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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Summary

The 'Miller' design of mixing inlet enables a cascade impactor to operate at constant flow rate whilst the inhaler-on-test can be evaluated at varying flow rates. Two studies forming part of a cross-industry assessment of mixing inlet internal losses are reported, the first evaluating continuous medication delivery of salbutamol via a nebulizer, the other examining bolus delivery of pMDI-actuated beclomethasone dipropionate (BDP). The nebulizer was subjected to a standard adult breathing profile (inspiratory/expiratory ratio = 1:1; tidal volume = 500 ml; respiration frequency = 15/min; peak inspiratory flow rate = 24 L/min). The pMDI was sampled at 30 L/min without mixing inlet and then at 40, 60 and 90 L/min with 10, 30 and 60 L/min compressed air added to the side-arm of the mixing inlet. In the nebulizer study, total mass recovered from a Next Generation Impactor (NGI) was 569.3 ± 82.2 µg. Average losses in the mixing inlet therefore represented 0.26% of the mass recovered from the impactor. In the pMDI study, total mass recovered from the NGI components was 78.1 ± 2.0 µg BDP/actuation, and the mass recovered from the mixing inlet interior surfaces was 0.6 ± 0.2 µg BDP/actuation for measurements at 40, 60 and 90 L/min. Internal losses within the 'Miller' mixing inlet are <1% of the total mass of medication sampled by the impactor, and, from the pMDI study, these losses did not change significantly when the flow rate was increased through the mixing inlet to the impactor from 40 to 90 L/min.

Key Message

The 'Miller' mixing inlet enables a cascade impactor to operate at constant flow rate for emitted aerosol aerodynamic particle size distribution (APSD) determination whilst an inhaler-on-test can be evaluated mimicking patient breathing. Our cross-industry study evaluated internal losses within such mixing inlets, testing a representative nebulizer and a pMDI product.

Introduction

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 inhaler, simulate a controlled inhalation flow rate-rise time profile [1]. The 'Miller' patented design of mixing inlet [2,3] (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 [4]. Its value became evident when Olsson *et al*. [5] were able to demonstrate good *in vitro-in vivo* correlations for budesonide aerosols delivered by pMDI, nebulizer and dry powder inhaler, mimicking adult use. The mixing inlet is located downstream of the inhaler mouthpiece and therefore subjected to a fixed flow of compressed air often but not always combined with a varying flow of air supplied by the breathing simulator on the inlet side during each respiratory cycle [4,5]. This process ensures that the aerosol emitted from the inhaler-on-test experiences the desired inhalation-exhalation flow profile whilst the impactor downstream can operate at constant flow rate. To date, no systematic studies have been undertaken to quantify potential internal losses of medication-containing particles during passage through this device. The 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. The findings from the evaluations of pMDI and nebulizer products are reported as the first phase of this investigation.

Materials and Methods

(a): Nebulizer Testing

Participant C investigated internal losses in a mixing inlet (Copley Scientific Ltd., Nottingham, UK) using an eFlow® vibrating membrane nebulizer (PARI, Starnberg, Germany) delivering a salbutamol solution (5 mg/2.5 ml fill) as the test device (Figure 1).

