Aptar pharma

PRESCRIPTION DIVISION

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

Fabienne Després-Gnis, Geralllt Williams

**Aptar Pharma**, route des Falaises, 27100 Le Vaudreuil, France

## 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 ($FPF_{\leq 5.0\mu m}$) 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 data for DPIs at the development stage, and which could lead to significant savings in both cost and time during development of OIPs.

## MATERIALS AND METHODS

Measurements of fine particle dose ($FPD_{\leq 5.0\mu m}$) and $FPF_{\leq 5.0\mu m}$ 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.

***Figure 1a:*** *FSI*

***Figure 1b:*** *NGI*

## ANALYSIS AND RESULTS

### Emitted Dose and Fine Particle Dose comparison between NGI and FSI

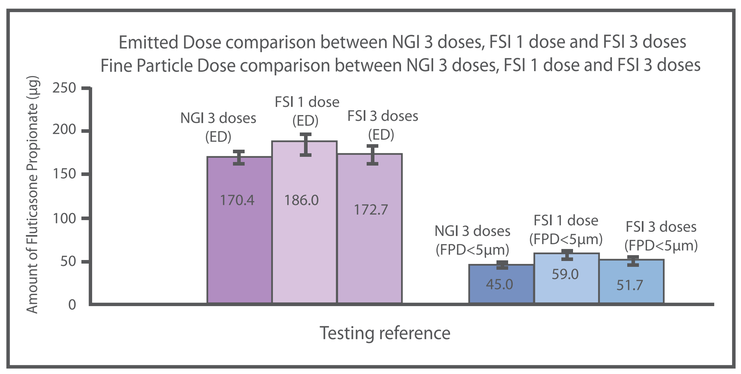


***Figure 2:*** Emitted Dose and Fine Particle Dose comparison between NGI and FSI
Error bars correspond to ±SD over the 5 data at each series of NGI and FSI

ED and FPD were each substantially comparable between NGI and FSI, both testing with 3 doses (Figure 2). However, the mean values of both metrics were slightly higher with both ED and FPD when testing with a single dose, so that a difference of approximately 10 µg existed between FSI – single dose and FSI - 3 consecutive doses. Measures of FPD and ED from the FSI – single dose tests were approximately 15 µg larger compared with equivalent data from the NGI with 3 consecutive doses.
In addition, it should however be noted that the method of calculation for FPD≤5.0 µm is different between CITDAS software (log-probit interpolation) for NGI and the single stage cut off calculation for FSI.

### 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 coat uniformly the pre-separator base with the solution usually used to coat the cups of the NGI, using a 1% v/v solution of glycerol in ethanol.

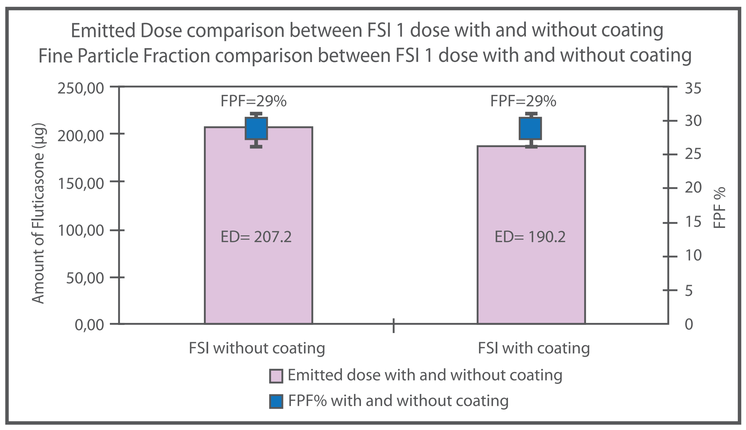


***Figure 3:*** Comparison of FSI with and without coating
Error bars correspond to ±SD over the 5 data at each series of FSI

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. 4kPa pressure differential and inhalation volume of 2 L was used to compare with single dose FSI measurements for the same DPI.

