Ind. J. Pharm. Edu. Res., 2023; 57(3):640-647.
https://www.ijper.org

Review Article

Inhalable Microparticulate System for Tuberculosis: An Updated Review

Mallamma T*, Prakash Goudanavar

Department of Pharmaceutics, Sri Adichunchanagiri College of Pharmacy, Adichunchanagiri University, B G Nagara, Karnataka, INDIA.

ABSTRACT

Antibiotic efficiency declines in TB treatment and bacteria develop resistance over time due to numerous barriers such as lung mucus and biofilms surrounding the microbe. To tackle drug-resistant tuberculosis, there is a critical need for the discovery of novel medications and the repurposing of existing drugs with new mechanisms of action. Despite these challenges Vascular drug delivery shows promise as a potential treatment option for tuberculosis due to its ability to achieve high medicine levels at the infection site with reducing toxicities. The inhalable antitubercular Microparticles (MP) are directly bound in a thick mucin mess network in the lungs, that allows for high concentrations at the site of action while limiting systemic distribution, resulting in more effective therapy with lower required doses, side effects and rapid elimination by mucociliary clearance. there are several challenges in obtaining a such formulation to meets all of the criteria for physico-chemical, aerodynamic, and biological properties, which is why only a small number of the investigated systems can reach the clinical trial phase and proceed to everyday use. The current study focuses on methods to create inhalable Microparticles for antitubercular drug delivery systems by using different carriers to the lungs, stressing how drug bioavailability, Drug Deposition might be affected by the route of administration. Additionally, the advantages and disadvantages of the novel distribution techniques and Evaluation parameters are explored.

Keywords: *Mycobacterium tuberculosis* (MTB), Inhalable Microparticles (MP), Multidrug-Resistant Tuberculosis (MDR-TB), Aspect Ratio (AR), Metered Dose Inhalers (MDI).

Correspondence:
Mallamma T
Assistant Professor, Department of Pharmaceutics, Sri Adichunchanagiri College of Pharmacy, Adichunchanagiri University, B G Nagara-571448, Karnataka, INDIA.
Email: mallammareddy89@gmail.com

Received: 23-09-2022;
Revised: 30-11-2022;
Accepted: 31-03-2023.

INTRODUCTION

The disease known as Tuberculosis (TB), which is brought on by the bacterium *Mycobacterium tuberculosis* and typically affects the lungs, is the 13th chief source of death globally and the 2nd deadliest infectious killer (later to COVID-19).[1] *Mycobacterium tuberculosis* is the culprit. When tuberculosis patients cough or sneeze, they may release bacteria into the air, increasing the risk of the disease spreading. Displaying similar symptoms, such as a hacking cough, a fever, and breathing difficulties, e.g A total of 1.5 million deaths were attributed to tuberculosis in 2020 (Including 2,14,000 people with HIV).[2] In 2020, just approximately one person out of every three who had drug-resistant tuberculosis received treatment for their condition. In 2020, 86% of all newly diagnosed tuberculosis cases worldwide were found in the 30 countries with the most significant TB burden. Eight countries accounted for two-thirds of newly diagnosed tuberculosis cases: South Africa, Pakistan, Nigeria, Bangladesh, India, China, Indonesia, the Philippines, and Pakistan.[3] From 2015 to 2020, the number of people who were ill with tuberculosis on a global scale decreased by 11% (relative to population), which is little over halfway to the milestone of 20% that was set for 2020.[2] Because of the thick permeability barrier created by the outer membrane, which collaborates with additional resistance mechanisms, including multi-drug efflux, *Mycobacterium* TB has intrinsic resistance to a wide range of antibiotics.[4]

To treat infected patients with mycobacterial strains susceptible to certain drugs, a minimum of 6-9 months of conventional anti-tuberculosis therapy is required. It is only in regions of the body that have adequate blood flow that it is possible to get therapeutic concentrations of medication [Figure 1]. Lesions, granulomas, or tubercles are examples of inadequately vascularized regions that can be found in the lungs. Granulomas provide a protective environment for mycobacteria, and it is possible that standard therapy will not reach therapeutic levels within the granulomas.[5] The initial intensive phase of drug-susceptible tuberculosis disease involves the simultaneous administration of a minimum of 3 medications in order to decrease the quickly dividing bacillary burden. In the continuation phase, a minimum of two drugs are used to sterilize lesions containing fewer and slower-growing bacilli.[5]

DOI: 10.5530/ijper.57.3.78

Copyright Information :
Copyright Author (s) 2023 Distributed under Creative Commons CC-BY 4.0

Publishing Partner : EManuscript Tech. [www.emanuscript.in]

In addition, some complications arise when oral anti-TB treatment cannot achieve a high medication concentration in the lung. A high dose over a protracted length of time is required to accomplish this. It is possible that this will lead to an increase in the severity of toxic effects, the degradation of medications before they reach their target location, and poor patient compliance.[6] Several researchers have transformed anti-TB medications into particles that can be delivered to the pulmonary system. Incorporating drugs into particles increases their stability and protects them from things like enzymatic degradation. In addition to enlightening the bioavailability of hydrophobic medicines, this permits drug targeting to particular organs, cells, or receptors and circumvents numerous lung clearance processes.[7]

Particulate-based pulmonary systems were created using a variety of carriers, including liposomes, solid lipid nanoparticles, polymeric micro/nanoparticles, micelles, and cyclodextrins, to overcome these challenges. Systems have demonstrated substantial potential for enhancing therapeutic effectiveness and medication absorption in the deep lung.

