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Across the pulmonary epithelial barrier: Integration of physicochemical properties and human cell models to study pulmonary drug formulations

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ABSTRACT

During the process of inhalable formulation development a deep knowledge of the physicochemical characteristics of the drug and formulation components and the biological properties of the airways is necessary.
For example, the solubility and lipophilicity of a drug may affect therapeutic efficacy by changing the residence time of the microparticles at the airway surface. Furthermore, the properties of microparticles, such as shape, size and density, as well as the diseases of the respiratory tract, delivery device and inhalation manoeuvre will have an impact on where these microparticles are deposited.
The airway epithelium is involved in the pathogenesis and treatment of respiratory diseases. Epithelial cells are directly exposed to the environment and respond to xenobiotics. In some cases, they are the site of action for drug molecules or the drug molecules might need to be transported across the epithelium to arrive at the site of action. The drug particles deposited on the respiratory epithelia have to interact with the mucus lining, dissolve and get transported through this layer. Despite advances in in vitro testing of respiratory epithelial permeability, there is little known about how and where drugs are absorbed at a cellular level and how long they reside in the lung. Therefore, pulmonary permeability assessment of drugs may provide insights that will allow formulations to be developed with optimised therapeutic outcomes.
This review focuses on the integration of these physicochemical characteristics with the biological factors to provide a better understanding of the fate of microparticles after deposition on the epithelial cells.
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Contents

Abbreviations: ACI, Anderson cascade impactor; ASP^+, fluorescent organic cation 4-(4-(dimethylamino)styryl)-N-methylpyridinium iodide; BCRP, breast cancer resistant protein; CFTR, cystic fibrosis transmembrane conductance regulator; CYP, cytochrome P; DPI, dry powder inhaler; FITC, fluorescein isothiocyanate; MRP, multidrug resistance-associated protein; MSLI, multistage liquid impactor; NSAIDs, non-steroidal anti-inflammatory drugs; NHBE, normal human bronchial epithelial cells; OAT, organic anion transporter; OATP, organic anion transporting polypeptide; OCT, organic cation transporter; OCTN, organic cation/carnitine transporter; PEPT, proton-coupled oligopeptide transporter; P-gp, P-glycoprotein; pMDI, pressurised metered dose inhaler; SAECs, small airway epithelial cells; TEER, transepithelial electrical resistance; TSI, twin stage impinger; ZO-1, zonula occludens protein-1.

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1. Introduction

Drug delivery by inhalation is becoming one of the most important routes for non-invasive systemic delivery of drugs (Labiris & Dolovich, 2003). Some of the main advantages of administering drugs via inhalation are the avoidance of liver first pass metabolism, reducing potential side effects and achieving a quick onset of action. Although technical knowledge and new devices and formulations have enabled the efficient deposition of particles into the deep lung, improving drug deposition efficiency may not always translate into a more effective inhaled medicine (Usmani et al., 2005). The clinical effects are not only dependent upon effective aerosol generation and deposition but also upon pulmonary absorption and effectiveness; despite the importance of this fact, not much is known about the fate of aerosol particles after deposition on the respiratory epithelia (Patton et al., 2010).

Development and evaluation of novel aerosol formulations require knowledge of the deposition and transport of drug molecules across the epithelial cell layer. The mechanisms responsible for transport of molecules depend on the region that the inhaled particles are deposited in, as well as the physicochemical characteristics of the drug molecule/formulation. Lipid solubility, molecule size, and $pK_{a/b}$-dependent ionisation have been considered as the main factors in determining the absorption of drug molecules (Olsson et al., 2011). Recently, however, it has become evident that physicochemical properties alone are not the only factors affecting the extent of drug absorption. Many cells have specialised membrane transport mechanisms for the entry or exit of drug molecules (Gumbleton et al., 2011). Furthermore, the physiochemical properties of drugs could be altered through addition of different excipients, combination drugs and changing the drug's solid state for targeted therapy and control of drug absorption in a predictable manner. Fig. 1 summarises the different biological and drug physiochemical factors that could influence drug transport across the respiratory epithelial barrier.

Prior to contact with the epithelial cells, drug particles delivered to the respiratory tract have to overcome the non-epithelial pulmonary barrier of surfactant, alveolar macrophages, mucus and the mucociliary escalator (Fig. 2).

1.1. Surfactant

Surfactant is a constituent of the lung lining fluid comprising a mixture of phospholipids and proteins secreted by Clara cells and alveolar type II cells. The interactions between the particle/drug and surfactant can modify the solubility and therefore the absorption of the drug (Fehrenbach, 2001).

