Assessment of Abbreviated Impactor Measurement (AIM) Methods for Nebulizer Characterization

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SUMMARY

Background: There is a need to expand the AIM Concept to the evaluation of wet aerosol generators such as nebulizers. **Methods:** Aerosols formed from aqueous droplets containing salbutamol from a vibrating membrane electronic nebuliser (investigational eFlow®), have been evaluated, comparing the performance of the fast screening impactor (FSI) used both cooled and at ambient conditions with that of a cooled full-resolution Next Generation Pharmacopeial Impactor (NGI). Laser diffractometer (LD)-based measurements were also made. **Results:** Substantially equivalent values of the respirable fraction (RF, volume %<5 µm) were obtained by LD, cooled NGI (controls) and the FSI operated both cooled and at room ambient temperature [83 ± 2%, 78 ± 5%, 73 ± 5% and 77 ± 5%, respectively]. The effect of making measurements under cooled or room ambient conditions was sufficiently small to be ignored with the FSI. As expected, the LD provided data almost instantaneously, but this method is non-specific for active pharmaceutical ingredient, hence the requirement for cascade impaction based measurements for this class of inhaler. The main time saving with the FSI was associated with the reduced number of samples that are generated for API assay by this procedure, allowing sample analysis time to be reduced to almost a third of that needed for NGI determinations. Additionally, data processing time was halved and experimental time was reduced from 8 hours to either 7 or 5 hours, depending on whether or not cooling of the FSI took place. **Conclusion:** The FSI when used as described in this presentation has the potential to provide accurate estimates of fine droplet fraction from nebulisers.

INTRODUCTION

The evaluation of droplet aerodynamic particle size distributions (APSDs) from the various types of nebulising system is an important requirement in assessment of performance. As a result standards have been developed defining methodology based on the multi-stage cascade impactor (CI), because droplet size is directly traceable to mass of active pharmaceutical ingredient (API) (1, 2). A European Pharmacopeia monograph is also in development that will mandate the use of the multi-stage CI (3). A key aspect in all these standards is the maintenance of a common constant flow rate of 15 L/min from the nebulizer, whether sampled directly (3) or indirectly (1, 2) by the CI. The AIM concept to date has been applied almost entirely to the evaluation of pressurised metered dose inhalers, where findings have been promising (4). However, it is already known from one series of experiments that care is required in the design of abbreviated CIs when low volatile species are present (in this case, ethanol (5)), so that the evaluation of such systems with aqueous formulations associated with nebulizers presents a challenge to avoid introducing bias associated with improper aerosol handling by the measurement equipment. The present study is an evaluation of an abbreviated NGI concept, in which a vibrating membrane nebulizer was used as the aerosol generation source. These devices are capable of producing very high droplet concentrations (6), therefore providing a significant challenge for the measurement equipment in the context of the avoidance of bias caused by either evaporative of condensation effects during transport from the nebulizer to the measurement equipment.

MATERIALS AND METHODS

The aerosol investigated in this proof-of-concept study was generated using an aqueous solution formulation (500 µg/ml salbutamol (albuterol)) as a representative API, nebulised by the investigational eFlow® electronic nebuliser (PARI GmbH, Starnberg, Germany), customized to generate an aerosol with a mass median aerodynamic diameter (MMAD) close to 3 µm (Figure 1).

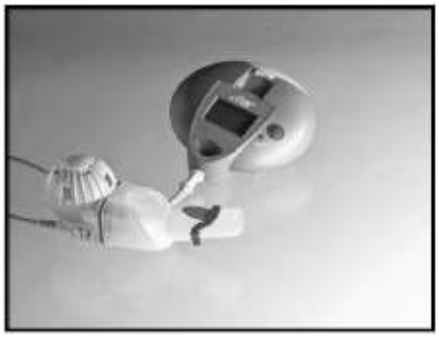

Figure 1: eFlow® vibrating membrane electronic nebuliser

In the first part of the study, full resolution NGI analysis was conducted to provide benchmark data, using a flow rate of 15 L/min, which corresponds to a tidally breathing adult patient (1). The effective cut-off diameters (ECDs) based on the archival calibration at this flow rate (7) were used. Droplet size distribution measurements were also conducted in parallel by laser diffractometry (LD) using a MasterSizer-X system (Malvern Instruments, Malvern, UK). Environmental conditions were tightly controlled within 23 ± 2°C and 50 ± 5 % RH. As impactor sizing of liquid aerosols can be subject to droplet evaporation during the sizing process (8, 9), the NGI was cooled to 18 ± 0.5°C in order to conduct the sizing process at thermal equilibrium with the aerosol generated by the nebulizer used in this study.