The selection of drug carriers is significant; however, it is also very important to take into consideration other factors, such as the physico-chemical properties of the drug, the inhalation device that is being used, the region that is being targeted, the severity of the condition, as well as the nature and stability of the carrier. In order to get around the pulmonary clearance processes and provide greater therapeutic effectiveness and regulated drug release, particle-based drug delivery systems have developed as a new and promising alternative to conventional inhaled medications. In order to produce formulations for inhalation, it is necessary to tailor and perfect several factors, such as the aerodynamic size and shape of carriers, as well as the surface characteristics of those carriers [Table 1]. The majority of inhalation treatments that are currently being used have poor therapeutic efficacy and substantially adverse effects [Figure 2] because their half-lives are quite short, and their drug bioavailability at the targeted site is relatively low. Inhaled drugs have a relatively short half-life and poor drug bioavailability as a result of the primary processes that lead to their removal. Enzymatic breakdown, fast systemic adsorption, and mucociliary and alveolar macrophage clearance are all components of the pulmonary clearance process.[9]

In this review, we will concentrate mainly on the creation of polymeric microparticles. Because they preferentially deposit in the deep lung for pulmonary delivery and because they do not agglomerate when subjected to shear force.[9]

The Microparticles (MPs) are spherical particles made of a continuous matrix and range in size from 1 to 1000 mm. Although many materials have been found to be able to create MPs, polymeric carriers perform better than other drug delivery methods, like liposomes in terms of stability, drug Loading Capacity (LC), delayed drug release, longer pharmacological activity, and storage properties. The particles may be made to preferentially deposit in particular lung regions since polymers are relatively flexible. The polymeric matrix may be made from synthetic or natural polymers. Examples of natural polymers include a variety of polysaccharides, proteins (such as albumin, gelatin, and collagen), and gelatin. Renewable resources are used to create natural polymers. They are biocompatible and biodegradable in part due to their highly organized structure.[11]

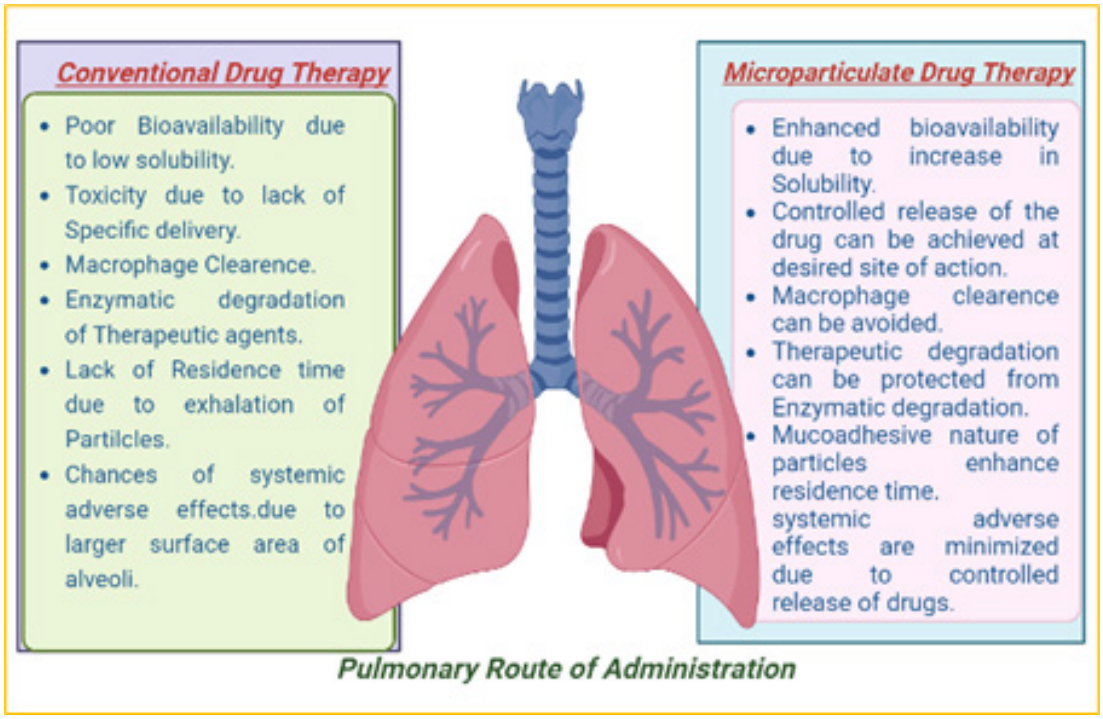

Figure 1: Difference in Pulmonary route of Administration.[8]

