and possibly shorten the duration of treatment. Continuing developments to improve carrier design, aerosol performance, and formulation stability underpin the use of PDDS as a promising strategy for enhancing TB management. Future advancement of clinical translation and device refinement will be instrumental in bringing these technologies into standard therapy and furthering international TB control programs

Keywords:Tuberculosis (TB), Multidrug-resistant tuberculosis (MDR-TB), Extensively drug-resistant tuberculosis (XDR-TB), Pulmonary drug delivery system (PDDS), Dry powder inhalers (DPI), Inhalable formulations, Targeted drug delivery

1. INTRODUCTION

Tuberculosis is an airborne infectious disease caused by Mycobacterium tuberculosis that predominantly targets the lungs. The emergence of drug-resistant strains multidrug-resistant (MDR-TB) and extensively drug-resistant (XDR-TB) strains—has been a major challenge to global efforts at TB eradication. Standard treatment for TB frequently necessitates frequent dosing over long durations, which typically results in patients taking medication irregularly as a result of side effects, compromising the effectiveness of treatment.[1][2]

Pulmonary delivery overcomes these issues by allowing targeted lung treatment using non-invasive inhalation methods. This method targets the medication to the infection site, avoids liver metabolism, and allows lower doses and less adverse reaction. Carrier systems have now refined these preparations further with sustained drug release that can reduce dosing frequency and enhance patient compliance.[4] Significantly, dry powder inhalers (DPIs) are convenient to use, as they are more stable than liquid or suspension drugs and easier to handle and store. The focus of this review is on the distinctive aerosolization properties of inhaled dry powder TB treatments. Through the identification of different anti-TB agents, it explores drug deposition patterns within the lungs. Findings of recent research indicate that DPI formulations have the ability to tremendously improve therapeutic efficacy by enhancing drug concentrations in lung tissues.[6] Administering TB drug via the pulmonary route serves to concentrate the drug where it is needed most and restrict its spread to other parts of the body, thereby maximizing efficacy while containing the risk of systemic side effects. But for effective therapy, drug particles need to deposit onto the epithelial surface in the lungs, and the active constituents of their drugs should be capable of traversing multiple biological barriers—like surfactant and mucus films, epithelial cells, basement membranes, and capillary endothelium—before they are absorbed. Of these, the surfactant layer inside the alveoli is the major one and also the prime target for treatment of the lungs.[3][7] This layer not only decreases surface tension in alveoli, enhancing gas exchange, but is also challenging to drug stability and solubility. Although surfactant may slow down drug particles, it will also increase the dissolution of some agents, improving their absorption and therapeutic potential in systemic delivery.

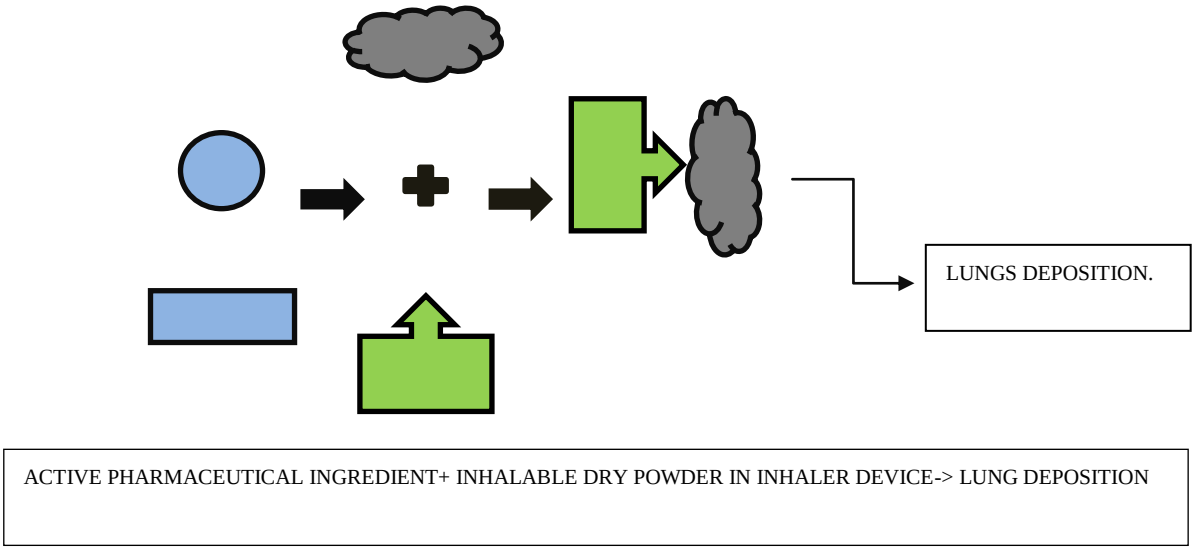

Fig. 1-Inhalable dry powder formulations for anti-tubercular treatment.

