Optimising the Aerodynamic Performance of Spray Dried mRNA Lipoplexes in Mannitol or Lactose Matrix

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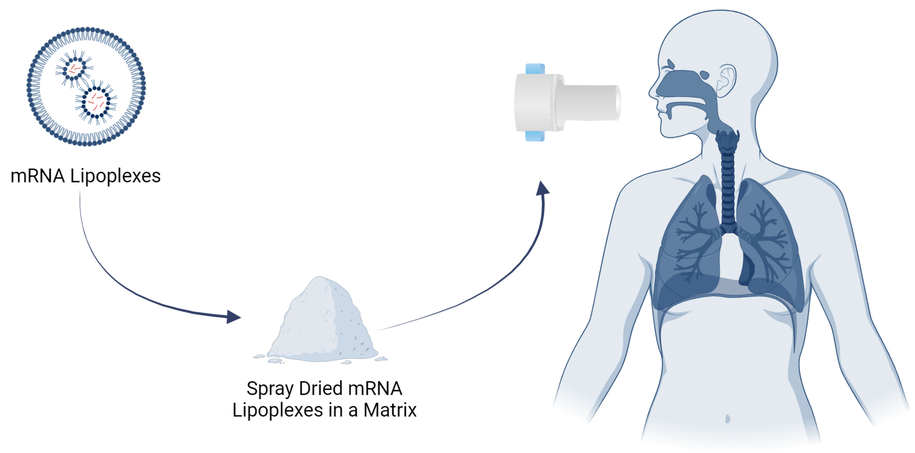
Objective:

Formulation of an Inhalable Dry Powder Platform for mRNA Therapeutics



- Many respiratory pathogens enter the body through the respiratory tract
  →The lungs and the mucosal immune system are promising targets for therapeutic interventions
- Liquid vaccines face the risk of chemical degradation and physical instability
  →Solid formulations can secure stability without challenging storage conditions. Since spray drying offers continuous manufacturing with high production capacity, we chose spray drying as production technique.

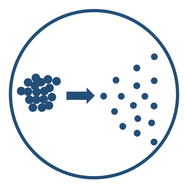
Previous Work:
- Spray drying at an outlet temperature of 50°C in mannitol matrix
  → efficient transfection
- Aerodynamic assessment of the formulation exhibited a FPF (fine particle fraction, aerodynamic diameter < 5 µm) of 35% and a powder residue of 22% in the capsules.

→ Optimisation of Aerodynamic Performance and Increasing Detachment by Co-Spray Drying with L-leucine

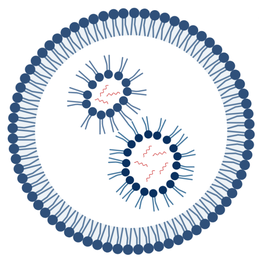
Hypothesis:

Surface Hydrophobicity ↑↓
Electrostatic Interactions ↓

→ FPF ↑
Dispersibility ↑
Capsule Residue ↓

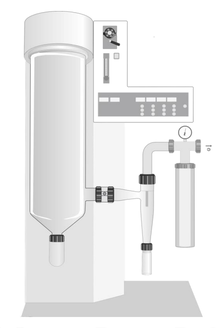


Experimental:



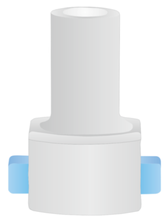
Firefly Luciferase mRNA
incorporated in Lipoplex
(Lipids DOTAP, DOPE)

+ Mannitol or Lactose
→4% (w/w) dispersion
+ 5% L-Leucine

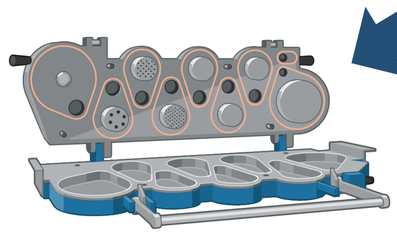


Mini Spray Dryer B-290
Inlet Temp.: 120 °C
Oulet Temp.: 50 °C

Spray Dried Powder
(mRNA Lipoplexes in Mannitol or Lactose Matrix and L-Leucine)



RS01 Dry Powder Inhaler
5 Capsules (20 mg each)

