Use of "Smartphone" technology to characterise and aid development of a standardised shake for the *in vitro* analysis of MDIs

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Summary

The through-valve analysis of suspension based Metered Dose Inhalers (MDIs) is susceptible to differences between operators, resulting in biases and seemingly random variability, especially when undertaking though valve delivered dose testing and Aerodynamic Particle size Distribution (APSD) by Cascade Impaction (CI). Often, key sources of data variability are device handling factors such as the frequency and intensity of shaking applied to the can during analysis. The aim of this study was to assess whether accelerometer data captured from a standard domestic smartphone could be applied to develop a standardised shake for use by laboratory personnel in order to reduce this variability. This is desirable in order to increase confidence in results and to improve the likelihood of success when transferring methods between development laboratories and production sites and outsourcing partners. 5 different shakes were investigated and the total on impactor, throat dose and fine particle dose parameters were compared for differences through the life of the MDI and spread of results to determine the most favourable shake. A standardised shake was developed using characteristics of frequency and duration of shake determined from accelerometer data collected by a smartphone. This could be provided to trainees in the form of written instruction and/or video footage.

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.

Many commercially available MDIs are suspension formulations due to the problem of achieving drug solubility in the current range of commercially available hydrofluoroalkane (HFA) propellants. In a suspension MDI, the drug is relatively insoluble in the propellant and particles are maintained as a slurry inside the can[1]. When formulated in this way the drug is likely to cream or sediment according to the relative densities of drug and propellant present and so must be re-suspended by shaking prior to use[2].

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[3]. Adopting a standardised approach to MDI shaking often helps to minimise this variability.

Advances in modern smartphone technology provide the opportunity to use a low cost generic method to characterise analyst shaking inputs to aid the development of standardised shaking methods without the need for costly bespoke instruments. 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 and verify 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). 10 actuations were collected at each stage of life using a flow rate of 30L/min and dissolved in 25:75 v/v ethanol:water using the Gentle Rocker (Copley Scientific). Sample solutions were analysed by HPLC using a validated in-house method. 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 – see 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 and discussion

The NGI data for TOI, throat dose and FPD were assessed for each of shakes 1 to 5 – see Table 1 and Figure 2.

Table 1: NGI results (Total on impactor (TOI), Throat dose, Fine particle dose (FPD)) for shakes 1 – 5

		TOI (µg/act)		Throat (µg/act)		FPD (µg/act)	
Shake	BOL/EOL	Mean	%RSD	Mean	%RSD	Mean	%RSD
1	BOL	105	3.1	44	15.6	56	6.5
	EOL	96	4.8	41	6.6	49	11.5
2	BOL	106	6.2	43	8.1	56	12.1
	EOL	97	4.3	39	5.6	51	4.4
3	BOL	104	2.8	42	4.6	55	5.6
	EOL	96	3.5	42	9.9	48	6.6
4	BOL	102	3.0	42	5.9	53	6.6
	EOL	100	0.5	40	4.1	52	2.9
5	BOL	108	5.4	41	11.7	60	8.8
	EOL	99	5.4	44	9.4	49	5.6