2. PULMONARY DRUG DELIVERY SYSTEM.

The pulmonary pathway is becoming more differentiated for both systemic and local pharmaceutical uses, due to its minimally invasive character and ability to avoid first-pass hepatic metabolism. The anatomy of the lungs their huge absorptive surface area, strong vascular tree, and thin mucosal lining render them a particularly suitable location for effective drug delivery [1]. Pulmonary drug delivery systems are generally divided into categories like nebulizers, dry powder inhalers (DPIs), and metered dose inhalers (MDIs). DPIs have emerged as one of the fastest-growing segments over the last few years. For example, DPI market size is approximated to be at USD 20.36 billion in 2024 and growing to around USD 32.04 billion by the year 2033 with a compound annual growth rate (CAGR) of approximately 5.2 % between 2025–2033.

DPIs deliver micronized drug particles, generally below 5 µm diameter by matching the inspiratory effort of the patient to ensure deep lung deposition, rendering them an effective alternative to propellant-based systems [6][7]. Comparison of DPIs and MDIs brings into perspective some of the advantages of the former. Despite pressurized MDIs' overpowering presence in the market with an approximate 80% current usage, MDIs have issues in use in practice and in environmental consequences. MDIs usually contain chlorofluorocarbon propellants, which are the source of ecological damage [4]. Additionally, proper MDI use requires precise coordination of device activation and inhalation, a need that results in less-than-ideal drug delivery. Other restrictions are high drug retention in the oropharynx, lack of counters for doses, and irregular mixing where devices are not sufficiently shaken. DPIs, by contrast, are propellant-free, depend entirely on breath-activated systems, have dose counters for monitoring, and deliver mostly solid dosages, which reduces contamination from device parts. DPIs are thus considered a superior, environmentally friendly, and patient-centered option in inhalation therapy [7]. DPIs are preferred because they release medication directly in a powder form without the use of propellants, which increases chemical stability, particularly critical for biologic medications sensitive to temperature and moisture.

New formulations utilize specially designed particles and carrier materials to enhance how the powder flows, disperses, and deposits deep in the lungs, maximizing efficacy while minimizing drug waste [8]. Technical innovations now encompass breath-actuated and power-assisted inhalers that minimize patients' effort during inhalation, making medicines more user-friendly, particularly in children or those with poor lung function. Computer simulations enhance airflow and particle shape within devices to maximize delivery efficiency. Spray drying and jet milling formulation techniques enable control over particle size and properties to achieve high drug loads and prolonged release profiles. Advanced excipients like amino acids or polymers also protect the active drug, enhancing shelf life and lung deposition [6][5].

3. DIFFERENT BIOLOGICAL BARRIERS AND FACTORS AFFECTING LUNG DRUG DELIVERY.

Conventional methods of drug delivery are hampered by first-pass metabolism, which minimizes the concentration of active drug entering circulation, and general side effects to the whole body. Due to this, administering drugs via direct inhalation through the lungs has attracted interest, particularly in the treatment of respiratory diseases such as tuberculosis.[9] This approach allows for the drug to have a greater concentration at the site of infection and restrict its distribution all over the body, which can increase efficacy and lower side effects. The drug particles need to settle on the inner surface of the lung's epithelial membrane in order to become effective. After settling there, the active ingredients need to be absorbed before being metabolized or eliminated. Yet the respiratory system does contain a number of protective layers that drugs need to cross. These are the mucus and surfactant layers, the epithelial cells, the basement membrane, and the lining of the capillaries.

Specifically, the alveolar area in the lungs is the primary target for most inhaled drugs. The surfactant layer here is part of the air-to-blood barrier. It lining's the alveoli, reducing surface tension to facilitate breathing and enhance the effectiveness of oxygen exchange between the lungs and blood

vessels. Drugs must be durable in this setting, having stability to prevent enzymes from degrading them or immune cells engulfing them, but also capable of dissolving enough to travel through to the bloodstream if necessary.[11] The surfactant is a barrier, but it is also beneficial because it enhances the drug's solubility and availability for absorption. The mucus surface is another defense mechanism, keeping particles and noxious agents trapped. In addition, small hair-like structures known as cilia remove mucus and trapped material from the lungs. In order to minimize drug loss due to this clearing action, additives may be used to enhance the penetration of the medicine through the lung barriers.[12]

The surfactant will be a barrier, but it can also be beneficial by enhancing the solubility and availability of the drug for absorption. The mucus covering layer acts as another barrier, which catches particles and toxic agents. In addition to that, small hair-like features referred to as cilia assist in removing mucus and trapped material out of the lungs. To limit drug loss due to this clearing process, some additives may be incorporated into the drug to enhance its penetration through the lung barriers. The epithelial cells form another barrier.[10] In the alveoli, these cells are tightly packed, allowing very small particles—smaller than 100 nanometers—to pass through freely. The airway's epithelial lining, made up of stacked cells joined by tight connections, limits the passage of larger particles. Only very small drug particles can pass through directly, use specialized transporters, or slip between cells to reach deeper tissue.

