UNIVERSITI TEKNOLOGI MARA

PHYSICOCHEMICAL EFECTS OF LACTOSE MICROCARRIER ON INHALATION PERFORMANCE OF RIFAMPICIN IN POLYMERIC NANOPARTICLES

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AUTHOR'S DECLARATION

I declare that the work in this thesis was carried out in accordance with the regulations of Universiti Teknologi MARA. It is original and is the result of my own work, unless otherwise indicated or acknowledged as referenced work. This thesis has not been submitted to any other academic institution or non-academic institution for any degree for qualification.

I, hereby, acknowledge that I have been supplied with the Academic Rules and Regulations for Post Graduate, Universiti Teknologi MARA, regulating the conduct of my study and research.

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ABSTRACT

This study investigated the effects of size, size distribution, specific surface area, surface roughness, crystallinity, and fine content (< 5 μm fraction) of lactose microcarrier on the pulmonary inhalation profiles of rifampicin encapsulated in polyvinylpyrrolidone nanoparticles (194.77 ± 9.52 nm). The spherical lactose was modified through solvation and reprecipitation processes using aqueous ethanolic solution with different ethanol contents. The reprecipitated lactose had smaller particle size, wider size distribution, larger specific surface area, more elongated shape, smoother surface texture and lower crystallinity than the unprocessed lactose. They contained fine particles of sizes smaller than 5 μm of which none was found in the unprocessed lactose. Cascade impactor and scanning electron microscopy analysis of lactose-nanoparticle blends indicated that unprocessed lactose carried nanoparticles through surface adsorption and pore immersion methods. The small, less crystalline and elongated processed lactose carried nanoparticles through surface adsorption and encapsulation via inter-lactose aggregation. The aggregative tendency of these lactoses increased with reduced size and crystallinity and a increased surface roughness that provided more active sites for particulate interaction. This improved the fine particle dose, fine particle fraction, percent dispersed, percent inhaled of nanoparticles due to their ability to remain attaching to lactose during aerosolization, and detach for deep lung deposition in late time domain unlike those immersed in pores of unprocessed lactose. Overall, a lactose fine content amounting to less than 9 % or more than 12 % was detrimental to aerosolization. Excessive fine reduced nanoparticle attachment. Suboptimal fine content discouraged nanoparticle detachment and deposition.

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CHAPTER ONE
INTRODUCTION

1.1 BACKGROUND OF STUDY

1.1.1 Pulmonary Drug Delivery

Pulmonary drug delivery has received considerable attention from researchers as an effective and convenient alternative route of drug administration to the conventional oral and injection modes. Pulmonary delivery enables to target drug directly to lung for both local and systemic treatment [1, 2]. Local delivery of medication to the lungs is highly desirable, especially in cystic fibrosis, asthma, chronic pulmonary infections or lung cancer patients. It offers several advantages including delivery of high drug concentrations directly to the target region, rapid clinical response, improving efficacy and reducing systemic side effect. Pulmonary delivery is also an attractive option systemic treatment because the respiratory region mainly alveoli provides an enormous surface area (80 to 100m^2 /adult) and highly permeable membrane for the absorption of medication into the blood to achieve maximum systemic uptake to the target region. It is a non-invasive 'needle-free' delivery system and suitable for wide range of substances from small molecules to very large proteins. Large protein molecules which degrade in the harsh gastrointestinal conditions and are eliminated by first-pass metabolism in the liver can be delivered via pulmonary route if deposited in the respiratory zone of the lungs [1].

The fate of delivered medication depends on the mechanism and rate of elimination in the respiratory tract. Upon therapeutic agent depositing in the lung, its elimination is immediately initiated thereby reducing the initially high local drug concentration in lung tissue [3-5]. Generally, multiple daily inhalations up to 9 times are required to compensate for the rapid decay of drug concentrations [6]. Apart from the pulmonary morphological aspects and ventilatory parameters, drug formulation and the design of potential carrier system with specific physicochemical properties such as size, shape, surface chemistry, and bioadhesive properties are very crucial to bypass the clearance mechanisms of the lung thereby providing prolonged residence times to therapeutic agent within the respiratory tract [7]. Alternative strategies