

Effect of MUNODA Device on Aerosol Delivery by Small Volume Nebulizer With Aerosol Mask & Non-Rebreathing Mask Interfaces

Objectives. Compare the effects on aerosol delivery to a bench model of simulated breathing of a standard small volume pneumatic jet medication nebulizer (Hudson MicroMist) under the following test configurations:

- (1) connected to a standard aerosol mask (primary baseline for comparison);
- (2) “slipped under” the edge of a standard nonrebreathing mask and positioned at ~45° tilt;
- (3) connected to one limb of the MUNODA device while the other limb of the MUNODA device (with the spring-loaded check valve) is connected to the reservoir bag of the nonrebreathing mask.

Abbreviations Used in This Report.

^{99m}Tc	Refers to the isotope Technetium-99m
DTPA	Diethylene triaminepenta-acetic acid
f	Frequency (breathing rate) in breaths/minute
F&P	Fisher & Paykel
GE	General Electric
I:E	Inspiratory-to-Expiratory time ratio
IM	Inhaled Mass
mCi	millicuries
NRB	Non-rebreathing (mask)
NSS	Normal Saline Solution (0.9%NaCl)
psig	pounds per square inch, gauge
RM	Residual Mass
SVN	Small Volume Nebulizer
VT	Tidal Volume in mL

Methods. This study was an *in vitro* test of aerosol delivery with 3 different test configurations, each using the same nebulizer as a control, and each representing a different device interface to the simulated patient. The study goal was to simulate aerosol delivery with each of the 3 methods and measure the outcomes in terms of Inhaled Mass, Residual Mass and other parameters.

Equipment & Supplies:

- Normal saline solution (NSS), 3 mL
- Technetium^{99m}-DTPA (~0.5 – 5 mCi)
- ‘H’-sized medical air cylinder with 50 psig regulator and back-pressure compensated 0 – 15 L/min flowmeter
- ‘E’-sized oxygen cylinder with fixed orifice flowmeter/regulator with an 8 L/min setting
- Pari #041B0522 Filter Pads and compatible filter holders
- GE MaxiCam Gamma Scintigraphy Camera and associated computer
- Harvard 615-type piston ventilator (breathing pattern simulator)
- F&P plastic demonstration head (head model) with 22-mm simulated mouth opening

Devices:

- One (1) Hudson #1883 MicroMist small volume nebulizer
- One (1) Airlife #1206 adult disposable aerosol mask
- Two (2) Airlife #1203 adult disposable nonrebreathing masks
- Two (2) MUNODA multifunction devices

Procedures:

- **Common to each test run:**

- Using the gamma camera, the 'room background' radioactivity was determined and recorded immediately prior to each test run, and subsequently subtracted from each measurement prior to mass calculation.
- 3 mL of NSS was drawn into a 5 mL syringe and 3 to 5 drops of ^{99m}Tc -DTPA was added to the syringe to render radioactivity between 0.5 and 1.5 mCi.
- The contents of the syringe were expressed into the cup of the Hudson MicroMist small volume nebulizer through the top of the nebulizer and gently swirled for a few seconds to achieve thorough mixing.
- The nebulizer was placed on the gamma camera and counted for 1-minute to obtain the value for the nebulizers Initial Charge (counts). The data and image were saved in the gamma camera computer.
- After determining the nebulizer's Initial Charge, the nebulizer was attached to the device under test and operated according to the study protocol below.
- The delivery tubing from the portable oxygen cylinder was connected to the nebulizer but not turned on at this time.
- A Pari aerosol collection filter, "IM Filter" (Inhaled Mass Filter), was placed inside the head model and connected to the "mouth" port to capture aerosol that was inhaled by the test model.
- The other side of the "mouth" port inside the head model was connected via a length of flex tubing to the Harvard pump sinusoidal breathing simulator which was set at a breathing rate of 15/min, tidal volume of 500 mL and I:E ratio of 1:1.
- After ensuring all connections were correct and tight, the Harvard Pump was turned on to commence simulated respiration through the nebulizer assembly.
- The oxygen cylinder's fixed orifice flowmeter was set at 8 L/min and a stopwatch was activated to commence the start of the experimental test run.
- The nebulizer was allowed to run for exactly 8 minutes and then immediately turned off. [Preliminary testing determined that a reliable complete run time for this nebulizer would be 8 minutes for all tests ("sputtering" had been heard and visualized, no further aerosol was being created and emitted (no mist was forming in the nebulizer and no large drops were falling)]. The nebulizer was not tapped during any test runs because (1) this is subjective and leads to uncontrolled variations in test protocol and (2) tapping a nebulizer has been shown to not actually be significantly effective with respect to increasing inhaled dose.
- After the predetermined treatment time of 8 minutes had elapsed, the test was stopped and the various device components, starting with the Residual Mass in the nebulizer and the Inhaled Mass filter were measured individually in the gamma camera.
- The nebulizer was thoroughly washed in running tap water after each experiment, to remove residual radioactivity, then dried prior to the subsequent experiment.