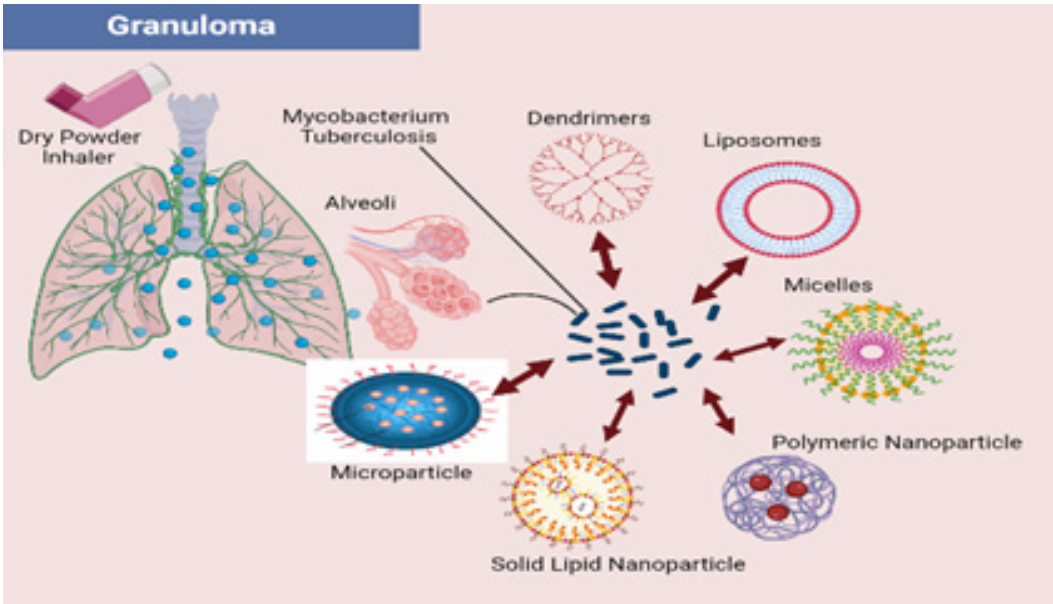

Figure 2: Different Carrier system for Pulmonary drug delivery to treat TB.

Table 1: Significant characteristics of important drug carriers.[10]

Carriers	Features
Microparticles	Excellent pulmonary deposition and widespread bioavailability after administration Inhalation, low drug encapsulation for some medications, low drug encapsulation for others.
Liposomes	Consisting of lipids that are physiological in nature a poor encapsulation rate of polar pharmaceuticals that are targetable to macrophages, issues with burst release of medicines, and a limited shelf life.
Nanoparticles	A high level of drug encapsulation with favourable pulmonary and systemic bioavailability.
Solid lipid nanoparticles	Natural carrier-based formulation features excellent drug encapsulation, favourable pulmonary deposition, high systemic bioavailability, and a long shelf life.

PULMONARY DRUG DEPOSITION AND BIOAVAILABILITY FACTORS

Particle Size

An aerosol's PM can range from 0.001 to greater than 100 mm. Depending on the size of the particles, there are different ways for particles to fall from the air.

Diffusion

Due to Brownian motion, particles will move from a region with a high concentration to a region with a low concentration. Diffusion is the term for this. Particles with a diameter smaller than 0.5 mm reach the alveoli through a process known as diffusion.

Sedimentation

Sedimentation is the process by which particles of aerodynamic sizes ranging from one millimeter to five millimeters become lodged in the alveoli and bronchioles, which are very small airways that experience minimal airflow. The gravitational forces, the speed of the particles, and their aerodynamic sizes all affect sedimentation.

Impaction

By impaction, particles bigger than 5 mm get stuck in bronchial areas. Aerodynamic diameter and mass have a significant effect on impact [Figure 3]. The Impact is most common way that dry powder inhalers and metered dose inhalers put down their Medicine (MDI).[12]

Methods for creating Inhalable microparticulate powders

The methods outlined in the Table 2 have shown that they can successfully develop carrier systems with acceptable aerodynamic diameters by using a wide range of polymers based on synthetic or natural substances.[13] Tables 3 and Figure 4 list the most popular production methods for inhalable microparticulate Drug delivery systems.

