Ultrasonic and Mesh Nebulizers Are Not the Same – Delivery of a Budesonide Suspension

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Summary

Mesh nebulizers are driven by a piezo-element and use ultrasonic frequencies to vibrate the mesh. The vibration of the mesh causes aerosol generation as the liquid passes through it. Ultrasonic nebulizers, by contrast, produce ultrasonic waves directly into the solution causing aerosol to be produced at the liquid surface. Since both use ultrasonics to generate the aerosol, confusion between the 2 types of nebulizers and their differing performance can occur. It is known that ultrasonic nebulizers are unable to deliver suspension formulations such as budesonide and this perception of inability to deliver budesonide can incorrectly be assumed to be the same for ultrasonically driven mesh nebulizers.

We compared an ultrasonic nebulizer, the Flores Medical GmbH Aerosonic Mobil 3060 nebulizer, and an ultrasonically driven mesh nebulizer, the Philips Respironics I-neb Adaptive Aerosol Delivery (AAD) System nebulizer, when delivering budesonide (2 mL of 250 µg/mL fill) to highlight the performance differences between the mesh and conventional ultrasonic devices. Nebulizer performance was assessed in terms of delivered dose, delivered dose output rate, total gravimetric output, mass median diameter, mass median aerodynamic diameter, and aerodynamic particle size distribution (APSD). These performance parameters were compared for the 2 devices against the delivery of a solution of salbutamol (2.5 mL of 2 mg/mL fill).

The Aerosonic Mobil 3060 and the I-neb AAD System nebulizers delivered 714 µg and 1079 µg of salbutamol respectively. With budesonide, the Aerosonic Mobil 3060 delivered 9.2 µg and the I-neb AAD System nebulizer delivered 109 µg. APSD data indicated the low delivery by the Aerosonic Mobil 3060 was a consequence of it being unable to deliver the suspended particles.

The results demonstrated that both nebulizer types are capable of delivering solutions but that the ultrasonic nebulizer cannot effectively deliver budesonide, whereas the mesh nebulizer can.

Introduction

Ultrasonic nebulizers have been reported to have low outputs of suspensions such as budesonide. [1-3] Mesh nebulizers are used to deliver budesonide, but published data on the delivery of budesonide from mesh nebulizers is limited. In this study, we compared the key *in vitro* performance parameters of the ultrasonic and the mesh nebulizer.

Method

An Aerosonic Mobil 3060 ultrasonic nebulizer (Flores Medical GmbH, Probstzella, Germany) and an I-neb Adaptive Aerosol Delivery (AAD) System mesh nebulizer with a 0.5 mL dosing chamber (Respironics Respiratory Drug Delivery (UK) Ltd, Chichester, UK) were characterized for dose output to filter (over 1 minute and to the end of treatment) using the ASL 5000 breathing simulator (IngMar Medical Ltd, Pittsburgh, PA, USA). Each nebulizer was run 20 times to determine the 1 minute output rate, total output to filter, treatment time, and mass median diameter (MMD). Mass median aerodynamic diameter (MMAD), aerodynamic particle size distribution (APSD) and mass balance (the sum of the drug in the nebulizer connector and NGI as a percentage of the initial fill drug mass) were determined in triplicate. Since the objective of the study was to compare gross differences in the delivery of different formulation types, rather than inter-device variability, a design including a single representative example of each device type with a high n for each test was chosen.

Particle size:

Nebulizers were characterized by laser diffraction with the Malvern Mastersizer (Malvern Instruments Ltd, Worcestershire, UK). Each nebulizer was charged with 2.5 mL of 5 mg/2.5 mL salbutamol sulphate solution (Salamol Steri-Neb, IVAX Pharmaceuticals, West Yorkshire, UK) directly from the respule or 2 mL of 250 µg/mL budesonide (Pulmicort, Astra Zeneca, Luton, UK). The Malvern Mastersizer was set up with an extraction flow of 30 L/min and shroud air of 10 L/min. The device under test was connected to the flow cell using an elastomeric-lipped ISO connector (Intersurgical Ltd., Wokingham, UK) and the join was sealed with parafilm. Data were measured for 3 time points, with a 20 second delay between each measurement. Data for each run were averaged to provide mean MMD and fine particle fraction.

