Keep Breathing! SMIs Deliver More

SMIs Deliver Higher Single Breath Doses Than Nebulisers

Takeaway Message
MRX004 SMI delivers single breath doses 3 to 5 times higher than nebulisers.

We contend that nebulisers are serial SMIs and only achieve mg delivered doses because of repeat dosing.

In short, Keep Breathing!
SMIs deliver more – Q.E.D.

For many years, nebulisers have been the preferred choice for respiratory drug developers needing an inhaler to deliver high doses to the lungs. This preference is largely due to nebulisers' ability to deliver a continuous stream of aerosol that can be inhaled via natural, tidal breathing over several minutes, thereby seemingly facilitating the delivery of high doses. However, a shift in perspective reveals a superior alternative: the soft mist inhaler (SMI), particularly the MRX004. SMIs deliver medication as a fine mist, which can be deeply inhaled in a single breath, offering greater efficiency and convenience (www.mrx004.com).

Delivering High Doses To The Lungs – Nebulisers Are A Legacy Technology

To understand why an alternative to nebulisers is desirable, it is important to recognise their limitations. Nebulisers are bulky devices that require an external electric power source to aerosolise a drug solution. The patient sits and inhales for several minutes, making the use of a nebuliser a time-consuming process. This is compounded by the high level of manual handling required through the assembly of the device, dispensing of the dose, and cleaning and maintenance of the nebuliser. Nebulisers are not portable inhalers, unlike pMDIs, DPIs and SMIs.

Nebulisers are comparatively wasteful. The need for electricity creates a demand for power that is unnecessary for purely mechanical devices like SMIs. In addition to spare parts requiring changing (metering chambers, tubing, masks), the aerosol is continuous, meaning that the patient is only breathing in half of the emitted dose. The other half is exhaled, wasting valuable drug product and contaminating the air around the patients. Nebulisers rely on tidal breathing to deliver the drug to the lungs; this is characterised by shallow breathing with a breathing cycle of about 15 breaths (inhale/exhale cycle) per minute, each characterised by an inhalation/exhalation cycle, or 6 effective inhalations per minute. This translates into a 4 seconds breathing cycle and an inhalation duration of 2 seconds. A single dose from a nebuliser therefore takes 2 seconds to be delivered; bear that number in mind.

The efficiency of a nebuliser is characterised by the fine particle fraction delivered to the deep lung, *i.e.* the proportion of droplets below 5 mm. Typically this is about 30%, in some exceptional cases 50%, once the losses from exhalations are discounted.

Are Nebulisers Serial SMIs? – The Challenge Of Comparing SMIs And Nebulisers

SMIs, such as Merxin Ltd's MRX004, deliver drugs to the lung by producing a slow-moving mist that patients inhale via a bolus or deep inhalation. Unlike nebulisers, SMIs deliver a discrete metered dose upon activation rather than a continual stream. In the case of MRX004, each dose is delivered in 1.5 seconds. No drug is wasted during exhalation, as an entire unit dose is delivered in a single, deep inhalation, rather than requiring the patient to sit and breathe with the device for an extended period as with a nebuliser.

The precise dosing capability of SMIs allows developers to accurately determine the amount of drug delivered with each activation. This precision has sometimes led to the perception of SMIs as a low-dose format. However, this is only the case if we limit the SMI to single doses. By administering multiple activations in sequence – similar to how nebulisers deliver medication over multiple continuous breaths – SMIs can effectively deliver high drug doses to the lungs. In this context, it is possible to see a nebuliser as a serial SMI, delivering drug over multiple continuous breaths where an SMI delivers doses one breath at a time.

What matters therefore is to compare the single dose delivered by an SMI with the single dose delivered in one inhalation by a nebuliser.

Thinking in this way, a fair comparison of SMIs and nebulisers requires comparing them breath-for-breath, single dose for single dose, metered dose for metered dose. However, doing so from existing literature is difficult as there is a wide variety of performance characterisation across nebulisers, droplet size, formulation concentration, physical properties, and drug wastage during exhalation, as well as a paucity of single breath/dose measurements. To make the task of accurate comparison even more difficult, the *in vitro* performance testing requirements for nebulisers and SMIs in the EU and US Pharmacopoeias are not aligned; nebulisers are averaged over the therapy's duration (a timescale of minutes), while SMIs are assessed on a single spray (a matter of seconds). Traditionally the output of nebulisers is given in mL/min, not corrected for fine particle fraction and breathing cycles, while the output of portable inhalers (pMDIs, DPIs and SMIs) is quoted in weight of the fine particle dose (droplet/particles below 5 µm) of API per metered dose ex-device delivered at a fixed flow rate.

Taking these limitations into account, the best way to make a direct comparison of a nebuliser with an SMI is to calculate the fine particle dose (FPD) of a single breath for each. For an SMI, this value can be calculated from a single activation and is already standardised. For nebulisers, a new calculation is required, and this is what we are going to use in this article.

