4-17-2023

Inhaled Microbiomics, Pharmaceutical Formulation and Disease Considerations in Patients with Cystic Fibrosis

David A. McChesney

Aidan Leyba

Mohammad Razmjoo

Pavan Muttil

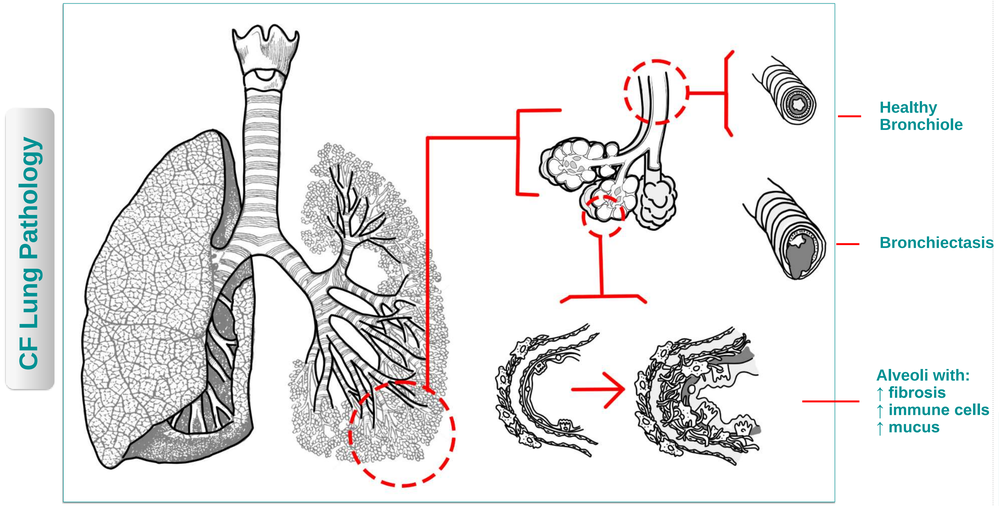
Inhaled Microbiomics, Pharmaceutical Formulation and Disease Considerations in Patients with Cystic Fibrosis

David A. McChesney, Aidan Leyba, Mohammad Razmjoo, Pavan Muttil, Department of Pharmaceutical Sciences, College of Pharmacy, University of New Mexico

INTRODUCTION

Cystic Fibrosis (CF)

- Chronic disease, with estimated frequency between 1/3000 and 1/6000 new births (1).
- New treatments have significantly prolonged patient's life expectancy.
- With almost 3-fold increases in life expectancy, there is a new aging patient population with CF. These patient's quality of life are often in direct relation to their exacerbations.



Microbiomics of the respiratory tract

- Key data has shown that decreased bacterial diversity with an increase in bacterial abundance is a sign of poor CF prognosis (2).
- CF has important anatomical changes as it relates to the microenvironment (viscosity, pH, oxygen/blood supply) and structure (fibrosis and bronchiectasis) of the respiratory system (3).
- Thus, CF is seen to have characteristic microbiomic changes as it relates to the inhabitance, virility, and abundance of bacteria (4,5).

Hypothesis

- Formulations which contain appropriate doses and species of a healthy respiratory microbiome, offer a viable inhaled therapy option to slow CF progression and morbidity.

METHODS

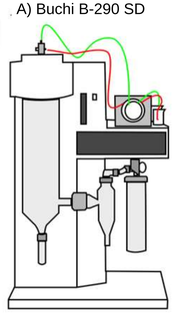
Spray Drying (SD)- Buchi B-290 Mini

- Bottom-up manufacturing process used to formulate microparticles (MPs) in the 1–10-micron size range.
- Used to engineer MPs containing drugs and vaccines compatible with pulmonary delivery.

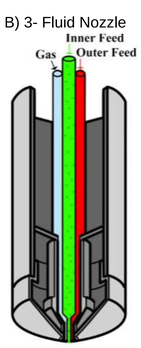
Formulation Design

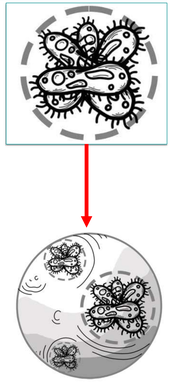
- SD dry powders containing:
  - Bacteria of a healthy respiratory microbiome
  - Mannitol for osmotic effect
  - Sodium for mucus lysing effect
  - Citrulline
  - Tobramycin

