Comparison of Different Nebulizers to Allow More Effective Decision Making

S Moore, J Richardson and C Gutteridge
Covance CRS Ltd. (formerly Envigo CRS Ltd.), Huntingdon, UK

Introduction

Covance CRS Ltd. has many years' experience of performing nonclinical inhalation toxicology programmes involving the generation of pharmaceutical and biopharmaceutical liquid formulations and suspensions for exposure of rodent and non-rodent species. Over the past ten years, we have seen a marked increase in the nonclinical testing of liquid formulations and the number of potential nebulizers available for this testing. Each of these nebulizers promises to provide a more effective method of delivery or increased patient compliance than either its predecessor or competitor. To make an effective decision on selecting an appropriate nebulizer, other information is also required. This can include disease target, test article and formulation properties, study design and dose levels. The most common (pneumatic or jet) nebulizers work by delivering compressed air through a jet causing a region of negative pressure (Venturi principle). The formulation to be aerosolised is entrained into the air stream and is sheared into a liquid film. This film is instable and breaks into droplets due to surface tension forces. A baffle is placed in the aerosol stream, producing smaller particles and causing larger particles to return to the liquid reservoir (to be recycled). With such a variety of nebulizers available to the preclinical aerosol technologist, it is difficult to differentiate on face value the facts from fiction, when only the manufacturers marketing material is used as a reference. As a consequence of this, Covance CRS Ltd. performed a direct comparison of the different types of readily available jet nebulizers, in order to evaluate nebulizer output.

Method

A wide range of jet nebulizers were compared. These are listed in Table 1 with their recommended operating conditions.

Table 1. Manufacturers recommended operating conditions

Manufacturer	Model	Recommended Airflow (L/min)	Recommended Priming Volume (mL)
Apex Medical Corp	Reusable Jet (EVO medical solutions)	>5.0	
Mallinckrodt	Raindrop	6 – 8	<10
Medex	Aeromist	8 – 15	<10
Pari	LC-D	6 – 8	2.5
Pari	LC Plus	4.2	2.5
Pari	LC Sprint	6	<8
Pari	LC Star	3.5 – 8	2.5
Profile	Sidestream	6 – 8	>2 and <10
Profile	Ventstream	6 – 8	3
Teleflex medical	Hudson Micro-mist	6 – 8	>6
Teleflex medical	Hudson Updraft II	8 – 12	>8
Trudell medical International	AeroEclipse II	7 – 8	>6
Westmed	HEART	10 – 15	>240
Westmed	MiniHeart (Lo-Flo)	1 – 2	8
Westmed	MiniHeart (Hi-F lo)	30	30
Wright	NA	5	-

The same procedure was used throughout this evaluation to ensure a direct comparison between individual nebulizers. The airflow through the nebulizer was initially calibrated. Each nebulizer was then primed with 0.9% Phosphate buffered saline (PBS) and generated for a period of 10 mins. The nebulizer and contents were weighed before and after the generation period and the data recorded. The airflow through the device was then amended and the experiment repeated. The priming volumes and airflow ranges evaluated are specified in Table 2.

Animal experiments were conducted according to the Animals (Scientific Procedures) Act, 1986, and 2012 amendments following local ethical approval. Work was conducted in AAALAC accredited facility

Table 2. Experimental operating conditions

Model	Recommended Airflow (L/min)	Recommended Priming Volume (mL)
Reusable Jet (EVO medical solutions)	3 – 29	6
Raindrop	3 – 27	8
Aeromist	5 – 27.5	20
LC-D	3 – 15	6
LC Plus	3 – 15	6
LC Sprint	3 – 17	6
LC Star	3 – 13	6
Sidestream	3 – 29	10
Ventstream	19 – 25	8
Hudson Micro-mist	3 – 21	6
Hudson Updraft II	5 – 20	10
AeroEclipse II	3 – 13	6
HEART	5 – 27.5	40
MiniHeart	3 – 13	8
Wright	3 – 23	8

Results

The results have been presented for low (3 – 8 L/min), medium (7 – 14 L/min) and high (12 – 28 L/min) airflow ranges and solely Pari nebulizers. The data shows that there is a wide variety of generation rates (g/min) for the various nebulizers selected.

Using an airflow of 3 L/min (Figure 1), the lowest generation rate was <0.05 g/min for the Wright and EVO nebulizers. The highest generation output at the same airflow for the Mini-Heart nebulizer was over three times higher at 0.15 g/min. All nebulizers apart from the Wright device gave a linear increase in output from 3 L/min to 7 L/min.

