Inhaler Performance at High Altitude

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Particle Engineering

Introduction

Dry powder (DPIs) and pressurized metered dose (pMDIs) inhalers must operate reliably in a variety of environments and are typically only tested near laboratory conditions. Little is known about device performance at reduced pressure associated with high altitude [1,2]. Testing was conducted to determine the in vitro lung dosage of a variety of different inhaler devices at a number of different altitudes. The data collected provides a good relative understanding of how the dosage of inhaler devices will change with altitude.

Method and Materials

❑ pMDI Testing

- Data for five devices, Symbicort®, Airomir™, Ventolin®, QVAR™, and Apo-Salvent, were collected at elevations of 670m, 2450m, 3260m, and 4300m.
- Properties of the inhalers are given in **Table 1.**
- A constant inspiratory flow rate of 30 L/min was used at all locations.
- The flow profile consisted of an initial 0.5 s period to allow for the flow stream to become uniform, followed by one actuation and a 6 second inhalation period, resulting in a total volume of 3 liters.

❑ DPI Testing

- Data for two devices, Turbuhaler® and Ventolin® Diskus®, were collected at elevations of 670m, 2450m, 3260m, and 4300m.
- Properties of the inhalers are given in **Table 1.**
- Since breathing profiles of patients inhaling from a DPI at reduced ambient pressure are unknown, two possible scenarios were tested:

a) Matched Flow Rate

- The volumetric flow rate was kept the same for all altitudes for each device.
- A constant inspiratory volume of 2.4 liters was used.

b) Matched Pressure Drop

- The pressure drop across each device at each altitude was kept constant at 4kPa.
- Resistance of each device was expected to change with altitude and thus the volumetric flow rate changed
- As the flow rate changed, with a 3 liter inhalation volume, the length of each test changed.

❑ Test conditions were maintained at 22 ±1.7 °C, 49.3 ± 9.2 %RH. For simulation of aircraft cabin conditions silica gel dried air was used.

Results

Test apparatus

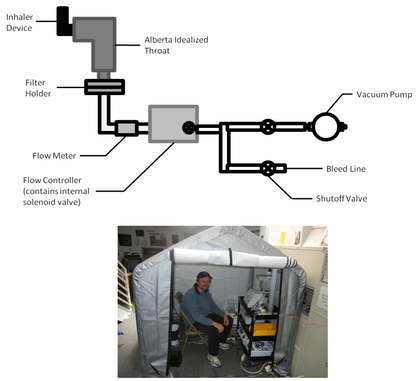


Table 1: Important properties of inhalers tested.

Product	Propellant	Label Dosage (µg)	Format
Symbicort	HFA 227ea	Budesonide 160[a] Formoterol 4.5[a]	Suspension pMDI with Povidone K25 and PEG 1000
QVAR	HFA 134a	Beclomethasone Dipropionate 100	Solution pMDI with Ethanol
Ventolin	HFA 134a	Salbutamol Sulfate 100	Suspension pMDI without excipients
Airomir	HFA 134a	Salbutamol Sulfate 100	Suspension pMDI with Ethanol and Oleic Acid
Apo-Salvent	HFA 134a	Salbutamol Sulfate 100	Suspension pMDI with Ethanol and Oleic Acid
Ventolin Diskus	NA	Salbutamol Sulfate 200	DPI with Lactose carrier
Bricanyl	NA	Terbutaline Sulfate 500	DPI without excipients

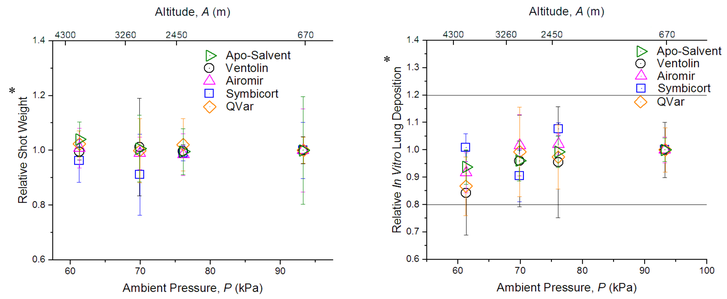
Absolute in vitro lung doses of pMDIs

Inhaler	Mean Dosage (µg)			
Altitude (m)	**670**	**2450**	**3260**	**4300**
Symbicort® Gravimetric assay	1,140±20	1,230±30	1,030±110	1,150±60
Symbicort® Chemical assay	338±27	423±28	304±38	359±22
Ventolin®	63.8±6.5	61.0±13	61.3±10.8	53.8±9.8
Airomir™	56.3±3.0	57.5±2.3	57.3±6.3	51.5±4.0
QVAR™	67.8±3.0	67.3±3.8	65.0±5.0	63.5±4.3
Apo-Salvent	62.8±5.0	61.3±7.3	62.3±10.3	54.5±6.8