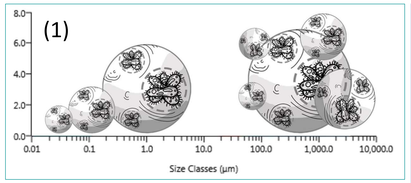
A) Buchi B-290 SD

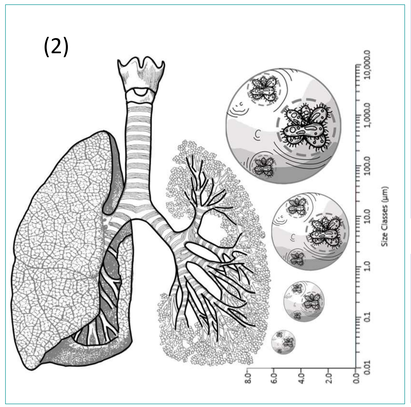


B) 3- Fluid Nozzle









Powder assessments

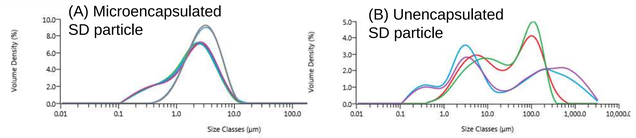
- Assessment for process optimization, yield, and manufacturing consistency.
- (1) Particle size distribution (PSD) via laser diffraction.
- (2) Mean mass aerodynamic size (MMAD) via next generation particle impactor.
- (3) Particle morphological assessment via scanning electron microscopy (SEM)

Pharmaceutical assessments

- Bacterial loading, viability, and survival post SD
- Epithelial cell studies
- Animal studies (CFTRtm1Unc)

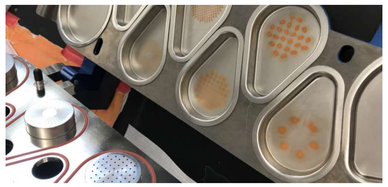
RESULTS

(1) PSD



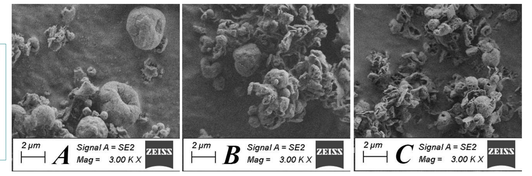
(2) MMAD

S	1	2	3	4	5	6	7
um	8.1	4.5	2.8	1.7	0.9	0.6	0.3

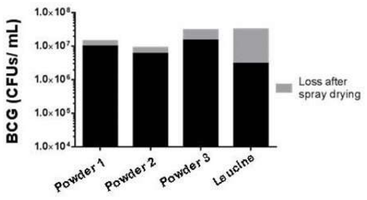


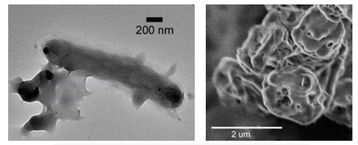
(3) SEM

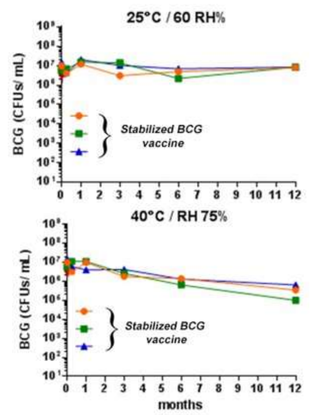
(A) Microencapsulated SD particle
(B) Unencapsulated SD particle
(C) Un-optimized SD pump system



Bacterial Assessments







Future Directions

- Optimization of dry powder formulation containing bacteria and key additives in the treatment of CF.
- Evaluation in animal models, including CF models.
- Understand the interactions of inhaled microbes with the host microbiome, immune system, and health status.

powder

BIBLIOGRAPHY

1. Scotet V, L'Hostis C, Férec C. The Changing Epidemiology of Cystic Fibrosis: Incidence, Survival and Impact of the CFTR Gene Discovery. Genes (Basel). 2020 May 26;11(6):589. doi: 10.3390/genes11060589. PMID: 32466381; PMCID: PMC7348877.
2. Hilty M, et al. Disordered microbial communities in asthmatic airways. PLoS One. 2010 Jan 5;5(1):e8578. doi: 10.1371/journal.pone.0008578. PMID: 20052417; PMCID: PMC2798952.
3. Bai TR, et al. Structural changes in the airways in asthma: observations and consequences. Clin Sci (Lond). 2005 Jun;108(6):463-77. doi: 10.1042/CS20040342. PMID: 15896192.
4. Hilty M,et al. Disordered microbial communities in asthmatic airways. PLoS One. 2010;5:e8578
5. (22) Price KE, et al. Unique microbial communities persist in individual cystic fibrosis patients throughout a clinical exacerbation. Microbiome. 2013;1:27.

COLLEGE of PHARMACY