The Influence of Environmental Factors on Pressurized Metered Dose Inhaler Performance

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Introduction

While performance testing of pressurized metered dose inhalers (MDIs) is typically conducted at controlled laboratory conditions, patients may utilize their inhalers at locations with substantial variations in temperature, humidity, or atmospheric pressure (e.g. at altitude). Since effective drug delivery from MDIs relies on adequate atomization and evaporation, *in vitro* evaluations were conducted while varying device and ambient temperature, humidity, and altitude to assess the influence of these factors on the *in vitro* lung dose. Additionally, mechanistic models were used to aid in interpretation of the results.

Materials & Methods

➢ *In Vitro* Lung Dose Testing

- The Alberta Idealized Mouth-Throat Model with a downstream filter classified MDI aerosols into respirable and non-respirable fractions.
- Filter deposition was assayed chemometrically or gravimetrically to determine *in vitro* lung dose; all experiments conducted at 28.3 std L/min air flow.
- A custom environmental chamber allowed manipulation of inhaler or air temperature[1] and relative humidity[2] (RH); a mobile test station was used to conduct high-altitude tests on Mt. Evans, Colorado[3].
- Save for high-altitude tests and experiments where RH was deliberately varied, all testing was conducted with RH ≲ 1%.

➢ Mechanistic Models

- A model was developed to estimate the influence of MDI temperature on droplet size.
- Mass median initial droplet diameter was correlated to temperature and formulation using the equation[4]

$$d_{0,50} \approx d_{c,50} = 416\,\frac{\sigma_{pa}}{p_{mc}}$$

- A quasistationary single droplet evaporation model including Stefan flow was implemented in C++ to evaluate the effect of gas temperature and vapor partial pressure on the evaporation rate of propellant droplets.
- Droplet equilibrium temperature was obtained by solving the equation[5]

$$\frac{\Delta H_v}{c_p} = \frac{(1-Y_s(T_{eq}))^{1/Le}\,(T_\infty - T_s)}{(1-Y_\infty)^{1/Le} - (1-Y_s(T_{eq}))^{1/Le}}$$

- The evaporation rate is then given by

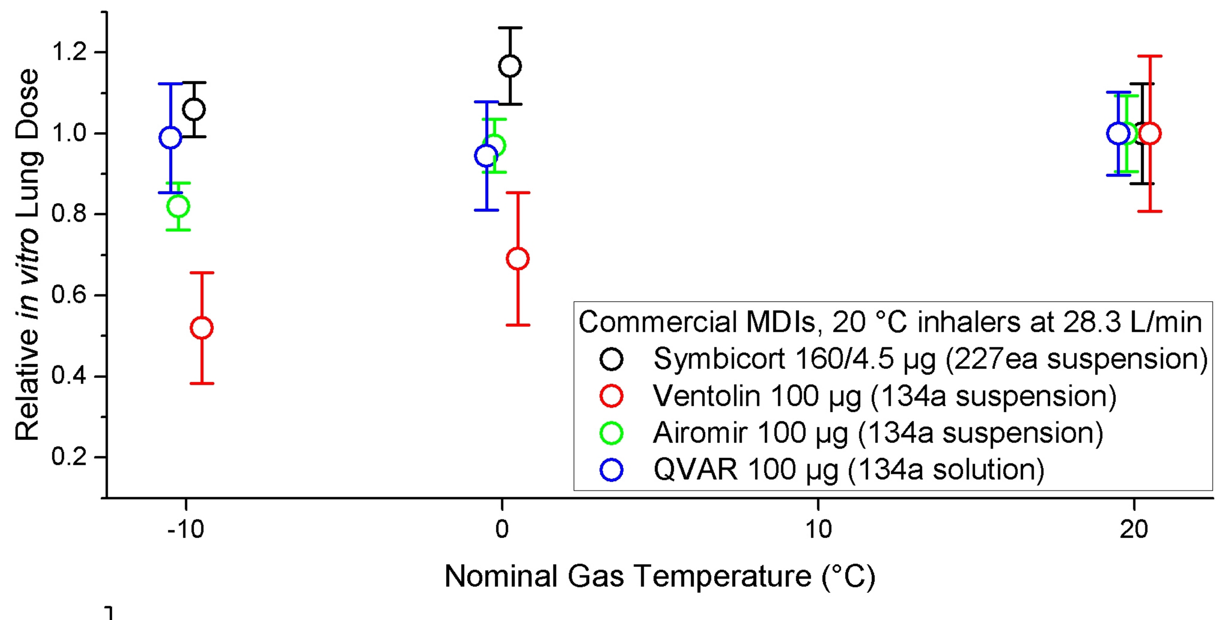
$$\kappa = 8D\,\frac{\rho_g}{\rho_l}\ln\left(\frac{1-Y_\infty}{1-Y_s(T_{eq})}\right)$$