To assess APSD, budesonide and salbutamol aerosols were characterized using a next generation impactor (NGI) at 15 L/min. Measurements were made in triplicate.

Output to filter:

The nebulizers were characterized using the ASL 5000 breathing simulator. Each nebulizer was charged with 2 mL of 250 µg/mL budesonide suspension or 2.5 mL of 2 mg/mL salbutamol. The ASL 5000 was set to reproduce an adult breathing pattern (tidal volume = 500 mL; inhalation:exhalation ratio = 1:1; 15 breaths per minute). A filter was placed at the end of a short piece of elephant tubing attached to the ASL 5000, inside a fume hood. The nebulizer under test was attached to the filter using a 22 mm elastomeric-lipped ISO connector and the join was sealed with parafilm. The nebulizer was run for 1 minute and the filter was removed. A new filter was attached and the nebulizer was run until the end of the treatment, as indicated by the nebulizer. The Aerosonic Mobil 3060 nebulizer automatically powered off after approximately 3 minutes of treatment, whereas for the I-neb AAD System nebulizer, the end of treatment was indicated by the device at the end of aerosol generation. The filters were processed to extract the drug which was then quantitated by high performance liquid chromatography analysis.

Results

Table 1: Results summary for output to filter, MMD, and MMAD (n=20 for MMD and n=3 for NGI).

Results Summary												
Testing	Budesonide						Salbutamol					
	Aerosonic Mobil 3060 nebulizer			I-neb AAD System nebulizer			Aerosonic Mobil 3060 nebulizer			I-neb AAD System nebulizer		
	Mean	SD [a]	% RSD [b]	Mean	SD [a]	% RSD [b]	Mean	SD [a]	% RSD [b]	Mean	SD [a]	% RSD [b]
Treatment time (s)	261	1.12	0.43	397	26.81	6.75	248	25.93	10.46	367	31.91	8.69
Output rate (µg on filter after 60 s)	3.17	0.70	22.16	9.54	1.74	18.26	203	29.84	14.65	109	15.09	13.72
Total delivered dose to filter (µg)	9.23	1.66	17.95	109.05	6.34	5.82	714	112.15	15.71	1079	50.90	4.71
Emitted gravimetric dose (mg)	450	90.77	20.16	558	11.73	2.10	755	77.76	10.30	564	7.72	1.37
MMD [c] (µm)	4.71	0.08	1.80	4.62	0.18	3.88	4.43	0.15	3.37	4.95	0.19	3.89
MMAD [d] (µm)	1.38	0.17	12.52	5.01	0.25	4.97	3.68	0.06	1.66	4.80	0.24	5.09
GSD [e]	1.96	0.11	5.67	1.74	0.07	3.92	2.01	0.03	1.56	1.80	0.03	1.69
Mass balance (%)	93	7.71	8.28	101	3.35	3.32	101	8.65	8.53	96	3.26	3.39

[a] Standard deviation (SD); [b] relative standard deviation (RSD); [c] mass median diameter (MMD); [d] mass median aerodynamic diameter (MMAD); [e] geometric standard deviation (GSD).

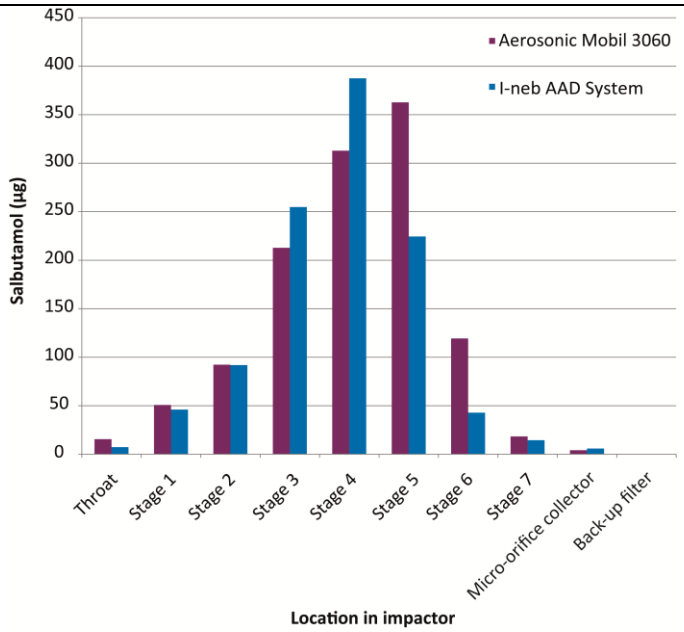

Figure 1: Stage deposition of salbutamol.

