Effect of Inhaler Parameters on the Aerosol Performance of D-LAK Peptide/Capreomycin Co-spray Dried Powder for Pulmonary Delivery

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Introduction

- Tuberculosis (TB) is an infection disease caused by *Mycobacterium tuberculosis (Mtb).* It mainly affects the lung. Drug-resistant TB becomes a global challenge[1].
- D-LAK120-A peptide is a synthetic antimicrobial peptide with anti-TB activity[2]. Capreomycin is a second-line antibiotic combating drug-resistant *Mtb*. Previous study suggested that D-LAK120-A peptide could potentiate the efficacy of capreomycin when used in combination[3].
- Capreomycin and D-LAK peptide are not orally available. Delivery through the pulmonary route can achieve high drug efficacy with low systemic toxicity.

Aims

- This study aims to formulate capreomycin and D-LAK120-A peptide as inhalable dry powder by spray drying with different drug content and mass ratios.
- The effect of different dry powder inhalers (DPIs) and flow rates on their aerosol performance were investigated.

Methods

D-LAK120-A + Capreomycin + Mannitol
(all dissolved in water)
(total 8 formulations: Table 1)

Spray Drying

- Inlet temperature 80 ℃;
- Nitrogen atomization flow rate 742 L/h;
- Aspiration 38 m³/min;
- Liquid feed rate 2.1 mL/min.

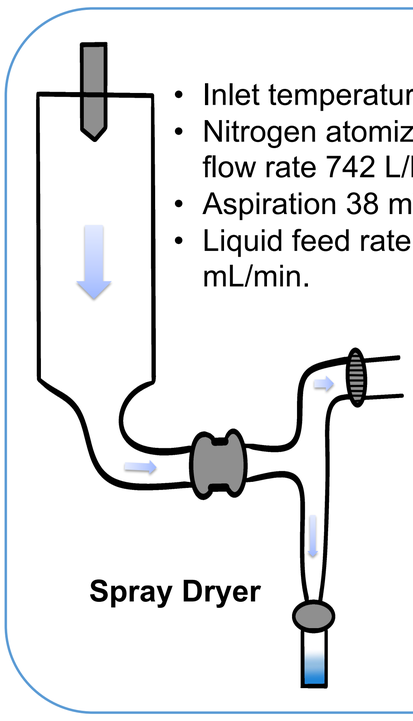

Table 1 Composition of different spray-dried formulations

Sample	Cap* (%, w/w)	Peptide (%, w/w)	Mannitol (%, w/w)
A0	0	2.0	98.0
A1	0.5	2.0	97.5
A2	0.5	4.0	95.5
A3	1.0	4.0	95.0
A4	1.0	8.0	91.0
A5	2.0	8.0	90.0
A6	2.0	16.0	82.0
A7	4.0	16.0	80.0

*Cap - capreomycin (sulfate)

All formulations

Aerosol performance

- Next Generation Impactor (NGI)
- Breezhaler®
- Flow rate: 90L/min
- Pressure drop: 3.4 kPa

Selected formulation

Aerosol performance with different inhaler parameters


Breezhaler®


High-resistance(HR) Osmohaler®

Handihaler®

Table 2 The operation condition of NGI

Inhaler	Flow rate (L/min)	Pressure drop (kPa)	Time duration (s)
Breezhaler®	90	3.4	2.7
Breezhaler®	60	1.5	4.0
HR-Osmohaler®	50	3.4	4.8
Handihaler®	33	3.4	7.3

Results and Discussion

- In figure 1, all formulations had similar EF values of around 80% and similar FPF within 40~45% (Breezhaler® , 90 L/min).
- No noticeable correlation between the aerosol performance and total drug content, or the mass ratio of two drugs.
- More than 15% (with respect to the recovered dose) of powder deposited at the throat of NGI in most powder formulations.

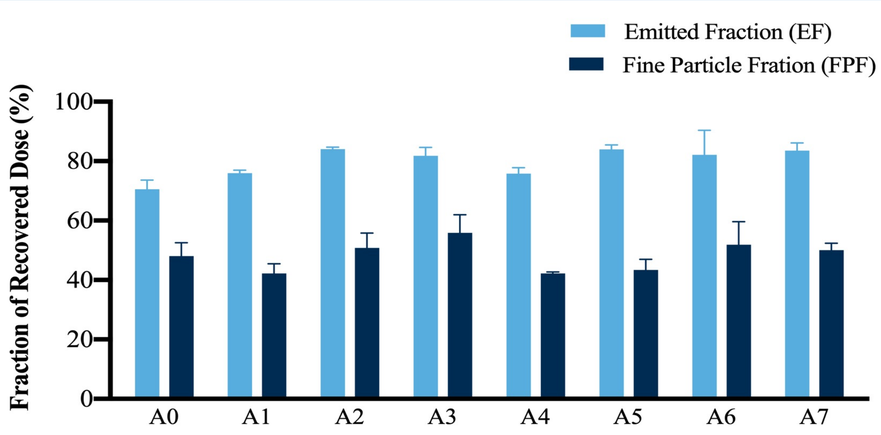

Figure 1 *In vitro* aerosol performance of all formulations evaluated by the NGI (Breezhaler® at 90 L/min)