Current Treatment

First-line therapy in the United States consists of the drugs Rifampicin (RIF), Pyrazinamide (PZA), Isoniazid (INH) and Ethambutol (EMB). It is possible that EMB will be substituted with streptomycin periodically in countries other than the United States in an effort to conserve money.[5]

Aminoglycoside antibiotics, cycloserine, Ethionamide, and fluoroquinolones are among the medications in the second-line

category. The three most common aminoglycoside antibiotics are amikacin, kanamycin, and streptomycin. Levofloxacin and moxifloxacin are fluoroquinolone antibiotics, and capreomycin sulphate is a cyclic polypeptide antibiotic that is effective against MTB.[5]

BEAT (Building Evidence for Advance treatment against Tuberculosis) study – using Bedaquiline, Delamanid, Linezolid, and Clofazimine, to reduce XDR TB treatment to 6–9 months from the current duration of 18 months.

Modified BPaL regimen (BDQ, Pretomanid, and Linezolid), a three-year study was initiated in October 2021 as a pilot in 10 sites across the country.

HICON-R study- High dose of Rifampicin (25mg/kg) in comparison to the conventional regimen of 10 mg/kg.[16]

Characterization of Inhalable microparticle

Morphology

The performance of microparticles *In vivo* is significantly influenced by their size. Particles having a size larger than 100 nm are kept at the administration site until they are consumed by phagosomes and removed. Lymphatic absorption and junction deposition are particularly apparent between 10 and 80 nm.[17]

Particle Size Analysis

Microparticles with a diameter higher than 3 m have commonly had their particle size analysed using either a Coulter counter or the laser Light Diffraction (LD) method. Dynamic laser light scattering yields the Polydispersity Index (PDI), which depicts the distribution of microparticles in the lower size zone.[17]

Coulter Counter

A Coulter counter is an essential piece of equipment for particle analysis of microparticles intended for intravenous administration since it calculates an average particle number per volume unit for various size ranges.[18]

Image Analysis

Image analysis performed with the use of a microscope might be able to provide a more accurate estimate of the shape (light or scanning electron microscopy). Roundness, Aspect Ratio (AR), and the diameter of the Feret all contribute to the formation of the shape. Cascade impactors may be employed to analyse the aerodynamic size distribution (an indication of particle deposition during inhalation of Powders, aerosols, and sprays). Along with particle size, particle shape and density also have an impact on the flow of particles.[19]

Physico-chemical Characteristics

Zeta-Potential Analysis

Particle surface charges are what determine their physical properties. (such as an inclination to aggregate); Hyaluronic acid, polyalginic acid, and polymethacrylic acid are examples of naturally occurring compounds with polysaccharide bases that have negatively charged surfaces that attract tissues in inflammations and are hemocompatible, which has a substantial impact on their biological performance. Chitosan and poly-l-lysine are examples of positive-charged mucoadhesive, non-hemocompatible microparticles.[20] To determine zeta potential and particle size, using photon correlation spectroscopy. The Brownian motion of the particles is used to calculate dynamic light scattering. The aggregation potential of surface-charged microparticles in suspension can be determined with the help of zeta potential tests. These tests can also be used to evaluate whether or not a surface-charged molecule is encapsulated or deposited on the surface (over 30 mV stable suspended particles due to repulsion).[21]

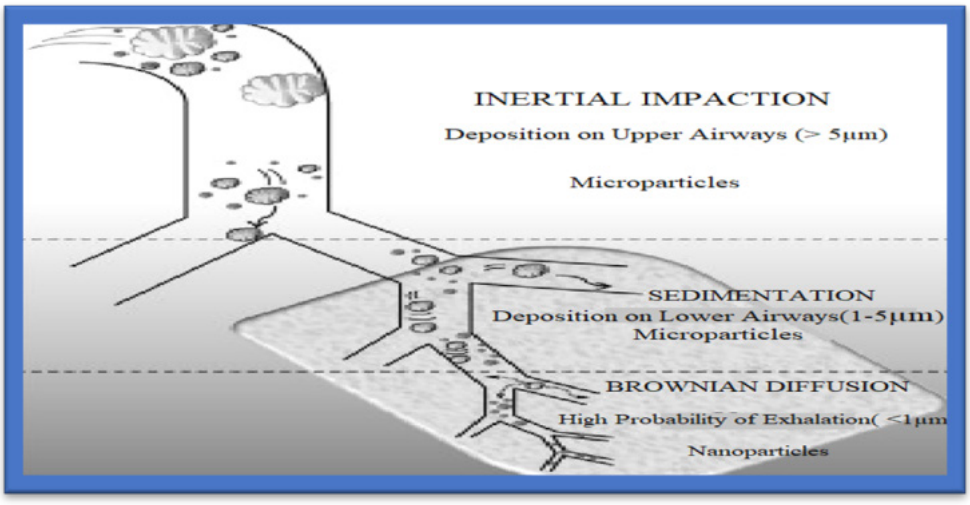

Figure 3: Mechanism of Deposition of Particulate System. [13]