- **For the Aerosol Mask test configuration:**

- The aerosol mask was placed on the head model, taking care to position it symmetrically and minimize leakage around the edge of the mask.
- The nebulizer was inserted into the appropriate port of the aerosol mask and operated accordingly.
- The nebulizer was operated with oxygen at 8 L/min for the E-cylinder.



- **For the Nebulizer “Slipped Under” the Non-Rebreathing Mask test configuration:**

- The NRB was placed on the head model, taking care to position it symmetrically and minimize leakage around the edge of the mask.
- The nebulizer was “slipped under” the edge of the mask on one side of the head model and tilted approximately 45° from true vertical.
- The nebulizer was operated with oxygen at 8 L/min from the E-cylinder.
- The NRB mask was supplied with medical air from the H-cylinder at a flowrate of 10 L/min.



- **For the MUNODA/NRB Mask test configuration:**

- The NRB was placed on the head model, taking care to position it symmetrically and minimize leakage around the edge of the mask.
- The reservoir bag was removed from the mask and placed into the vertical limb of the MUNODA device, opening the one-way valve.
- The nebulizer was inserted into the offset limb of the MUNODA device but maintained in a vertical position.
- The nebulizer was operated with oxygen at 8 L/min from the E-cylinder.
- The NRB mask was supplied with medical air from the H-cylinder at a flowrate of 10 L/min.



- **Analysis:**

- At the conclusion of each test run, the **Nebulizer Residual** activity was determined by removing it from the test setup, placing it on the gamma camera and counting the emitted gamma activity for 1 minute, whereupon the total gamma counts and time were recorded and an image saved.
- Next, the **Inhaled Mass** filter’s activity was similarly measured on the gamma camera.
- In some tests, other parts of the tested configuration (such as the mask, the reservoir bag, or the MUNODA device) were similarly measured on the gamma camera. This was done in selected tests to render a complete “Mass Balance” accounting of the fate of the Initial Charge at the conclusion of the test run.

- In some tests, the head model was situated on a stand facing the front of the gamma camera and aligned with the nose of the model exactly centered on the camera head at a distance of approximately 1-inch. This was done in selected tests as part of the Mass balance determination and to render image of radioactive aerosol deposited on the “face” of the head model.
- All measurements were entered into an Excel spreadsheet to record the data and correct it for the radioactivity gamma decay factor for ^{99m}Tc that occurred between the time the Nebulizer Charge was recorded and the time of each subsequent measurement.

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Results

The table below summarizes the mean Inhaled Mass, Residual Mass and Mass Balance results for the 3 different test configurations. The Inhaled Mass and Residual Mass were measured directly. A Mass Balance of 100% was assumed such that the difference between 100% and the sum of the IM and RM estimate the "Other Losses," or aerosol that was generated and emitted from the nebulizer but not directly measured. When these losses cannot be directly measured, they are inferred in order to account for 100% of the radioactivity (which represents drug dose) initially placed in the nebulizer. These losses are typically comprised of (1) aerosol that is generated and emitted during the exhalation phase and is lost to the room and, (2) aerosol that is generated and emitted during the inspiratory phase but escapes to the room through ports in the mask and/or around the edges of the mask when a perfect seal cannot be obtained. "Other Losses" represents **wasted aerosol**: aerosol that has been generated by the nebulizer, and emitted from the nebulizer, but was not inhaled and not deposited on any portion of the device or system.

