

Use of “Smartphone” Technology to Characterise and Aid Development of a Standardised Shake for the *In Vitro* Analysis of MDIs

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Introduction

Device handling factors such as analyst shake and force to fire inputs are often a key source of variability when performing *in vitro* analysis of MDIs for stability or batch release. In the context of a CRO, it is often not cost-effective to invest in expensive custom built automated technology and it is therefore necessary to rely on human operators to perform the analysis consistently.

Differences in shaking inputs between operators may result in different biases and seemingly random variability. It has been identified that one source of variability in CI measurements is MDI handling, including frequency and intensity of shaking.¹ Adopting a standardised approach to MDI shaking often helps to minimise this variability.

The aim of the study was to investigate whether the shake used during the *in vitro* NGI cascade impactor analysis of MDIs has an effect on critical data points, to characterise the shakes used using a smartphone accelerometer and to develop a standardised shake using the data produced.

Experimental Method

Salamol MDIs (100µg salbutamol sulphate, 200 actuations, IVAX Pharmaceuticals Ireland) were tested at beginning and end of life using the Next Generation Impactor (NGI, Copley Scientific). The operator was provided with brief outlines of 5 different shakes, chosen to represent a wide variety of handling styles. A total of 6 MDIs were tested using each shake; the same shake was used consistently throughout the life of each MDI including for manual waste firing. Following each NGI collection the shake was characterised using a 3 dimensional trace from an accelerometer app (Physics Toolbox Accelerometer, Vieyra Software) on an HTC Wildfire™ smartphone. Five different shaking methods were studied the details of which are summarised below.

- ▶ Shake 1: Can vertical, shake quickly using an up-and-down motion
- ▶ Shake 2: Can vertical, shake slowly using an up-and-down motion
- ▶ Shake 3: Can horizontal, shake from side to side
- ▶ Shake 4: Can vertical, shake in an arc pivoting from the elbow
- ▶ Shake 5: Can horizontal, shake in an arc pivoting from the wrist

The axes of the smartphone were determined and the operator was coached to match the shake of the smartphone as closely as possible to that of the MDI to ensure that the accelerometer traces were consistent (Figure 1).



Figure 1. Maintaining consistency between inhaler and smartphone use.

For each NGI run, total on impactor (TOI), fine particle dose (FPD) and throat dose was determined, and the change through life calculated for each MDI.

These results and the spread of data for each set of 6 MDIs were assessed and the most favourable shake determined. Characteristics of the shake were measured using the accelerometer data which were subsequently used to develop a standardised shake procedure.

Results

The NGI data for TOI, throat dose and FPD were assessed for each of shakes 1 to 5 (Figures 2 to 6).

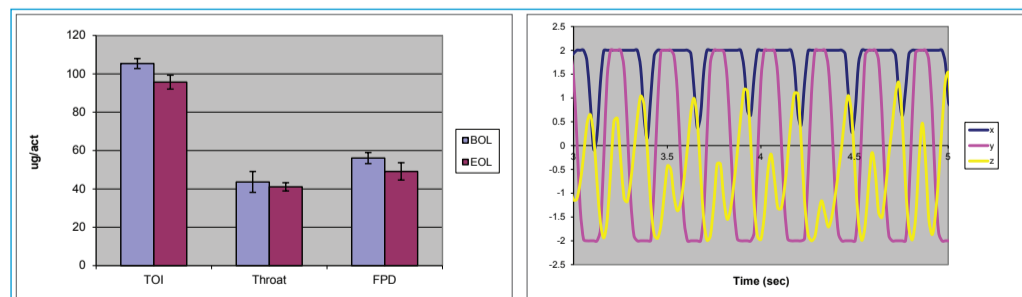


Figure 2. Shake 1 results and accelerometer trace.

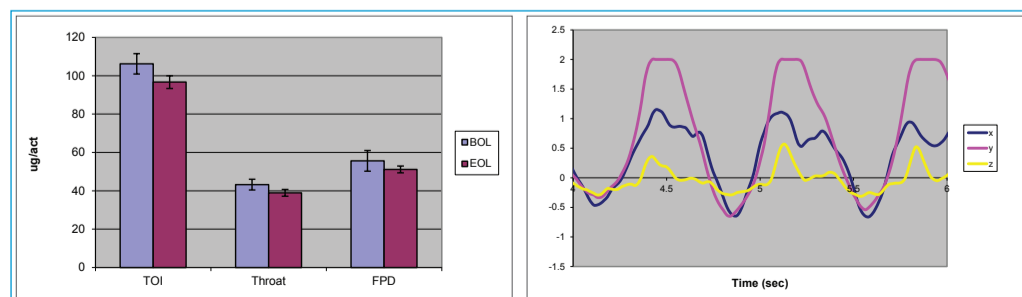


Figure 3. Shake 2 results and accelerometer trace.

