In vitro bioequivalence evaluation of pMDI spacer devices

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Summary

We report a experimental design template and results of in vitro bioequivalence evaluation of 3 pMDI spacer devices tested with 3 pMDI drugs. Devices tested include MDI SpaceChamber and SpaceChamber Plus non-antistatic devices, and AeroChamber Plus Flow Vu Antistatic device. Guidelines for testing spacer devices are not clear on how many samples of each device to test, and how many replicates of each to test, and what flow rates of cascade impactor should be used. Guidelines are more clear that 3 drugs should be tested. After considerable internal debate we chose to test 6 samples of each device in triplicate to obtain suitably robust statistical measures. Further, we chose to apply 2 flow rates for NGI cascade impaction at 15 L/min and 30 L/min to approximate both child and adult inhalation rates. Normative and Cumulative aerosol size distributions were processed using validated SolAero Ltd software. From the cumulative size distributions, estimates of MMAD and GSD were calculated along with Respirable Fraction defined as aerosol within 0.5 to 4.7 um size range. **R**es**u**lts of aerosol size metrics obtained are highly repeatable with low inter and intra variation. We conclude that experienced and skilled aerosol science technical support are important in obtaining highly repeatable results. In vitro bioanalytical data demonstrate the devices tested give comparable performance and are therefore interchangeable without the risk of delivering significantly different doses to the same patient were they to change device for another for ease of use patient choice reasons.

Introduction

We undertook to design and carry out in vitro equivalence testing of a new spacer device and compare this to an existing and approved predicate spacer device. Both spacer devices have been developed to improve deposition of inhaled pMDI aerosols within the respiratory tract. We have carried out a series of aerosol measurements to evaluate the MDI Space Chamber Plus device in comparison to the Trudell AeroChamber Plus Flow-Vu Antistatic Valved Holding Chamber at SolAero Ltd that houses an established cGMP aerosol laboratory. The important elements of this comparison included exhaustive cGMP aerosol output and size testing using **n=3** samples from each device design, tested in triplicate, using aerosol size analysis from an NGI impactor at both 15 L/min and 30 L/min flow rates, with each of 3 pMDI drug aerosol formulations including Ipratropium Bromide (Atrovent HFA, Boehringer Ingelheim, 17 μg per actuation) Salbutamol (Ventolin HFA, GSK, 90 μg per activation), and Beclomethasone dipropionate (QVAR, TEVA, 80 μg per activation).

We believe this work is important to publicise for two reasons. Firstly, we present an experimental in vitro bio-equivalence experimental design template that represents best practices in drug aerosol science to an interpretation of current regulatory guidelines. Secondly, we present valuable in vitro data describing a high degree of measurement repeatability when conducted in an established aerosol laboratory with skilled technical support.

Experimental Methods.

A series of aerosol size experiments using the NGI cascade impactor were undertaken to collect data on the two MDI spacers (Space Chamber Plus and Compact Space Chamber Plus) along with the predicate spacer device (AeroChamber Plus Flow-Vu Anti-Static Valved Holding Chamber) in order to evaluate spacer equivalence and inter- and intra- variation of the test spacers in comparison to the predicate device. In addition, the pMDI used was also tested by itself without spacer device. The method used to prime spacers before the onset of testing followed manufacturers' guidance. The MDI spacers are each primed by washing in mild detergent followed by air-drying. The AeroChamber Plus Flow-Vu Antistatic Valved Holding chambers did not require priming, as per manufacturer's instructions.

A summary of pMDI aerosol testing using the NGI cascade impactor includes:

a) pMDIs were primed according to manufacturer's recommendations prior to initial aerosol sizing experiments.
b) Aerosol was emitted from pMDIs and directed into the a NGI cascade either directly alone or directly through a test spacer. The number of activations used and total calculated drug available were:
    i. Ipratropium bromide: 17 μg per actuation x 12 activations = 204 μg.
    ii. Salbutamol: 90 μg per activation x 6 activations = 540 μg.
    iii. Beclomethasone dipropionate: 80 μg per activation x 6 activations = 480 μg.

