Meeting Aerosol Delivery Standards from Mesh Micropump Nebulizers for a Test Item Formulated in Ultrapure Water – A Case Study

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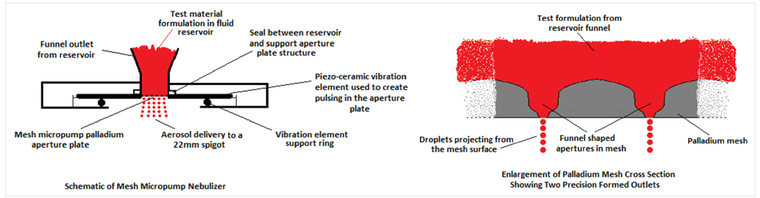
Introduction

Initial technical trials delivering an oligonucleotide test material formulated into ultrapure water using a partner-designated clinical mesh micropump delivery platform identified two nebulizer performance challenges that were each capable of limiting the required nonclinical program. The partner had been working with the nebulizer manufacturer to obtain sufficiently reliable delivery within the scope of the clinical program, but while able to generate the test item with high efficiency for required clinical periods of generation, the selected platform was subject to frequent delivery failures. Each occasion of stoppage required attending staff to either repeatedly intervene by tapping the reservoir, to invert the unit while tapping it until generation resumed or to manually clean the aerosol outlet spigot.

Mesh micropump aerosol generation was considered essential to the delivery of the intact oligonucleotide to the respiratory tract.

Principle of Mesh Nebulizer Aerosol Generation

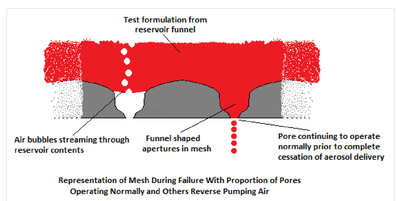
The nebulizer platform used in this work has a 5mm palladium vibrating mesh surface that is perforated with precision-formed, funnel-shaped holes with approximately 50 perforations per mm^2. When vibrated at high frequency (over 125,000 times per second), the mesh acts as a pump, actively drawing fluid from the reservoir through the perforations and projecting a low-velocity aerosol stream from the underside of the nebulizer. In clinical use, the output is commonly directed into the inspiratory limb of respiratory circuits, mouthpiece or a patient facemask. In the nonclinical studies conducted by Labcorp, nebulizer output was directed into a stream of carrier air for delivery to the animal breathing zone. Due to the low formulation concentration available, the combined output from several units was necessary to maximize the delivered aerosol concentration.



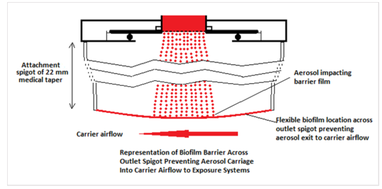
Challenge Statement

Delivery of the required multiples of the anticipated clinical dosages to satisfy regulatory requirements in the nonclinical phase had been calculated to require aerosol generation from multiple mesh nebulizer units for exposure periods of up to 6 hours. Early Labcorp investigations showed increasing aerosol concentration into the airflow required for the animal exposures while using the combined output from three nebulizers, but no additional benefit from adding a fourth unit due to increased droplet:droplet interactions.

Trials into rodent exposure systems demonstrated that, using any individual nebulizer, aerosol generation could be anticipated to variably reduce significantly or to discontinue altogether within intervals ranging from a few seconds to several minutes. The most rapid delivery failures were observed to associate with the presence of fine bubbles rising from the nebulizer mesh surface through the reservoir contents. Air bubbles were not observed in the reservoirs during periods of satisfactory operation; consequently this observation was concluded to be an indicator of the nebulization failure. Vibration of an affected unit would reinitiate aerosol generation and eliminated the bubble stream. It was concluded that presence of the bubbles represented reverse operation of the nebulizers with air transitioning from the outlet side of the palladium foil to the reservoir side of the mesh surface. As the test item concentration in formulation was low (0.5mg/mL) and prepared in ultrapure water, it was further concluded that high formulation surface tension was bridging the “pores” in the mesh surface, encouraging air to pump in the reverse direction of the intended fluid flow.



A second and lower frequency failure occurred due to the formation of a flexible test material bubble across the 22mm nebulizer outlet. This failure generally occurred after periods of aerosol production that exceeded the operational interval that could be reliably obtained without technician intervention to address reverse air pumping described previously. As mesh micropump nebulization is achieved without parallel air delivery through the nebulizer, the test item film was presenting an impaction barrier to aerosol droplets leaving the mesh and wholly preventing delivery to the lateral carrier airflow delivering the aerosol to exposure systems.