In the second part of the investigation, a FSI (model 185, MSP Corp., St. Paul, MN, USA), based on the design of the NGI pre-separator, but with the effective cut-off diameter (ECD) for the fine/coarse mass fractions at 5.0 µm aerodynamic diameter (10), was modified to operate at the required 15 L/min rather than the design flow rate of 30 L/min, by plugging alternate impactor nozzles (3 of 6) in the insert plate. This arrangement allowed the flow rate through the apparatus to be halved while retaining the same ECDs as if it had been used at 30 L/min where calibration data are available, thereby avoiding the potential to introduce bias by extrapolating cut-point sizes. Two series of experiments were performed with the FSI, one with and one without cooling this impactor, in order to assess the impact of conducting the measurements at ambient conditions, and to investigate if droplet evaporation occurs to such an extent that it may have biased the results. All tests were conducted using three nebulisers each tested in duplicate (n = 6 for each test). Samples were analysed for albuterol content by reversed phase HPLC-UV spectrophotometry (Waters Alliance).

In order to enable direct comparison of the aerodynamic size distribution patterns obtained from laser diffractometry and cascade impaction, analysis of the mass frequency was conducted as proposed by Dunbar and Mitchell (11). In brief, the mass frequency as a function of the aerodynamic diameter is calculated from the drug mass deposited on the different impactor stages according to the following expression:

$$Mass\ Frequency\ (d_{a,i}) = \left[\frac{m_i}{M_E}\right] * \left[\frac{1}{\Delta ECD_i}\right]$$

Where m_i is the mass on stage i, M_E is the total emitted mass, ΔECD_i is the difference between the ECD of the preceding stage *i-1* and stage *i* (i.e. the stage size width) and $d_{a,i}$ is the aerodynamic diameter associated with stage *i* (calculated as the arithmetic mean of the upper and lower boundary size for that stage).

RESULTS

Using the concept of differential mass frequency, the APSD measured by LD and NGI can be compared directly. Figure 2a shows the “bell shaped” mass frequency curve and Figure 2b shows the corresponding “S shaped” cumulative mass fraction curve for the same data obtained by LD. The NGI data (also shown) are substantially equivalent to the results obtained using LD.

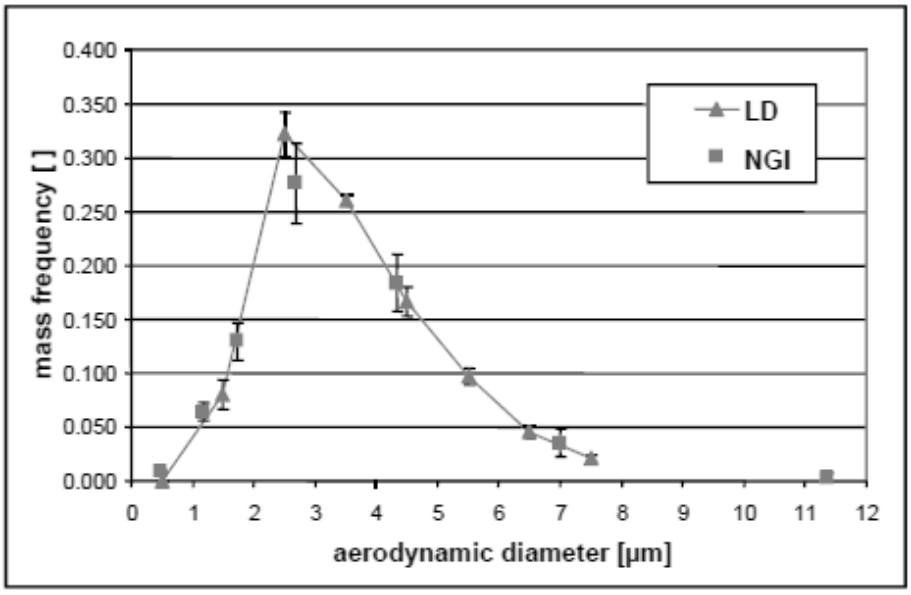

Fig.2a: Mass frequency plot comparing results from cascade impaction and laser diffractometry (n=6).

