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SUSTAINED RELEASE MICROPARTICLES INHALATION FOR TUBERCULOSIS TREATMENT: PRESENT ISSUES AND PROSPECTS

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Abstract

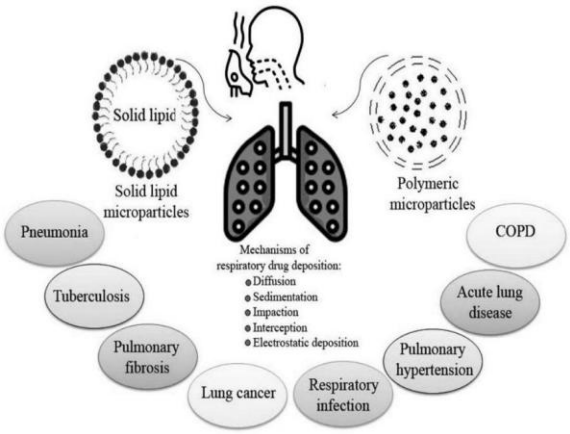
Mycobacterium tuberculosis, the primary cause of tuberculosis in humans, is a transmissible airborne disease. One of the most significant medical advances of the 20th century was the development of medications to cure tuberculosis. It makes sense to create strategies for administering antitubercular medications orally, or through the respiratory system. The pulmonary route lowers systemic toxicity, necessitates a lower dose, and has instantaneous drug release, first pass hepatic metabolism, and side effects. Presently, the most prevalent patterns in study aim to offer the optimal dry powders in the appropriate fraction for inhalation, which can release the medication before it is eliminated through natural mechanisms.

Introduction

A Greek pharmacist, Pedants Disco-rides, introduced the concept of inhaled application during the first century (1). Antiseptic aerosol therapy, e.g. boiling tar vapors, became a popular anti-tubercular medication in the middle of the 20th century, although it hardly had any therapeutic value. Since then, anti-tubercular inhaled therapy has come a long way to a stage of experimental reality with potential clinical applications. The importance of the subject stems from the fact that tuberculosis (TB) continues to be a leading killer disease- causing millions of deaths annually(2). Oral therapy using the currently employed anti- tubercular drugs is very efficient but is still associated with several significant drawbacks. More than 80% of TB cases are of pulmonary TB alone and high drug doses are required to be administered because only a small fraction of the total dose reaches the lungs after oral Administration. Decades of research in the field of medicine and pharmacy resulted in the development of many drugs and active pharmaceutical ingredients (API) (3) Inhalation therapy for lung diseases, especially asthma, was first recognized in India around 2000 DC by Ayurvedic medicine(namely daturaroots)that was later found to contain broncho dilating alkaloids. Later examples of inhalable therapies were found in ancient Egypt and Greece, followed by, e.g. medieval Spain. The discovery of the 18th and 19th centuries in medicine resulted in the development of modern ceramic inhalers or nebulizers utilizing medicated vapors or steam(4) Nowadays, inhalable formulations of various bronchodilators or corticosteroids are accessible for patients suffering from respiratory diseases such as asthma and COPD (5) Tuberculosis (TB) is one of the major health concerns in the world, with at least 10 million people being infected each year. It is an infectious airborne disease caused by *Mycobacterium tuberculosis,* which is transmitted from person-to-person via the air droplets. *M. tuberculosis* is mainly affecting the lungs causing pulmonary tuberculosis, but it can also adversely affect intestine, bones, joints, and other tissues of the body causing extra-pulmonary tuberculosis.

TB can be classified into two groups, which are latent TB and active TB. People with latent TB show asymptomatic and is not transmissible while people with active TB show noticeable symptoms and the disease can spread to others. In 2018, it was estimated globally that 10 million people were affected by TB with approximately

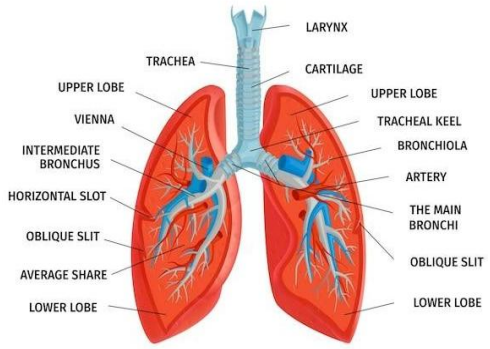
1.5 million people dying from the incidence based on the data reported by WHO. As compared to previous years, there was an estimated 1.6% decline in the average TB incidence rate per year from 2000 until 2018 and 2% between 2017 and 2018. The number of TB deaths was decreased by 11% between 2015 and 2018 (6). In 2020, 86% of all newly diagnosed tuberculosis cases worldwide were found in the 30 countries with the most significant TB encumbrance. Eight countries accounted for two-thirds of newly diagnosed tuberculosis cases: South Africa, Pakistan, Nigeria, Bangladesh, India, China, Indonesia, the Philippines, and Pakistan(7). From 2015 to 2020, the number of people who were ill with tuberculosis on a global scale decreased by 11%, which is a little over halfway to the milestone of 20% that was set for 2020(8). To treat infected patients with mycobacterial strains hypersensitive to certain drugs, a minimum of 6-9 months of conventional anti-tuberculosis therapy is required (9)