Let us assume that the entire content of a nebule is delivered in a single sitting, so we can use the following formula to calculate the FPD per breath:

$$FPD = \frac{DOSE}{TIME} \times DURATION \times FPF$$

Here, TIME is the time taken for the entire dose to be delivered during nebulisation (usually of the order of minutes). DOSE is the dose contained in the nebuliser (typically 1 mg in a 1 mL nebule). The DOSE/TIME ratio is in fact the output of the nebuliser and is a physical limitation of the nebuliser. FPF is the fine particle fraction of the delivered dose (typically 30% for nebuliser due to

inefficiencies and tidal breathing that do not promote deep lung deposition). DURATION is the length of one breath, which as mentioned above is defined as 2 seconds by the US Pharmacopeia and ISO standards.[2]

Using this formula in conjunction with available literature, one can calculate a theoretical FPD per breath emitted from a nebuliser. Assuming a nebule concentration of 1 mg/mL and a nebule volume of 1 mL to normalise the calculations, the DURATION of the inhalation is fixed at 2 seconds as per the pharmacopoeia. One can calculate the FPD by varying the TIME and FPF. The theoretical range of nebuliser FPDs are listed in Table 1.

Assuming a 50% FPF and a TIME of 8 minutes, the FPD per breath of an average nebuliser is 1.67 µg.

Where CONCENTRATION is the API bulk concentration in the cartridge and MC is the volume of the metering chamber (15 µL).

MRX004 has a FPF of 70%. If we assume an API bulk concentration of 1 mg/mL, the unit dose per breath is 10.5 µg, or about 5 times the single breath FPD of a nebuliser (cf 1.67 µg).

Theoretical FPDs of MRX004 for a range of FPFs are listed in Table 3.

Recent publications at DDL 2023 on the FPD of MRX004 can be compared with theoretical values. The experimental FPD per inhalation of MRX004 SMI for Dornase Dornase Alfa (2.5 mg/ 2.5 mL) was 6.28 µg[4] and Salbutamol 5 mg/mL was 35.1 µg, or 7 µg

FPD µg	Time – min						
FPF – %	2 min	4 min	5 min	8 min	10 min	12 min	15 min
30%	5.00	2.50	2.00	1.25	1.00	0.83	0.67
40%	6.67	3.33	2.67	1.67	1.33	1.11	0.89
50%	8.33	4.17	3.33	2.08	**1.67 µg**	1.39	1.11
60%	10.00	5.0	4.00	2.50	2.00	1.67	1.33
70%	11.67	5.83	4.67	2.92	2.33	1.94	1.56

Table 1: Theoretical FPD per inhalation range of nebulisers as a function of the required nebulisation TIME (fixed by the nebuliser hardware) and a range of FPFs. The nebule concentration is assumed to be 1 mg/mL in a 1 mL nebula.

Nebuliser	FPF (<5µm) %	FPD (<5µm) µg
MicroBase µSMI	44.3 ± 1.7	0.26 ± 0.01
Aerogen Solo	47. ± 5	0.30 ± 0.04
Philips Innospire Go	51 ± 1	0.21 ± 0.02
PARI eRapid	36 ± 2	0.10 ± 0.01

Table 2: Experimental FPDs per inhalation for commercial nebulisers.[3]

FPF – %	FPD – µg
45%	6.75
50%	7.50
55%	8.25
60%	9.00
65%	9.75
70%	**10.50**

Table 3: Theoretical FPD range for MRX004 SMI as a function of FPF.

Most nebulisers are not so efficient; assuming an FPF of 30% and 12 minutes required nebulisation time, the FPD becomes 0.83 µg per breath. This can be compared with the data from Table 2 with effective experimental FPDs for a small selection of commercial nebulisers. The experimental FPDs of these commercial nebulisers is much lower than the theoretical ones calculated in Table 1.

Keep Breathing – SMIs Are The Portable Inhaler Of Choice For High Doses

Let us now turn to the MRX004 SMI. The FPD per breath for an SMI is calculated thus:

$$FPD = CONCENTRATION \times MC \times FPF$$

when normalised to 1 mg/mL (assuming no effect on the aerosolisation process from the dilution). This is 3 to 4 times higher than nebuliser single breath FPDs.

This demonstrates that MRX004 SMI outperforms nebulisers on a single inhalation basis by delivering a unit dose up to 5 times higher. Add to this that the plume duration of MRX004 is 1.5 seconds but a nebuliser single breath is 2 seconds, and that SMIs deliver their payload to the deep lung when nebuliser aerosols deposit mostly in the upper respiratory track, it is then obvious what a superior inhaler MRX004 SMI is and that SMIs can achieve much higher doses than nebulisers.

We therefore contend that nebulisers are serial SMIs and only achieve mg delivered doses because of the repeat dosing. In short, Keep Breathing! SMIs deliver more.

More work is required to establish a direct experimental comparison between SMIs and nebulisers, but this initial review demonstrates that by viewing nebulisers as serial SMIs and comparing them on a breath-for-breath basis, most available nebulisers struggle to compete with SMIs. If patients just keep breathing and take multiple doses from an SMI, they can benefit from all the advantages of SMIs as a patient-friendly delivery device,[1] along with excellent efficiency for delivering high doses to the lungs.

REFERENCES

1. Aqrawe Z, Rogueda P, Murnane D, Eng B, "Soft Mist Inhalers Versus Nebulisers: Delivery Equivalence & Future Therapies". ONdrugDelivery, Issue 158 (Apr 2024), pp 24–28.
2. US Pharmacopeia. (1601) Products for Nebulization – Characterization Tests.
3. Hsiao S et al, "A Novel Contact-triggered Vibrating Mesh Nebulizer: Aerodynamic Performance and Drug Distribution of Suspension Drug Delivered with MicroBase µSMI". RDD 2018, 2018, Vol 2, pp 459–462.
4. Antoniak D et al, "Inhaled biologics: from nebules to SMIs – Dornase alfa in MRX004". Poster Presentation at DDL 2023.

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