Comparison of Aerosol Particle Size Measured by Two Methods Using Three Brands of Mesh Nebulizer

L. Slator¹, Y. Degtyareva¹, L. Hardaker¹, D. von Hollen² & J. Pritchard¹

¹ Respironics Respiratory Drug Delivery (UK) Ltd, a business of Philips Electronics UK Limited, Chichester, West Sussex, UK
² Respironics, Inc., a Philips Healthcare Company, Murrysville, PA, USA

Summary

We compared the particle size and fine particle fraction (FPF, % ≤5 µm) of 3 mesh nebulizers using cascade impaction with a Next Generation Impactor (NGI) and a modified laser diffraction method with a Spraytec particle sizer. Three of each nebulizer brand (InnoSpire Go [production equivalent], Aeroneb Go, and MicroAir U22) were tested with 1 mL of 5 mg/2.5 mL salbutamol sulphate in triplicate with a 15 L/min constant flow rate. NGI tests: the nebulizer was connected to the NGI and run until treatment completion; samples from the NGI were analyzed via high performance liquid chromatography. Spraytec tests: the Spraytec was set up with the inhalation cell fitted with the sheath flow collar with ports open, the flow straightener component fitted and connected to a vacuum pump such that there was 15 L/min flow at the inlet adapter ferrule. The nebulizer was connected to the inlet adapter ferrule; the nebulizer was run and stopped after 60 seconds of data measurements following a 10-second prime. The differences between the results of the NGI and Spraytec particle sizer were within 0.5 µm for particle size and 5% for FPF. The InnoSpire Go produced aerosols with the smallest particle sizes (mean ± standard deviation: 3.99 ± 0.26 µm MMAD and 4.17 ± 0.22 µm VMD) and largest FPFs (64.4 ± 4.42% and 63.4 ± 3.74%, respectively); the MicroAir U22 produced the largest particle sizes and smallest FPFs (9.83 ± 0.43 µm MMAD and 6.30 ± 0.19 µm VMD, and 41.3 ± 3.83% and 36.7 ± 1.62%, respectively). Span and geometric standard deviation were lowest for the InnoSpire Go. The modified Spraytec method has potential for use as a routine method in the future.

Introduction

Different methods can be used for determination of particle size; cascade impaction has traditionally been the most commonly used method of assessing aerosol droplet sizes and is recommended in regulatory guidelines, but laser diffraction is also a popular method due to the speed and ease of analysis compared with cascade impaction. We compared the particle size and fine particle fraction (FPF) measurements of 3 different mesh nebulizers determined with a standard cascade impaction method using a Next Generation Impactor and a modified laser diffraction method using a Spraytec, when performed at the same constant extraction flow rate to confirm the acceptability of the new method.

Methods

Three of each of the InnoSpire Go (A), Aeroneb Go, and MicroAir U22 nebulizers (Figure 1) were tested in triplicate with 1 mL of 5 mg/2.5 mL salbutamol sulphate (Salamol; IVAX Pharmaceuticals, Castleford, UK). Each nebulizer was tested with a Next Generation Impactor (NGI) and a Malvern Spraytec laser diffraction system, each set to a 15 L/min constant extraction flow rate. Before each of the tests, the nebulizers were cleaned in warm soapy water, rinsed, and air-dried, and all equipment and solutions were stabilized to ambient conditions for at least 2 hours before use.

For the NGI tests, a vacuum pump attached to the NGI was set to an extraction flow of 15 L/min. An InnoSpire Go nebulizer was filled with 1 mL of salbutamol sulphate solution, the mouthpiece was attached to the NGI via a custom connector, and the join was sealed with Parafilm (Alcan Packaging, Neenah, WI). The nebulizer and timer were started simultaneously. At the end of nebulization, the nebulizer and timer were stopped simultaneously, and the vacuum pump was stopped after a further 10 seconds. Samples were eluted from the NGI induction port, collection cups, custom connector, nebulizer, and back-up filter using volumes of diluent appropriate for analysis by high performance liquid chromatography. The nebulizer was disassembled, cleaned in warm soapy water, and air-dried. The test was performed in triplicate with the other 2 InnoSpire Go nebulizers. The test was also performed in triplicate with 3 Aeroneb Go and 3 MicroAir U22 nebulizers. NGI data analysis was performed using Copley Inhaler Testing Data Analysis Software (CITDAS; Copley Scientific Ltd., Nottingham, UK), and the results reported were mass median aerodynamic diameter (MMAD), geometric standard deviation (GSD), and FPF (% ≤5 µm). The CITDAS summary data was checked to ensure the data was unimodal.

The Spraytec was set up with the inhalation cell fitted with the sheath flow collar with ports open, the flow straightener component and the inlet adapter ferrule. A vacuum pump provided an extraction of 22 L/min through the inhalation flow cell as measured at the inlet adapter ferrule. The inhalation flow cell was then adjusted so as to allow a combined secondary sheath air flow of 7 L/min (±0.3 L/min) into the inhalation cell from either side, resulting in a 15 L/min extraction at the inlet adapter ferrule, which provided the same flow rate through the nebulizers as used in the NGI method. The sheath air flow of 7 L/min ensured that the aerosol was transported...
across central portion of the flow cell. The InnoSpire Go nebulizer was filled with 1 mL of salbutamol sulphate solution and connected to the Spraytec via a connector. The nebulizer and timer were started simultaneously, and data acquisition on the Spraytec was started after 10 seconds. Data acquisition, nebulizer, and timer were stopped after 70 seconds of nebulization. The nebulizer was disassembled, cleaned in warm soapy water, and air-dried; the test was performed in triplicate and with the other 2 InnoSpire Go (A) nebulizers. The test was also performed in triplicate with 3 Aeroneb Go and 3 MicroAir U22 nebulizers. The results reported were volume median diameter (VMD), FPF, and span of delivered aerosol calculated using Spraytec software version 3.2.