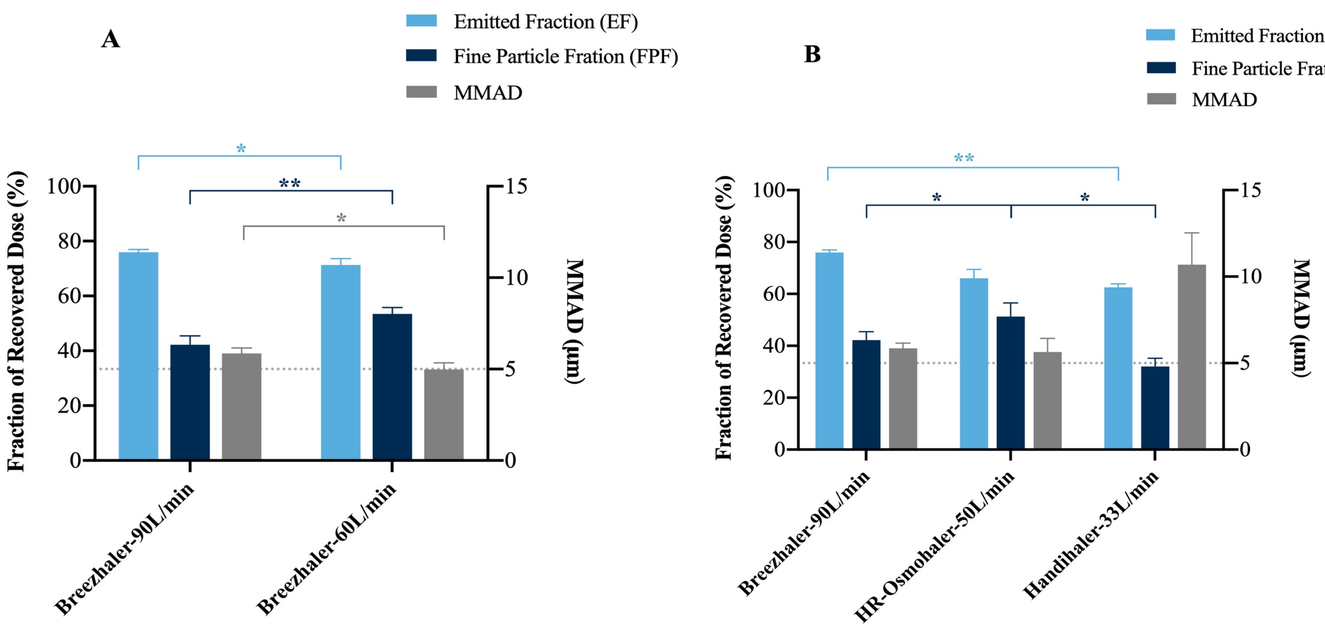

Figure 2 In vitro aerosol performance of formulation A1 evaluated by the NGI.
Figure 2A: Breezhaler® at 90 or 60 L/min. (Student t-test was applied);
Figure 2B: Breezhaler® at 90 L/min, HR-Osmohaler® at 50L/min and Handihaler® at 33L/min with the same pressure drop. (One-way ANOVA was applied.)

- Formulation A1 dispersed at a lower flow rate using Breezhaler® had a significantly lower EF but higher FPF of over 50%. The MMAD was significantly smaller (below 5 μm) (Figure 2A).
- The EF of formulation A1 decreased as the flow rate decreased (Figure 2B). Using Handihaler® showed lowest EF, followed by HR-Osmohaler® and then Breezhaler®.
- The HR-Osmohaler® operated with a flow rate of 50 L/min showed the best higher FPF (around 50%) and the smallest MMAD.
- These spray dried particles need a high airflow rate to exit the capsule and inhaler. But a high airflow rate may laed to more inertial impaction losses in the proximal airways.

- **MMAD:** mass median aerodynamic diameter.
- **EF:** emitted fraction, the percentage of the emitted dose with respect to the recovered dose.
- **FPF:** fine particle fraction, the percentage fraction of fine particle (aerodynamic diameter less than 5.0 μm) dose with respect to the recovered dose.

Conclusions

- The aerosol performance of powder formulations was affected by inhaled device and airflow rate but not the drug content or ratio of the two drugs.
- The HR-Osmohaler® was a suitable inhaler. It can generate a moderate airflow rate, leading to good powder emission from the capsule and inhaler, reduction of inertial impaction and a high FPF.

Acknowledgement

This study was financially supported by the Health and Medical Research Fund (HMRF 18170972), Hong Kong SAR.

References

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