Mini Review
Volume 8:6, 2022

Journal of Lung Diseases & Treatment

ISSN: 2472-1018 Open Access

Inhaled Drug Particle Dissolution and Absorption in the Lungs

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Abstract

Dry powder inhalation therapy has been shown to be effective in treating localised lung diseases such as asthma, COPD, cystic fibrosis, and lung infections. The physicochemical nature and aerosol performance of powder particles are determined *in vitro* for dry powder formulations. There is a well-established relationship between particle properties (size, shape, surface morphology, porosity, solid state nature, and surface hydrophobicity) and aerosol performance of an inhalable dry powder formulation. In contrast to oral formulations, there is no standard dissolution method for assessing the dissolution behaviour of inhalable dry powder particles in the lungs. This review focuses on different dissolution systems and absorption models used to evaluate dry powder formulations. It includes an overview of airway epithelium as well as barriers to development. an *in vitro* dissolution method for inhaled dry powder particles, fine particle dose collection methods, various *in vitro* dissolution testing methods developed for dry powder particles, and models commonly used to study inhaled drug absorption.

Keywords: Dissolution • Absorption • Inhalation • Dry powders • Fine particle dose

Introduction

Although pulmonary drug delivery by inhalation has been used for many years, research in dry powder inhalers (DPIs) for both local and systemic drug delivery has advanced rapidly in the last decade. DPIs are monophasic solid particulate mixtures that were first developed in the 1970s. DPIs are simple to process, portable, more stable, environmentally friendly due to the lack of propellants, patient-friendly, and cost-effective. The majority of DPIs on the market have a short residence time and low drug bioavailability locally in the lungs, resulting in suboptimal local therapeutic effect.

One of the clearance mechanisms of inhaled drug particles from the lungs is the rapid dissolution of micron-sized particles and subsequent absorption of the drug into the systemic circulation. Therefore Many formulation strategies have been employed in order to increase the residence time of inhaled drugs at the site of action while reducing dosing and avoiding unwanted toxicities. Drug encapsulation in a particulate carrier system (liposomes, polymeric and lipid microparticles), increasing the molecular mass of the drug by conjugating with a ligand, and decreasing the solubility of the drug by conjugating with a low water-soluble, hydrophobic material are some approaches to prolonging the residence time of inhaled drug particles in the lung [1].

Literature Review

In Vitro dissolution testing of inhalable dry powder particles

The physicochemical nature and aerosol performance of powder particles are determined *in vitro* for dry powder formulations. There is a well-established relationship between particle properties (size, shape, surface morphology, porosity, solid state nature, and surface hydrophobicity) and aerosol performance of an inhalable dry powder formulation. In contrast to oral formulations, there is no standard dissolution method for assessing the dissolution behaviour of inhalable dry powder particles in the lungs. The Andersen cascade impactor is a high flow rate cascade impactor that is used to assess the aerodynamic size distribution of particles in pharmaceutical and toxicological applications. It is made up of a standard tubular induction port (IP) with a 90° bend, stages 0-7, and a filter stage. Each impactor stage has several nozzles that get smaller as the stage number increases, directing air and particles onto the collection plates.

Davies and Feddah, 2003 used a custom designed stainless steel ring with a stainless steel screen support filter to collect dry powder particles onto a glass fibre filter at the connection point of the induction port and inlet part of ACI. An induction ceremony is part of the ACI assembly. The impactor's port and base have only stage number zero. The main disadvantage of this method of collection is that the entire emitted dose is collected over the filter, which does not correspond to the size of the particles deposited in the deeper lung regions. collected aerodynamically classified particles with diameters of 4.7-5.8 m and 2.1-3.3 m on the filter membranes of ACI stages 2 and 4. They used an 8-stage ACI with stage 2 and stage 4 collecting plates turned upside down to arrange six polyvinylidene difluoride (PVDF) filter membranes (25 mm in diameter; 0.22 m pore size) for dose collection in this study. collected particles onto the regenerated surface in another study [2].

Models for pulmonary drug absorption

Under cell culture, the *in vitro* air-to-blood barrier is reconstructed using cell models in the Transwell or Snapwell system. summarises the various cell types used in *in vitro* lung barrier models. Many researchers are interested in stem cell-derived lung epithelial cells and "lung-on-a-chip" models. Most importantly, differentiation of human embryonic stem cells (ESC) or induced pluripotent stem cells (iPSC) to alveolar epithelial type II-like cells allows for large-scale production of alveolar epithelial cells. Air-liquid interface (ALI) culture can promote further differentiation of alveolar epithelial type I-like cells. Furthermore, a "lung-on-a-chip" microfluidic device has been developed as a lung model to study biological development and pathogenic responses of the lungs. The value of a one-of-a-kind six-well "lung-on-a-chip" prototype that can incorporate *in vitro* aerosol deposition The system is currently being investigated. This attempt appears to be interesting because it includes the presence of air, media flow, and breathing-like stretching that resembles lung movement. Ex vivo tissue models are used when *in vivo* or *in vitro* models cannot clearly explain the mechanism of drug transport or lung disposition kinetics [3].