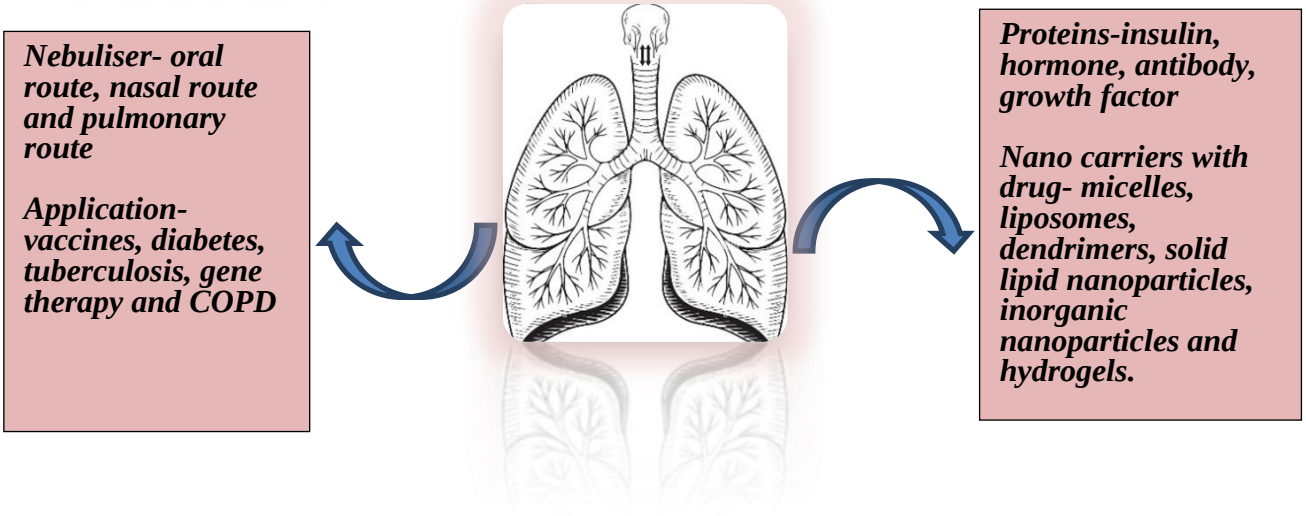

Fig. 2- Biological barriers in lung delivery system.

4. DRUG DELIVERY ROUTES AND APPLICATION.

4.1. Pulmonary Route-

The pulmonary route is generally used to transport medications directly to the lungs, making it an excellent choice for treating respiratory ailments such as asthma, chronic obstructive pulmonary disease (COPD), cystic fibrosis, and TB. This technique is increasingly gaining popularity for systemic drug administration, particularly for medications that require a quick beginning of action. Pulmonary medication administration is beneficial because it provides direct access to the lungs, resulting in localized therapy with less systemic adverse effects.Moreover, the vast surface area of the alveoli and the thin epithelial barrier allow for fast absorption into the circulation. [15] However, this approach has drawbacks, including the necessity for specialist devices such as inhalers, nebulizers, and dry powder inhalers. The effectiveness of pulmonary delivery depends on the particle size of the drug formulation, which must be optimized to reach the lower respiratory tract, patient compliance and proper inhalation techniques are critical for successful drug delivery. [16]

4.2. Oral Route-

The oral route is the most popular and commonly recognized mode of medication administration due to its ease and non-invasive nature. It is used to provide a wide variety of medicinal substances, including analgesics, antibiotics, hormones, and vitamins. Oral drug delivery is recommended due to its ease of administration, making it ideal for self-administration and long-term therapy. [13] Medications taken orally are subjected to first-pass metabolism in the liver, which might diminish their bioavailability. This route has a later beginning of effect than other routes, such as pulmonary or nasal administration. [17].Oral medications can also induce gastrointestinal adverse effects, such as discomfort or nausea, depending on the formulation and dose. Despite these obstacles, advances in drug formulation, such as enteric coatings and sustained-release tablets, have increased the efficacy and tolerability of oral drugs.

4.3. Nasal Route-

The nasal route is a potential option for local and systemic medication administration. It is particularly useful for medications that are poorly absorbed or require immediate therapeutic effects. The nasal cavity's highly vascularized mucosa and porous endothelium membrane allow for rapid absorption into the systemic circulation, avoiding first-pass metabolism. [18] This method is frequently utilized for local therapies such decongestants, antihistamines, and corticosteroids for allergic rhinitis. It is also used for systemic distribution of hormones (e.g., insulin, progesterone), analgesics, and CNS-targeting medicines since it may cross the blood-brain barrier. Nasal medication delivery is noninvasive, allowing for self-administration and increased patient compliance. It has drawbacks such poor drug retention in the nasal cavity, possible discomfort, and inconsistent absorption because of physiological elements like nasal secretions and mucociliary clearance. Recent developments have improved the stability and efficacy of nasal medication delivery methods, including nasal sprays, gels, powders, and liposomal formulations. [19] Each route—oral, nasal, and pulmonary—offers special benefits and uses in medication administration. The oral route is still the most practical and popular way for systemic distribution, while the pulmonary route is best for quick and targeted therapy of respiratory disorders. The nasal route is unique because it may carry medications straight to the central nervous system (CNS) or systemic circulation, avoiding first-pass digestion. Despite their challenges, ongoing research and technological advancements continue to optimize these routes for better therapeutic outcomes. [19] [20].