1.2. Alveolar macrophages

Alveolar macrophages play a significant role in the fate of inhaled therapeutics. They serve as the first-line of host defence against inhaled particulate molecules. Alveolar macrophages are capable of producing a wide range of pro- and anti-inflammatory cytokines. The macrophages are cleared from the alveoli to the bronchioles by the lining fluid, and then from the airways by the mucociliary escalator (Nicod, 2005).

1.3. Mucus/mucociliary escalator

Mucus, as part of the mucociliary clearance system is secreted from serous and goblet cells and is composed of water, glycoproteins, proteins, salt and lipids (Thiriet, 2011). Mucus is the first barrier to absorption of the drugs in the airways. Microparticles deposited in the respiratory tract need to be wetted and dissolved prior to drug absorption to occur; therefore the thickness of the mucus layer determines the concentration of the drug in the lining fluid and impacts on the fate of deposited microparticles (Labiris & Dolovich, 2003). The ability of inhaled particles to penetrate the mucus barrier depends on particle size, solubility, lipophilicity and charge (Hamm et al., 1992; Samet & Cheng, 1994).

To study the interaction and fate of microparticles in the airways, respiratory epithelial cell culture models have been developed effectively

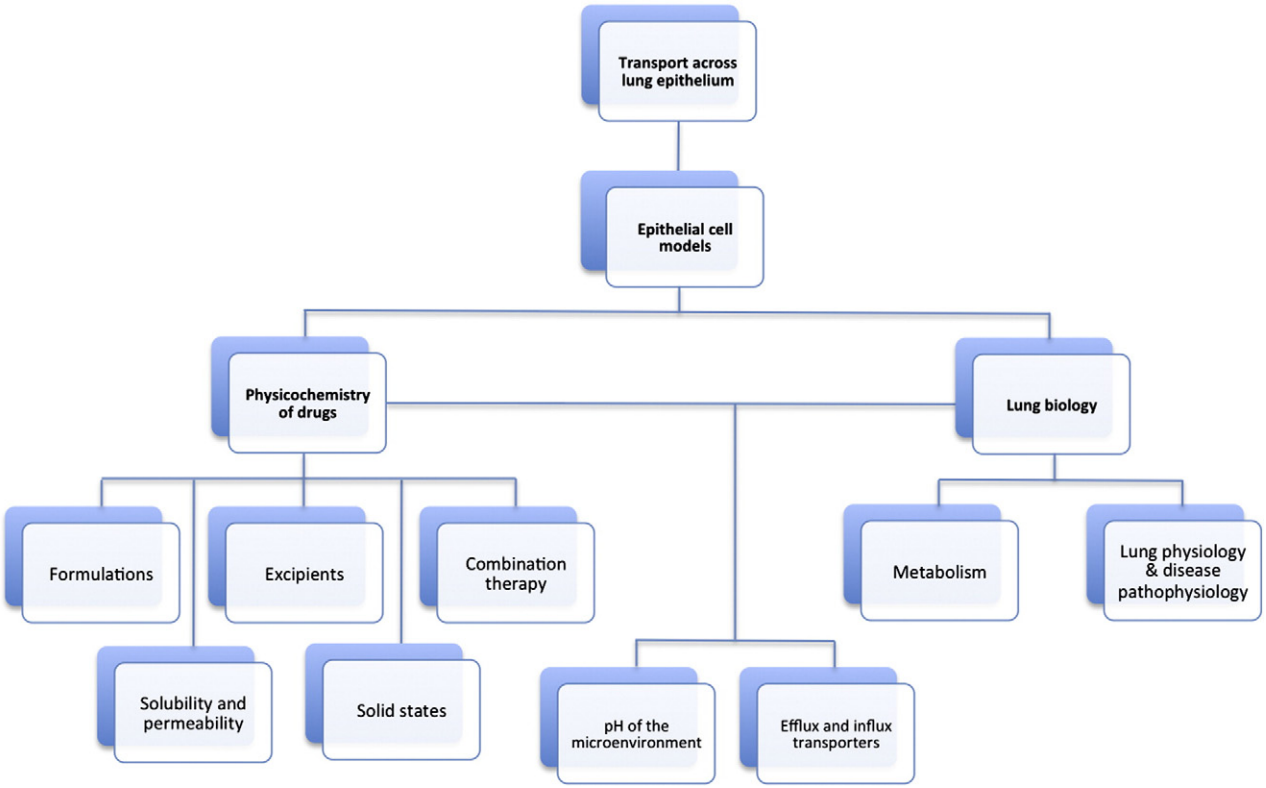

Fig. 1. Summary of the different factors that could influence drug transport across respiratory epithelial barrier.

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