Assessing the Variability of In Silico Lung Deposition Predictions When Inhaling from Soft Mist Inhalers with Various Air Flow Resistances

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Background

When selecting a suitable inhaler for effective drug delivery, it is crucial to consider both particle/droplet size and inspiratory flow rate achievable with a specific device. Inspiratory flow rate varies significantly among inhalers [1] due to different flow resistance. Novel SMIs, such as the pre-filled syringe SMI (PFSI®) [2, 3] offer a customizable range of flow resistances to suit specific patient populations. Slow and deep inhalation is known to result in high lung deposition and determining the optimal device resistance is a critical design consideration.

This study assesses inspiratory flow patterns and drug lung deposition of healthy volunteers and patients with pulmonary arterial hypertension (PAH) using SMIs with different flow resistance.

Method

- Studies were conducted with a SMI mock-up of various flow resistance between 0.047 and 0.125 $\mathrm{kPa}^{0.5} \cdot \mathrm{min/L}$ (Table 1) which compare favorably with other inhalers (Handihaler = 0.058; Dreamboat = 0.093 $\mathrm{kPa}^{0.5} \cdot \mathrm{min/L}$).
- Individual inhalation flow profiles were assessed in 35 healthy volunteers (group 1; age 30.5 ± 11.9) and 15 patients with PAH of functional class II, III and IV (group 2; age 36 – 83).
- Study subjects were instructed to inhale as slowly and deeply for 5 seconds or as long as comfortable with each inhaler and flow patterns were recorded via an integrated flow sensor.
- Lung deposition associated with each flow resistance was estimated using a lung deposition model (Mimetikos Preludium); the lung model morphology was scaled to FRC = 3000 mL and inspiratory flow profiles where according to the measured inhalation profiles with a 1:1 in/ex ratio.
- Two different aerosol droplet size distributions with volumetric mean diameter (VMD) of 4.5 µm and 5.5 µm (GSD = 1.4) were simulated to represent typical soft mist inhalers [3, 4].

Results

Inspiratory Flow Profiles

- Average Inspiratory Flow (AIF) decreases with increasing flow resistance for all study groups.
- Average Inspiratory Time (AIT) increases with increasing inhalation flow resistance.
- PAH patients (A*) achieve a similar AIF, but a lower AIT when compared to healthy subjects (A).

Table 1: *Classification of resistor models and equivalent flow resistance*

Group	Resistor Model	Used by	Resistance, R ($\mathrm{kPa}^{0.5}$·min/L)
1	E	Healthy volunteers	0.047
	D	Healthy volunteers	0.066
	A	Healthy volunteers	0.099
	B	Healthy volunteers	0.125
2		PAH patients	0.099

Resistance calculated as $R=\sqrt{\Delta P}/Q$, where ΔP is the pressure drop across the SMI mouthpiece and Q is the volumetric flow rate

- Population averaged flow profiles are nearly rectangular, typical for inhalers, with a sharp rise to peak inspiratory flow followed by a period of nearly constant inspiratory flow.
- In all cases, AIT is longer than the aerosol bolus (3.5 seconds) ensuring that a complete and deep inhalation of the medication is achieved.
- Patient to patient variability in inspiratory flow significantly decreases for increasing flow resistance.

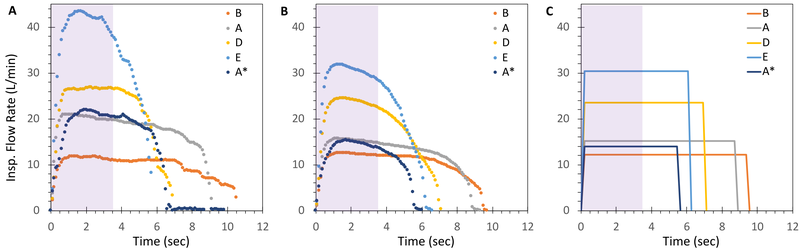

Figure 1: *(left) Example of individual flow profiles of Group 1 and Group 2; (middle) Average measured inhalation flow profiles; (right) Modelled inhalation flow profiles used for deposition calculation.*

