A Microphysiological Model of Human Lung Airway for Evaluating Dissolution and Permeability of Inhaled Drugs

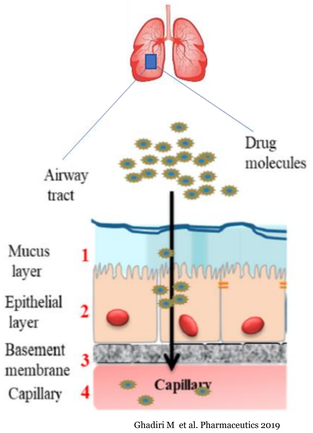
Shekh Rahman, Robert Geiger, Md Shadiqur Rashid Roni, Isra Tariq, Omnia Ismaiel, Kevin Ford
Division of Applied Regulatory Science, Office of Clinical Pharmacology, Office of Translational Sciences, Center for Drug Evaluation and Research

Abstract

Current cellular in vitro models have limitations replicating the structure and function of human lungs and thus do not reliably predict clinical parameters such as lung dissolution and permeability for inhaled drugs. To improve the development and evaluation of drugs intended to act locally in the lungs, there is a need for more accurate models. Microphysiological systems (MPS), which mimic the structure and function of human tissue and organs in a laboratory setting, are gaining attention as an alternative to traditional models. We evaluated a lung airway model created using a multi-well PhysioMimix MPS-T12 plate to determine if it can reliably predict lung dissolution and permeability of two locally acting inhaled drugs: fluticasone furoate (FF) and albuterol sulfate (AS). The model was generated by co-culturing primary human lung epithelial and endothelial cells. The intracellular and extracellular concentrations of drugs were measured using LC-MS/MS. Due to the lipophilic properties of FF (logP: 4.13), we observed significant intracellular concentrations for epithelial and endothelial cells. However, we also observed a loss of 72-92% of FF due to non-specific bindings (NSB). The results of AS demonstrated an apparent permeability of ~8×10^{-6} cm/s but very low intracellular concentrations (< 1% cellular uptake). Overall, the MPS model demonstrated potential to be useful tool for evaluating clinical properties for some inhaled drugs currently in use or under development.

Introduction

- Systemic plasma concentrations are generally analyzed for the evaluation of inhaled drugs, which does not provide information on how drugs penetrate lung tissues
- Conventional cellular models lack relevant physiological properties



Ghadiri M et al. Pharmaceutics 2019

Lung MPS:
- Devices designed to form cellular barriers
- Forms a tight epithelial monolayer with cell-mediated transport and functional polarity
- Produces mucin and cilia

Key drug parameters:
- Epithelial solubility
- Lung cell permeability

- Project goal: Assess the reliability of lung MPS for estimating clinical parameters and accelerating the development of locally acting generic inhalation drugs
- Project hypothesis: The epithelial solubility and the ability of drugs to permeate lung cells when inhaled, as measured using lung MPS can be predictive of clinical data

Materials and Methods

Multi-well MPS-T12 consumable plate (CN Bio, UK) is used with Transwell insert to create a MPS model (Figure 1). The primary human lung cells grown in an air-liquid interface (ALI) and fluid flow in each well allow recapitulation of human-specific lung structure and functions.

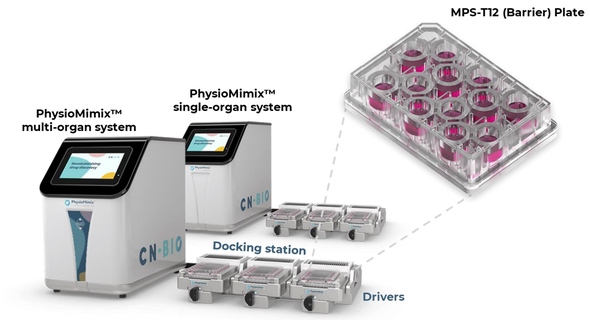
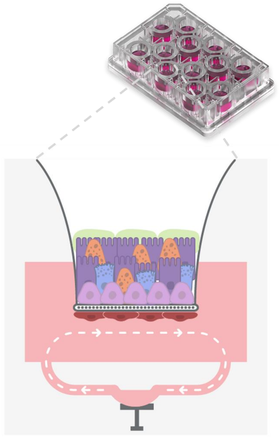


Figure 1. Transwell-based MPS-T12 platform.

Human lung airway model is generated by co-culturing primary human lung bronchial epithelial and microvascular endothelial cells (Figure 2). The model was characterized by evaluating cell confluency, cell-type composition, cilia beating, tight junctions, transepithelial electrical resistance (TEER), mucus production, and barrier function using FITC-dextran.



