

Conference Paper

Development of Liposomal Dry Powder Inhalation to Increase the Effectiveness of Tuberculosis Therapy

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ORCIDRaditya Weka Nugraheni: <https://orcid.org/0000-0001-6449-6357>**Abstract.**

Tuberculosis (TB) is one of the most threatening infectious diseases for Indonesian people. The number of TB patients in 2020 was estimated at 845,000 people with 98,000 deaths. One of the factors that causes difficulty in TB therapy is the lack of adherence and the slow development of new antibiotics when antibiotic resistance appears. The development of nanotechnology-based preparation has the potential to increase the therapeutic effectiveness of the active ingredients, such as in the dry powder inhaler form, which allows the active ingredients to be delivered efficiently to the lungs as the target organs.

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1. Introduction

TB is an infectious disease caused by *Mycobacterium tuberculosis* and typically attacks the lungs (pulmonary TB) can also attack other organs (extrapulmonary TB). The spread of TB infection can occur through the cough droplets of TB patients that spread in the air and are inhaled by other people [1]. Based on the CDC report (Centers for Disease Control and Prevention), one third of the world's population has been infected with TB. In 2014, 9.6 million people in the world suffered from TB disease and there have been 1.5 million TB-related deaths globally. TB is also a major killer for patients living with HIV [2].

Tuberculosis (TB) therapy as one of the deadliest diseases in the world is already available, but generally the failure of therapy is caused by low adherence which will lead to resistance of infectious agents to drugs. Most of the active ingredients have low bioavailability, so large doses are needed and use with high frequency, this is also related to the incidence of side effects that arise. Treatment failure will lead to poor outcomes and large costs. Researchers believe that nanomedicine can be

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a solution in overcoming this challenge, because the discovery of new antibiotics is not as fast as the rate of resistance of microorganisms to drugs [3]. Development opportunities are still wide open, active research continues to be carried out, in terms of delivering antibiotics with nanomaterials has several advantages: controlled and uniform distribution in target tissues, increased solubility, controlled and sustained release, increased patient compliance, minimized side effects, and increased internalization [4].

Rifampicin and isoniazid along with ethambutol and pyrazinamide are the two main drugs (first line) in TB therapy that are still the mainstay of the world. Isoniazid (INH) has bactericidal activity, works specifically to inhibit the synthesis of mycolic acid which is a component of virulent bacterial cell walls. Rifampicin is also bactericidal because it works by inhibiting transcription by binding to bacterial DNA-dependent RNA-polymerase. Failure of first-line therapy is generally caused by poor patient compliance with this therapeutic regimen. TB therapy with first-line drugs is carried out for 2 months of the intensive period (rif/inh/eta/pza) and 4 months of the continuation phase (rif/inh), with very large daily drug doses [1].

Delivery of TB first-line drugs locally via the inhalation route is expected to produce large concentrations in the area of infection so that it can reduce the duration of therapy, which in turn can reduce the risk of side effects and therapy failure [1]. In this literature review, we will discuss the potential development of inhaled dry powder (DPI) preparations for tuberculosis drugs such as rifampin and isoniazid with nano-sized dry liposome carriers.

1.1. Particle Deposition in the Respiratory Tract

There are three main deposition mechanisms in the lower respiratory tract: (1) Inertial impaction experienced by large particles measuring >1 micron in the upper part of the tracheobronchial region (TB), the probability of inertial impaction depends on the momentum of the particle (the product of mass and velocity of the particle). Particles with a large mass and large velocity will exhibit a large impaction; (2) Particle sedimentation is controlled by gravity, which is important in areas with low airflow velocities such as in the bronchioles and alveoli. The fraction of particles deposited by this mechanism depends on the duration of the particles in the region; (3) Brownian diffusion is more significant for particles less than 1 micron in size. These submicron particles will be randomly hit by gas molecules, allowing for collisions with the airway walls. The probability of deposition increases with decreasing particle size. The prevalence of

Brownian motion is also increased in areas with low airflow velocity, such as the alveoli [5].

In general, large aerosol particles (>5 microns) are deposited in the upper airways, medium-sized particles (1-5 microns) are deposited in the smaller airways and bronchioles, while very small or submicron particles reach the bronchioles more effectively, terminals and alveoli. In relation to TB therapy, it is expected that drug particles encapsulated in liposomes can reach the alveoli and be internalized into macrophages because TB germs that are intracellular are able to settle in macrophages [1].

1.2. Liposome Bilayer Components for Delivery to the Lungs

Liposomes are carriers that are quite possible to target lung organs because they are well tolerated by the body and relatively not immunogenic. In addition, liposomes can be phagocytosed by immune cells, including macrophages, so that they can deliver antimicrobial drugs to these cells [1].