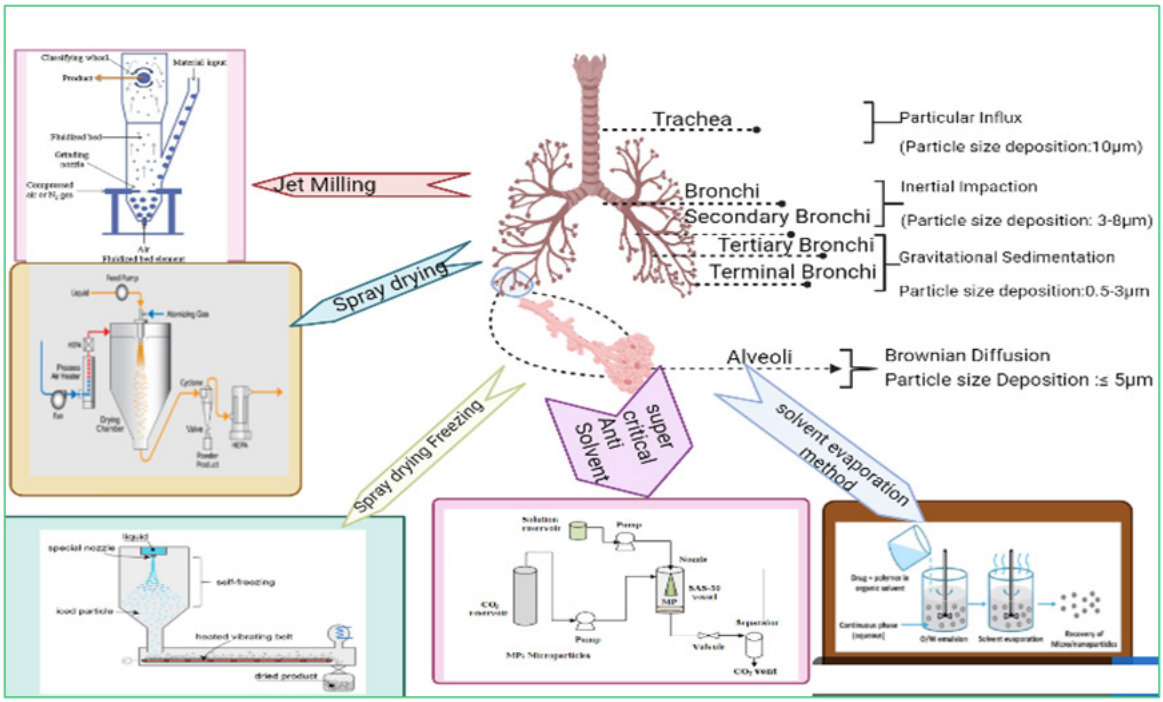

Figure 4: Methods of Preparation of Inhalable Microparticle.[15]

Table 2: Formulation Development of Inhalable Microparticles for TB:[14]

Materials	Category	Functions
PLGA poly(lactic-co-glycolic) acid, sodium carboxymethyl cellulose, sodium alginate, and sodium hyaluronate, chitosan, poly(butylcyanoacrylate), poly(lactic acid), and poly (lactic-co-lysine graft lysine).Sugars(mannitol, glucose monohydrate, trehalose, dextrose, maltose,sorbitol, maltitol and xylitol) lipids, amino acids(Leucine, trileucine).	Polymers.	Improved aerosol efficiency.
Poloxamer, polysorbates and sorbitanes SPC, sodiumtaurocholate and sodium glycocholate.	Surfactants.	Production of light and porous particles.Helps in dispersion or dissolution of drugs.
Trichloromonofluoromethane Dichlorodifluoromethane Dichlorotetrafluoroethane, Sorbitan trioleate Menthol, Ethanol Aqua, Glycerol Polyvinyl pyrrolidone K30Polyethylene glycol 600, Polyvinyl Alcohol (PVA), Acetic acid.	Solvents.	To make miscible.
α–phosphatidylcholine and PVP S 630 D, Methyl paraben and Propyl paraben.	Stabilizers.	Long-term conservation of products.
Salts of bile, including sodium salts of cholate, deoxycholate, glycocholate, glycodeoxycholate, taurocholate, and taurodeoxycholate, among others.	Absorption Enhancers.	They increase tran-cellular transport makes it more permeable.
Glutaraldehyde, sodium hydroxide, formaldehyde, ethylene glycol, di-glycidil ether, and sodium tripolyphosphate are all examples of cross-linking agents.	Cross –Linking agents.	
L-leucine and Stearic acid.	Flow enhancers or surface coating material.	Producing a shell to limit inter-particle contact improves the powder's flowability and dispersibility.