Primary epithelium on apical side includes:
- Ciliated cells
- Goblet cells
- Club cells
- Basal cells

Primary microvascular endothelium on basolateral side

Figure 2. Human lung airway modeling using primary human lung epithelial and endothelial cells (source of schematic: CN Bio, UK).

Results and Discussion

MPS model demonstrated human-relevant structure and function of lung tissue e.g., 3D structure and multicellular composition, ciliation, and mucus layer formation (Figures 3 and 4). TEER and low amounts of dextran permeating across the epithelial barrier are an indication of proper lung tissue formation. Perfused co-culture model demonstrated some differences in cell population, ciliation, barrier permeability, and mucus secretion as compared to static co-culture model.

The transport rate and apparent permeability of AS was found to be higher than other in vitro studies but lower than data generated from in vivo studies (Figures 5A-5C). The apparent permeability was higher in the perfused co-culture condition compared to the static co-culture model.

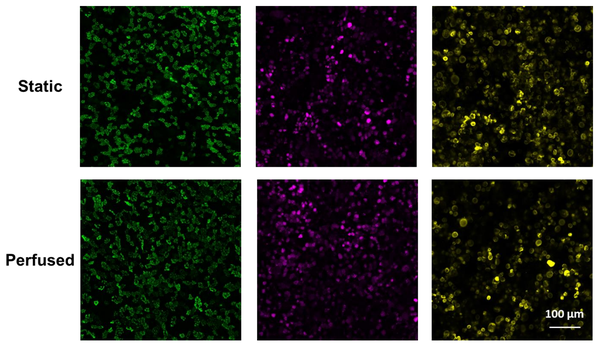


Figure 3. Formation of lung epithelium with ciliated cells (green), mucus-producing goblet cells (magenta), and basal cells (yellow).

A

Cells	Static	Perfused
Ciliated (%)	31 ± 2	34 ± 4
Goblet (%)	23 ± 2	24 ± 3
Club (%)	23 ± 3	21 ± 2
Basal (%)	29 ± 5	24 ± 3

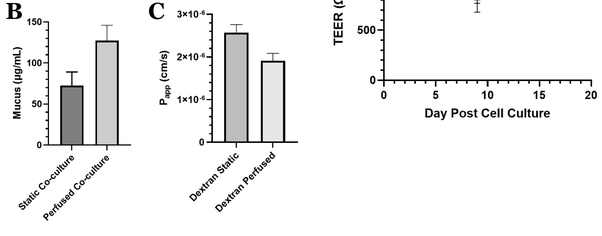


Figure 4. Characterization of lung tissue in terms of (A) cell population, (B) production of mucus, (C) apparent permeability (P_{app}) of FITC-dextran (3 kDa), and (D) transepithelial electrical resistance (TEER).

NSB to the MPS device materials affected the permeability of FF, resulting in close to zero permeability across the epithelial barrier (Figure 5D).

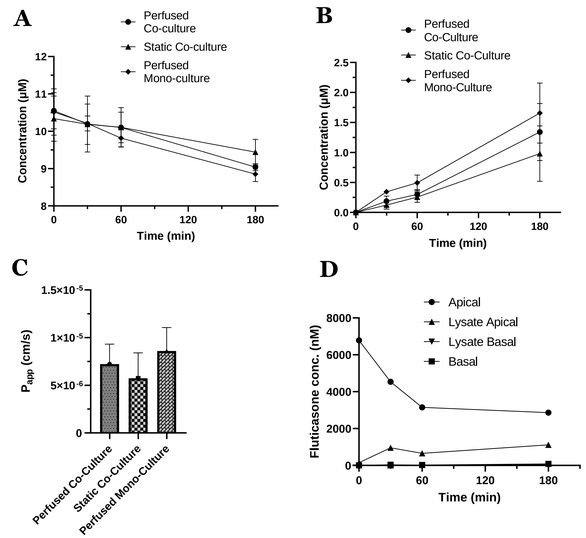


Figure 5. (A) Transport profiles of AS in apical compartment. (B) Transport profiles of AS in basolateral compartment. (C) Apparent permeability (P_{app}) of AS. (D) Transport profiles of FF for perfused co-culture condition.

Conclusion

This study represents an assessment of a MPS model as an alternative to traditional cellular models of human lung airway for the pharmacokinetic assessment of locally-acting inhalation drugs. The model demonstrated potential as a screening tool for drugs that have similar physiochemical properties to AS (high water solubility, logP: 0.4). However, the permeability study of FF suggested that the MPS model may have limitations in predicting the lung dissolution and permeability of inhaled drugs with similar physicochemical properties to FF (low water solubility, logP: 4.13). The utility of MPS model will be further assessed by evaluating permeability and cellular uptake for additional inhaled drugs e.g., olodaterol hydrochloride and formoterol fumarate. The data/results of this study could be used in the development of a draft guidance on MPS performance standards and quality control criteria.

Disclaimer

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