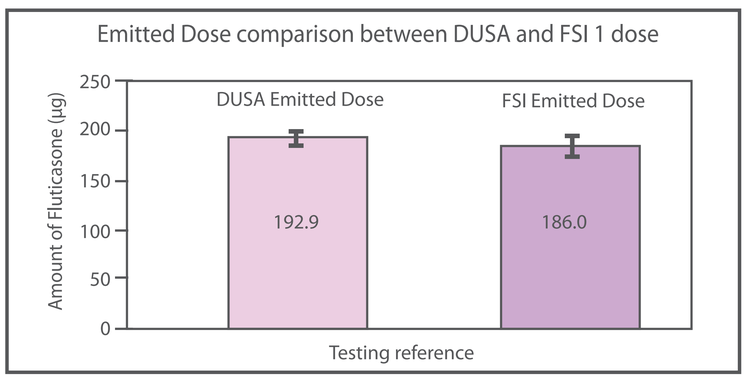


***Figure 4:*** Comparison of DUSA and FSI 1 single dose
Error bars correspond to ±SD over the 5 data at each series of DUSA and FSI

This time, values of ED by both systems were similar (Figure 4), indicating that the FSI equipment used in this way could potentially be applied to evaluate dosage uniformity when performing fast screening of a new product. Importantly, by delivering only one dose per test, more measurements in a given time are possible when performing through life studies.

### Effect of Comparison of testing parameters for the NGI and FSI

Additionnal parameters such as sealing integrity (Table 1), air flow resistance (Table 2) and inter-stage drug loss (Table 3) associated with the FSI were verified and compared with equivalent values from the NGI. The following observations are pertinent:

1. **Sealing integrity ($\Delta_{AP}$), (kPa):** Both FSI and NGI were evaluated with several mouthpiece adapters of the same design on the same equipment.

2. **Equipment air resistance (cm $_{H20}$ $^{1/2}$.lpm$^{-1}$):** Both measurement systems were tested at 35 lpm with the same mouthpiece adapter on the same equipment, and sealing integrity was checked prior to test.

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 the NGI.

| FSI (n=5) | | NGI (n=4) | |
|---|---|---|---|
| Mean | 0.34 | Mean | 0.41 |
| SD | 0.08 | SD | 0.03 |

***Table 1:*** Sealing integrity

| FSI (n=3 | | NGI (n=3) | |
|---|---|---|---|
| Mean | 0.12 | Mean | 0.19 |
| SD | 0.00 | SD | 0.00 |

***Table 2:*** Equipment air resistance

| FSI 1 dose (n=3) | | NGI 3 doses (n=5) | |
|---|---|---|---|
| Mean | 0.6 | Mean | 1.7 |
| SD | 0.33 | SD | 1.03 |

***Table 3:*** Interstage drug loss

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 well 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).

| | Test duration (min) | HPLC analysis duration (min) | Solvent quantity (ml) |
|---|---|---|---|
| NGI | 60 | 140 | 300 |
| FSI | 25 | 63 | 200 |
| Gain (%) | **58** | **55** | **33** |

***Table 4:*** Time-Savings

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 slightly 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

[1] United States Pharmacopeial Convention. Chapter 601. Aerosols, metered-dose inhalers, and dry powder inhalers. In: USP30-NF25. Rockville, MD: USP; 2007:220-240
[2] European Pharmacopeia. Section 2.9.18 – Preparations for inhalation:Aerodynamic assesment of fine particles, 5th Edition, Council of Europe, Strasbourg, 2005, pp 2799-2811
[3] Mitchell, J.P, Nagel, M.W, Avvakoumova, V. Mackay, H, Ali, R. The abbreviated impactor measurement (AIM) concept: Part 1 – Influence of particle bounce and re-entrainment-Evaluation with a “Dry” Pressurized metered dose inhaler (pMDI)-Based Formulation, AAPS PharmSciTech. Apr 2009, Vol. 10, No1:243-251
[4] Stobbs, B, McAulay, E, Bogard, H, Monsallier, E. Evaluation of the fast-screening impactor for determining fine particle fraction of Dry Powder Inhalers, DDL 20, 2009, pp 158-161