Table 3: Methods that are utilized in the production of Inhalable microparticulate dry powders.

Technique	working principle	Process Advantages	Process Disadvantages
Emulsion/solvent evaporation.	The drug and polymer are first dissolved in an organic solvent, and then an aqueous solution containing a dispersion stabiliser is added. After emulsion sonication, the solvent is evaporated.	Preserves the physicochemical characteristics of the polymer.	A size distribution of the microparticles that is rather broad Employing organic solvents as a method Difficult to scale up A method with two stages.
Spray-Drying (SD).	Spraying a feed into a hot drying media causes it to change from a fluid condition to a dried particle form.	Process for producing continuous, quick, easy and repeatable. No last drying stage, extremely versatile simple to scale, increased drug incorporation compared to previous methods.	Higher polydispersity compared to alternative methods. Expensive machinery and circumstances.
Supercritical anti-solvent.	After the drug and the polymer have been dissolved in an organic solution, the supercritical fluid, such as SCO_2, performs the role of an anti-solvent by assisting in the precipitation of the microparticles.	Single-step process.	Scaling up the use of organic solvents is challenging. Expensive intensive labour.
Anti-solvent Precipitation/SD.	Using a drug and anti-solvent solution one drop at a time to a polymer solution while rapidly mixing the two solutions together (e.g., ethanol, diethyl ether). The drug-loaded microparticles are then sprayed with excipients, resulting in the production of composites.	Low cost.	two-stage procedure organic solvents are used a challenge to scale up.
Ionotropic gelation/SD.	A cross-linking agent (such as TPP or CaCl2) is introduced drop by drop to a polymer solution which also includes a drug while the solution is being agitated. The drug-loaded microparticles are then spray dried with or without excipients to form microcomposites.	Prevents the usage of hazardous chemicals that are utilized in chemical cross-linking.	A two-step procedure, a challenge to scale up.

Physical Properties

Density

The ability of particles to float and how quickly they break down or swell are both influenced by their density. The psychometric method can be used to determine this value using helium gas.[22]

Porosity

Processes involving water absorption, swelling, reconstitution, and release are influenced by microparticle porosity. This parameter may be directly monitored with mercury porosimeters.[23]

Flowability and Compressibility Studies

In the case of dry particles, flowability, Carr's index, Hausner ratio, and angle of repose are significant factors.

Mechanical Test

The tensile strength and elasticity of microparticles can be evaluated with the help of a texture analyzer. This device measures the compression force in proportion to the distance and computes the maximum compression force and hardness, both

of that indicate the mechanical resistance of the layer or matrix structure.[24]

Swelling

One can do an swelling equilibrium research to investigate how dry particles behave under various circumstances.The initial particle diameter (di) and the initial particle diameter after reconstitution (ds) are used to determine the swelling index (S percent),as shown below.[25]

$$S(\%) = ds + di + 100)$$

Wetting Property

Measurements of the contact angle can be used to determine the level of wetting ability possessed by the excipients.[24]

Drug Entrapment Efficiency

The efficiency of actual drug loading and entrapment (also known as encapsulation) can be used to evaluate the success of drug loading: The following formula is used to get the value of entrapment efficiency: Entrapped drug content (EE, percent) (mg) 100 mg of possible drug content.

$$\text{Drug Entrapment Efficiency} = \frac{\text{Practical Drug Content}}{\text{Theoretical Drug Content}} \times 100$$

Numerous factors, such as the process type and conditions, affect the optimal entrapment efficiency (100%) of the system.[25]

Drug Release

The *in vitro* Dissolution Test for Multiparticulates USP 42-NF 37 provides an overview of several different methods for manufacturing multiparticulate products. Coated beads that do not dissolve can be utilized with the compendial rotating basket (USP Apparatus 1), the reciprocating cylinder (USP Apparatus 3), or the flow-through cell if sink conditions are maintained (USP Apparatus 4). Ionic polymers have varying degrees of activity depending on the pH. It is possible to evaluate whether the release of the drug is independent of or reliant on the ionic strength of the medium by employing a number of the processes outlined in the pharmacopeia. The medium can be hydrochloric acid, phosphate, or acetate buffer with or without enzyme, and its pH can range anywhere from 1.2 to 7.5 on the physiological scale, but this might vary depending on how the polymer is delivered or how it behaves in the medium (for example, swelling or ionization) (IEP). It is feasible to use surfactants, typically in quantities higher than their CMC value. You are permitted to utilize a spinning bottle, dialysis tubes, or a compact device equipped with a mini-paddle as non compendial pieces of equipment. Understanding the *in vitro* release mechanisms, such as erosion, osmotic release, diffusion, or a mixture of these, can be accomplished by using the models proposed by Fick, Higuchi, Korsmeyer-Peppas, Weibull, and Kopcha.[26]