Methods – Initial Trials

The program partner had advised that most nebulization failures could be addressed by sharply tapping the nebulizer reservoir. Initial aerosol generation trials confirmed the partner findings and demonstrated that even during periods of moderately reliable individual nebulizer operation it was not possible to obtain a consistent aerosol concentration from three units operating in parallel without intervention from technical staff. Close observation of the units together with a continuous cycle of tapping the reservoir and wiping the outlets proved essential. Throughout early aerosol trials, the time interval preceding nebulization failure was unpredictable, requiring constant close attention for every system. Due to the requirement to operate multiple systems in parallel for periods of over 6 hours, manual agitation was not considered a feasible solution.

The solution, based on prior Labcorp experience with powder delivery systems, required one of our technical staff to visit an “Adult” store and purchase a “personal massager” device. The “massager” was dismantled to access the electromagnetic vibration unit that was then attached to the side of a single nebulizer. This addition dramatically improved the reliability of the generation platform/test item delivery combination, but the vibration was excessive, continuous and unpleasantly loud. Purchase and reconfiguring multiple “massagers” was considered but rejected as a range of low-voltage, haptic-feedback devices had been identified by the Labcorp Innovation Engineering Services group. These low-cost vibration devices, commonly used in cell phones to indicate an incoming call, were of an appropriate size and energy to allow direct attachment to individual nebulizers.

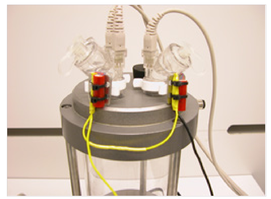


Figure 1. Prototype haptic-feedback device vibrators attached in series.

In the early trials using the prototype Labcorp-manufactured shaker mechanism, continuous vibration of the reservoirs was used and the shakers were wired in series. While providing consistent aerosol delivery, sequential wiring was associated with frequent individual shaker mechanism failure due to breakages in the fine direct current wiring and the cessation of operation for all connected units. To reduce this attrition rate, the unit power was cycled through electrical supply interrupter units and the shaker units were wired individually. The optimal interruption rate was found to be 4 seconds operation within a 12-second operational cycle.

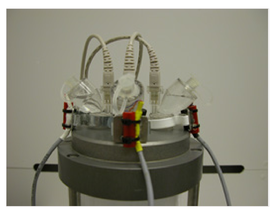


Figure 2. Individually wired haptic feedback vibrators.

During Maximum Tolerated Dose Inhalation studies, it became evident that even with the modified operational cycle and separate power supply, the units were still subject to vibration damage during the long exposure times. In the early versions, the haptic-feedback vibrators were attached to reservoirs with electrical zip ties. To prevent wiring damage, the shaker elements were housed in plastic casings and fully embedded in epoxy resin. This enhanced energy transfer from the shakers to the nebulizers and eliminated the wiring fragility issue.

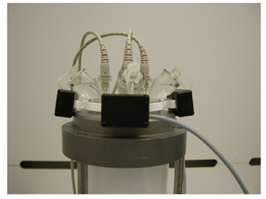


Figure 3. Encapsulated nebulizer vibrators.

Results

By developing the shaker/vibrator units it was possible to reliably run multiple nebulizers to each exposure system for periods of greater than 6 hours per exposure day. It remained necessary to monitor output at regular interval due to the residual occurrence of biofilm formation over the nebulizer outlets. The modified nebulizers were used successfully for two programs that required rat and nonhuman primate exposures which were conducted in alignment with animal welfare regulatory requirements in an AAALAC-accredited facility.

Table 1. Rodent Exposure System 28-Day Study (three nebulizers)

	Total Test Item Delivered Dose (mg/kg)			
Group	Target	Males	Females	Mean
1	0	0	0	0
2	0	0	0	0
3	0.7	0.74	0.8	0.77
4	3.75	3.89	4.2	4.05
5	6.4	6.35	7.05	6.7

Table 2. Nonhuman Primate Exposure System 28-Day Study (three nebulizers)

	Total Test Item Delivered Dose (mg/kg)			
Group	Target	Males	Females	Mean
1	0	0	0	0
2	0	0	0	0
3	0.2	0.34	0.34	0.34
4	0.5	0.64	0.64	0.64
5	0.9	1.24	1.24	1.24

Conclusions

Mesh micropump nebulizers can provide high efficiency aerosol generation for fragile test items and are generally simple to operate. Aerosol is produced without the reflux, vehicle evaporation/test item concentration and importantly, for fragile materials, without the shear that occurs in compressed air nebulizer systems.

Mesh micropump units can though for some formulation types be negatively impacted by factors including progressive mesh blockage, reverse pumping of air into the reservoir and biofilm formation over the outlet spigot.

In the programs described in this poster reliable generation was obtained from the partner specified mesh platform by the addition of Labcorp designed and manufactured reservoir vibration units. Labcorp experience and methods using the nebulizers in these programs was subsequently shared with the nebulizer manufacturer.

Larger studies requiring the combined output from four nebulizers are planned in 2022.

Acknowledgements

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