High-dose Antibiotics Inhalers for Acute Lower Respiratory Tract Infections in Primary Care

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1. Background

- Acute lower respiratory tract infections (LRTIs) are a primary public concern with rapid morbidity and considerable mortality[1].
- LRTIs are one of the major lung diseases caused by pathogenic bacteria, viruses, which are mainly associated with pneumonia, bronchitis, influenza (Fig 1).
- Some environmental substances (tobacco smoke, air pollution, dust in Fig 1) could also cause inflammation, damage the lung cells and lead to the lung infections[2].

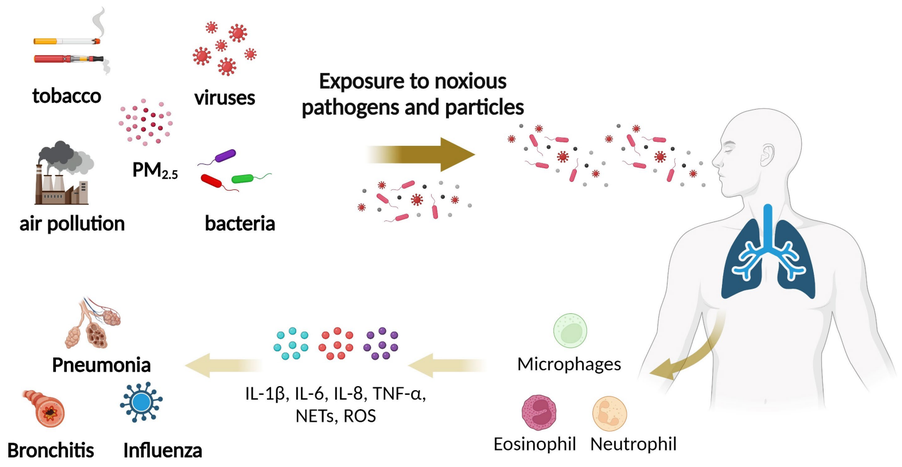

Fig 1. Schematic of development of acute lower respiratory tract infections (Biorender)

2. Problem Statement

- Dry powder inhalers (DPI) are devices for pulmonary drug delivery, which exhibit significantly advantages in delivering aerosolised drug particles into the deep lung.
- Particle flowability, drug payload, aerosolisation, controlled release and antimicrobial resistance pose significant challenges for the deployment of DPI formulations for lung diseases.
- Confinement engineering of the particles is required for pulmonary route administration.

3. Research Objectives

Objective 1- Design carrier-free pharmaceutical products, obtain high-dose antibiotic DPI formulations and explore their performance via the Orbital inhaler (Aptar).

Objective 2- Assess the performance of various excipients, polymers and surfactants to develop DPI formulations with sustainable release characteristics.

Objective 3- Design and optimise multidrug particles for enhanced therapeutic effect.

4. Methodology

Electrospray drying (ESD) is a versatile technique commonly used in producing the homogenous monodisperse particles under the electrostatic forces (Fig 2). The advantage consists of rapid, controlled disintegration of dry particles and particle size production at ambient atmosphere[3].

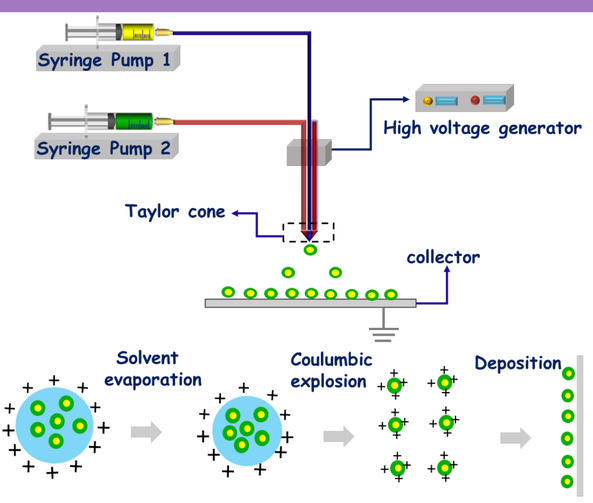

Fig 2. Schematic of electrospray drying

1. Materials synthesis and analysis

- Utilise ESD to generate inhalable monodisperse DPI of suitable & combination antibiotics with well-tuned and controlled physicochemical properties.
- Characterise physicochemical performance of DPI formulations like supramolecular structures, particle size & morphology, powder flowability, etc. Some of the common characterisation techniques are shown in Fig 3.