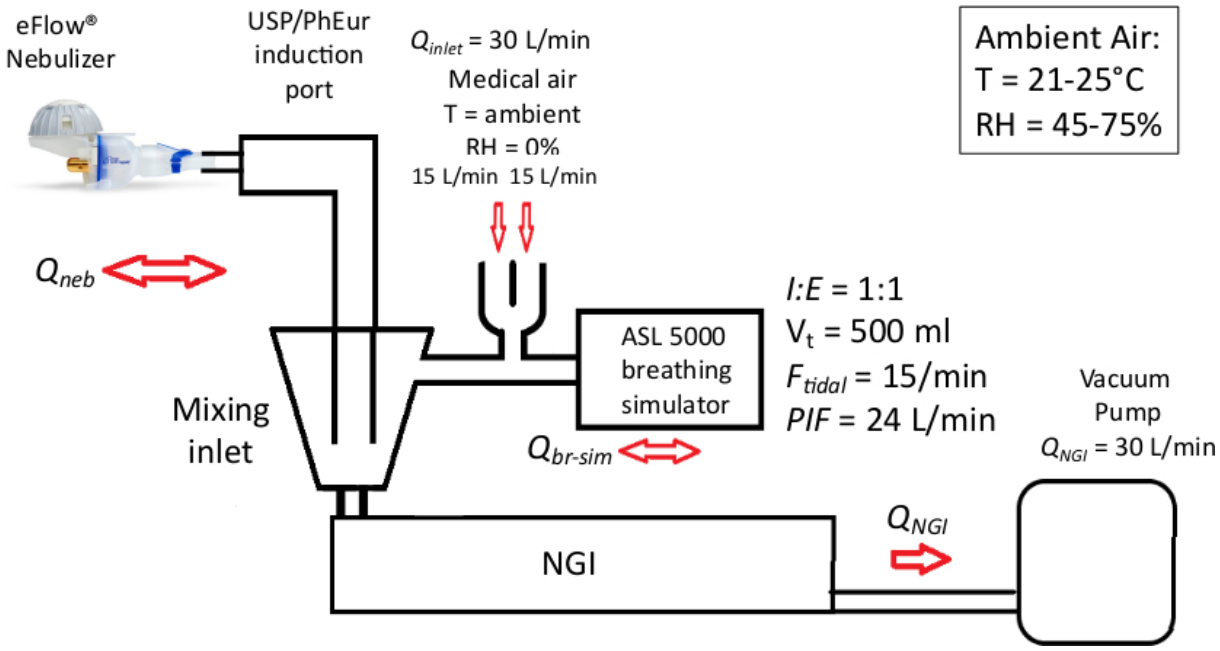

Figure 1: Test Arrangement Used by Participant C to Study Internal Losses in a Mixing Inlet

A standardized 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 (*PI*F) = 24 L/min) was realized at the nebulizer mouthpiece using a breathing simulator (ASL 5000, Ingmar Medical, Pittsburgh, PA, USA). The droplet stream from the nebulizer was transported to the mixing inlet via a USP/PhEur Induction Port and a fixed supplementary flow of medical-grade air (Q_{inlet} = 30 L/min) was introduced into the flow entering the 'T'-piece of the inlet from the breathing simulator via two parallel ports that merged via a 'U'-piece just before entry to the 'T'-piece, each supplying 15 L/min. 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).

Results:

Mass deposition profiles for the three replicate measurements are presented in Figure 2. The total mass