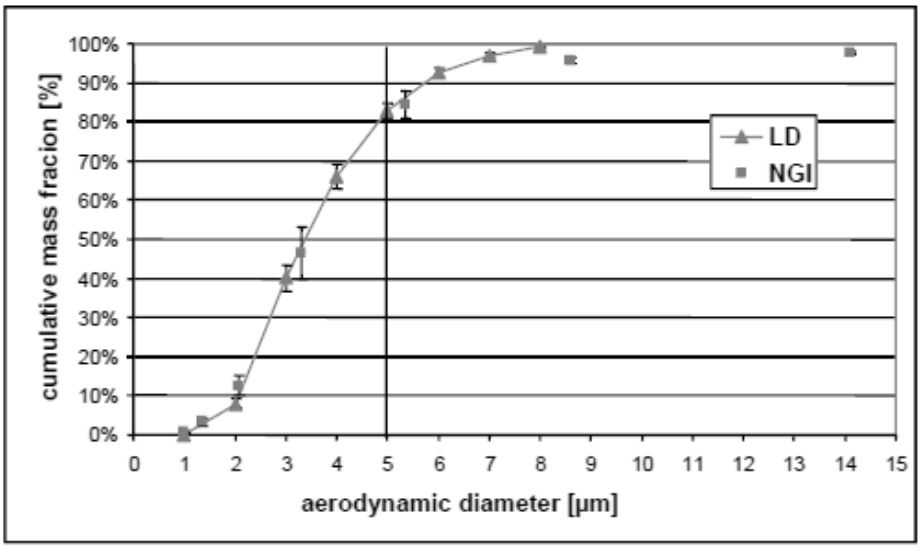

Fig. 2b: Cumulative mass fraction comparing results from cascade impaction and laser diffractometry (n=6). The vertical line at 5 µm indicates the droplet size below which droplets are typically considered to be respirable.

Substantially equivalent values of the respirable fraction (RF, volume % <5µm) were obtained by LD, cooled NGI (controls) and the FSI operated both cooled and at room ambient temperature (Figure 3). There appears to be a slight trend towards reduced RF for the FSI when cooled, however, the difference in the mean result is in the order of a standard deviation and is not likely to be of practical relevance. In the case of the FSI with the eFlow® electronic nebuliser, the effect of conducting the test under cooled or room ambient conditions was sufficiently small to be ignored in practice.

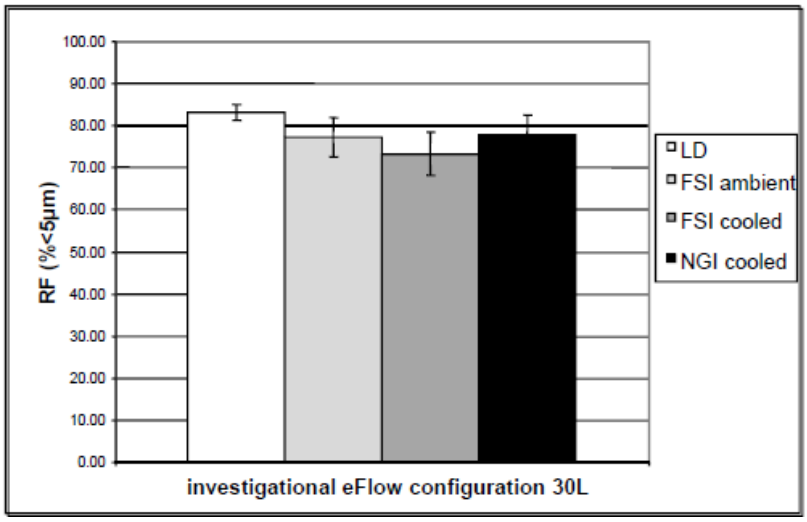

Fig. 3: Respirable Fraction [% <5µm] measured by LD, NGI and FSI at ambient and cooled conditions (n=6, error bars = 1 SD).

One of the important aspects of the AIM concept is the ability to reduce the time per measurement so that either measurement productivity in the test laboratory is increased, or in the case of oral inhaled product testing, more units in a batch can be evaluated (greater coverage), leading to better decision making concerning batch disposition (11). Part of the present study therefore involved an assessment of the required time to perform 6 replicate analyses using the respective methods. This analysis included comparing the times for the performance of the aerosolization experiment, the analysis of the samples and the data processing, with the outcomes as shown in Table 1. It should be noted that no sample analysis time is required for the LD method, as this test involves purely presenting the droplet stream to the light path between laser source and concentric ring-diode detector array (12). Thus, droplet size distribution data are available within milliseconds once the aerosol has been interrogated by this technique.

In the comparison of the efficiency of the different test methods, it should be considered that 'Experimental' and 'Data Processing' are so-called "hands-on" time, which requires an operator to be fully attentive to the process for the whole duration. In contrast, 'Sample Analysis' in this case mainly represents non-operator involved "machine time", where the samples are processed by a largely automated HPLC system. It can therefore be seen that the LD method is by far the most time efficient procedure, requiring less than a tenth of total analysis time compared to a full resolution NGI test and a quarter of the hands on time (2.5 h versus 10 h for experimental plus data processing time).