**Nebulizers tested**

<table>
<thead>
<tr>
<th>3 × InnoSpire Go</th>
<th>3 × Aeroneb Go</th>
<th>3 × MicroAir U22</th>
</tr>
</thead>
<tbody>
<tr>
<td>(production equivalent; Respinorics Respiratory Drug Delivery [UK] Ltd, Chichester, UK)</td>
<td>(Aerogen Limited, Galway, Ireland)</td>
<td>(Omron Healthcare, Kyoto, Japan)</td>
</tr>
</tbody>
</table>

**Laboratory equipment**

| Next Generation Impactor (NGI; Copley Scientific Ltd, Nottingham, UK) | Malvern Spraytec (Malvern Instruments Ltd, Malvern, UK) |

**Figure 1 - Nebulizers and laboratory equipment used in the study.**

**Results**

The results for the MMAD and VMD for the 3 nebulisers with the NGI and Malvern Spraytec are shown in Figure 2. The results for the FPF for the 3 nebulisers with the NGI and Malvern Spraytec are shown in Figure 3.

Median mass balance for the NGI tests was 97.6% (range 94.6 to 99.4%).

The mean results for MMAD from the Next Generation Impactor and VMD from the Spraytec were similar for each of the nebulizers tested (Figure 2); the mean FPF for each nebulizer was also similar for the 2 methods (Figure 3). Mean particle size was smallest for the InnoSpire Go (A) nebulizers and largest for the MicroAir U22 nebulizers (Figure 2). Mean fine particle fraction was largest for the InnoSpire Go (A) nebulizers and smallest for the MicroAir U22 nebulizers (Figure 3).
Figure 2 - Mean particle size from the NGI shown as mass median aerodynamic diameter (MMAD) (white) and mean particle size from the Spraytec shown as volume median diameter (VMD) (grey) for each of the nebulizers tested (n = 9). Error bars show the standard deviation about the mean.

Figure 3 - Mean fine particle fraction (% ≤5 µm) as tested via the Next Generation Impactor (white) and Spraytec laser diffraction system (grey) for each of the nebulizers tested (n = 9). Error bars show the standard deviation about the mean.
Table 1. Span and geometric standard deviation results for each of the nebulizers tested.

<table>
<thead>
<tr>
<th></th>
<th>InnoSpire Go (production equivalent)</th>
<th>Aeroneb Go</th>
<th>MicroAir U22</th>
</tr>
</thead>
<tbody>
<tr>
<td>Span (SD)</td>
<td>1.39 (± 0.02)</td>
<td>1.59 (± 0.04)</td>
<td>1.73 (± 0.06)</td>
</tr>
<tr>
<td>Geometric standard deviation (SD)</td>
<td>1.82 (± 0.01)</td>
<td>2.10 (± 0.03)</td>
<td>2.07 (± 0.07)</td>
</tr>
</tbody>
</table>

The results for span and geometric standard deviation were lowest for the InnoSpire Go (A) nebulizer (Table 1).

Discussion

The differences between the mean particle size measurements (Figure 2) and the mean FPF measurements (Figure 3) produced by the 2 methods varied between the nebulizers but the differences were all relatively small; the differences between the particle size results were all within 0.5 µm, and the differences between the FPF results were all within 5%. This relative consistency between the VMD and MMAD results, and the FPF results, indicates that the Spraytec method is suitable for use as an indicator of aerodynamic particle size distribution when large numbers of samples need to be tested. Furthermore, these different methods of droplet sizing at a constant flow rate could be used to produce comparable results when testing mesh nebulizers, as found in a number of other studies that used various types of nebulizer and measurement systems.[3,4,5]

The small particle size and high FPF of the aerosol produced by the InnoSpire Go (A) nebulizers compared with the other nebulizers suggest that it would produce more particles likely to penetrate deeper into the lungs compared with the other nebulizers tested.[6,7] Furthermore, the smaller span and GSD in the results for the InnoSpire Go indicated a particle size distribution closer to a mono dispersion; mono disperse aerosols have the potential for preferential deposition to specific areas of the lungs.[6]

Conclusion

The droplet size and FPF results for each of the nebulizers when tested with the NGI and Spraytec methods were generally comparable for the formulation tested; therefore, the modified laser diffraction method could potentially be used as a routine method for the determination of mesh nebulizer particle size characteristics in the future. The InnoSpire Go (A) nebulizers produced the smallest particle size and largest FPF compared with the Aeroneb Go and MicroAir U22 nebulizers.

A The InnoSpire Go nebulizers used in the tests were production equivalent devices.

References

1. European Pharmacopeia 7.3 (2012): General Chapter 2.9.44. Preparations for nebulization: Characterisation