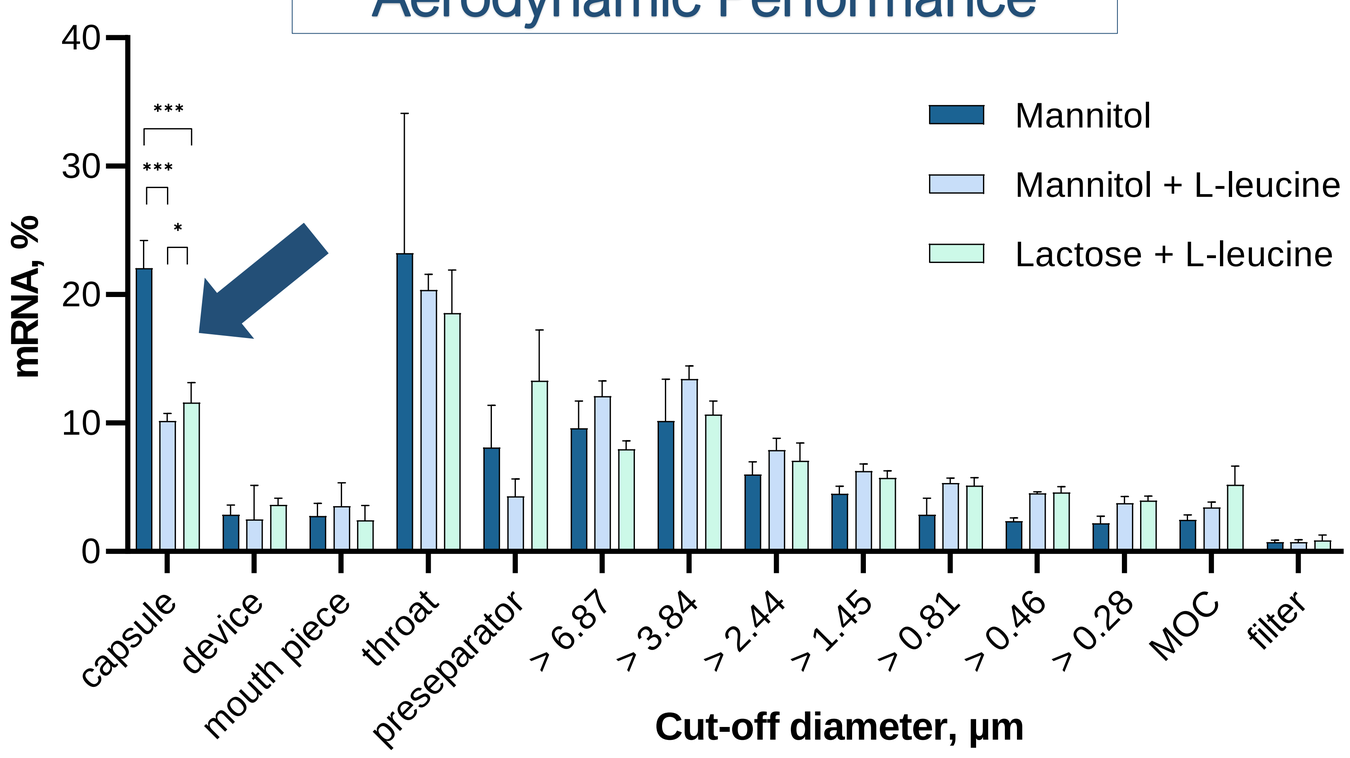


Next Generation Impactor
(Apparatus E, Ph.Eur.)
Flow Rate: 80 l/min

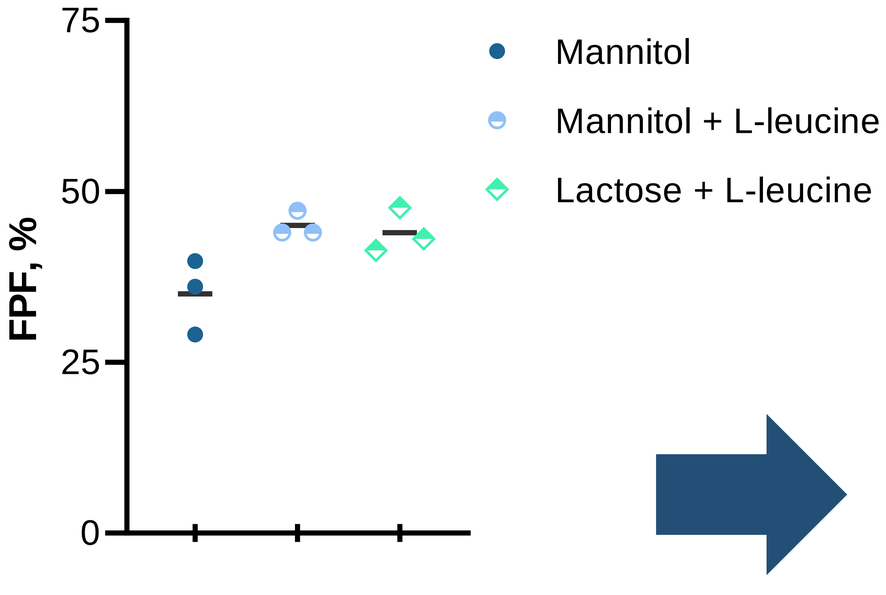
created with BioRender.com

Results:

Aerodynamic Performance



*Deposition profiles of the spray dried formulation in mannitol matrix, with or without the addition of L-leucine and in lactose matrix with L-leucine, error bars show standard deviation of 3 NGI measurements *p < 0.05; ***p < 0.001.*



Fine particle fraction (FPF) of the spray dried formulations. Symbols represent individual values and lines show mean of 3 NGI measurements.

Residue in the capsules and fine particle fraction (FPF) of the spray dried formulations with mannitol or lactose matrix after the addition of L-leucine (+) in comparison to the spray dried mannitol-based formulation without L-leucine (-).

Matrix	L-leucine	Capsule Residue, %	FPF, %
Mannitol	-	22	35
	+	10	45
Lactose	+	12	44

Conclusion:

Co-spray drying with L-leucine achieved for both matrices:
- Significant reduction of powder residue in the capsules
- Considerably higher fine particle fraction (FPF)

by increasing surface hydrophobicity and thereby reducing electrostatic interactions

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