Experimental Evaluations of Internal Losses in 'Miller' Mixing Inlet Used to Enable Constant Flow Rate to a Cascade Impactor Whilst Allowing an Inhaler to be Tested for Emitted Aerosol Aerodynamic Particle Size Distribution (APSD) with Realistic Breathing Profiles

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EPAG European Pharmaceutical Aerosol Group www.epag.co.uk

BACKGROUND:

- Testing methods in the pharmacopeial compendia for the determination of APSD either operate the multi-stage cascade impactor at constant flow rate, or for dry powder inhalers, simulate a controlled inhalation flow rate-rise time profile
- The 'Miller' mixing inlet, developed in 2002, has since become in widespread use where it is desired to adopt a more clinically appropriate way of testing all classes of orally inhaled product

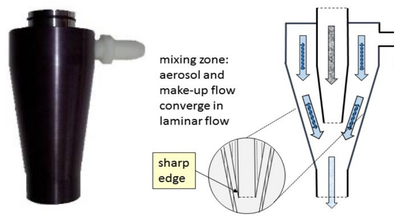

Figure 1 "Miller" Mixing Inlet

STUDY PURPOSE

- Systematic studies have not been undertaken to quantify potential internal losses of medication-containing particles during passage through the mixing inlet
- A cross-industry study undertaken by member companies of the European Pharmaceutical Aerosol Group (EPAG] has been undertaken to investigate mixing inlet losses with representatives of each major class of orally inhaled product
- A further purpose was to examine possible effects of losses in the mixing inlet on the cascade impactor-measured APSDs
- The findings from the evaluations of pMDI and nebulizer products are reported as the first phase of this investigation.

MIXING INLET IN USE

- The mixing inlet is downstream of the inhaler mouthpiece and throat model
- It is subjected to a fixed flow of compressed air, counterbalanced by the flow through the impactor provided by the vacuum source
- This flow is often but not always combined with a varying flow of air supplied by a breathing simulator on the inlet side during each respiratory cycle
- The aerosol emitted from the inhaler-on-test experiences the desired inhalation-exhalation flow profile whilst the impactor downstream operates at constant flow rate

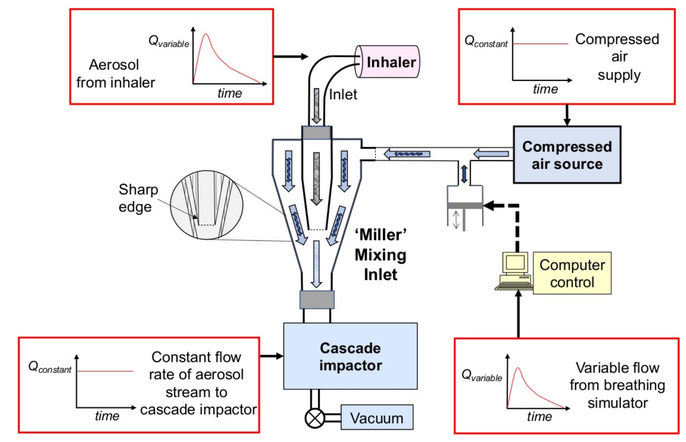

Figure 2: Mixing Inlet Used with Breathing Simulator
(The Mixing Inlet can also be used under constant flow conditions)

PART 1: NEBULIZER TESTING WITH BREATH SIMULATION

MATERIALS AND METHODS

- The breathing profile was realized at the nebulizer mouthpiece
- A breathing simulator (ASL 5000, Ingmar Medical, Pittsburgh, PA, USA) provided the varying flow via the side-arm of the mixing inlet
- The droplet stream from the nebulizer loaded with 2.0 mL of solution containing salbutamol (5 mg/2.5 mL) was transported to the mixing inlet via a USP/PhEur Induction Port
- A fixed supplementary flow of compressed medical-grade air (Q_{inlet} = 30 L/min) was also introduced
- A constant flow rate (Q_{NGI}) of 30 L/min was withdrawn from the base of the mixing inlet to a Next Generation Impactor (NGI)

STANDARD ADULT TIDAL BREATHING PROFILE

- inspiratory/expiratory (*I/E*) ratio = 1:1
- tidal volume (V_t = 500 ml)
- respiration frequency (F_{tidal} = 15/min);
- peak inspiratory flow rate (*PIF*) = 24L/min