Spray duration for pMDIs is unaffected by altitude

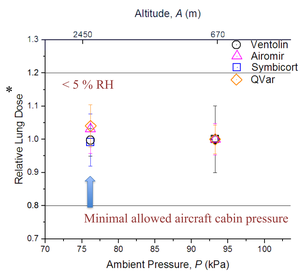
Inhaler	Time (s)	
Altitude (m)	**670**	**4300**
Symbicort®	0.18 ± 0.02	0.21 ± 0.02
Ventolin®	0.13 ± 0.01	0.15 ± 0.02
Airomir™	0.15 ± 0.01	0.15 ± 0.01
QVAR™	0.21 ± 0.02	0.21 ± 0.03
Apo-Salvent	0.16 ± 0.02	0.16 ± 0.01

pMDI shot weight and *in vitro* lung dose are unaffected by altitude

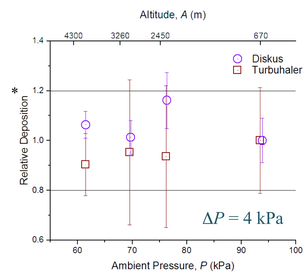


*Relative parameters are normalized by results obtained at an elevation of 670 m.

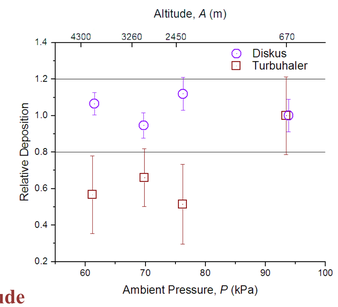
pMDI *in vitro* lung dose is maintained at aircraft cabin conditions



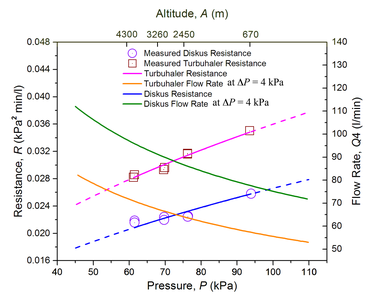
DPI *in vitro* lung dose is unaffected by altitude for matched pressure drop



DPI show device dependent reduction in *in vitro* lung dose for matched volumetric flow rate



DPI device resistance is a function of ambient pressure



DPI device resistance, *R*, as a function of ambient pressure, *P*:

$$R(P) = R_{\mathrm{ref}}\sqrt{\frac{P}{P_{\mathrm{ref}}}}$$

P_{ref}: Standard pressure, 100 kPa (~ sea level).
R_{ref}: Device resistance at standard conditions.

Conclusion

Collected data for most of the devices tested displayed little effect of altitude on measured *in vitro* lung dose. **Note:** The effect of reduced pressure on particle size distribution of the delivered aerosol was not tested in this study.

- ❑ All pMDIs tested delivered *in vitro* lung doses that were within ±20% of nominal dosage bands.
- ❑ Ventolin® Diskus ® displayed very consistent *in vitro* lung dose at all conditions tested.
- ❑ Bricanyl Turbuhaler ® was unaffected by altitude when tested under matched pressure drop conditions.
- ❑ Bricanyl Turbuhaler ® *in vitro* lung dose displayed a negative correlation with altitude when tested under matched flow rate.
- ❑ All pMDIs tested had consistent dosage when aircraft cabin conditions were simulated.
- ❑ Spray duration and shot weight of all pMDIs was unaffected by altitude.
- ❑ The device resistance of DPIs is affected by ambient pressure

References

1. Röggla G, Moser B. 2006. *The function of metered dose inhalers at moderate altitude.* J Travel Med. 2006; 13(4):248–248.
2. Cogo A, Fiorenzano G. 2009. *Bronchial asthma: advice for patients traveling to high altitude.* High Alt Med Biol; 10(2):117–121.

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