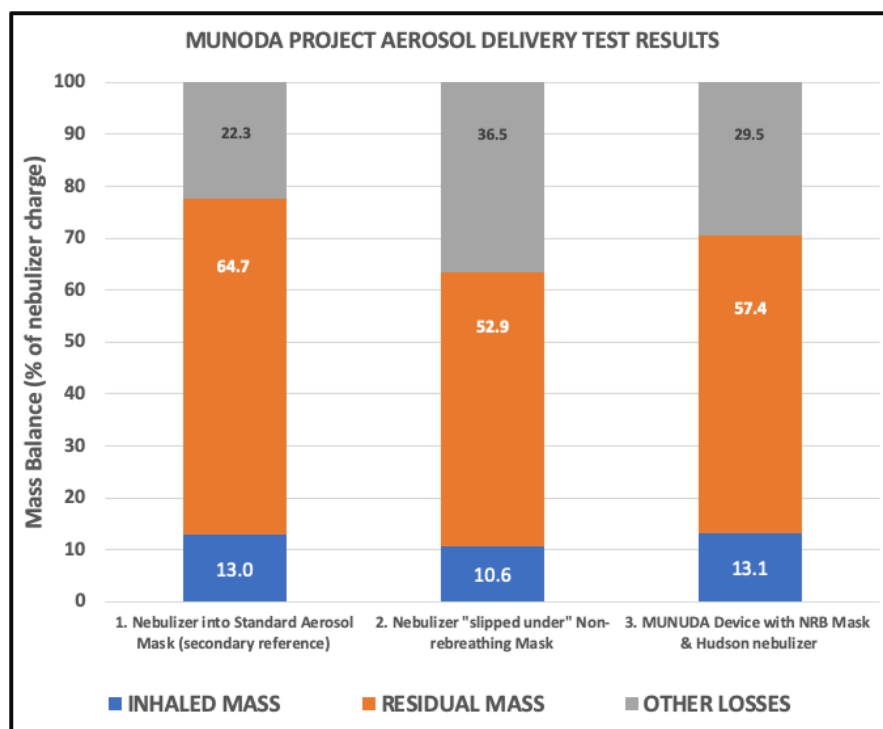
Summary of Inhaled Mass and estimated Mass Balance results, means of multiple test runs.