DPPC is a phospholipid with two palmitic acids attached to the phosphatidylcholine head group. This compound is the main surfactant component in the lungs and has been used clinically [6]. To increase the uptake of drug-containing liposomes by alveolar macrophages, cationic liposomes can be made by adding a positively charged lipid component. Positive surface charge can facilitate increased internalization of particles through the mechanism of phagocytosis into macrophages compared to neutral and negatively charged particles [7]. The lipid component of DPPC is a zwitterion with a positive charge due to the quaternary ammonium, and a negative charge for the phosphate group. Liposomes formed from DPPC have a negative zeta potential [8]. It should be noted that the combination of lipid bilayer components DPPC/DDA can form liposomes that have high colloidal and bilayer (molecular packing) stability with a ratio of 50% DDA or a molar ratio of 1:1. These liposomes were made using the thin film hydration technique using NaCl as a hydrating solution [9].

Liposomes can facilitate the simultaneous delivery of hydrophilic and lipophilic drugs because there is a lipophilic part of the acyl group and a hydrophilic part of the phosphate group. Hydrophilic drugs will be trapped in the middle of the liposome, while lipophilic drugs will be between the acyl chains. Rifampicin and INH are both water soluble, so hypothetically these two drugs will be encapsulated in the liposome core.

1.3. Production of Inhaled Dry Liposome Powder with Freeze Drying Technique

The production of inhaled dry liposomes can be carried out in 2 stages. The first stage is the preparation of a liposome suspension in water with various techniques that have been described previously [10, 11]. Furthermore, the liposomes were dispersed in a suitable carrier excipient and then dried using freeze drying, spray drying, or supercritical fluid (SCF) techniques to obtain an inhaled powder product. Inhaled powder is expected to have the ability to deliver drugs directly to the target in the lungs, high effectiveness in low doses, encapsulation effectiveness, and the ability to release drugs in a controlled manner, stability, and increase patient compliance [1].

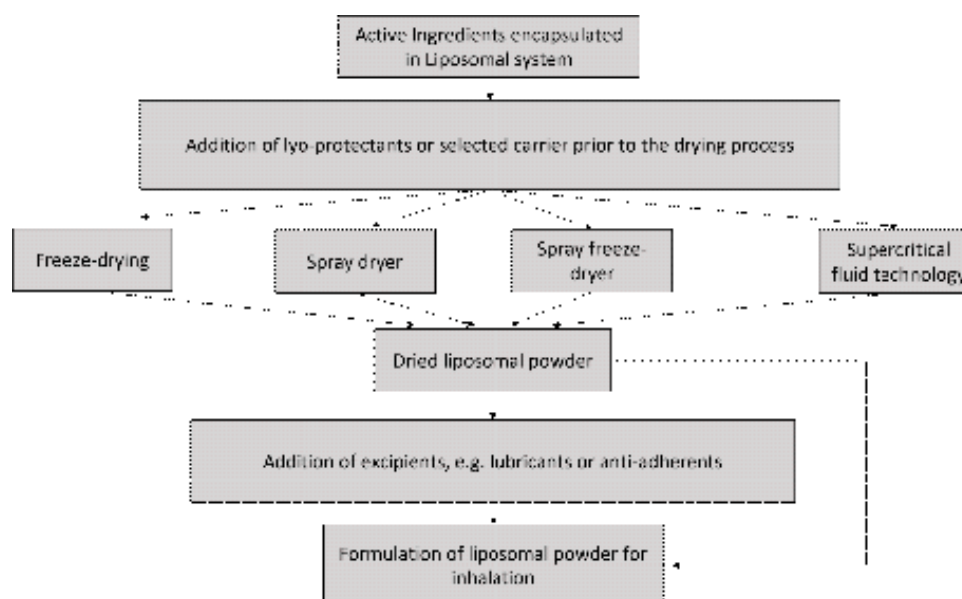


Figure 1: Inhaled Dry Powder Formulation.

Freeze drying and spray drying are one of the main techniques in the production of inhaled dry liposomes. Carriers that can be used include cryoprotectants from the saccharide group (sucrose, lactose, trehalose, dextrose, and maltose). Liposome dispersions containing cryoprotectants were frozen at -40°C and lyophilized for 48 hours to form a porous solid. The solid is sieved with a mesh number of 120 and a mesh number of 140. In addition to cryoprotectants in the internal phase, carriers can also be added to the outer phase such as lactose or lubricants. The addition is done after the lyophilized powder is sifted, then a carrier such as lactose is added with a very fine particle size (fines) [12].

1.4. Physical Characterization of Liposomes and DPI Final Products

Characterization of liposomes as primary carriers that bind directly to the active ingredient needs to be carried out before further processing, namely the lyophilization process. These characterizations include: (1) Determination of the concentration of active ingredients that are adsorbed on liposomes; (2) Liposomal morphology; (3) Determination of particle size and size distribution using dynamic light scattering (DLS) technique.

Meanwhile, for DPI, characterization is also carried out to ensure the quality of the product. Characterization for dry powder inhalation carried out include: (1) Determination of the angle of repose, because this parameter is related to the flow properties of the powder; (2) dispersibility index; (3) Determination of water content; (4) Fine Particle Fraction; (5) Particle morphology by SEM [12]. In addition to the physical characterization above, it is also necessary to test the activity of the preparation in vitro and in vivo to ensure that the preparation is effective, safe, and stable.

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