RESULTS

Mass deposition profiles for the three replicate measurements are presented in **Figure 3:**

- Total nebulizer-delivered mass of salbutamol (mean ± S.D.) = 624.3 ± 79.3 µg,
- 1.1 ± 0.2 µg and 0.4 ± 0.1 µg were recovered from the interior surfaces of the mixing inlet and the 'T'-piece and associated tubing.
- Total mass recovered from the NGI was 569.3 ± 82.2 µg

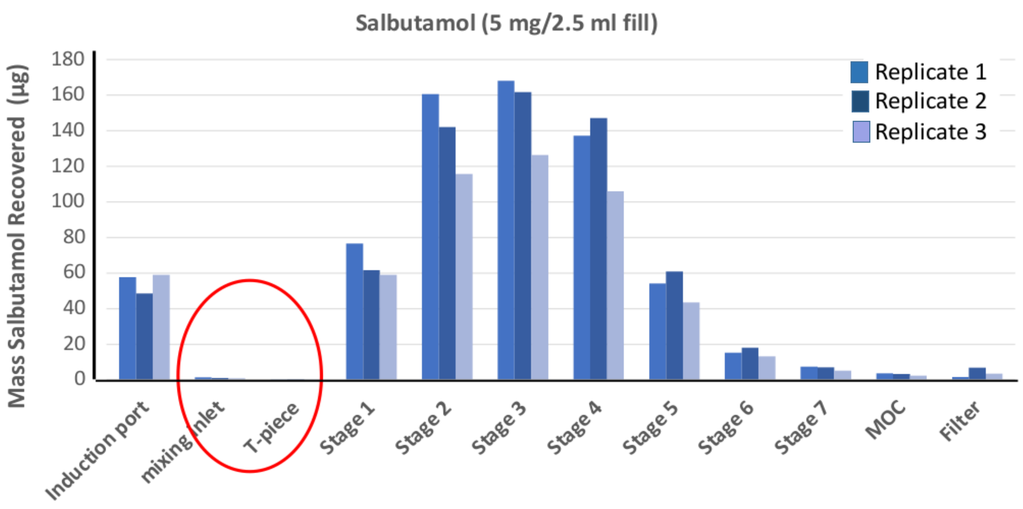

Figure 3: Mass Deposition Profile Through Sampling System

Average losses in the mixing inlet and associated connections represented 0.26% of the mass recovered from the impactor.

PART 2: PRESSURIZED METERED DOSE INHALER (pMDI) TESTING WITH SUPPLEMENTAL CONSTANT FLOW

MATERIALS AND METHODS

- The aerosol ex mouthpiece of the pMDI-on-test (beclomethasone dipropionate (BDP) 80 µg/actuation ex mouthpiece) was sampled by NGI with external filter directly at 30 L/min following the procedure in the pharmacopeial compendia
- The mixing inlet setup was inserted at the other sampling conditions and fixed additional flows of 10, 30 or 60 L/min were introduced (Q_{inlet}) for measurements made with Q_{NGI} at 40, 60 and 90 L/min respectively
- All flow rates were kept constant during medication delivery from the nebulizer