4.4. Transdermal route-

has emerged as a novel strategy for delivering anti-tubercular drugs through the skin using patches, microneedles, or Nano carrier-based systems. This approach offers several benefits, most notably its non-invasive nature and ability to provide sustained drug release over an extended period. By bypassing the gastrointestinal tract, it avoids first-pass hepatic metabolism and enhances the bioavailability of drugs that are otherwise unstable or poorly absorbed when taken orally. From a patient perspective, transdermal formulations reduce the burden of daily oral dosing and can potentially be developed as long-acting patches, such as once-weekly systems, thereby improving adherence to lengthy TB treatment regimens. Despite these advantages, limitations exist, including the restricted penetration of large and hydrophilic drugs like isoniazid and rifampicin through the skin, the potential for local irritation or allergic reactions, and limited drug loading capacity in patches. Current research is exploring microneedle patches and nanoparticle-enhanced systems to overcome these challenges, positioning transdermal delivery as a promising future option to complement conventional TB therapy.

4.5. Targeted and novel drug delivery systems-

are being actively developed to enhance treatment outcomes by ensuring higher drug concentrations at the primary sites of infection, particularly the lungs and alveolar macrophages. Among these, the intranasal route is being investigated for both therapeutic and prophylactic purposes, especially in the delivery of TB vaccines, as nasal administration can stimulate both systemic and mucosal immune responses. Another promising approach involves implantable or injectable depot formulations, often using biodegradable polymers, which provide long-term and controlled release of anti-TB drugs over weeks or months, thereby reducing the frequency of administration and addressing compliance issues common in multidrug-resistant TB. Also, nanotechnology-based systems such as liposomes, solid lipid nanoparticles, and polymeric nanoparticles are being designed to improve solubility, stability, and targeted macrophage delivery of first-line drugs like rifampicin and isoniazid. These advanced carriers protect the drug from degradation, enhance oral absorption, and reduce systemic toxicity. While many of these technologies are still under preclinical or clinical evaluation, they hold significant potential to shorten treatment duration, improve patient adherence, and minimize drug resistance, making them an important direction for the future of TB therapy.

5. NOVEL APPROACHES FOR DRY POWDER INHALABLE DRUG DELIVERY.

Table1-Liposomal and Proliposomal Formulations for Pulmonary Delivery: Methods of Preparation and Potential Therapeutic Benefits.

Drug	Preparation Method	Major Ingredients	Device & Conditions	Fine Particle Fraction (FPF %)
Amikacin Sulphate	Reverse Phase Evaporation (RPE) + Lipid Preparation (LP)	Hydrogenated Soy Phosphatidylcholine (HSPC) along with Chitosan (CS), Stearylamine	Twin Stage Impinger (TSI), Rotahaler, with Flow rate -2, 60 L/min	29.2 ± 2.10
Budesonide	Thin Film Hydration (TFH) + LP + Bead Milling (BM)	Egg includes Phosphatidylcholine, CS and α-Tocopherol[23]	TSI, Rotahaler, with Flow rate -2, 60 L/min[22]	20.69 ± 1.50
Dapsone	Thin Film Evaporation (TFE) + Spray Drying (SD)	Dipalmitoyl phosphatidylcholine (DPPC), CS and Hydrolysed Gelatin, DSPG	Andersen Cascade Impactor (ACI), with Flow rate -2, 28.3	75.6 ± 1.60