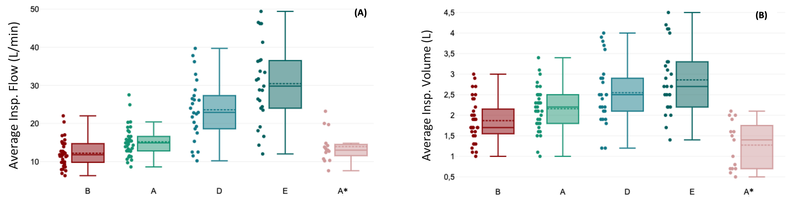

Figure 2: *Individual and mean inspiratory flow data at different flow resistances for health volunteers (A, B, D, E, Group 1) and PAH patients (A*, Group 2). (left): AIF (L/min) and (right): AIV (L)*

Modelled Lung deposition

- Modelled lung deposition (LD) is > 60% with low throat deposition for all cases irrespective of VMD and flow resistance due to the achieved slow and deep inhalation.
- LD decreases with decreasing flow resistance irrespective of VMD.
- Patient to patient variability in LD decreases notably with increasing flow resistance.
- Mean AIF and LD of the PAH group (A*) show no statistical difference from the healthy subject group: AIF = 13.9 L/min vs 15.2 L/min (p = 0.155); LD = 81.0% vs 89.1% (p = 0.130).
- Mean Average Inhalation Volume (AVI) is different between the two groups: AIV = 1.27 vs 2.16 L (p < 0.05) owed to the lower respiratory capacity of the PAH subjects.

Table 2: *Lung deposition at inspiratory flows associated with each air flow resistance (VMD = 4.5µm)*

Lung Deposition (%)	B	A	C	D	A*
Throat	5 – 12	7 – 15	8 – 25	11 – 32	5 – 14
Lung (LD)	88 – 95	85 – 93	74 – 91	67 – 88	70 – 89
Tracheobronchial	10 – 14	11 – 15	12 – 18	13 – 18	10 – 15
Bronchiolar	20 – 36	17 – 29	11 – 26	10 – 21	17 – 33
Alveolar	48 – 54	53 – 54	45 – 53	39 – 54	26 – 52
Exhaled	0 – 0	0 – 0	0 – 1	1 – 1	1 – 26

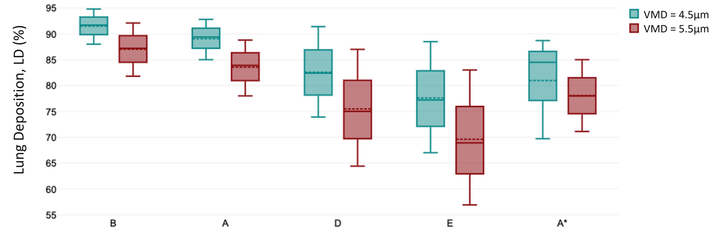

Figure 3: *Modelled lung deposition at different flow resistances for health volunteers (A, B, D, E, Group 1) and PAH patients (A*, Group 2) at VMD = 4.5µm and 5.5µm (GSD = 1.4).*

Conclusion

- Inhalers featuring different flow resistances influence the inhalation flow profile of patients.
- Measurements a lung deposition modelling indicate that inhalation at higher flow resistance leads to more consistent flow profiles and higher lung dose with lower patient to patient variability.
- All study subjects were able to perform appropriate inhalation maneuvers at all flow resistances with AIT of 6 – 10 seconds, with AIF of 12.2 – 30.4 L/min and AIV of 1.3 – 2.9 L.
- Small differences in lung deposition are observed for different particle size distributions.
- Emphasizing good inhalation technique is crucial for effective treatment. Selecting an inhaler device such as the PFSI® soft mist inhaler with customizable flow resistance is thus important for predictable aerosol delivery to the lungs.

References

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