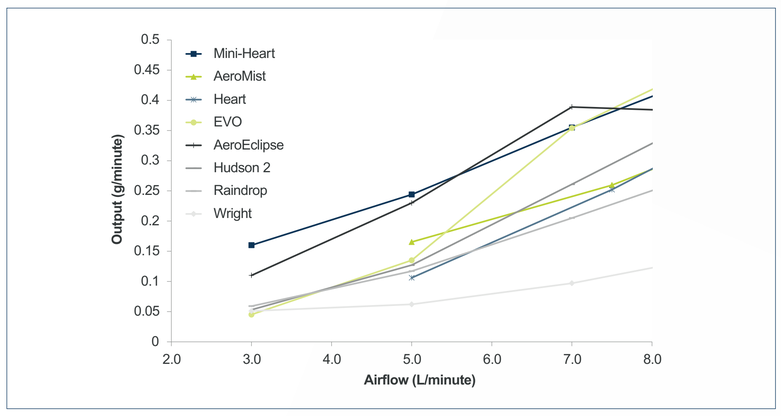

Figure 1. Nebulizer output from 3 to 8 L/min

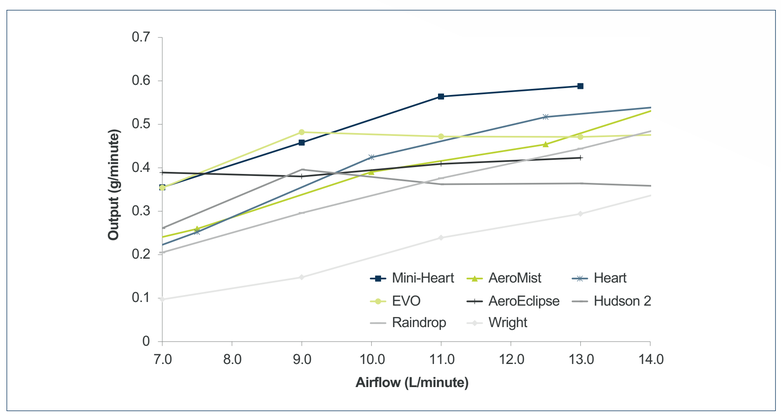

Figure 2. Nebulizer output from 7 to 14 L/min

At airflows up to 12 L/min, the outputs from several devices either did not increase proportionately or gave no increase in output irrespective of any continued increase in airflow (Figure 2). This was particularly apparent for the AeroEclipse, Hudson 2 and EVO devices. A gradual decline in output was observed for the Raindrop and Mini-Heart.

Figure 3. Nebulizer output from 12 to 28 L/min

At airflows between 12 and 20 L/min (Figure 3), there were several devices that still gave a proportionate increase in output with increased with airflow. These included the HEART, AeroMist and Wright nebulizers.

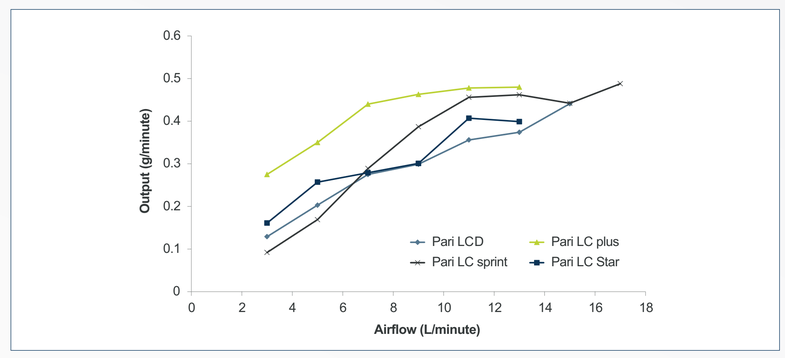

Figure 4. Nebulizer output from the four Pari nebulizers

The Pari series of nebulizers were also evaluated over a comparable airflow range. From the data presented in Figure 4, the Pari LC plus gave the highest output from 3 L/min to 13 L/min even though there was a gradual decline in the rate of output from 7 L/min. The decline in output was also observed for the Pari LC Sprint at airflows exceeding 10 L/min. However, a continual increase in output was observed using the Pari LC D up to an airflow of 15/Lmin. From the data, the device which gave the highest and most importantly, consistent output over the range usually used for jet nebulizers was the Mini-Heart. The Wright nebulizer gave the lowest output from those evaluated. To make an effective and informed decision selecting an appropriate nebulizer, further parameters and considerations are required.

These include:

- Study duration.
- Study objective.
- Dose levels.
- Number of animals being dosed simultaneously.
- Daily exposure duration.
- Amount of active test material available.
- Solution vs suspension.
- Active test material physical characteristics.
- Formulation excipients and concentrations.
- Airflow required for the animals.
- Limit of solubility.
- Surface tension or viscosity.
- Propensity of component aggregation.
- Minimum and maximum priming volume.
- Passiveness or vigorous nature of the refluxing action within the nebulizer.
- Temperature of the solution or suspension in the nebulizer during nebulisation.

Conclusions

This poster provides a direct comparison of the different delivery rates from individual nebulizers over a range of airflows. We are therefore able to predict with greater accuracy the formulation requirements and provide scientific expertise for recommendations for a given study design. This is of particular importance when an active drug is very expensive and nonclinical programme time lines are critical.

COVANCE
SOLUTIONS MADE REAL®