Drug	Preparation Method	Major Ingredients	Device & Conditions	Fine Particle Fraction (FPF %)
			L/min[26]	
Gemcitabine Hydrochloride	Supercritical Emulsification (SE) + LP	mPEG2000-DSPE, Trehalose, along with Saturated Egg Phosphatidylcholine	ACI, with Flow rate -3, 60 L/min[24]	56.12 ± 4.38
Ketotifen Fumarate	TFH + Freeze Drying (FD)	Phosphatidylcholine, CS and Sucrose	TSI,with Flow rate -2, 60 L/min (5 sec)	21.59 ± 1.53
N-Acetylcysteine	RPE + SD	Phospholipid and CS[25]	ACI, Handi Haler, with Flow rate -3, 28.3 L/min (8.5 sec)	35.34 ± 3.86
Recombinant Secretory Leukocyte Protease Inhibitor (rSLPI)	Rotary Evaporation (RE) + LP + Jet Milling (JM)	1,2-Dioleoyl-sn-glycero-3-[phospho-L-serine] and CS	TSI, Spinhaler, along with Flow rate -2, 60 L/min[27]	59.5 ± 5.40
Rifampicin	TFE + Chitosan & Carrageenan coating + SD	Soy Phosphatidylcholine (SPC) and HSPC, CS	NGI, Turbospin, along with Flow rate -2, 70 L/min[26]	51.1 ± 2.30
Salbutamol Sulfate	Vesicular Phospholipid Gel + LP + BM	SPC	TSI, Spinhaler, with Flow rate -2, 60 L/min	41.51 ± 2.22
Amiloride Hydrochloride	TFH + High-Pressure Homogenization (HPH) + SD	HSPC, CS and Mannitol[21]	ACI, Rotahaler, with Flow rate -2, 28.3 L/min	67.6 ± 0.60
Tacrolimus	TFE + HPH + SD	Hydroxy propyl Cellulose (HPC) and CS	ACI, with Flow rate -2, 28.3 L/min	71.1 ± 2.5
Isoniazid	Spray Drying (SD)	L-α-Soybean Phosphatidylcholine, CS and 90% Mannitol[25]	ACI, with Flow rate 60 L/min[28]	71 ± 2.0
Rifapentine	Spray Drying (SD)	HSPC and Stearylamine	ACI, with Flow rate -2, 60 L/min (4 sec)[28]	92.5 ± 1.5

Table 2- Strategies for pulmonary medication administration in TB therapy.

Type of formulation	Dosage form	Excipients used	Method of preparation	objective
Dry powder inhaler	Nanocarriers	l-leucine Valine	Spray drying method	To determine the influence of adding l-leucine and using an ethanolic The impact of solvent on the physicochemical and aerodynamic properties of nanospray-dried PZA-l-leucine powders. [29]
Dry powder inhaler	Micro carriers	DPPC -Hyaluronic acid -Ammonium bicarbonate	Spray drying method	Change the spray drying parameters to enhance the PZA formulation as large porous particles for pulmonary delivery. [33]

Type of formulation	Dosage form	Excipients used	Method of preparation	objective
		-D,l-leucine		
Dry powder inhaler	Phospholipid-based microparticles	DPPC -DSPE-PEG2k -l-leucine	Spray drying method	Create and enhance PZA spray-dried inhaler powders based on phospholipids. [36]
Dry powder inhaler	Polymeric microparticles	Chitosan -TPP -l-leucine -Lactose	Spray drying Method	Prepare and describe chitosan microspheres loaded with INH for pulmonary administration. [32]
Dry powder inhaler	Lipid-polymer hybrid nanoparticles	Soy Lecithin -DSPE-PEG2k -PLGA -Mannitol	Spray drying Method	Spray-dried lipid-polymer hybrid nanoparticles are what we want to use to provide antitubercular medications to the lungs. [39]
Dry powder inhaler	Solid lipid nanoparticles	Compritol -Tween 80 -Poloxamer 407	Homogenization and ultra sonication	to use EMB-loaded SLNs to measure pulmonary DPI in order to treat tuberculosis. [40]
Dry powder inhaler	Polymeric nanoparticles	Chitosan	Nano spray drying method	The goal is to test the effectiveness of a dry powder formulation containing EDH and chitosan in treating TB by targeting AMs.[38]
Dry powder inhaler	Polymeric microcarriers with nanosize drug	Chitosan	Spray drying method	To provide injured lungs EDH in the form of DPI, a hollow chitosan carrier was created. [44]
Dry powder inhaler	Polymeric microparticles	PLGA	Spray drying method, O/W emulsion, lyophilization	Enhancing the RIF content of primary nanoparticles and investigating the usage of leucine and arginine to produce low-hygroscopic nanocomposite particles are the objectives. [43]
Dry powder inhaler	Nanostructured lipid carriers	Oleic acid -Stearic acid -Tween 80 -Phospholipon 80H	Microemulsion technique	Tuftsin-modified peptide was used to functionalize RIF NLC in order to improve TB treatment. [41]

Type of formulation	Dosage form	Excipients used	Method of preparation	objective
Dry powder inhaler	Microcarriers with nanosize drug	Sodium Hyaluronate	Spray drying Method	Our objective is to develop respiratory microparticles loaded with sodium hyaluronate nanocomposite RIF, INH, and VPM to fight against mycobacterial pulmonary infections and antibiotic resistance. [46]
Dry powder inhaler	Polymeric microparticles	Chitosan -TPP -Lactose	Spray drying Method	The objective is to develop and evaluate a DPI for RFB based on chitosan microparticles. [47]
Dry powder inhaler	NA	NA	Spray drying Method	By co-spray drying hygroscopic KNM powder with hydrophobic RIF, the study seeks to enhance its aerosolization for the treatment of respiratory infections. [43]
Dry powder inhaler	NA	Acetone -Methanol	Spray drying method	The inhalable crystalline and amorphous dry powder forms of RFP were compared in vitro. [45]
Dry powder inhaler	Microcarriers	LBG	Spray drying Method	To create inhalable LBG microparticles as a dual antibiotherapy for TB. [47]
Dry powder inhaler	Proliposomes	HSPC -l-leucine -Cholesterol -Stearyl amine	Spray drying Method	Create proliposomes loaded with RFP and formulated with DPI to treat TB. [46]