Fig;1 Mechanism of respiratory drug deposition

1. Anatomy and physiology of the lungs:

To achieve both local and systemic effects, the lungs represent the main organs of the respiratory system which give the desired route for the direct administration of drugs to the desired site of action. The lungs are cone-shaped, paired organs that are connected to the trachea by the left and right bronchi. The lungs are located within the thoracic cavity and separated from each other spine as protection. The surface of the lungs is covered by two thin protective membranes, the by mediastinal structures. The lungs are enclosed by ribcage, sternum, and parietal and visceral pleura. There is a space in between the two protective membranes known as the pleural cavity, which consists of lubricating fluid that helps to reduce the friction produced when the two protective membranes slide over each other duringrespiration [(10)]. In each lung, the bronchi are branched into smaller bronchioles, which end in tiny air sacs, called alveoli.



Fig;2. Human lung Anatomy

Alternatively, expiration is a passive process and is dependent on the elasticity of the lungs and the thoracic cage. During inspiration, the contraction of the diaphragm and intercostal muscle and the diaphragm relax during expiration, which allows the lungs to recoil back to their original dimensions (11).

2. Modes of respiratory drug delivery:

A favorable way of delivering drugs to the lungs is the aerosolization of the drugs as fine powders with the aid of dry powder inhalers (DPIs). Alternatively, the drug may be first solubilized/suspended in an aqueous medium and later aerosolized (liquid aerosolization or nebulization) through a nebulizer. A nebulizer requires a dispersing force (either a jet of gas or ultrasonic waves) for aerosolization (12). The frequency of nebulization was thrice daily whereas the duration was dictated by practical considerations and smear conversion times which ranged from 9 to 122 days.

It was observed that 86% of the patients with drug-susceptible TB and 58% of the patients with drug-resistant TB underwent smear conversion during the study period, suggesting that residual aminoglycosides in sputum expectorated from pulmonary cavities could inhibit intra- cavitary bacillary growth and prevent transmission, though not necessarily affecting the bacteria inside the macrophages.

Pulmonary delivery of liposome-encapsulated ATDs

Liposome-encapsulated drugs are especially effective against intracellular pathogens and their demonstrated advantages include:(13)

(i) The ability to formulate biologically active molecules

(ii) the ability to encapsulate hydrophilic compounds

(iii) Reduction in toxicity of the active agent

(iv) Increased therapeutic index

(v) Increased stability of labile drugs

(vi) Improved pharmacokinetics

(vii) Increased delivery to target tissues

(viii) The feasibility of nebulization (14).

3. Types of inhalable microparticles

Microparticle-based drug delivery systems have appear as the most significant approach for the treatment of respiratory disorders owing to improved drug therapeutic

index, prolonged biological half-life, and reduced toxicity (15). They are micron-size particles wherein the drug is physically and uniformly dispersed and encapsulated by walls of synthetic and natural polymer films of variable thickness and degree of permeability acting as a release rate controlling substance (16).

Polymeric microparticles.

Polymeric microparticles are particulate dispersion or solid particles with sizes ranging from 1-1000 um. They are naturally or synthetically derived polymers and are bio-compatible and biodegradable such as polylactic acid, polybutylcyanoacrylate, poly (lactic acid-co-lysine) graft, chitosan, poly lactic-glycolic acid (PLGA)] (17) conducted in-vitro and in-vivo studies on docetaxel-loaded chitosan micro spheres and found increased bioavailability and sustained release with minimum systemic toxicity (18).

- Solid lipid microparticles (SLMs).

SLMs have spherical shapes and sizes in the range of 1 to 1000 µm. They are lipid matrices composed of glyceride, fatty acid, fatty alcohol, and solid wax (19), possessing high melting points. In recent years, SLMs could serve as a good alternative and acceptable method for pulmonary drug delivery. Currently, for the development of inhalable SLMs, cisplatin was mixed with a solubilized lipid and PEGylated component using high-pressure homogenization and spray-dried (20).

Cyclodextrin complex microparticles.