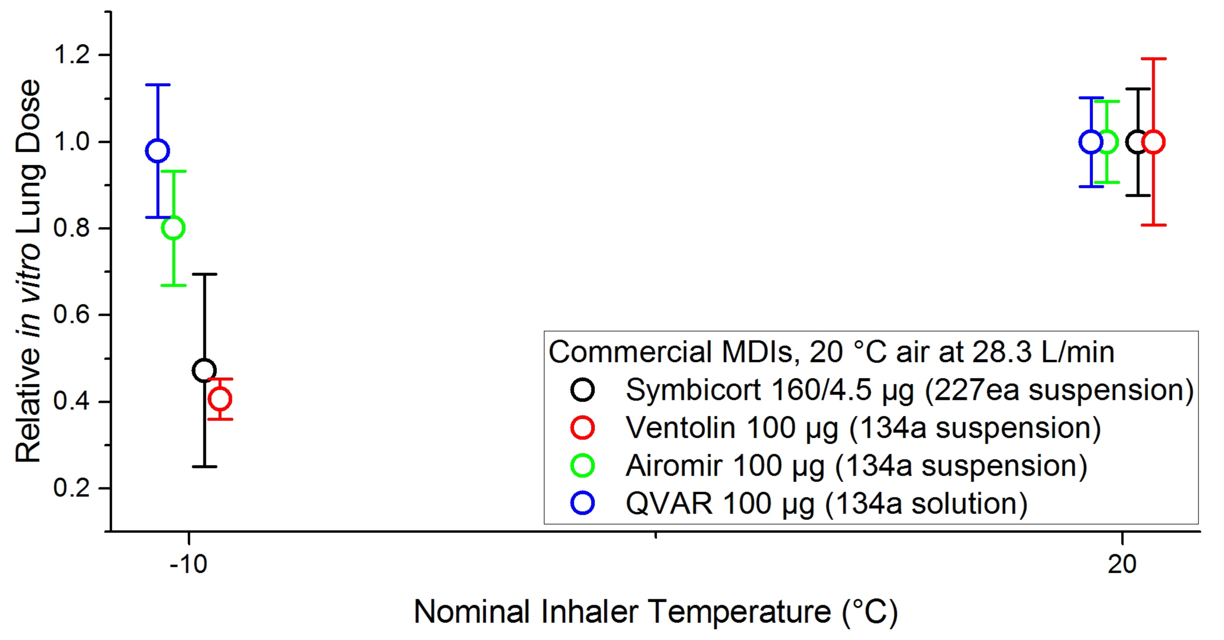
- All gas-phase properties were evaluated at

