Effect of ambient temperature and humidity on the *in vitro* regional lung deposition of solution and suspension MDIs

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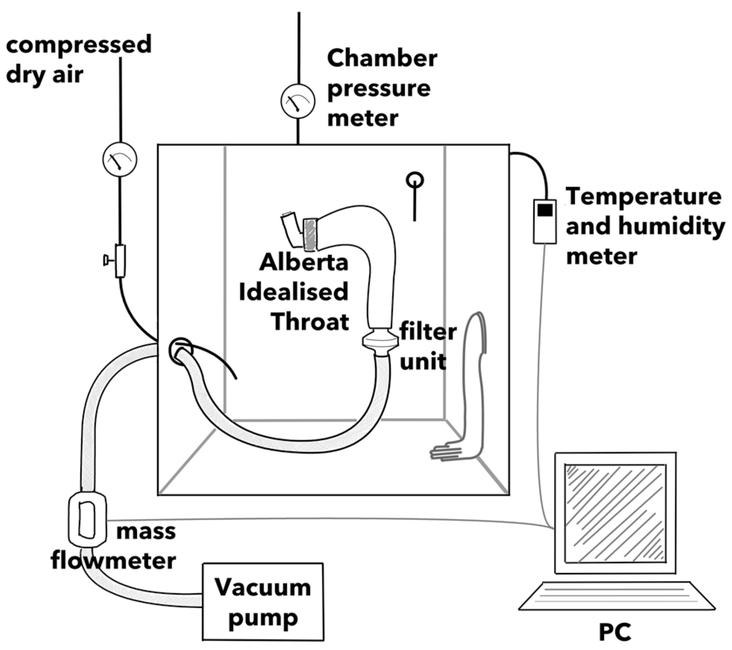
INTRODUCTION

Pressurised metered dose inhalers (pMDIs) are used and stored by patients in a variety of climates. Previous *in vitro* studies of temperature and humidity effects on aerosol delivery have employed experimental setups only representing mechanical ventilation for intubated patients, and only studied salbutamol sulfate pMDI suspensions (see [1] for a recent review). In this study, we will use the Alberta Idealised Throat, a replica developed from MRI and CT scans of human subjects, to measure mouth-throat deposition and subsequent lung deposition. The study will look at the effect of relative humidity (RH) and temperature on the aerosol delivery of both solution and suspension pMDI formulations.

MATERIALS AND METHODS

Three pMDI formulations were chosen for study:

- Beclomethasone dipropionate (BDP), 13% w/w ethanol, 1.3% w/w glycerol in HFA-134a (**"BDP HFA134a"**; solution formulation)
- BDP and 13% ethanol in HFA-227a (**"BDP HFA227"**; solution formulation)
- Fluticasone propionate in HFA-134a (**"Flixotide Evohaler"**; suspension formulation)



The pMDIs were tested in the setup shown above, according to the following experimental matrix:

	BDP HFA134a, Flixotide Evohaler		BDP HFA227	
Temperature (°C)	20	40	20	40
RH (%)	0, 35, 80		0, 35, 80	0, 80
Flow rate (L/min)	28.3, 60, 90		28.3	

Drug deposition was quantified in the throat and filter by chemical assay.

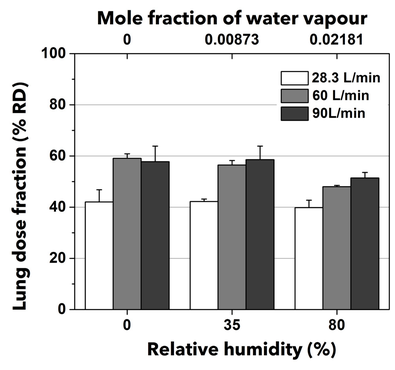
- The mass collected in the filter was defined as "lung dose"
- The total mass recovered from throat and filter was defined as "recovered dose" (RD)
- Statistical analysis by one-way ANOVA (significance when $p < 0.05$)

RESULTS

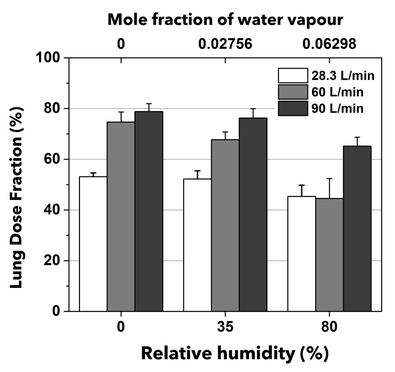
BDP HFA134a

- General increase in mouth-throat deposition and decrease in lung dose fraction between 35 to 80% RH, at 60 and 90 L/min
  - Up to a 35% decrease in lung dose fraction at 40°C, 60L/min
- General decrease in mouth-throat deposition, and increase in lung dose fraction when temperature raised from 20 to 40°C
- General increase in lung dose fraction between 28.3 and 60L/min flow rate