c) Aerosol passing through the NGI impactor impacts on the impactor 'throat' – a right angled tube simulating the human throat – and subsequently passes through the throat into the body of the NGI impactor where aerosol deposits on the various stages on the basis of its aerodynamic size. There are a total of 7 impaction stages in the NGI, as well as an MOC (micro-orifice collector) stage and a final filter. Each of the stages has a 'cut-point' which describes the aerosol size collected for a given flow rate (both 15 or 30 L/min used in this work)
d) After collection, aerosol residue deposited in the throat, cascade stages, MOC and final filter were quantitatively desorbed using known volumes of appropriate HPLC mobile phase solution.
e) Quantification of the drug from each sample was undertaken by HPLC against known USP drug standards.
f) Results were processed into aerosol size distributions using proprietary SolAero Ltd software, from which relevant aerosol size parameters were extracted.
g) Regulatory guidance from the FDA and Canada teach that analysis and reporting of relevant aerosol size parameters should not include the residue found in the NGI impactor throat. Though the impactor throat can contain significant amounts of drug, it is not considered to have a size fraction and confounds interpretation of results. The size fractions calculated and described in this report consider the aerosol collected within the NGI (i.e. stages 1-7, MOC and filter), but excluding the throat, as per FDA guidance. Size fractions and aerosol size parameters included:
    - Mass Median Aerodynamic Diameter (MMAD) for all size distributions interpolated from the Cumulative Undersize Distribution plot
    - Calculated Geometric Standard Deviation (GSD) for all MMADs interpolated from the cumulative undersize distribution $GSD = (d_{84.13}/d_{15.87})^{0.5}$
    - Particle size fraction, %, greater than 4.7 um
    - Particle Fraction (FPF, %) as cumulative size less than 4.7 um
    - Particle Size Fraction % as cumulative size less than 1.0 um
    - Particle Size Fraction % as cumulative size less than 0.5 um
    - Calculated mean, SD, SEM and 95%CI for each set of 3 results for each pMDI as well as on each pMDI and spacer sample, and similarly for each set of n=9 composite results for each pMDI with all 3 spacer samples of the same design.
h) The total delivered dose is calculated as the sum of drug aerosol residue collected in the NGI impactor stages plus NGI throat plus final filter.
i) The % total delivered dose was calculated by dividing the total delivered dose (h) by the theoretical available maximum drug emitted (b).
j) The % respirable dose was calculated by multiplying the % respirable fraction (i.e the proportion of aerosol between 0.5-4.7 μm determined from the cumulative size distribution) by the total delivered dose (h).

Experimental Results

SolAero Ltd internal software was used to process and present aerosol size distribution results from NGI impaction stages. Figure 1 plots results for a typical pMDI size distribution, in this case Spacer Chamber Plus with Salbutamol. The plots show two expressions of the experimentally obtained pMDI aerosol size distribution. The x-axis defines nebulized aerosol droplet size between 0.1 to 100 μm in a lognormal scale. The diamonds present a normative plot of the same size distribution whose shape indicates a near symmetrical lognormal distribution typical of many pMDI drug aerosol size distributions. The cumulative size distribution (triangles) plot the cumulative mass of size fractions obtained from an NGI cascade impactor (15 L/min flow) and relate to the left y-axis (Cumulative undersize %). From the cumulative size plot, the MMAD can be determined as the size intercepting the 50% cumulative mass, which in this example is 2.5 μm. . The MMAD was defined as the diameter at which 50% of the particles by mass were larger and 50% were smaller. The GSD is a measure of the spread of an aerodynamic particle size distribution and calculated as follows: $GSD = (d_{84.13}/d_{15.87})^{0.5}$ where $d_{84.13}$ and $d_{15.87}$ represent the diameters at which 84% and 16% of the aerosol mass are contained. In this case the GSD is calculated to be 1.6 (no units). Interpolation of intercepts between the left y-axis of the cumulative mass distribution allows estimation of any size parameter, including: the % aerosol mass in the Particle Fraction (PF) less than 0.5 μm (%PF<0.5 μm) of 1.5%, the PF% < 1μm at 3%, the % PF <4.7 μm at 90% and any other parameter of interest..

A summary of results of in vitro assessment of bioequivalence from the 3 spacer devices tested is presented in Table 1. Comparative metrics describing the aerosol testing were extracted from the cumulative size distributions, and mean results calculated along with 95% Confidence Intervals for MMAD, GSD, delivered dose, delivered dose as respirable aerosol, proportion of the aerosol as Fine Particle Fraction (0.5 - 4.7 um), total delivered dose as a % of dose as a fraction of total released dose from actuator valve, and percentage of released dose as respirable aerosol.

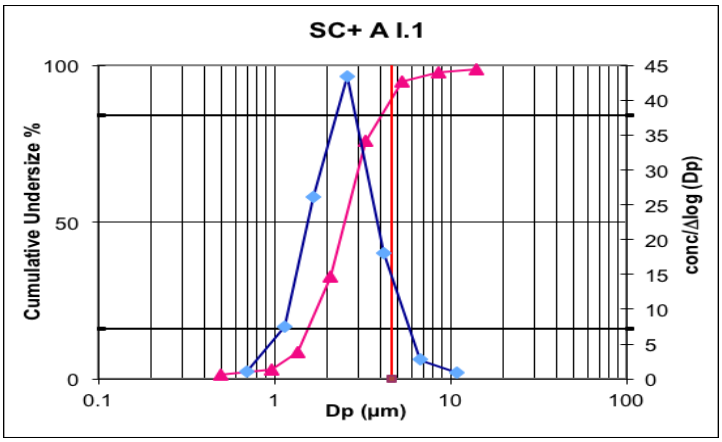

Figure 1 Aerosol Size Distribution. Data set obtained from a Salbutamol pMDI aerosol delivered through a primed MDI Spacer Chamber plus device through an NGI cascade impactor at a 15 L/min flow rate.