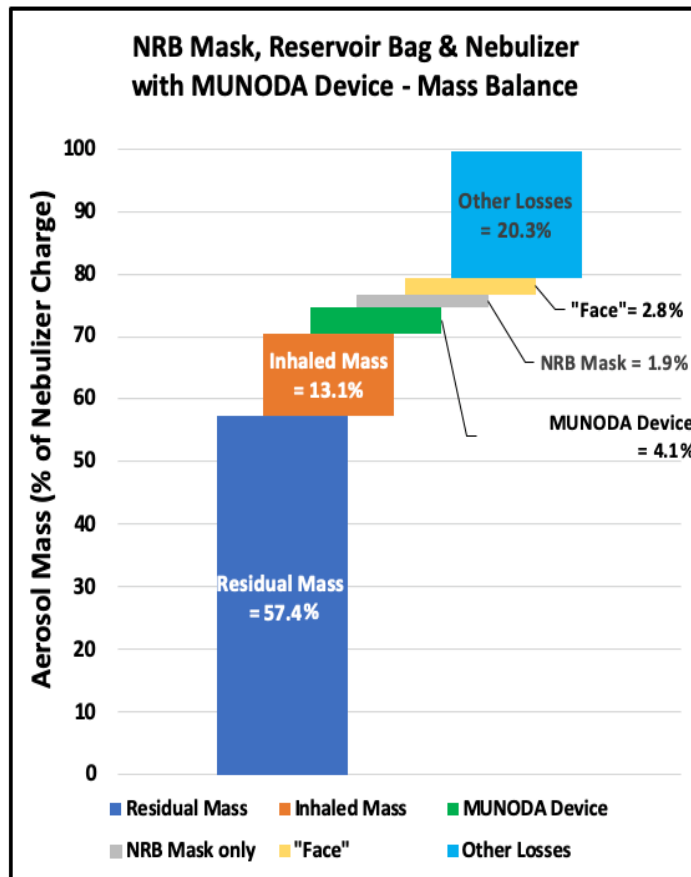
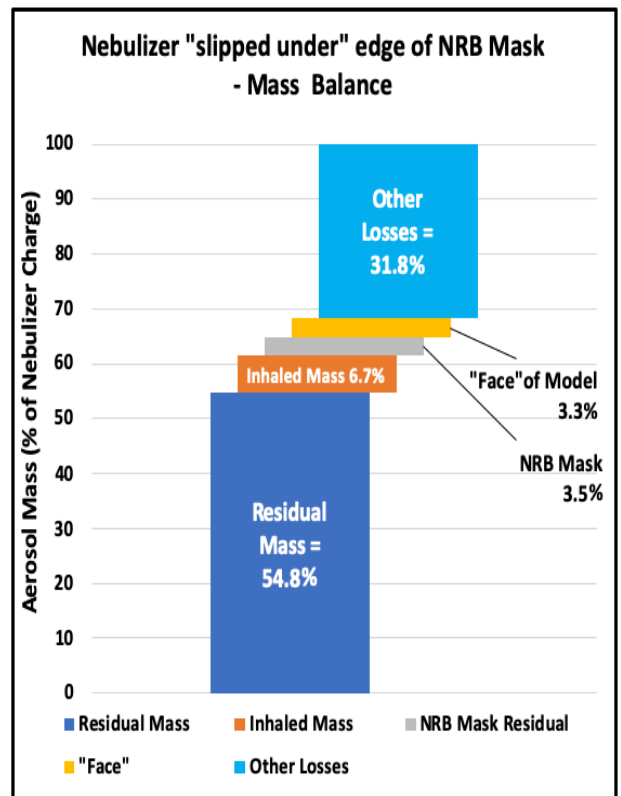
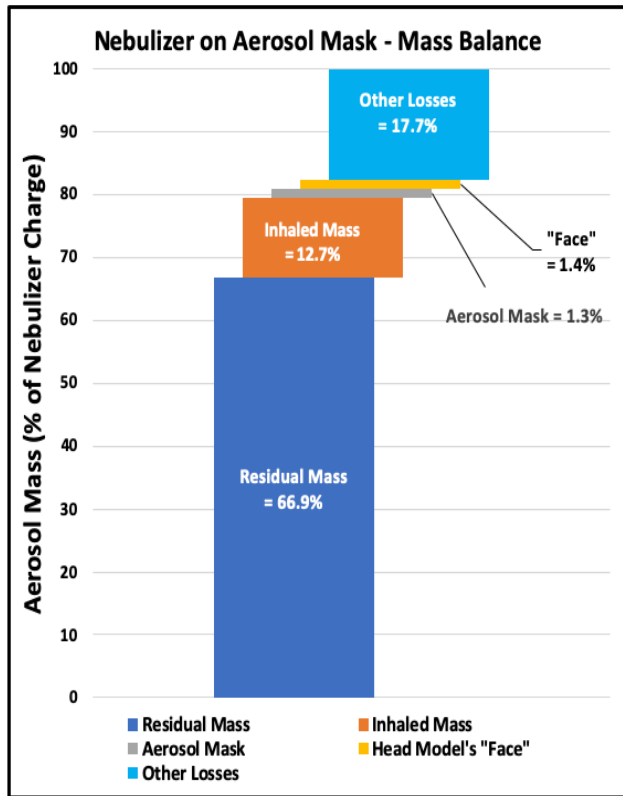
Test Configurations:	RESULTS			
	INHALED MASS	RESIDUAL MASS	OTHER LOSSES	Mass Balance %
	(% of neb charge)	(% of neb charge)	(% of neb charge)	
1. Nebulizer into Standard Aerosol Mask (secondary reference)	13.0	64.7	22.3	100
2. Nebulizer "slipped under" Non-rebreathing Mask	10.6	52.9	36.5	100
3. MUNUDA Device with NRB Mask & Hudson nebulizer	13.1	57.4	29.5	100

Conditions:

1. Same Hudson MicroMist nebulizer used for all configurations.
2. Nebulizer filled with 3 mL radiolabeled normal saline.
3. Nebulizer operated at 8 L/min with medical air @ 50 psig.
4. When used, NRB mask operated at 10 L/min with oxygen @ 50 psig.
5. Breathing pattern & simulation supplied by Harvard #615 piston ventilator: sinusoidal flow wave, f = 15 breaths/min, VT = 500 mL, I:E = 1:1.

In addition to the Inhaled Mass and estimated Mass Balance determination for the 3 test configurations shown above, the comprehensive Mass Balances that were determined once for each test configuration are shown graphically below. All colored data points sum to 100%.