Dissolution Test for Inhaled Particles

Conduct tests to determine how well-inhaled particles dissolve. There is a possibility that the particles will become lodged in the tracheobronchial tract if they are of a certain size, density, and shape. Because the mucus layer that acts as a medication absorption site has such a small volume, and because the process of regeneration of the absorption layer is distinct from that of the gastrointestinal tract, other dissolving techniques have been developed. USP 2, the spinning paddle apparatus, can be utilized with a few modifications. A specific container is utilized, the medicine is put inside, and a 150 mL dissolving media is employed. It is agitated with a little paddle. The use of a dialysis bag is another option. A semipermeable dialysis bag that is filled with the drug is placed in a dissolving media. Even though it maintains both static and sink conditions, the approach does not simulate the transition from liquid to gas.[27]

Other Studies

Spectrometry

Research with the Fourier-Transform Infrared (FT-IR) and Powder X-ray Diffractometry (PXRD) techniques can be carried out to investigate the intramolecular changes resulting from microencapsulation.[28] Investigations using Nuclear Magnetic Resonance (NMR) show how complexation alters polymer structure.[29]

Thermoanalytical Methods

Thermogravimetry (TG) and Differential Scanning Calorimetry (DSC) are effective tools for studying the thermal behavior of polymers. In both the manufacturing and release processes, the measured glass transition temperature is crucial.[24]

Biocompatibility

An MTT (Methylthiazolyldiphenyl-tetrazolium bromide) assay, a tetrazolium-based colorimetric assay, was effective for determining the cytotoxicity of hydrophilic polymers.[30]

CONCLUSION

The strategy will only work if high local therapeutic doses can be given to the lungs without giving too much drug to the body as a whole, which could help bacteria become resistant to drugs. Pleuropulmonary clearance mechanisms, rapid systemic absorption, metabolic breakdown, and control over where and how quickly the medication is deposited are the key factors that make it difficult to get pulmonary drug administration to operate successfully. One major challenge is ensuring that the particles are delivered to the correct site in the lungs and remain there long enough to release their medicine. Future research in this area should focus on optimizing particle size and shape to improve delivery efficiency, as well as developing new formulations that can release medicine over an extended period of time. The

efficiency of the therapies provided by the Inhalation based pulmonary systems in boosting medication bioavailability and absorption in the deep lung was excellent. Therefore, there is still much effort to be made to close the clinical and technological gaps and turn these Inhalation based pulmonary methods into Pharmaceuticals.

ACKNOWLEDGEMENT

I would like to thank for the assistance provided by Dr. Prakash Goudanaver, HOD and Professor, Department of Pharmaceutics, was greatly appreciated. I wish to extend my special thanks to Dr. Raghavendra Naveen, Assistant Professor, Department of Pharmaceutics, SACCP, ACU.

CONFLICT OF INTEREST

The authors have no conflicts of interest to declare.

ABBREVIATIONS

TB: Tuberculosis; **MTB:** *Mycobacterium tuberculosis*; **MP:** Inhalable Microparticles; **MDR-TB:** Multidrug-resistant tuberculosis; **AR:** Aspect ratio; **MDI:** Metered Dose Inhalers; **RIF:** Rifampicin; **PZA:** Pyrazinamide; **INH:** Isoniazid; **EMB:** Ethambutol; **PVA:** Polyvinyl alcohol; **LD:** Laser light diffraction; **PDI:** Polydispersity index; **FT-IR:** Fourier-transform infrared; **PXRD:** Powder X-ray diffractometry; **NMR:** Nuclear magnetic resonance; **TG:** Thermogravimetry; **DSC:** Differential scanning calorimetry; **MTT:** Methylthiazolyldiphenyl-tetrazolium bromide.