6. BENEFICIAL ASPECTS.

The application of dry powder inhalers (DPIs) as a drug delivery system is increasing, especially in respiratory diseases such as TB. To help in the control of the global TB pandemic, this research examined various DPI formulations containing one or more anti-TB drugs. Well-organized aerosolization method is one of the key features of DPI formulations, enabling the study and quantification of the deposition of particles in the lungs upon inhalation. [29] Most DPI formulations contain carriers, which improve the flow properties of drug particles and aid in decreased dosage inconsistency. Improved powder handling during manufacture and regulated medication deposition in the lungs are also facilitated by this. Besides this nano and micro technologies are usually employed to enhance medication solubility, which increases bioavailability and enhances therapeutic effect. Since DPI carriers, l-leucine, mannitol, chitosan, and lactose are commonly studied excipients. L-leucine is a favorite since it improves the efficacy of anti-TB drugs in aerosol state. [30]

Leucine is prone to forming a depot at the air-water interface during spray drying, which prevents the entry of solvent vapor. Reduced particle density is a consequence of the effect of this behavior on particle geometry. Leucine also enhances process efficiency by reducing particle sticking to spray drying equipment surfaces. Based on the literature, DPI formulations typically contain sugar-based transporters such as lactose and mannitol. The hygroscopic nature of mannitol accelerates drug degradation, while lactose is valued for its biocompatibility and biodegradability. Generally, MPC-mannitol is superior to crystalline mannitol since the latter type creates smooth spheres that favor particle agglomeration and lower the fine particle fraction (FPF) but both ensure improved powder flow.[30][31] Most significant are phospholipid carriers, such as proliposomes based on mannitol and soybean phosphatidylcholine or its porous counterpart. By enhancing the bioavailability of hydrophobic drugs, the biocompatible phospholipid bilayer enhances therapeutic effectiveness. [29] By providing targeted delivery to specific tissues and stimulating absorption by alveolar macrophages, the entrapment of anti-TB drugs into such carriers may augment antimycobacterial action and reduce systemic toxicity. Due to their ability for sustained release, polymeric carriers such as chitosan, polyvinyl alcohol (PVA), and poly(lactic-co-glycolic acid) (PLGA) are preferred in the formulation of DPI. Studies show that the release of medication from polymeric carriers typically entails a long, controlled release period following an initial rapid release period.[32]

7. ADVANCEMENT IN PULMONARY DRUG DELIVERY SYSTEM AND FORMULATIONS.

Treatment of respiratory diseases like asthma and chronic obstructive lung disease (COPD) has long depended extensively on inhalation therapy. It has now even found application in the treatment of bacterial diseases like tuberculosis (TB) and other infections of the lungs.[37] More effective treatment methods are urgently required, as evidenced by the development of resistant TB strains. Through maintenance of high local drug levels in lung tissue with lowered systemic exposure and side effects, pulmonary drug delivery offers a promising approach. Novel pulmonary delivery devices like dry powder inhalers (DPIs) have raised the possibility of effective anti-TB therapy.[38]

Nanoparticle-based formulations are critical for the optimization of medication delivery and overcoming the biological barriers in the lung. Sophisticated carriers facilitate the delivery of biological agents, including peptides and nucleic acids, and medications to the alveolar macrophages, which are often the residence of Mycobacterium TB. With the development of multidrug-resistant tuberculosis (MDR-TB), the most lethal form of bacterial infection of the lungs, these new approaches are particularly vital. Investigations into synergistic activities of capreomycin and antimicrobial peptides in powdered form for inhalation present promising alternatives to conventional therapy.[47]

In an effort to stabilize biological compounds such as plasmid DNA and ensure good aerosol properties for pulmonary administration, dry powder formulations employing particle engineering methods such as spray freeze drying (SFD) and thin-film freezing (TFF) have demonstrated great potential [39][40]. Knowing the dissolving kinetics of aerosol powders is critical in making formulations with optimal pharmacokinetic profiles. These methods offer precise regulation of particle shape and size, which is crucial for efficient lung depositing and therapeutic activity. The integration of computer modeling and in vitro dissolution studies enhances targeted TB treatment formulation design by forecasting systemic drug exposure from pulmonary delivery. Whereby the advanced technical advancements have enhanced intratracheal delivery procedures in small animal models, preclinical animal research is still necessary to determine the safety and immunogenicity of inhale vaccines and therapies. New population pharmacokinetic methods measuring regional lung deposition are useful for bioequivalence assessment of inhaled drugs and facilitate regulatory evaluation.[45][46]