20°C



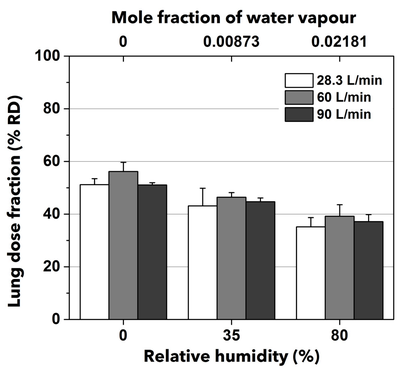
40°C



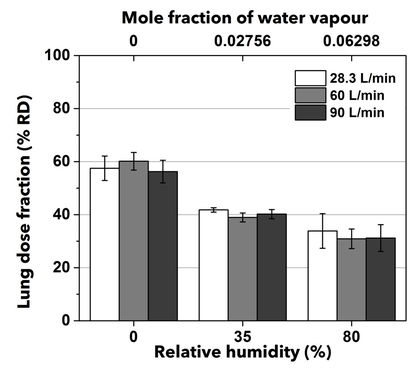
Flixotide Evohaler

- General increase in mouth-throat deposition and decrease in lung dose fraction between 0 to 80% RH
  - Up to a 50% decrease in lung dose fraction at 40°C, 60L/min
- No significant difference in mouth-throat deposition or lung dose fraction when temperature raised from 20 to 40°C
- No significant change in lung dose fraction corresponding to flow rate

20°C

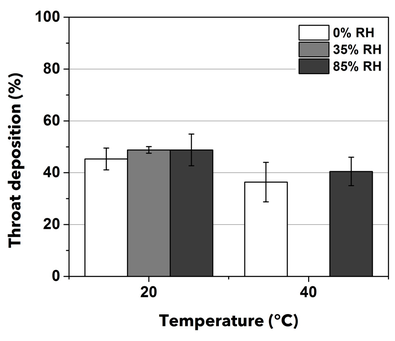


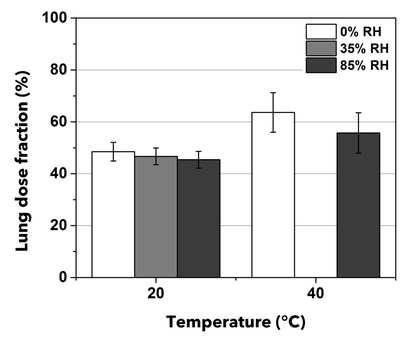
40°C



BDP HFA227

- No significant difference in mouth-throat deposition or lung dose fraction corresponding to RH
- No significant difference in mouth-throat deposition or lung dose fraction when temperature raised from 20 to 40°C
  - Except increased lung dose fraction at 0% RH





CONCLUSIONS

Effect of relative humidity

Increasing RH led to reduced lung dose fraction

- Likely due to condensation of water vapour on residual dry particles
- Condensation leads to increased particle diameter, and thus increased mouth-throat deposition

Effect is strongest in the suspension formulation, and weaker in the solution formulations

- Flixotide estimated to produce 1 particle per 30 droplets, compared to 1 particle per droplet for solution formulation[2]
- Flixotide also shown to produce colder plume temperature compared to a solution formulation similar to BDP HFA134a[3]
- The relatively few, cold, residual particles are susceptible to greater condensation than residual particles from the solution pMDI formulations

Effect of temperature

Increasing temperature increased lung dose fraction only for BDP HFA134a (and a weak non-significant increase for BDP HFA227)

- May be related to ethanol content
- Increased temperature leads to decreased droplet evaporation time
- Finer droplets reach the filter, thus increasing lung dose fraction

Flixotide suspension may have already short droplet evaporation time, without ethanol or glycerol to retard evaporation

- Hence no effect of temperature

Practical implications

Patients are commonly advised to store pMDIs below 25-30°C. However, this study shows that lung delivery may still be affected by environmental conditions at the point of drug dosage, particularly in humid climates.

REFERENCES

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3. Brambilla G, Church T, Lewis D, and Meakin B: Plume temperature emitted from metered dose inhalers. Int J Pharm. 2011;405:9–15.