Towards More Realistic In Vitro Nebulizer Testing

Uwe Schuschnig, Andrea Winzen, Benjamin Heine, Nicolas Schwenck and Stefan Seemann

PARI Pharma GmbH, Gräfelfing, Germany

Background

- Standard methods for nebulizer testing have limitations:
  - Droplet size is determined at constant flow rate
  - Delivered Dose is determined at standardised breathing pattern ex mouthpiece
  - Dead space volume of respiratory tract not considered
- First test setup combining impactor, breath simulation with realistic inlet geometry and breathing pattern published 2003 [1]
- In *vivo in vitro* correlation of new method validated 2013 [2] for inhalers
- Experimental setup adopted for nebulizers, peak inspiratory flow rate up to 30 l/min 2017 [3]

Objective

We present a setup with a flow rate of 45 l/min and test the effects of variable respiratory dead space volume and breathing pattern on the aerosol performance of two differently designed vibrating membrane nebulizers (Figure1).

Material and Methods

- Two vibrating membrane nebulizer types, the Philips InnoSpire Go (ISG) and a PARI eFlow investigational nebulizer (EIN) with ~90 ml aerosol chamber were used
- Breathing pattern I:E variation (1:2; 1:1; 2:1) of standard adult pattern (Figure 2)
- Respiratory tract dead space volume 90 vs. 150 ml
- DoE with 36 experiments
- Test substance 2 ml isotonic saline
- Stage deposition determined by conductometry [4]

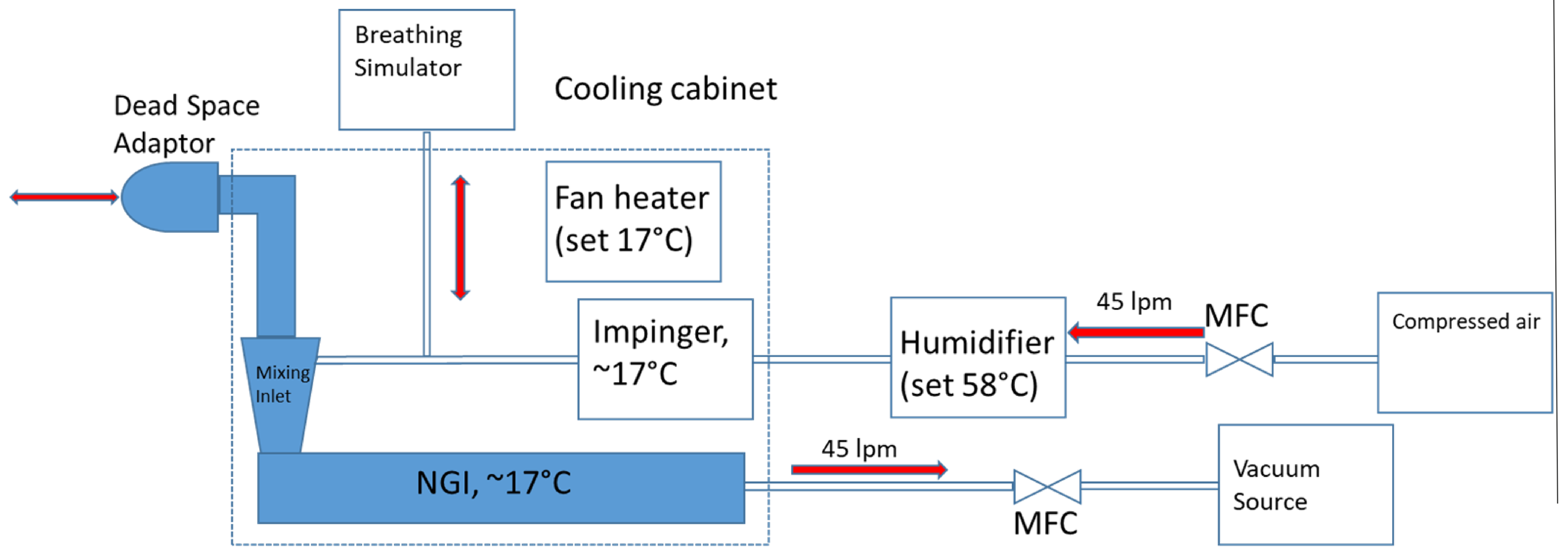

Figure 1: Experimental setup (NGI= Next Generation Impactor MFC= mass flow controller)