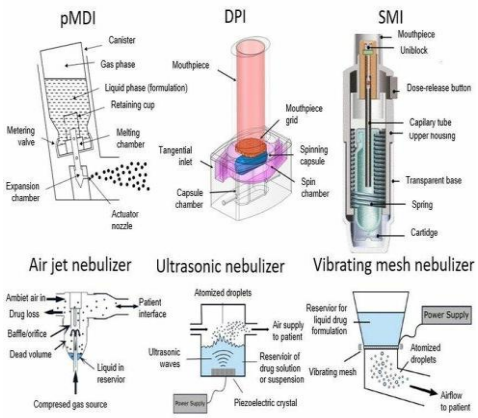
Cyclodextrins (CDs) like α-, β- and γ-CDs are composed of cyclic oligosaccharides that are cyclic polymers of α-D-glycopyranose. Because of their high complexation efficiency, high loading capacity along with low cost of production, β-CDs are frequently used for pharmaceutical applications. Due to their exceptional structure, having an external layer comprising hydroxyl groups along with the lipophilic internal cavity (21), they result in the inclusion of complexation formation with the hydrophobic drugs. To decrease the drug irritation following pulmonary delivery CDs have proven to be excellent solubilizing agents in aerosol preparations of poorly water-insoluble drugs (22).

4. Recent Advancements in inhalable microparticles:

Therefore, studies had been conducted to explore the potential of microparticles in pulmonary drug delivery and developed inhalable sustained-release microparticles for co- delivery of doxorubicin along with TRAIL (type II transmembrane protein that stimulates programmed cell death in numerous carcinoma cells) for the treatment of metastatic lung carcinoma.

Composed different types of inhalers:

Throughout the years, many systems to deliver drugs by inhalation have been invented. The choice of devices used for this purpose often plays a critical role in the management of obstructive lung diseases (23).



5. Requirements for microparticles as dry powder for inhalation:

After inhalation, microparticles (MP's) may be exhaled or deposited in the respiratory tract. If MPs will remain in upper or lower airways is influenced by the manufacturing method, their physicochemical properties, and the other factors mentioned above (24). The two parameters that characterize drug carriers are encapsulation efficiency (EE) and loading efficiency (LE). The EE determines how much of the drug used for the manufacturing of the formulation has been encapsulated, while the LE shows how much of the formulation's mass consists of the drug itself. It is important to maximize the EE, by optimizing the manufacturing process as it allows us to obtain the particles in a repeatable manner and minimize the drug losses in the manufacturing process. EE is calculated using the equation (25).

$$EE = \frac{\text{weight of encapsulated drug in microparticles}}{\text{initial weight of the drug}} \text{ X } 100$$

While LE is expressed by equation

$$LE = \frac{\text{weight of the drug in microparticles}}{\text{Weight of microparticles}} \text{ X } 100$$

MPs based on polysaccharides:

Polysaccharides are natural, biodegradable, non-toxic, and functional biomacromoleculesthat are composed of a large number of monosaccharide units linked by glycosidic bonds (26).

MPs based on proteins:

Proteins are made from a long chain of amino acids connected to each other with a covalent peptide bond. There are 20 types of amino acids in proteins with different chemical structures and properties. Each type of protein has a unique sequence of amino acids that are the same from one molecule to another (27).

5. Production methodology of inhalable microparticles

5.1 : Emulsion polymerization technique.

Emulsion polymerization is a simple process in which the monomers are stabilized by using surfactants and are dispersed in an aqueous phase. The obtained microparticles display a low polydispersity index and produce high yields (28).

6.2. Dry coating technique.

In this technique, the prepared microparticles are

lyophilized and introduced into the Mechanofusion apparatus chamber simultaneously with lactose. This apparatus consists of a rotating chamber having 200-1600 rpm speed, a stationary blade, and a scrapper. Microparticles are adsorbed onto the surface of lactose, which can be easily deposited inside the lung (29).

6.3 Spray drying technique;

This technique was a breakthrough in the pharmaceutical industry over previous technologies. It is a dehydration method that has high speed, versatility, high encapsulation efficiencies, and is easy to scale up. Parameters that influence the size and morphology of the microparticles are inlet-outlet temperature, nozzle diameter, air or solution volume mixture,
pressure, feed rate, and type of atomizer.

6. Challenges and future perspectives;

Respiratory drug delivery systems certainly have the potential for anti-tubercular inhaled therapy. The requirements for fewer drug doses as well as a low dosing frequency are definite advantages. However, some key issues still need to be addressed. The possibility of variable deposition of an inhaled formulation in the lungs needs to be considered and is a matter of concern because it could result in sub-optimal drug concentrations in certain lung regions. If this does occur to a significant extent then treatment response could be impaired. However, delivery vehicles with good systemic bioavailability could overcome this potential problem (29).

Conclusion

Due to the huge absorptive surface area, first-pass metabolism clearance, and extremely thin diffusion layer that alters quick drug absorption at the target site, pulmonary drug delivery is becoming increasingly related these days. The most popular medication targeting systems available today involve administering drugs directly into the lungs through inhalation, mostly using pressurized metered-dose inhalers and dry powder inhalers. As a result, in the years to come, inhalable microparticles with aerodynamic dimensions of 1 to 5 μm may be successfully and effectively investigated for the treatment of respiratory conditions such asthma, lung cancer, cystic fibrosis, COPD, pneumonia, chronic bronchitis, and tuberculosis.

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