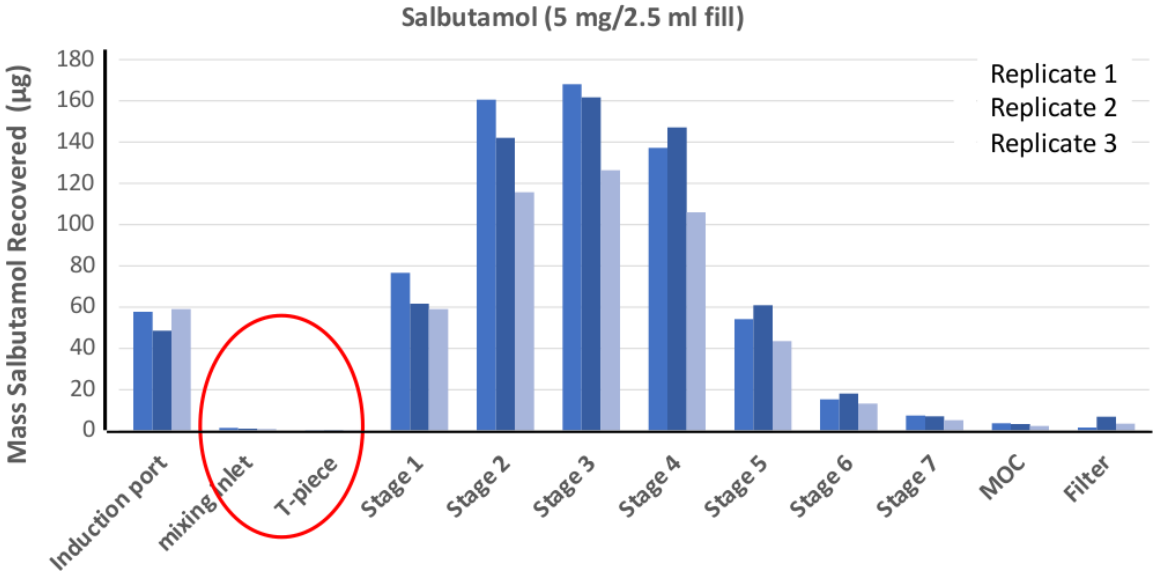

Figure 2: Mass Deposition Profile for eFlow®-Nebulizer Simulating Adult Tidal Breathing at the Mouthpiece; Salbutamol Recovered from the Induction Port and Components of the NGI Operated at 30 L/min and Including Recovery from the T'-piece Entry for Side Arm Air and Mixing Inlet Interior Surfaces

of salbutamol (mean ± S.D.) delivered from the nebulizer (n = 3 replicates) was 624.3 ± 79.3 µg, of which 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. The total mass recovered from the NGI was 569.3 ± 82.2 µg, so that the average losses in their mixing inlet and associated connections therefore represented 0.26% of the mass recovered from the impactor.

(b) pMDI Testing

Materials and Methods

Participant A evaluated the delivery of pMDI-delivered solution-formulated BDP (Qvar® 80 µg/actuation ex actuator), sampling at a fixed flow rate (Q_{mdi}) of 30 L/min at the mouthpiece throughout the study as its purpose was to explore how losses in their mixing inlet might vary with increased sampling flow rate to the impactor (Q_{NGI}). The test arrangement is shown in Figure 3 and this participant used a Mark-II mixing inlet (Copley Scientific Ltd.). The aerosol ex mouthpiece of the pMDI-on-test was sampled by NGI with external filter directly at 30 L/min following the procedure in the pharmacopeial compendium[1]. 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.

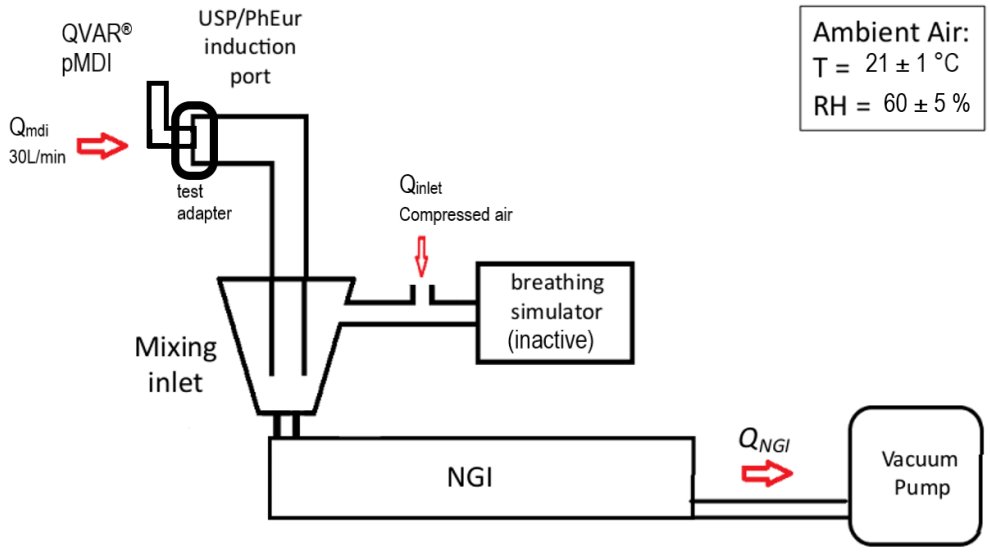

Figure 3: Test Arrangement Used by Participant C to Study Internal Losses in a Mixing Inlet

Results

Mass deposition profiles for the five replicate measurements at each condition are presented in Figure 4. The total mass of BDP recovered from each test (mean ± SD) was 98.2 ± 2.4% of label claim ex actuator, equivalent to an average of 78.6 µg BDP/actuation. The total mass recovered from the NGI components was 78.1 ± 2.0 µg BDP/actuation, and the mass recovered from the mixing inlet interior surfaces was 0.6 ± 0.2 µg BDP/actuation for measurements 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.