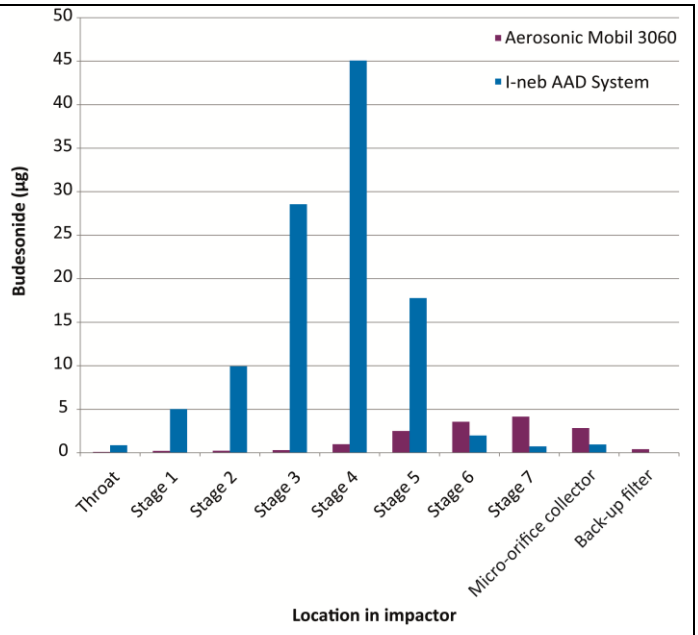

Figure 2: Stage deposition of budesonide.

Discussion

As shown in Table 1, the particle size by laser diffraction was comparable between the 2 devices with both salbutamol and budesonide; for example, the mean MMD of the Aerosonic Mobil 3060 nebulizer and I-neb AAD System nebulizer respectively with budesonide was 4.71 µm and 4.62 µm, and with salbutamol it was 4.43 µm and 4.95 µm. The MMAD values for the Aerosonic Mobil 3060 nebulizer and I-neb AAD System nebulizer respectively with budesonide were 1.38 µm and 5.01 µm, and with salbutamol they were 3.68 µm and 4.80 µm. For the I-neb AAD System nebulizer, the apparently larger particle size of budesonide as measured by NGI is as expected. Laser diffraction measures the size of aerosol droplets which include small droplets that do not contain particles of budesonide and thus underestimates the particle size of drug containing aerosol. [4] The NGI method measures the drug so that the underestimation that the laser gives by measuring the small empty droplets is overcome. For the Aerosonic Mobil 3060 nebulizer, the very low particle size of the budesonide measured by NGI compared with laser diffraction is surprising as it contradicts what would be expected, but as discussed later, may be related to the inability of the Aerosonic Mobil 3060 ultrasonic nebulizer to aerosolize budesonide suspension particles.