	Experimental	Sample Analysis	Data Processing	Total
6 x LD	1.5 h	negligible	1 h	2.5 h
6 x FSI cooled	7 h	6.5 h	1 h	14.5 h
6 x FSI ambient	5 h	6.5 h	1 h	12.5 h
6 x full resolution NGI	8 h	18 h	2 h	28 h

Table 1: Approximate time (h) required for the different stages of the determination of RF

The main time saving with the FSI was associated with the reduced number of samples that are generated for API assay by this procedure, allowing the sample analysis time to be reduced to almost a third of that needed for a full resolution NGI determination. Although these savings are only associated with "machine" time, they can make a significant difference when it comes to the question of whether the results from an experiment are available on the next day or whether an additional day has to pass until the outcome of a change to a device or a formulation can be fully assessed. Additionally, data processing time was halved by comparison with the NGI and Experimental time was reduced from 8 for full resolution NGI assessment to either 7 or 5 hours, depending on whether cooling of the FSI is deemed to be necessary or not.

CONCLUSIONS

There was good agreement between a full resolution NGI, LD and a FSI abbreviated impactor with respect to the measurement of respirable fraction of droplets generated from a vibrating membrane nebulizer. Operating the current model of the FSI at 15 L/min can be accomplished by blocking off 3 of the 6 nozzles. The difference in result obtained cooled or at ambient conditions was small for the nebulizer and formulation investigated here but the need for cooling should be assessed on a case by case basis. LD was the most efficient test method followed by the FSI. For the FSI the main time saving lies in the reduced number of samples which are generated, thus leading to a significant reduction of HPLC analysis time and data processing time.

REFERENCES

1. Comité Européen de Normalisation. Respiratory therapy equipment — Part 1: Nebulizing systems and their components, EN 13544-1: 2001, Brussels, Belgium.
2. International Standards Organization. Anaesthetic and respiratory equipment — Nebulizing systems and components ISO 27427:2009, Geneva, Switzerland.
3. European Directorate for Quality in Medicines and Health Care (EDQM). Preparations for nebulisation: Characterisation, general chapter 2.9.44. Pharmeuropa 2006;18(2):280-2.
4. Copley, M. *et al.* Implementing the AIM Concept: Streamlining the Testing of Inhaled Drug Products by Using an Abbreviated Impactor Measurement Method. *Inhalation*, 2010;4(1):7-11.
5. Mitchell, J.P. *et al*. The abbreviated impactor measurement (AIM) concept: Part 2 – Influence of evaporation of a volatile component – evaluation with a "droplet producing" pressurized metered dose inhaler (pMDI)-based formulation containing ethanol as co-solvent, *AAPS PharmSciTechnol*, 2009;10(1):252-57.
6. Knoch, M. and Keller, M. The customised electronic nebuliser: A new category of liquid aerosol delivery systems. *Expert Opin. Drug Deliv. Syst*. 2005;2(2):377-390. Marple, V.A. *et al*. Next Generation Pharmaceutical Impactor : A New Impactor for Pharmaceutical Inhaler Testing. Part III. Extension of Archival Calibration to 15 L/min, Journal of Aerosol Medicine, 17, 4, 2004, p. 335-343.
7. Finlay, W.H. *et al.*, Undersizing of droplets from a vented nebulizer caused by aerosol heating during transit through an Anderson impactor, *J. Aerosol Sci.*, 1999;30(1):105-109.
8. Jauernig, J. *et al*., Validation of a test set-up utilizing the 28.3 l/min Andersen Cascade Impactor (ACI) for the aerodynamic assessment of nebulized aqueous formulations, RDD VIII, Tuscon, USA, 2002, Proceedings vol. 2, p. 537-539.
9. Stobbs, B. *et al.* Evaluation of the Fast Screening Impactor for determination of fine particle dose in dry powder inhalers, Drug Delivery to the Lungs-20, The Aerosol Society, Edinburgh, UK, 2009: 158
10. C. Dunbar and J. Mitchell, The interpretation of data from cascade impactors, *Drug Delivery to the Lungs-15*, The Aerosol Society, London UK, 2004:75-78.
11. Tougas, T.P. *et al.* Improved quality control metrics for cascade impaction measurements of orally inhaled drug products (OIPs), AAPS PharmSci Technol., 2009; 10(4):1276 – 1285.
12. Mitchell, J.P. *et al.* Laser diffractometry as a technique for the rapid assessment of aerosol particle size from inhalers. J. Aerosol Med., 2006;19(4):409-433.