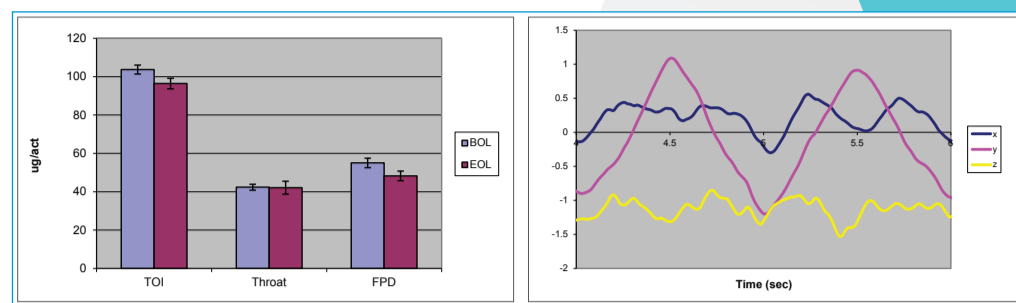


Figure 4. Shake 3 results and accelerometer trace.

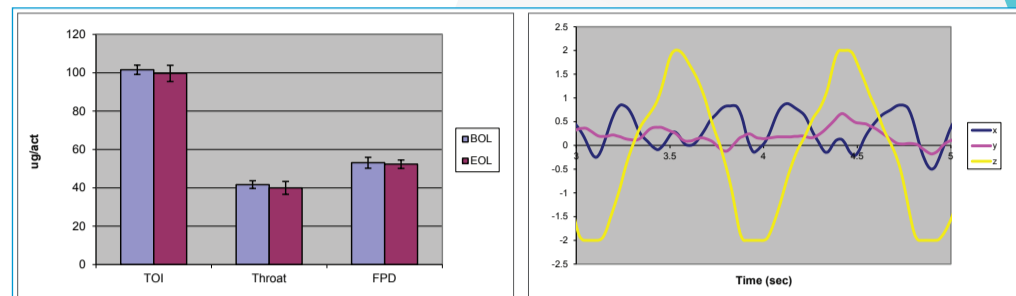


Figure 5. Shake 4 results and accelerometer trace.

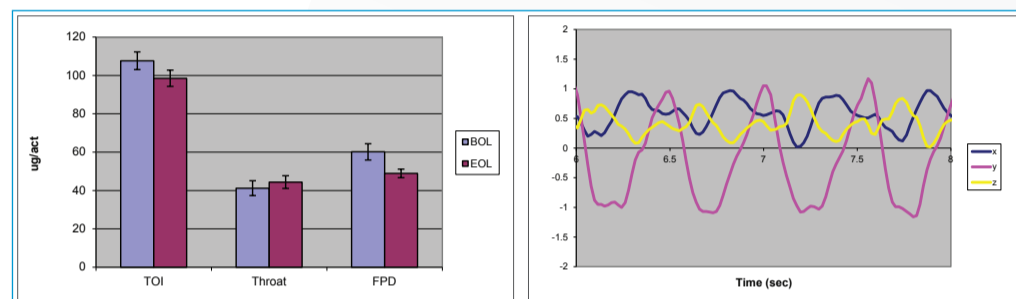


Figure 6. Shake 5 results and accelerometer trace.

Discussion

It was determined that in terms of the differences between results at the beginning and end of life of the MDIs and the spread of data, shake 4 gave the most consistent and desirable results. It is suggested that the reason this shake was so effective is that it provided excellent mixing whilst keeping the valve in constant contact with the suspension.

The average frequency and duration of the shake was determined from the accelerometer traces. Using this information in conjunction with the original instruction to the operator, the standardised shake was described as follows:

“Hold the inhaler as follows:



Keeping your elbow still and holding the canister so the mouthpiece is pointing away from you, shake the canister in an arc for 5 seconds at 1 cycle per second (i.e. using a windscreen wiper-like motion).”

Conclusions

The method described above demonstrates that using a smartphone pre-loaded with a suitable accelerometer “App” may provide a low-cost generic tool for characterising and controlling can shaking inputs – one aspect of inter-operative variability when performing through-valve analysis of MDIs. Providing written instructions for easy reference, along with video footage of an experienced analyst performing the procedure, could be an invaluable training aid. Incorrect performance of the shake could be diagnosed by comparing accelerometer traces collected by trainees with those of an ideal shake, allowing the shake to be corrected during training and method familiarisation exercises. This may increase the success rate when undertaking the transfer of methods between development laboratories and production sites and outsourcing partners.

Acknowledgements

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Reference

1. Bonam, M, Christopher, D, Cipolla, D, Donovan, B, Goodwin, D, Holmes, S et al. Minimizing variability of cascade impaction measurements in inhalers and nebulizers. AAPS PharmSciTech. 2008 June; 9(2): 404-413. doi: 10.1208/s12249-008-9045-9.