RESULTS

The deposition profile is presented in **Figure 4:**

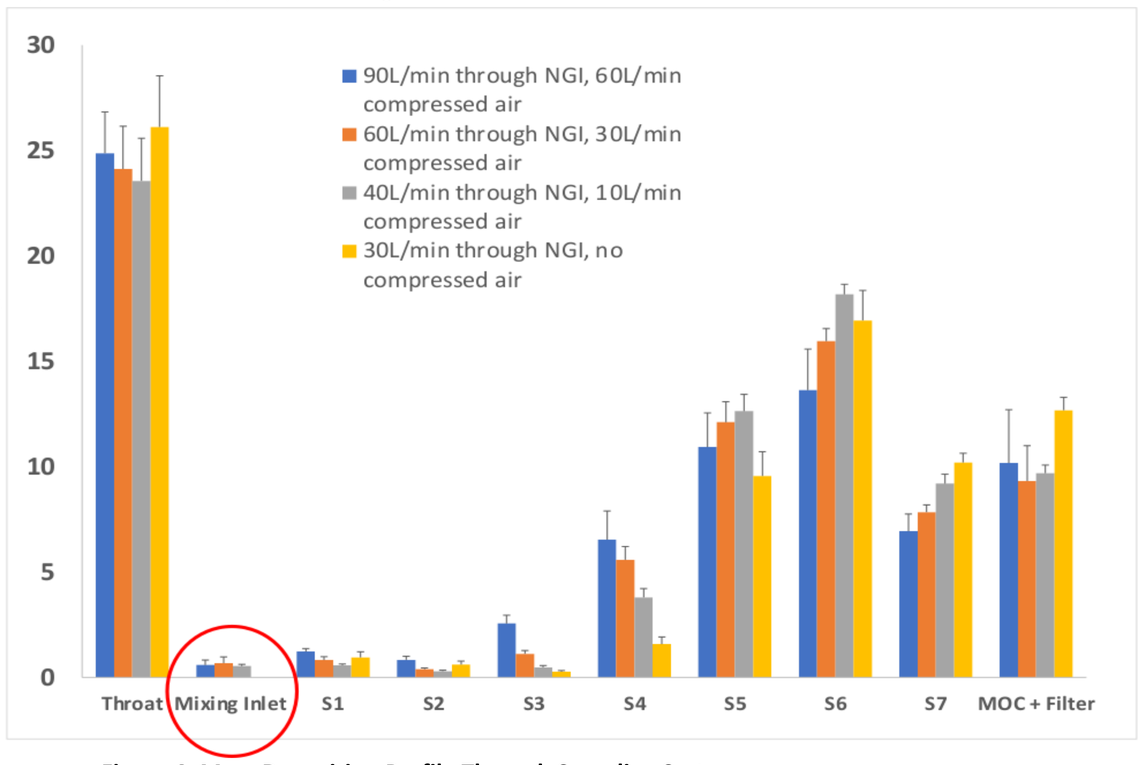

Figure 4: Mass Deposition Profile Through Sampling System
N.B. the stage cut point sizes (not shown) varied with the flow rate through the impactor

- Total mass of BDP recovered from each test (mean ± SD) = 98.2 ± 2.4% of label claim ex actuator
- Total mass recovered from the NGI components was 78.1 ± 2.0 µg BDP/actuation
- The mean mass recovered from the mixing inlet interior surfaces was 0.6 ± 0.2 µg BDP/actuation for measurements (Q_{NGI}) at 40, 60 and 90 L/min.
- The choice of sampling flow rate through the mixing inlet had an insignificant influence on these internal losses (1-way ANOVA, p = 0.62) that represented on average 0.8% of the total mass balance

1. **Average losses in their mixing inlet and associated connections represented <1% of the mass recovered from the impactor**

2. **Increasing the flow rate resulted in an expected shift in deposition profile to finer sizes but losses in the Mixing Inlet remained at a constant small mass fraction of the sampled total mass BDP ex inhaler**

DISCUSSION

- Both studies have shown that internal losses within the 'Miller' mixing inlet are less than 1% of the total mass of medication sampled downstream by an NGI, and as such, make < 20% addition to the overall losses that are required to be <5% of the mass balance in the methods for oral inhaler APSD determination
- The configuration used for the nebulizer evaluation was the more conventional arrangement where the nebulizer is subjected to a breathing profile whilst the impactor samples at constant flow rate
- In the nebulizer study, the broad range of ambient RH (45 to 75%) may have influenced APSD measurements due to differences in droplet evaporation kinetics; however, as the purpose was to define internal losses, the width of the RH window within which the measurements were performed may have been advantageous in terms of method robustness
- Importantly, the configuration used to evaluate mixing inlet losses when testing a pMDI enabled an explicit evaluation of the influence of total flow rate through the mixing inlet while keeping the flow through the inhaler constant (30 L/min) showing that the internal losses did not change significantly within the range explored (40 to 90 L/min)
- This DDL 2022 abstract is the forerunner of a much larger cross-industry assessment that will include dry powder inhaler assessments

CONCLUSION

The two studies reported have demonstrated that internal losses within the 'Miller' mixing inlet are <1% of the emitted mass from a representative nebulizer and a pMDI product

ACKNOWLEDGEMENT

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