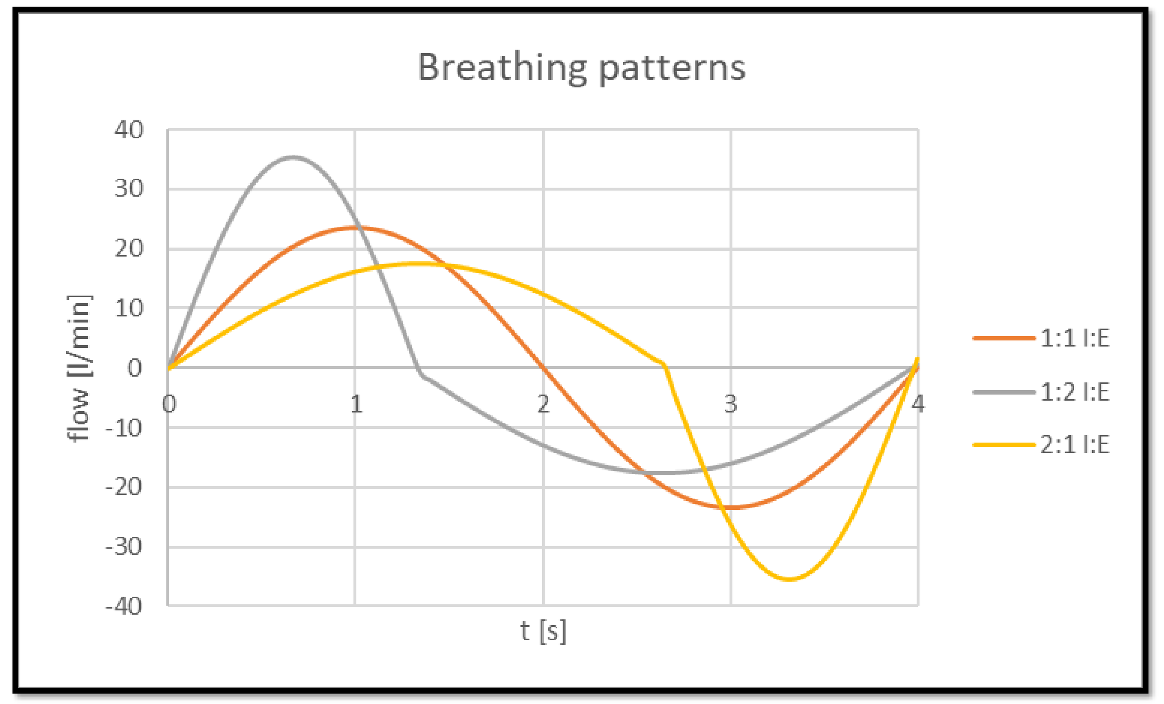

Figure 2: Breathings patterns tested in DoE; all patterns have 500ml tidal volume with a breathing frequency of 15 bpm; the I:E ratios of 1:2, 1:1 and 2:1 correspond to inhalation times of 1.33, 2 and 2.67 seconds

Results

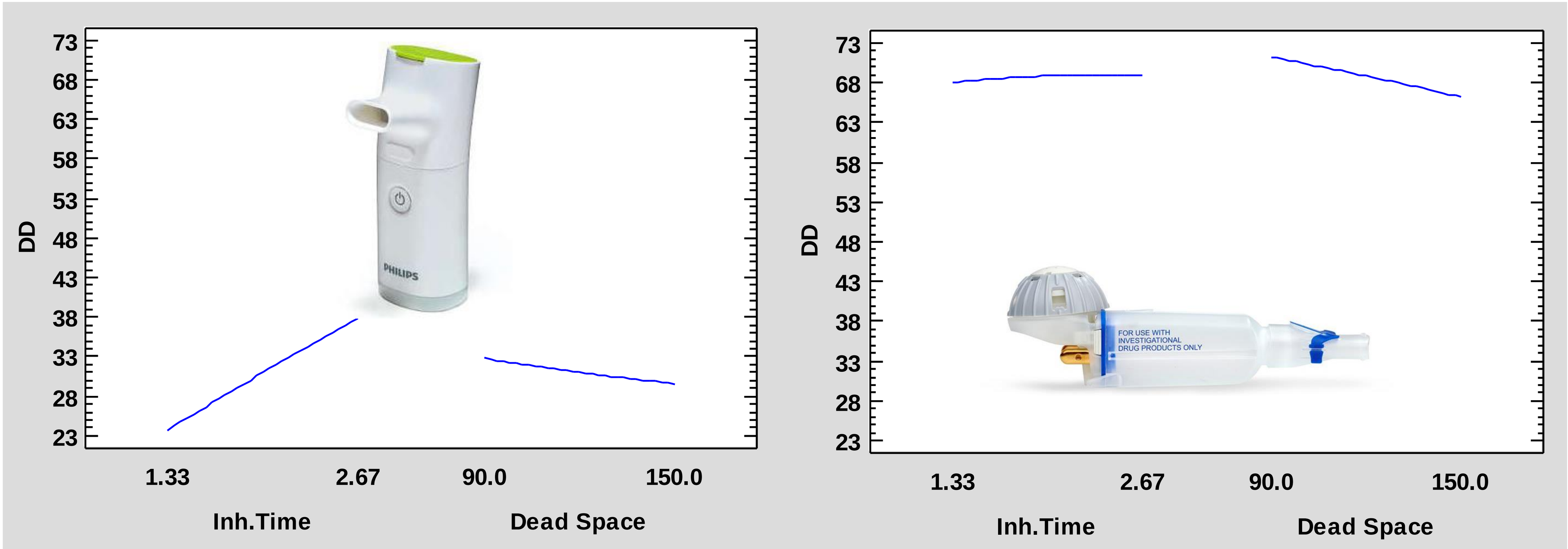

Figure 3: Main effect plots for InnoSpire Go (left) and eFlow (right). This plot shows the estimated Delivered Dose DD [%] as a function of inhalation time and dead space. In each plot, the factor of interest is varied, while the other factor is held constant at the central value.