The I-neb AAD System nebulizer had a higher delivered dose with both salbutamol (1079.65 µg compared with 713.96 µg) and budesonide (109.05 µg compared with 9.23 µg) than the Aerosonic Mobil 3060 nebulizer. In the case of the salbutamol, this reflects the fact that the I-neb AAD System nebulizer is breath activated, so it does not lose drug to exhalation. With budesonide, the delivered dose from the Aerosonic Mobil 3060 nebulizer was much lower than would be expected, even allowing for exhalation. Due to the size of the dosing chamber used, the amounts of both drugs delivered with the I-neb AAD System nebulizer are consistent with amounts delivered with jet nebulizers. [5,6] The Aerosonic Mobil 3060 nebulizer manual states that the device can nebulize suspensions: “The 3060 aerosonic® mobil can be used for the nebulisation of all water-based inhalation solutions, including suspensions, however not for solutions containing essential oils.” [7] However, the results from this study suggest that the Aerosonic Mobil 3060 nebulizer struggled to nebulize suspensions of budesonide. Not only did the Aerosonic Mobil 3060 nebulizer have a significantly lower delivered dose with budesonide, but it also had a notably lower MMAD of 1.38 µm. This result is somewhat surprising, as suspension formulations usually have higher MMADs than solutions. [8] It could be hypothesized that the budesonide collected in the NGI was from the small (circa 10%) [9] amount of budesonide dissolved in the solution and that the particles in the budesonide suspension were not aerosolized. The stage deposition data shown in Figure 2 supports this hypothesis as the deposition from the Aerosonic Mobil 3060 nebulizer is all on the lower stages, which is more typical of a solution. It is not clear, however, why the MMAD was much lower than for the salbutamol solution. It could reflect the budesonide particles modifying the way ultrasonic waves are transmitted through the solution and the consequent particle size generation. The comparison of the 2 nebulizers

suggests that the Aerosonic Mobil 3060 ultrasonic nebulizer may not be a viable method for the delivery of budesonide, whereas the I-neb AAD System nebulizer is.

Conclusion

- The I-neb AAD System mesh nebulizer is effective at delivering both budesonide and salbutamol.
- The Aerosonic Mobil 3060 ultrasonic nebulizer is inefficient at delivering the suspension formulation budesonide.
- The ultrasonically driven mesh nebulizer had significantly different performance characteristics to the conventional ultrasonic nebulizer and the 2 devices should not be confused.

References

1. Dahlbäck M: Behavior of nebulizing solutions and suspensions. J Aerosol Med Pulm Drug Deliv. 1994;7(1):S3-S6.
2. Berlinski A, and Waldrep JC: Effect of aerosol delivery system and formulation on nebulized budesonide output. J Aerosol Med Pulm Drug Deliv. 1997;10(4):307-318.
3. Nikander K, Turpeinen M, and Wollmer P: The conventional ultrasonic nebulizer proved inefficient in nebulizing a suspension. J Aerosol Med Pulm Drug Deliv. 1999;12(2):47-53.
4. Keller M, Lintz F-C, Walther E, and Knoch M: Effect of novel pharmaceutical formulation on nebulisation efficiency of an air jet and a new electronic nebuliser. [Abstract]. Presented at the International Society for Aerosols in Medicine 13th International Congress, Interlaken, Switzerland, September 17-21, 2001; J Aerosol Med Pulm Drug Deliv. 14:3;390 DOI: 10.1089/089426801316970358 (online only).
5. Berg EB, and Picard RJ: In vitro delivery of budesonide from 30 jet nebulizer/compressor combinations using infant and child breathing patterns. Respir Care. 2009;54(12):1671-1678.
6. Smaldone GC, Cruz-Rivera M, and Nikander K: In vitro determination of inhaled mass and particle size distribution for budesonide nebulizing suspension. J Aerosol Med Pulm Drug Deliv. 1998;11(2):113-115.
7. Aerosonic 3060 Instructions for Use: Edition 1106. Flores Medical GmbH, Probstzella, Germany.
8. Ziegler L, Nikander K, Hatley RHM, and Somaraju S: Characterization of nebulized budesonide using two different impactor methods. [Abstract]. Presented at the CHEST Annual Meeting Conference, Chicago, IL, October 20-25, 2007; Chest. 132:4;508b DOI: 10.1378/chest.132.4_MeetingAbstracts.508b (online only).
9. Keller M, Jauernig J, Lintz F-C, and Knoch M: Nebulizer nanosuspensions: Important device and formulation interactions. In: Dalby RN, Byron PR, Peart J, and Farr SJ (eds). *Respiratory Drug Delivery VIII (2002)*. Proceedings of Respiratory Drug Delivery 2002; May 12-16, 2002; Tucson, AZ. Virginia Commonwealth University, Richmond, VA; vol. 1, pp. 197-206, 2002.