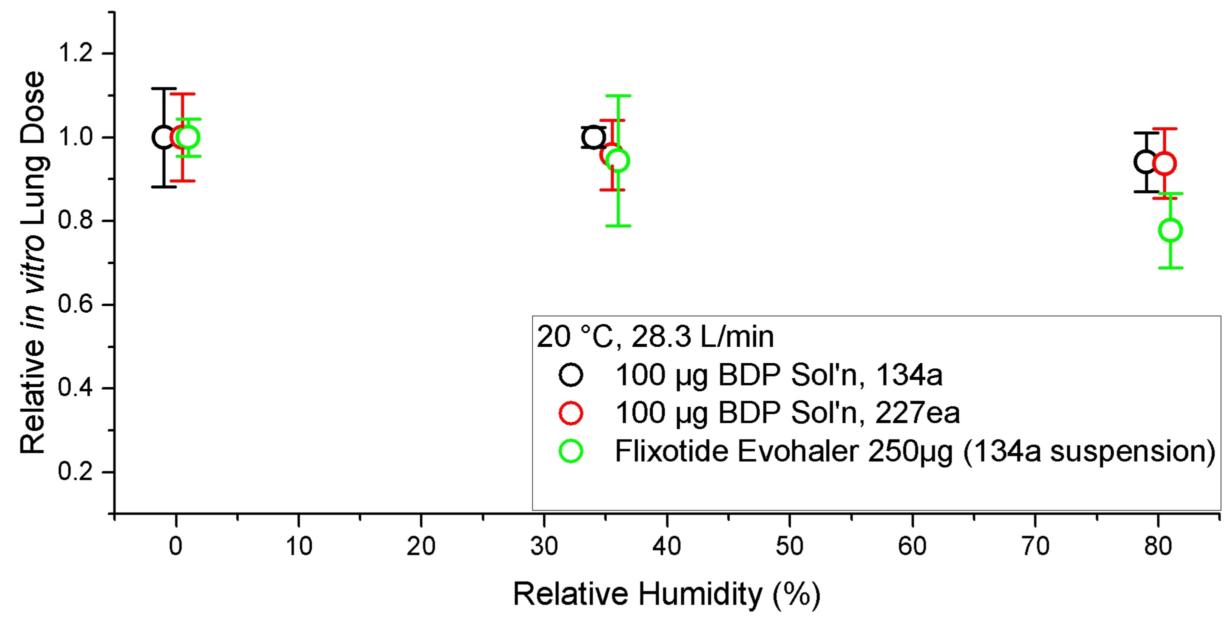
$$T_{1/3} = T_s + \frac{(T_\infty - T_s)}{3},\quad Y_{1/3} = Y_s - \frac{(Y_s - Y_\infty)}{3}$$