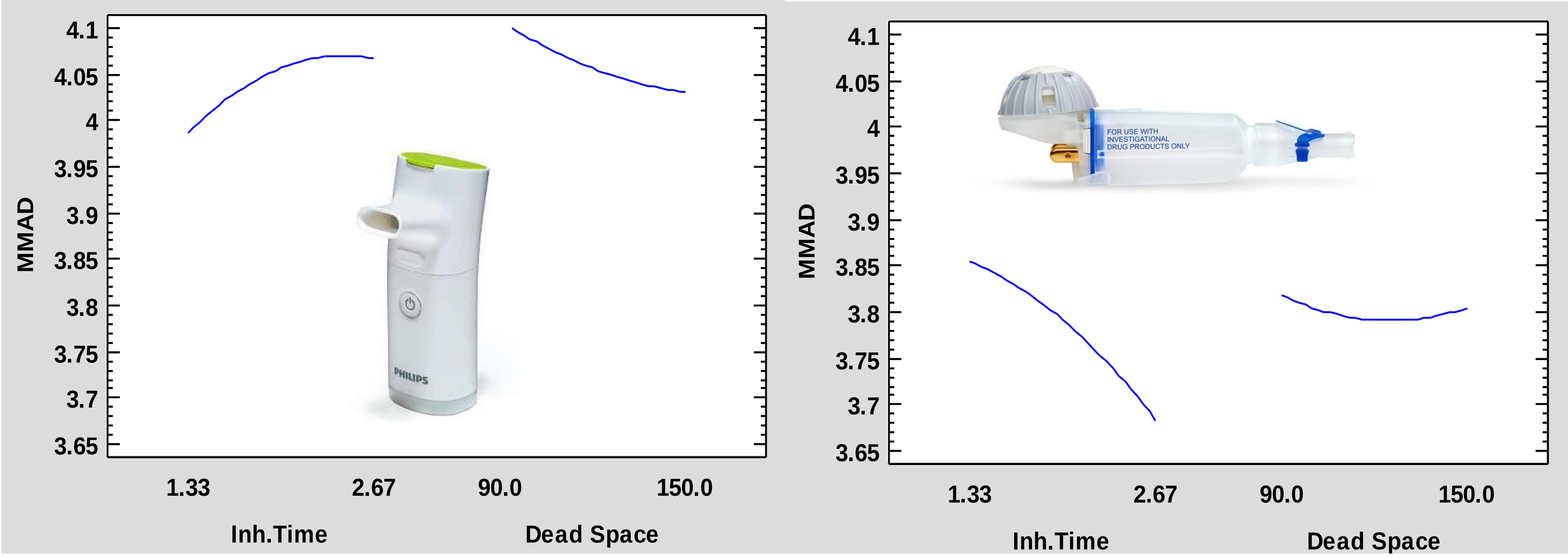

Figure 4: Main effect plots for InnoSpire Go (left) and eFlow (right). This plot shows the estimated MMAD [µm] as a function of each experimental factor. In each plot, the factor of interest is varied from its low level to its high level, while the other factor is held constant at central value.

Summary

- ISG, without aerosol storage, achieves lower delivered dose (DD) than EIN with aerosol chamber (31% vs. 69%)
- ISG is stronger affected by breathing maneuver (23% vs. 38% 1:2 vs. 2:1) than EIN (68% vs. 69%)
- Effect of increased dead space is lower for EIN than for ISG (7% vs. 10% relative DD reduction)
- Aerosol storage chamber increases delivered dose
- Aerosol storage chamber renders nebulizer less dependent on breathing maneuver and respiratory dead space

Conclusions

- Method worked well and delivered results which could be expected due to different nebulizer design
- Method is capable to detect even small changes in droplet size
- Combined approach for nebulizer characterization is a valuable tool to better understand nebulizer performance under dynamic conditions and to improve future device developments

References

[1] Janssens HM, de Jongste JC, Hop WCJ, Harm A. W. M. Tiddens: Extra-Fine Particles Improve Lung Delivery of Inhaled Steroids in Infants* Chest 2003;123;2083-2088

[2] Olsson, B., Borgström, L., Lundbäck, H., & Svensson, M. (2013). Validation of a general in vitro approach for prediction of total lung deposition in healthy adults for pharmaceutical inhalation products. Journal of aerosol medicine and pulmonary drug delivery, 26(6), 355-369.

[3] Marten Svensson, Elna Berg,Jolyon Mitchell, Dennis Sandell: Laboratory Study Comparing Pharmacopeial Testing of Nebulizers with Evaluation Based on Nephele Mixing Inlet Methodology, AAPS PharmSciTech (2017)

[4] Schuschnig U, Heine B, Knoch M: : How Cold Is Cold Enough? Refrigeration of the Next-Generation Impactor to Prevent Aerosol Undersizing JOURNAL OF AEROSOL MEDICINE AND PULMONARY DRUG DELIVERY Volume 34, Number 0, 2021

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