Discussion

These *in vitro* results express aerosol **delivery** to the airway opening of a surrogate breathing simulator (test lung) as a function of the breathing pattern and device configuration. These tests and results do not represent any determinations or estimates of aerosol deposition to the lung. *In vivo* deposition studies are typically conducted to ascertain actual intrapulmonary deposition and distribution.

The primary determinant in all of these tests is Inhaled Mass (IM), which represents that fraction of the nebulizer output that would have been inhaled into the test lung if it had not been captured on the measurement filter. IM is therefore defined as the percentage of the initial charge of drug placed in the nebulizer. The initial charge could be the 'volume' of drug solution placed into the nebulizer but that doesn't help determine what is being delivered to the patient. It makes better sense to work with the **mass** of the drug (in mg or µg) because that is how medication dosage is referred to.

In the case of these bench tests, the charge is actually an amount of radioactivity (gamma energy) emitted by the isotope Technetium (^{99m}Tc) which is placed in the nebulizer as a surrogate for the drug. Technetium behaves in the nebulizer identically to aqueous inhalation drug solutions and can be easily measured with appropriate instruments anywhere in the nebulizer, the capture filter, the face model, etc. The drug itself cannot. So, the Technetium is substituted for the actual drug and indicates how much 'drug' mass with which the nebulizer is charged, how much mass remains in the nebulizer after the treatment, and how much mass is delivered to the IM filter. The amount of drug **mass** (not volume) remaining in the nebulizer after the treatment has concluded is called the Residual Mass, and it is also expressed as a percentage of the initial charge placed in the nebulizer.

In theory, all of the radioactivity that is initially placed in the nebulizer should be accounted for (Mass Balance) at the conclusion of the treatment. However, this only happens in a completely closed system where aerosol cannot escape to the room. Therefore, the "Other Losses" reported herein refer to that portion of the initial charge that was aerosolized and emitted from the nebulizer but was not recovered or directly measured anywhere in the system. To the greatest extent possible, documentation of 'Other Losses' as aerosol having deposited inside the mask, or directly on the 'face' of the model, was done by measuring those parts on the gamma camera. However, during mask therapy a substantial portion of 'Other Losses' in Mass Balance is actually aerosol that leaks past the mask into the room air and is thus unrecoverable. Obviously, this is one of the known challenges of mask therapy for aerosol delivery and is often difficult to control.

Objective Description of Results. Referring back to the figures in the beginning of the results section ...

Test config #1 (Nebulizer into Standard Aerosol Mask). The mean IM was 13.0% and the RM slightly increased to 66.9%, which is one component of the decrease in IM compared to the "tee" nebulizer. In the particular test run highlighted by the bar graph, the 'Other Losses' portion of the aerosol mask Mass Balance is approximately equal to that amount that lost through the exhalation filter on the tee neb. So, that does not seem to be the cause of the decrease in IM. Instead, there is deposition inside the mask (1.3%) and on the face of the head model (1.4%), probably due to turbulence as the aerosol enters the mask cavity from the nebulizer. While not a great amount, along with the slightly increased RM, it contributed to the overall decrease in IM.

Test config #2 (Nebulizer 'Slipped Under' the Edge of the NRB Mask). The mean IM decreased to 10.6%, as a result of many factors. The RM also decreased substantially, probably as a result tilting the nebulizer. Presumably, tilting the nebulizer to a 45° angle allowed somewhat more solution to be aerosolized thereby decreasing the RM. However, the decrease in RM did not translate into increased IM because it was offset by other factors, chiefly the significant increase in 'Other Losses.' Inasmuch as Other Losses during mask therapy are due mainly to leaks around the mask, slipping the nebulizer under an edge of the mask exacerbates this problem by opening up a very large area for aerosol to escape. This is likely the primary factor for the decreased IM with this approach. In the example shown in the bar graph figure for this setup,

the IM for this particular test run was 6.7%, even though the average of all test runs was slightly higher at 10.6%. This indicates that there is also uncontrolled variation in IM using this method of aerosol delivery.

It also appears that a somewhat greater amount of aerosol was deposited inside the mask (3.5%) and on the face of the head model (3.3%) by using this unconventional technique. Ordinarily, this might not be considered significant, but when the 'Other Losses' are already so high, the mask and facial deposition losses that were exacerbated by this technique only serve to reduce IM even further.