8. EXPERT OPINION ON DRUG DELIVERY FOR TREATMENT OF TUBERCULOSIS.

Polymeric microparticles and nanoparticles used in dry powder inhaler (DPI) formulations have been extensively assessed for safety using cytotoxicity tests. Chitosan-based formulations, as reported, maintain cell viability rates of 80 to 90 percent with low toxicity on a range of lung-derived cell lines such as A549, Calu-3, and NR8383. [50] The chitosan-free formulations are generally more cytotoxic, reflecting the protective role of the carrier in minimizing any adverse effects. Once encapsulated in chitosan-TPP nanoparticles, rifampicin (RIF) shows considerably improved cytocompatibility compared to when RIF is unbound. Whereas free RIF exposure results in discernible detrimental effects at doses higher than 0.125 mg/mL upon 6 to 12 hours of incubation, macrophage cell viability remains nearer to 80–90% across a variety of doses of drugs. [54]

These findings have been validated by animal experiments using male Wistar rats; oral RIF administration showed considerable pulmonary toxicity, but neither RIF-loaded chitosan-TPP formulations nor control DPI products resulted in lung toxicity when administered by inhalation. Analogously, like these chitosan microparticles loaded with isoniazid (INH), little cytotoxicity has been observed in alveolar macrophage cell lines (AMJ2-C11 and

J774.1), establishing their suitability for pulmonary delivery systems. [52] [53] In pertinent immunological and lung epithelial cells, rifabutin-loaded chitosan carriers and rifampicin-loaded poly (lactic-co-glycolic acid) (PLGA) microparticles did not significantly affect cytotoxicity.

Further support of the safety of such carriers, polymeric DPI formulations embedding rifampicin (RIF) and pyrazinamide (PZA) in hydroxypropyl-beta-cyclodextrin (HBCD) matrices did not impair A549 cell viability. The doses below 1 mg/mL, rifampicin-loaded nanocomposites exhibited reduced cytotoxicity yet preserved intense anti-tuberculosis activity. [54]Under exposure to microparticles with RIF, INH, and verapamil (VPM), human monocyte-derived macrophages remained at full vitality up to five days of post-exposure; viability only decreased upon prolonged incubation. Research into the cytotoxicity of combination therapy indicated that formulations including both PZA and bedaquiline (BDQ) decrease the toxicity associated with BDQ alone.[55]

This could be due to the reduced BDQ ratio in certain combinations. Nevertheless, INH and rifabutin-filled locust bean gum (LBG)-based microparticle carriers suppressed A549 lung cell survival by approximately 60%, indicating that such formulation formulations require a more improvement. Assessments of co-spray dried formulations of hygroscopic kanamycin (KNM) with hydrophobic rifampicin (RIF) and crystalline rifapentine DPIs enhanced aerosolization performance and proved their safety and compatibility with lung epithelial cells. All these studies endorse the therapeutic promise of polymeric and the other lipid-based dry powder inhaler formulations to enhance TB treatment methods by providing strong proof of their relative safety for pulmonary delivery. [56]

9. CLINICAL ASPECT OF DRY INHALAER FORMULATION AGAINST FORMULATION.

A rising number of preclinical and clinical investigations have revealed promising improvements for pulmonary administration of anti-tubercular medicines in dry powder inhaler (DPI) formulations. The first anti-TB medication created as a microparticle DPI formulation was capreomycin. [58] Twenty healthy adults who used a portable inhaler device participated in a phase 1 single-dose, dose-escalation clinical study for this formulation. Although 20% of participants reported having a mild to moderate, temporary cough, the results showed that the medication was usually easily tolerated with no major side effects. Suggestively, serum drug concentrations beyond the minimal inhibitory concentration (MIC) of 2 µg/mL against Mycobacterium TB were obtained by inhaling a 300 mg dosage. [59]

A clinical-stage biopharmaceutical company launched a phase 1 clinical trial in July 2020 to assess an amikacin DPI formulation, administered via the CyclopsTM device, in patients with drug-susceptible tuberculosis. These results support possible use of inhaled therapy as a component of a regimen for multidrug-resistant tuberculosis (MDR-TB). Amikacin given by the pulmonary route is tolerated well, according to earlier research. A single 300 mg dosage during the study caused serum concentrations of M. tuberculosis to surpass the minimum inhibitory concentration (MIC). About 20% of individuals reported having a mild to severe, temporary cough. These findings further suggest that inhaled amikacin may be used as a mainstay of care for MDR-TB. [60] [61]