One of the most common methods is isolated perfused lung (IPL), in which the lung is isolated from the body and kept in an artificial system under certain

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Received: 03 November, 2022, Manuscript No. LDT-23-85318; **Editor Assigned:** 05 November, 2022, PreQC No. P-85318; **Reviewed:** 19 November, 2022, QC No. Q-85318; **Revised:** 24 November, 2022, Manuscript No. R-85318; **Published:** 02 December 2022, DOI: 10.37421/2472-1018.2022.8.165

experimental conditions. This distinguishes distribution, metabolism, and elimination from lung-specific evaluations. In an isolated organ experiment, the architecture and functionality of the tissue are closely maintained, increasing its resemblance to the *in vivo* state when compared to *in vitro* monolayer models from a single cell type. For lung disposition studies, an IPL prepared from small rodents is commonly used.In order to investigate absorption, *in vivo* studies in intact animal models are used. The distribution and pharmacodynamics of drug particles inhaled. Formulations are administered to conscious or anaesthetized animals using various types of delivery devices, with or without surgical intervention, in such models. Mice and rats have traditionally been used to study pulmonary pharmacokinetics. However, the use of larger animals such as guinea pigs, rabbits, dogs, sheep, and monkeys is limited due to the higher cost and logistics required for handling and housing. Regional drug delivery/distribution in larger animals can be achieved through the appropriate selection of aerosol size and inspiratory manoeuvres, allowing for the study of region dependent lung absorption and disposition [4].

Discussion

Although we have summarised various instruments and methods used for dissolution studies of inhaled drug particles, no standard method can be recommended for routine studies. As a result, sophisticated instruments for testing inhalable formulations are required. Furthermore, current small volume dissolution apparatus only accounts for dissolution studies in stagnant medium (simulated RTLF), ignoring the fact that mucociliary clearance occurs in the upper airways and that breathing results in the movement of alveoli and air sacs of the lungs. As a result, small volume dissolution instruments should be developed or upgraded to include fluid movement. Furthermore, *in vitro* cell-based models used for absorption studies are inconvenient for routine formulation testing. Therefore, They are always preferred over automated cell-free systems.

Various simulated RTLFs (dissolution media) used for *in vitro* dissolution studies, on the other hand, do not closely resemble the human RTLF. The composition and thickness of RTLF vary regionally and individually from one region of the respiratory tract to another. RTLF is high in mucus in the upper respiratory tract but low in surfactant in the lower respiratory tract. For example, patients with cystic fibrosis (CF) have highly tenacious (adhesive and cohesive) sputum. In addition to mucin (a regular component of normal mucus), CF sputum contains significantly more DNA and filamentous actin than healthy people's RTLF. As a result, there is a requirement. for simulated RTLFs based on region and disease. To mimic them, absolute concentrations of RTLF components must be determined, which is a difficult task. As a result, sophisticated methods (technology) are required to accurately determine them. Furthermore, components of simulated RTLF should always be chosen with cost and availability in mind, as this will aid in future commercialization [5].

Conclusion

In vitro dissolution testing is a well-known quality control test for determining the performance of a solid oral dosage form. Despite the fact that many studies have demonstrated the relationship between dissolution and pharmacokinetics of inhaled drugs, no approved methods for evaluating the dissolution behaviour of inhaled dry powder particles are available. The lungs' complex nature, with anatomical and physiological differences in the tracheobronchial and alveolar regions, presents a significant challenge in developing an *in vitro* dissolution method that mimics lung conditions. We summarised various dissolution methods and absorption models developed for evaluating the dissolution and absorption behaviour of inhaled drug particles in this review. Despite the fact that the recent methods used a small volume of dissolution medium, it only represents a particular region of the lung. Further advancements in dissolution methods that mimic the different regions of the lungs are required.

Acknowledgement

None.

Conflict of Interest

None.

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How to cite this article: Bastola, Basanth. "Inhaled Drug Particle Dissolution and Absorption in the Lungs." J Lung Dis Treat 8 (2022): 165.