Discussion

Both studies have shown that internal losses within the 'Miller' design of 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 [1]. The configuration used for the nebulizer evaluation was the more conventional arrangement as described by Olsson *et al*. [5], where the inhaler is subjected to a breathing profile whilst the impactor samples at constant flow rate. 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 be advantageous in terms of method robustness. However, pMDI configuration enabled a more explicit evaluation of the influence of total flow rate through their mixing inlet, showing that, with the range explored (from 40 to 90 L/min), the internal losses did not change significantly.

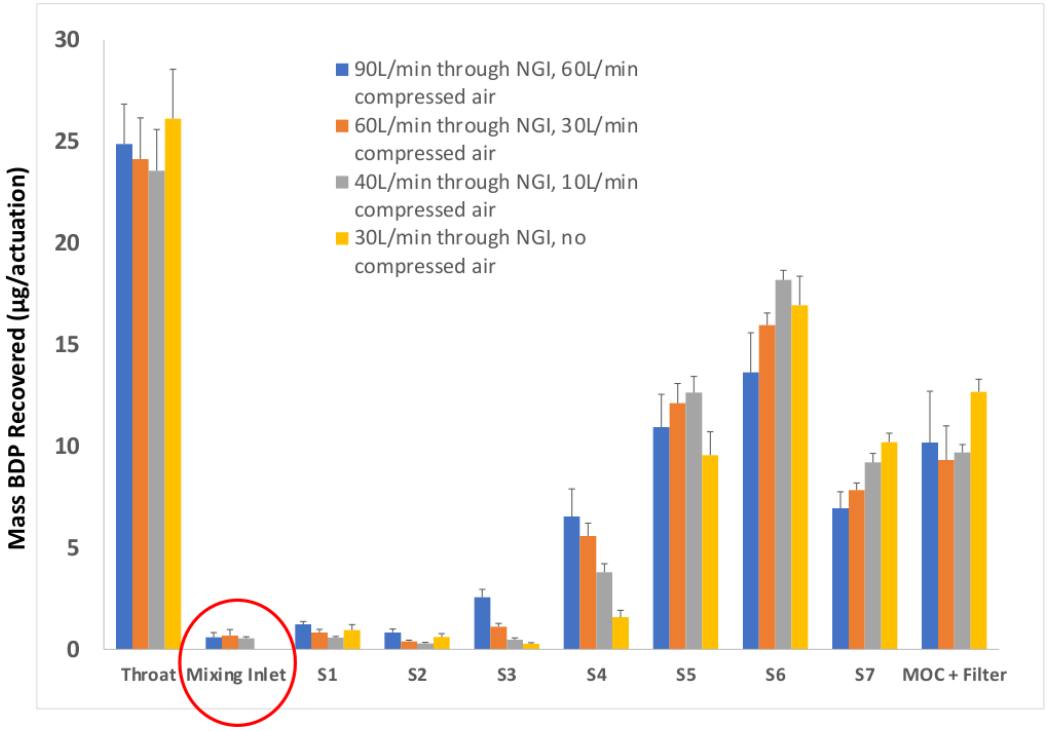

Figure 4: Mass Deposition Profiles for pMDI delivered BDP (100 µg/actuation ex valve) at 30 L/min ex mouthpiece via a Mixing Inlet to an NGI Sampling at 30, 40, 60 and 90 L/min with Added Compressed Air of 0, 10, 30 and 60 L/min Respectively to Side Arm of Mixing Inlet

This abstract is the forerunner of a much larger cross-industry assessment that will include dry powder inhaler assessments, thereby extending the work to include representatives of the major orally inhaled product classes.

Conclusions

The two studies reported have demonstrated that internal losses within 'Miller'-type mixing inlets are <1% of the mass balance emitted from representative nebulizer and pMDI products.

Acknowledgements

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