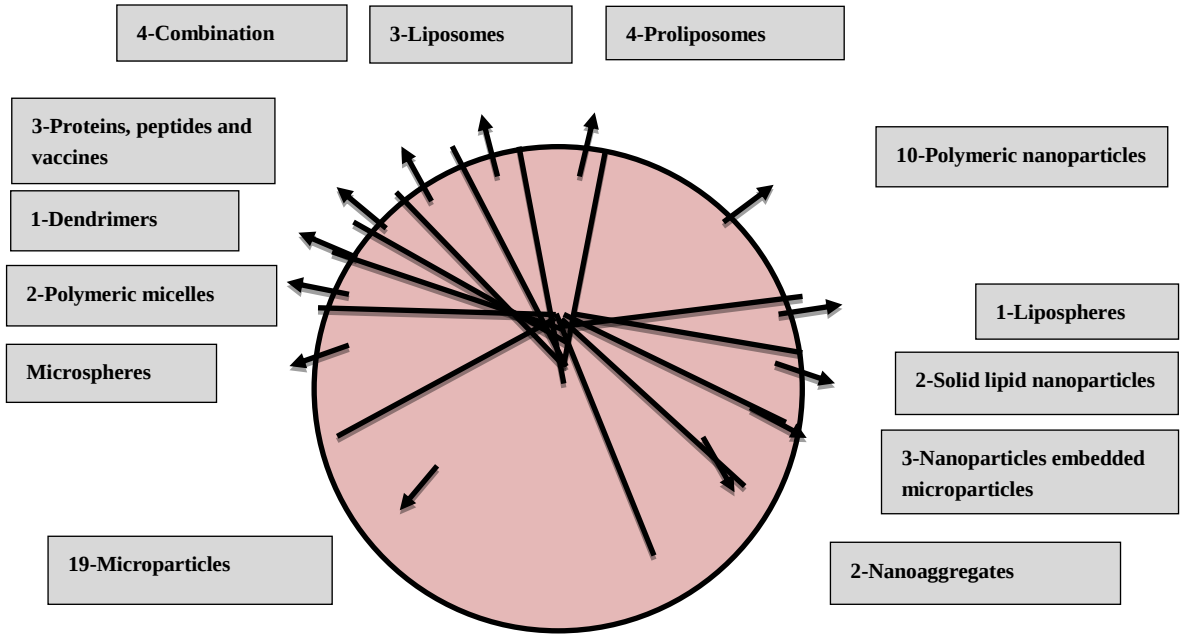

Fig. 3-Scientific Literature Trends on Dry Powder Inhalers for Tuberculosis.

10. CONCLUSION.

Tuberculosis (TB) is still a serious worldwide health issue, despite the availability of modern treatment regimens. While the condition is treatable, present treatment options frequently have significant limitations, including as lengthy treatment periods, heavy pill loads, patient noncompliance, and the rise of drug-resistant strains.[50] To address these issues, novel medication delivery techniques are being investigated. One interesting possibility is the use of inhalable polymeric dry powders for targeted pulmonary administration of anti-TB medicines. [50] These dry powder techniques have various benefits over traditional oral and parenteral delivery. By delivering medications directly to the lungs, the principal location of Mycobacterium tuberculosis (Mtb) infection, they can increase local drug concentrations while decreasing systemic adverse effects. Importantly, inhaled dry powders have a higher absorption by alveolar macrophages, the primary host cells harboring Mtb, resulting in more rapid pathogen clearance compared to oral or injectable methods. [48]

Recent studies have shown that these methods not only increase medication bioavailability but also give considerable advantages to patient quality of life. They are easy to store, stable under ambient circumstances, cost-effective to create, and simple to administer—all of which make them ideal for large-scale application in both low- and high-resource environments, developments in magnetic particle technology have created new opportunities for precise medication targeting.[49] Incorporating magnetic particles into inhalable formulations allows for site-specific administration within the lungs while also providing non-invasive, real-time imaging to assess therapy success. This combined role of pharmacological advice and patient follow-up marks a significant step forward in tailored tuberculosis care. Such strategies allow clinicians to tailor therapies to individual patient needs—whether focusing treatment on alveolar niches, infected macrophages, intracellular bacilli, or granulomatous lesions—thereby maximizing therapeutic efficiency while minimizing unnecessary drug exposure. Pulmonary delivery systems have the potential to integrate multiple therapeutic agents within a single formulation. [54] This combinatorial strategy may have synergistic benefits, such as combining direct bactericidal activity against Mtb with immunomodulatory activities that improve macrophage functionality. This may allow for shorter treatment durations, their multifactorial design, which includes particle size, aerodynamic characteristics, release profiles, and biocompatibility, must be meticulously tailored to achieve specific therapeutic goals. [55] Continuous progress in the creation of new anti-TB compounds should coincide with advances in delivery technology. The ultimate objective is to build simple, reliable, and patient-friendly pulmonary medication delivery devices that may be routinely applied in clinical practice, expediting worldwide efforts to eradicate tuberculosis. [57]

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