Test config #3 (NRB Mask & Nebulizer Interfaced via MUNODA device). When the MUNODA device was used to interface the reservoir bag and nebulizer to the NRB mask, the IM increased to 13.1% which is comparable to the value achieved with the aerosol mask. This was accomplished largely through reduction of 'Other Losses,' (decreased from 31.8 to 20.3%) which also managed to offset the losses on the face of the head model (2.8%), inside the NRB mask (1.9%), and inside the MUNODA device itself (4.1%).

Not all patients are able to use a mouthpiece, thus interfacing the small volume nebulizer with a mask is the next best option. For example, attaching the nebulizer to a standard aerosol mask is a commonly accepted solution which resulted in an Inhaled Mass delivery of 13.0% of the nebulizer charge, justifying use of the aerosol mask interface as the baseline mode in this study.

In some areas, a prevailing practice is to place the small volume nebulizer under the edge of the NRB mask on one side of the face, particularly when patients are already receiving high FIO₂ through a non-rebreathing (NRB) mask and aerosol therapy is subsequently prescribed. In the bench tested reported herein (test config #3), that procedure created a large gap in the seal of the mask to the face on that side which, presumably, also happens clinically with actual patients. That large gap argues against conventional respiratory therapy teaching with respect to the necessity of establishing a good seal for mask therapy: both for FIO₂ control as well as aerosol delivery. Although FIO₂ was not measured in this study, it would have been predictably and severely decreased.

Slipping a nebulizer under the edge of the NRB mask in a tilted position with a large gap in the mask seal, decreased mean aerosol delivery compared to the aerosol mask reference (10.6% vs 13.0%). The bar graphs show the **worst-case scenario** revealed in testing, an IM of 6.7%. Because the basic problem with this approach at the bedside is that actual inhaled mass is likely an unpredictable variable; a practitioner has no way of knowing whether this unconventional technique is rendering acceptable therapy, or worst-case therapy until and unless the patient deteriorates or fails to improve with therapy.

Limitations of This Study

This study has a number of limitations. First, only a single brand of SVN was utilized. There are multiple brands of SVN on the market and some may perform better or worse than the one used in this study. It was beyond the scope of this study to test multiple brands of small volume nebulizer.

Second, inasmuch as this was essentially a proof-of-concept study, only a few tests of each configuration were conducted. The sample size was therefore too small to make any meaningful statistical inferences as to significance of difference.

Third, only a single breathing pattern was used ($f = 15$ breaths/min; $VT = 500$ mL; $I:E = 1:1$). Arguably, this is a normal adult breathing pattern, although the I:E ratio of 1:1 tends to demonstrate "best case" aerosol delivery. More comprehensive testing might have included both adult and pediatric breathing patterns and shorter inspiratory times. Nevertheless, the breathing pattern was sufficient to prove the point that slipping an SVN under the edge of a mask decreases aerosol delivery.

Conclusion

Based upon limited testing, Inhaled Mass, as % of initial charge placed in the nebulizer, was determined for 3 test configurations: (1) an SVN into an aerosol mask setup, (2) an SVN slipped under the edge of an NRB mask and operated at a 45° angle, and (3) an SVN and reservoir bag interfaced to an NRB via the MUNODA device. Configuration 1 represented a typical clinical scenario and serves as a baseline or control. Configuration 2 is an unconventional technique for aerosol delivery in patients using an NRB mask. Configuration 3 is a suggested remedy for the unconventional technique embodied by Configuration 2.

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|--|-----------------|
| • Configuration 1 (SVN/aerosol mask): | Mean IM = 13.0% |
| • Configuration 2 (SVN slipped under NRB mask): | Mean IM = 10.6% |
| • Configuration 3 (SVN interfaced to NRB with MUNODA): | Mean IM = 13.1% |

Therefore, based upon limited testing, the unconventional technique of slipping a nebulizer under the edge of an NRB mask should be discontinued. Not only is it intuitively poor technique, but these results suggest that it can substantially diminish the Inhaled Mass of aerosolized medication delivered to a patient. These tests also suggest that the MUNODA device, used as described herein, can restore aerosol delivery during NRB mask therapy to levels comparable to the mean results rendered for the aerosol mask.

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