COMPARISON OF NEXT GENERATION IMPACTOR AND FAST-SCREENING IMPACTOR FOR DETERMINING FINE PARTICLE FRACTION OF DRY POWDER INHALERS

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INTRODUCTION

The US FDA, European and other regulatory agencies recommend the use of multi-stage cascade impactors (CIs) for determining the aerodynamic fine particle fraction (FPF≤5.0 μm) of orally inhaled drugs in regulatory submissions and for routine quality control of such commercial products. This is a labour intensive analytical method (1, 2) and provides detailed resolution of particle size which may not necessarily be needed for initial screening and development studies of inhaled products and devices (3). The present work was an investigation of the performance of a fast-screening impactor (FSI, Figure 1a), using a NGI (Figure 1b) to provide benchmark data. The FSI employs a single stage with an effective cut off diameter that collects all the fine particle fraction < 5.0 μm (FPF) in one stage (4). In addition, the incoming aerosol is fractionated into coarser particles depositing in the induction port (mouth/throat) and in the pre-separator. Adding up all these three mass components from the FSI provides the total emitted dose (ED). We present further evidence for the acceptability of the FSI as an abbreviated apparatus for gathering aerodynamic size-related measurements of dry powder inhalers (DPI) and provides detailed resolution of particle size which may not necessarily be needed for initial screening and development studies of such commercial products. This is a labour intensive analytical method (1, 2) and provides detailed resolution of particle size which may not necessarily be needed for initial screening and development studies of inhaled products and devices (3).

MATERIALS AND METHODS

Measurements of fine particle dose (FPD≤5.0 μm) and FPF≤5.0 μm were carried out with five measurements by NGI (3 consecutive doses), a similar number of measurements by FSI (3 consecutive doses) and five measurements by FSI with a single dose. Testing was performed at a flow rate of 35 L/min equivalent to approximately 4 kPa and an inhalation volume of 2 L, by one analyst evaluating several devices issued from the same batch.

Effect of coating the collection surface of the insert in the FSI below the impaction stage

To overcome the differences in FPD between the systems, it was decided to use a 1% v/v solution of glycerol in ethanol. The use of coating had an insignificant effect on FPF from single dose measurements (Figure 3).

Comparison of emitted dose data from the FSI versus a dose unit sampling apparatus (DUSA)

A DUSA (Copley Scientific Ltd, Nottingham, UK) sampling at 35 L/min equivalent to ca. 4 kPa pressure differential and inhalation volume of 2 L, was used to compare with single dose FSI measurements for the same DPI. Figure 4:

ANALYSIS AND RESULTS

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3. Interstage drug loss (wall losses, μg): The filter holder support was rinsed and collected drug assayed by HPLC after each of three replicate measurements by FSI with a single dose. Similarly, the complete NGI support was rinsed and drug product collected assayed as above after each of five replicates with NGI.

Both measurement systems provided equivalent and acceptable sealing integrity. However, air resistance through the NGI system was slightly higher as might be expected given the presence of individual stages with higher pressure drop associated with them than the single stage of the FSI. Inter-stage drug loss was slightly lower with FSI where only one dose was delivered, although both impactors were within the USP/Ph.Eur. acceptance criterion that inter-stage drug losses should be ≤5% of the total delivered drug mass into the impactor.

Estimating the time and cost advantages of FSI testing vs NGI testing

As the intention underlying the development of AIM-based equipment is to reduce unnecessary analytical input by eliminating the need for intermediate stage recovery, measurement time and solvent use were also considered during this overall study and compared with standard NGI testing (Table 4). Both FSI and NGI times are based on the equivalent of a single analyst operating a single measurement system (either abbreviated or full resolution). The use of the FSI allows a substantial reduction in the time per measurement as well as in the duration of drug assay-related activities. Furthermore, the consumption of solvents is greatly reduced, which is a positive aspect in terms of sustainable development and the “Green Chemistry” initiative.

CONCLUSION

Overall, the NGI and FSI gave substantially comparable results when tested with the particular DPI and powder formulation used for this comparative screening evaluation. Coating of collection surfaces within the FSI did not seem to influence the results significantly, and comparable results to those from DUSA testing were achieved by the FSI, when only a single dose was delivered. General performance characteristics were similar between the two impactors with the only difference being the slight lower air resistance of the FSI. Significant savings both in time and costs can be achieved with the FSI which could significantly accelerate development times for DPIs.

REFERENCES