Discussion

Inspection of the results from validation of priming (data not presented) show no unusual or inconsistent values in the reported data, and a consistent increase of gross aerosol from both the Space Chamber Plus and the Compact Space Chamber Plus after priming, as would be expected (data not presented).

Inspection of the results from NGI sizing of pMDI aerosol from all spacers with all drugs indicates relative consistency. Ipratropium pMDI results indicate a very fine aerosol distribution that thwarted calculation of the GSD of the MMAD, as the cumulative size distribution did not cross the 15.87% mark. The GSD is a measure of the spread of an aerodynamic particle size distribution and calculated as follows: $GSD = (d84.13/d15.87)^{0.5}$ where d84.13 and d15.87 represent the diameters at which 84% and 16% of the aerosol mass are contained. In the case of distributions obtained from Ipratropium, the cumulative distribution plot did not intersect with the d15.87 % and so the GSD is not be readily calculable, and in these instances the GSD was reported as Not Applicable (NA).

The guidelines for testing spacer devices are not clear on how many samples of each device to test, and how many replicates of each to test, and what flow rates of cascade impactor should be used. Guidelines are clearer that 3 drugs should be tested. After considerable internal debate we chose to test 6 samples of each device in triplicate to obtain robust statistical measures. Further, we chose to apply 2 flow rates for NGI cascade impaction at 15 L/min and 30 L/min to approximate both child and adult inhalation rates. Inspection of the data presented in the Table indicates consistent results for particle size and aerosol output metrics for all spacers tested. We worked to reduce variability within our in vitro testing methods to encourage narrow confidence intervals and make more obvious small differences between test devices.

Conclusions

We present highly repeatable aerosol size measurements with low inter and intra variation in results. We believe this is due in large part to testing undertaken in established aerosol laboratory with highly trained and skilled aerosol science technical support. Further, this in vitro bioanalytical data demonstrates the devices tested give comparable performance and are therefore interchangeable without the risk of delivering significantly different doses to the same patient were they to change device for another for ease of use patient choice reasons.

Table 1. Comparative pMDI aerosol Size and Output Results obtained from repeat testing using the NGI cascade impactor at 15 L/min.

Device	Mean MMAD, um (95% CI)	Mean GSD of MMAD (95% CI)	Mean total delivered dose, ug (95% CI)	Mean total respirable (0.5-4.7 um) dose, ug (95% CI)	Mean respirable fraction PF% (95% CI)	mean total delivered dose as % of dose actuated from valve	mean total respirable dose as % of dose actuated from valve
Ipratropium Bromide							
Ipratropium Bromide pMDI without spacer	0.7 (0.1)	NA*	93.55 (2.26)	51.14 (2.8)	54.7 (1.7)	45.86%	25.07%
Space Chamber Plus	0.9 (0.1)	NA*	130.50 (4.06)	85.26 (3.3)	65.3 (0.9)	63.97%	41.79%
Compact Space Chamber Plus	0.8 (0.0)	NA*	105.34 (2.60)	65.19 (2.1)	61.9 (0.7)	51.64%	31.96%
Aerochamber Plus Flow Vu Anti-static	0.8 (0.1)	NA*	92.14 (3.34)	55.28 (3.0)	60.0 (1.8)	45.17%	27.10%
Salbutamol							
Salbutamol pMDI without spacer	2.6 (0.11)	1.8 (0.08)	435.50 (70.82)	347.1 (43.3)	79.7 (3.3)	80.56%	64.28%
Space Chamber Plus	2.5 (0.04)	1.7 (0.02)	333.28 (39.31)	286.9 (36.3)	86.1 (0.9)	61.72%	53.13%
Compact Space Chamber Plus	2.3 (0.05)	1.6 (0.02)	287.82 (43.45)	253.4 (38.7)	88.0 (0.6)	53.30%	46.93%
Aerochamber Plus Flow Vu Anti-static	2.4 (0.03)	1.6 (0.01)	333.74 (23.80)	292.2 (19.2)	87.6 (0.7)	61.80%	54.11%
Beclomethasone Dipropionate							
Beclomethasone dipropionate pMDI without spacer	1.4 (0.07)	2.3 (0.12)	282.06 (20.05)	218.12 (16.3)	77.3 (2.4)	58.76%	45.44%
Space Chamber Plus	1.3 (0.02)	2.0 (0.01)	396.83 (13.00)	328.05 (9.9)	82.7 (0.8)	82.67%	68.34%
Compact Space Chamber Plus	1.3 (NA)	2.0 (0.03)	368.48 (14.05)	308.29 (12.7)	83.7 (1.0)	76.77%	64.23%
Aerochamber Plus Flow Vu Anti-static	1.3 (0.03)	2.0 (0.04)	376.99 (19.62)	316.25 (17.6)	83.9 (1.1)	78.54%	65.89%