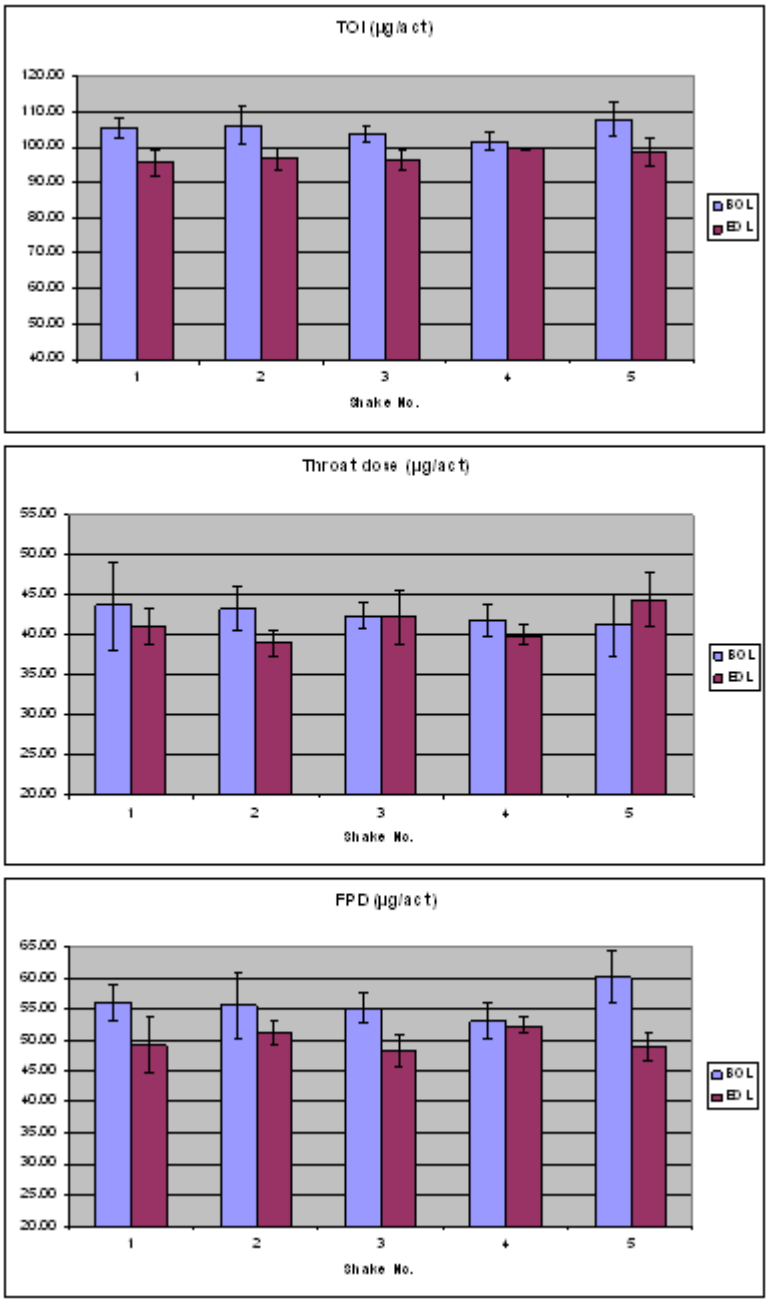

Figure 2: NGI results for shakes 1 – 5 (error bars show 95% CL)

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. Figure 3 shows typical accelerometer traces for shake 4. 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.

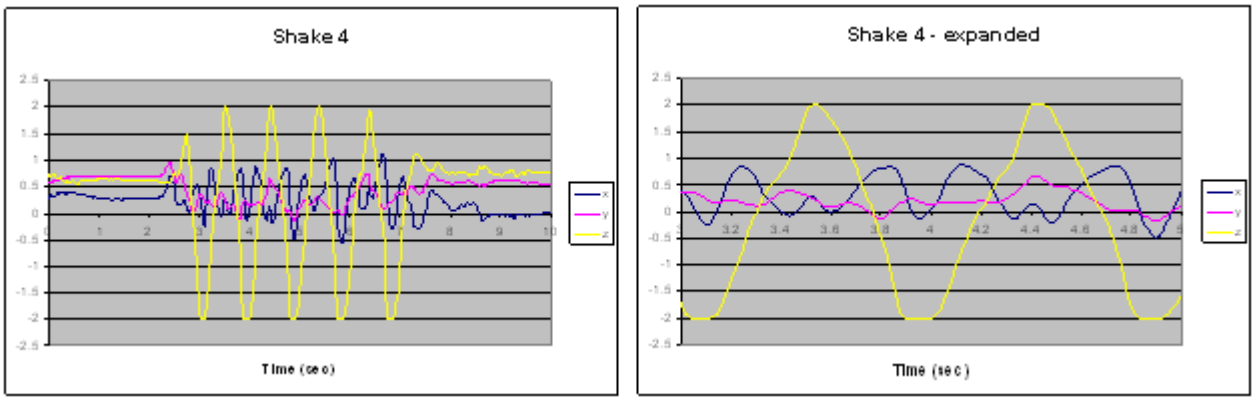

Figure 3: Typical accelerometer traces for shake 4

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.

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Acknowledgements

The author wishes to thank Jessica Allen of Covance Laboratories Ltd for performing the NGI analyses.