REFERENCES

1. https://www.who.int/news-room/fact-sheets/detail/tuberculosis
2. Tuberculosis deaths rise for the first time in more than a decade due to the COVID-19 pandemic. Available from: https://www.who.int/news/item/14-10-2021-tuberculosis-deaths-rise-for-the-first-time-in-more-than-a-decade-due-to-the-covid-19-pandemic
3. Tuberculosis(Availablefrom:https://www.who.int/news-room/fact sheets/detail/tuberculosis
4. Niederweis M, Danilchanka O, Huff J, Hoffmann C, Engelhardt H. Mycobacterial outer membranes: in search of proteins. Trends Microbiol. 2010;18(3):109–16.
5. Muttil P, Wang C, Hickey AJ. Inhaled drug delivery for tuberculosis therapy. Pharma Res. 2009;26(11):2401–16.
6. Gowda D V, Datta V, Kumar Gupta V. Formulation and Evaluation of dry powders containing anti tuberculosis drugs for pulmonary delivery. Indo Am J of Pharma Res. 2013;3:1239-48.
7. Misra A, Hickey AJ, Rossi C, Borchard G, Terada H, Makino K. Inhaled drug therapy for treatment of tuberculosis. Tuberculosis. 2011;91(1):71-81.
8. Singhvi G, Rapalli VK, Waghule T, Gorantla S, Pemmadi RV, Patel R. Microparticulate drug delivery systems for targeting respiratory diseases. 2020;1:337–57.
9. El-Sherbiny IM, El-Baz NM, Yacoub MH. Inhaled Nano and microparticles for drug delivery. [cited Jul 18 2022].
10. Pandey R, Khuller GK. Antitubercular inhaled therapy: opportunities, progress and challenges. J of Antimicrobial Chemotherapy. 2005;55(4):430–5.
11. Raquel F, Guerreiro H. Spray-dried polysaccharide microparticles aimed at pulmonary delivery of antitubercular drugs.
12. Smola M, Vandamme T, Sokolowski A. Nanocarriers as pulmonary drug delivery systems to treat and to diagnose respiratory and non respiratory diseases. Int J of Nanomedicine. 2008;3(1):1-19. PMID 18488412.
13. Miranda MS, Rodrigues MT, Domingues RMA, Torrado E, Reis RL, Pedrosa J. Exploring inhalable polymeric dry powders for anti-tuberculosis drug delivery. Mater Sci and Eng C Mater Biol Appl. 2018;93:1090–103.
14. Parumasivam T. Inhaled Antitubercular therapy: Dry powder formulations, device and toxicity challenges.
15. Xu Y, Liu H, Song L. Novel drug delivery systems targeting oxidative stress in chronic obstructive pulmonary disease: a review.J Nanobiotechnology. 2020;18(1):145.
16. Ministry of Health and Family Welfare Government of India Coming Together to End TB Altogether [internet].
17. Lengyel M, Kallai-Szabo N, Antal V, Laki AJ, Antal I. Microparticles, microspheres, and microcapsules for advanced drug delivery. Sci Pharma. 2019:87(3):89.
18. (PDF) Micro particles: An approach for betterment of drug delivery system.
19. Shekunov BY, Chattopadhyay P, Tong HHY, Chow AHL. Particle size analysis in Pharmaceutics: Principles, methods and applications. Pharma Res. 2007;24(2):203-27.
20. Hasırcı V, Hasırcı N. Fundamentals of biomaterials.Vol 338.
21. Chou DK, Krishnamurthy R, Randolph TW, Carpenter JF, Manning MC. Effects of Tween 20 and Tween 80 on the stability of Albutropin during agitation. J Pharm Sci 2005;94(6):1368-81.
22. Patel MA, AbouGhaly MHH, Schryer-Praga J, Chadwick K. The effect of ionotropic gelation residence time on alginate cross-linking and properties. Carbohydr Polym 2017;155:362-71.
23. Song M, Li N, Tiedt LR, Degennaro MD, de Villiers MM. Preparation and characterization of highly porous direct compression carrier particles with improved drug loading during an interactive mixing process. AAPS Pharm Sci Tech. 2010;11(2):698–707.
24. Lengyel M, Kállai-Szabó N, Antal V, Laki AJ, Antal I. review microparticles, microspheres, and microcapsules for advanced drug delivery. Scientia Pharmaceutica. 2019;87(3):20.
25. El-Say KM. Maximizing the encapsulation efficiency and the bioavailability of controlled-release cetirizine microspheres using Draper-Lin small composite design. Drug Des Dev Ther. 2016;10:825-39.
26. Ti li Aydin RS, Pulat M. 5-Fluorouracil encapsulated chitosan nanoparticles for pH-stimulated drug delivery: Evaluation of controlled release kinetics. J of Nanomater. 2012;2012:1-10.
27. Son YJ, McConville JT. Development of a standardized dissolution test method for inhaled pharmaceutical formulations. Int J Pharm. 2009;382(1-2):15-22.
28. Bhattacharya SS, Shukla S, Banerjee S, Chowdhury P, Chakraborty P, Ghosh A. Tailored IPN hydrogel bead of sodium carboxymethyl cellulose and sodium carboxymethyl xanthan gum for controlled delivery of diclofenac sodium.Polymer -Plastics Technology and Engineering. 2013;52(8):795-805.
29. Yang CH, Wang MX, Haider H, Yang JH, Sun JY, Chen YM, *et al*. Strengthening alginate/polyacrylamide hydrogels using various multivalent cations. ACS Appl Mater Interfaces. 2013;5(21):10418–22.
30. Sgouras D, Duncan R. Methods for the evaluation of biocompatibility of soluble synthetic polymers which have potential for biomedical use. J Mater Sci: Mater Med. 1990;1(2):61-8.

Cite this article: Mallamma T, Goudanavar P. Inhalable Microparticulate System for Tuberculosis: An Updated Review. Indian J of Pharmaceutical Education and Research. 2023;57(3):640-7.