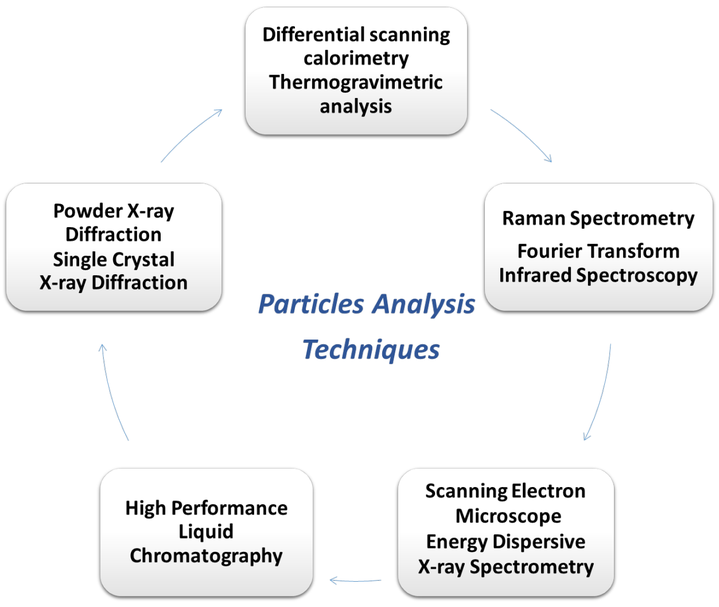

Fig 3. Common particle characterisation techniques

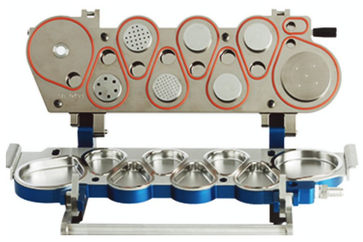

Fig 4. Schematic of Next Generation Impactor

2. In vitro pulmonary deposition

- Pulmonary aerodynamic deposition will be estimated via Next Generation Impactor (NGI) as present in Fig 4.
- Aerosols will be generated with the DPI using the Orbital inhaler device into NGI.
- Determine their aerosol performance via calculating emitted fraction, fine particle fraction and respirable fraction.

3. Antimicrobial activity determination

- The colony biofilms assay will be used to assess the antimicrobial activity (Fig 5)[4].

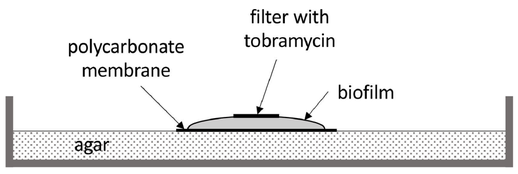

Fig 5. Schematic of the colony biofilm[4]

4. AI directed DPI formulations

- Machine learning (e.g. SVM, KNN, Random Forest, etc.) will be employed to optimise the process parameters.
- Predict and model the relationship between formulation variables.
- Optimise the critical quality attributes of the produced particles.

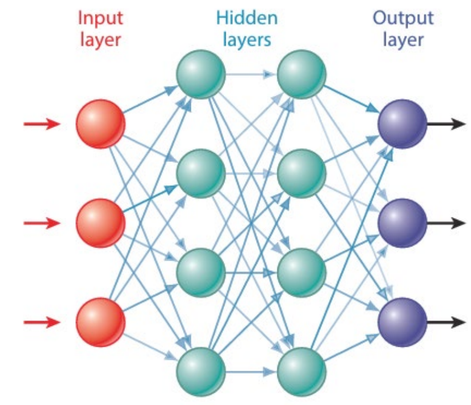

Fig 6. Example of machine learning model[5]

5. Responsible Innovation & Policy

- Formulate effective high-dose DPI products could alleviate acute airway infectious diseases and improve global healthcare in the future.
- Strengthen contemporary management practices and policies of antimicrobial drugs could contribute to reduce the antibiotic resistance.

6. Challenging

- Synthesis of pharmaceutical crystalline materials and determination of their supramolecular structures.
- Particle aggregation and aerodynamic deposition performance of DPI products.

[1] Flatby, H. M., et al., Risk of lower respiratory tract infections: a genome-wide association study with Mendelian randomization analysis in three independent European populations. *Clin Microbial Infec* **2022**, 28 (5), 732.e1-732.e7.

[2] Rahman Sabuj, M. Z.; Islam, N., Inhaled antibiotic-loaded polymeric nanoparticles for the management of lower respiratory tract infections. *Nanoscale Adv* **2021**, 3 (14), 4005-4018.

[3] Ee, L. Y., et al., Electrospray drying-mediated coating of cellulose nanocrystal. *Carbohydr Polym Technol Appl* **2023**, 6, 100345.

[4] Aljalamdeh, R., et al., The effect of particle size of inhaled tobramycin dry powder on the eradication of Pseudomonas aeruginosa biofilms. *Eur J Pharm Sci* **2021**, 158, 105680.

[5] Deng, X., et al., Emerging Applications of Machine Learning in Food Safety. *Annu Rev Food Sci Technol* **2021**, 12, 513-538.