Results

➢ *In Vitro* Lung Dose Testing



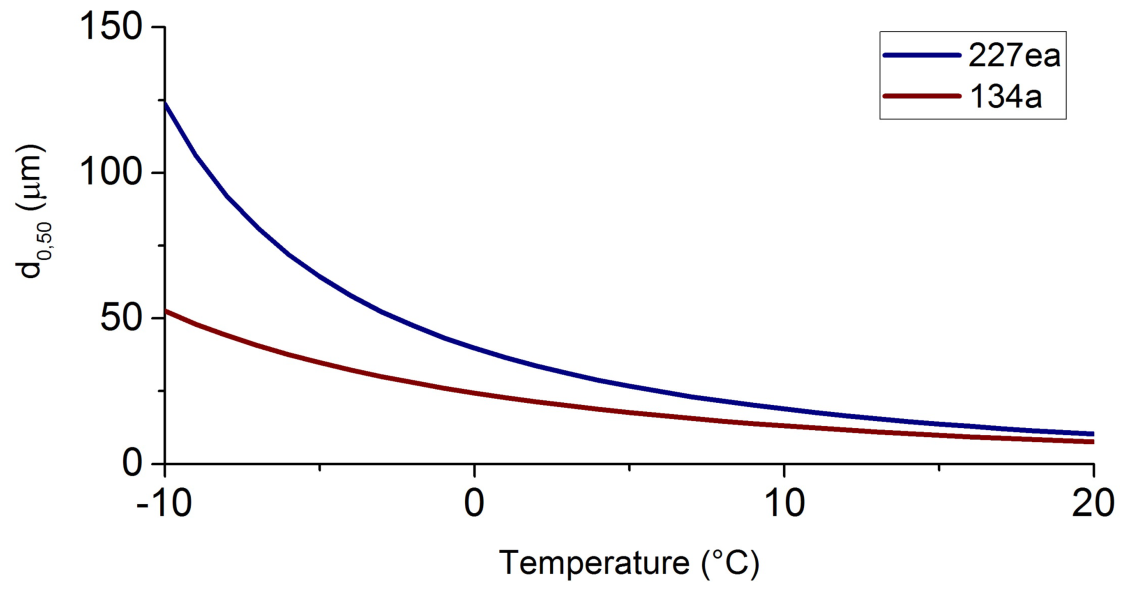




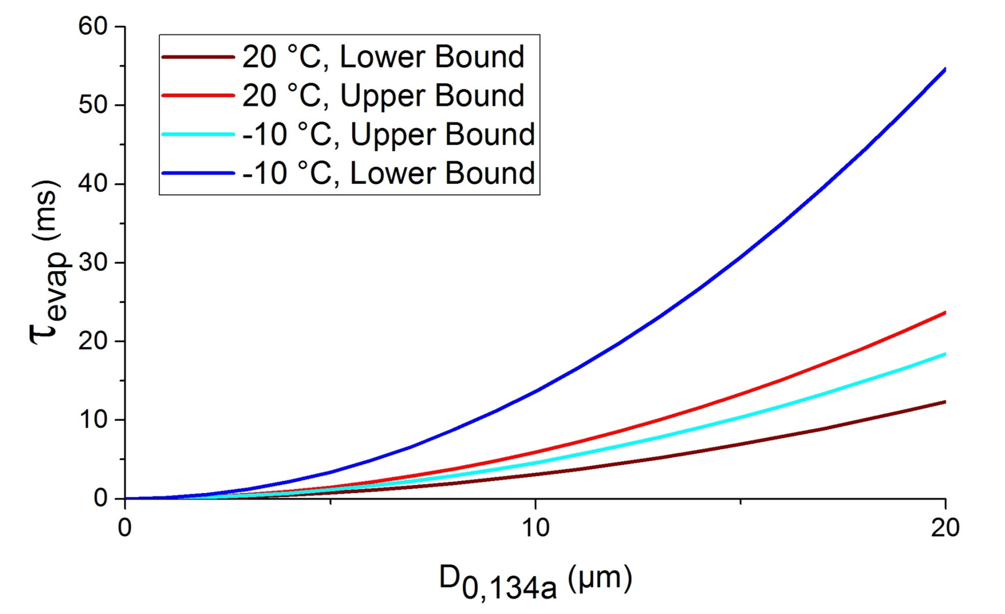
- Changing ambient pressure (61-94 kPa) had no significant effect on the tested MDIs.
- Decreasing the temperature of either the inhaler or the air may reduce the *in vitro* lung dose—some MDIs more susceptible than others.
- Increasing the RH of the air during testing may result in a reduction in *in vitro* lung dose, depending on MDI.

➢ Mechanistic Models

- Mouth-throat deposition depends on atomization (droplet diameter and spray momentum), aerosol dynamics (evaporation), and flow field (gas flow rate, mouth-throat geometry).



- Lower MDI temperature is expected to affect lung dose by decreasing propellant vapor pressure, thus coarsening the initial droplet diameter distribution and the residual aerosol.



Evaporation time vs. initial diameter for p134a droplets. "Lower bound" calculated at nominal air temperature, while "upper bound" calculated at an outlet condition assuming complete evaporation of propellant in an adiabatic process to provide an extremum case.

Conclusions

➢No significant effect of atmospheric pressure on *in vitro* lung dose was observed up to 4300 m elevation (~60 kPa atmospheric pressure).

➢Air temperature affects *in vitro* lung dose; the severity of the effect varied across the tested MDIs.

➢The device temperature also affected *in vitro* lung dose, with some MDIs more susceptible than others.

➢Increasing RH results in a small but significant reduction in *in vitro* lung dose for one inhaler type; others were unaffected.

➢Further experimental and theoretical work is needed to fully understand what factors lead to robust performance at low temperatures or high humidity.

➢Product developers and clinicians should be aware of these considerations to ensure patients obtain consistent performance regardless of environmental conditions.

References

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