A device screening method for predicting delivery of inhaled mRNA via a nebuliser

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Key Message

A device screening method is presented which takes aerosol parameters, deposition modelling, and post aerosolisation mRNA integrity data to predict lung deposition of functional mRNA as a percentage of fill dose. In the prediction performed here, the Aerogen Solo, Pari eFlow rapid, and the Resyca Pulmospray™ result in 12%, 2% and 51% lung deposition of functional mRNA, respectively.

Background

- COVID-19 accelerated mRNA technology considerably.
- A disadvantage of mRNA-based products is the delivery route, with most product being administered parenterally (needle fear).
- Pulmonary administration may be a better accepted delivery route capable of functional mRNA delivery.
- This study provides a method for prediction of functional mRNA lung delivery from different nebulisers , considering aerosol performance, lung deposition, and product integrity after nebulisation.

Methods

- Pulmospray™ (Resyca) device performance data generated according to ISO 27427.
- eFlow rapid (PARI) and Solo (Aerogen) device performance data collected according to ISO 27427 an EN13544-1 from their respective IFU's.
- Lung deposition modelled via Mimetikos Preludium V 1.1.7 (Emmace) using parameters as described in Table 1. Aerosol transport modelled according to Findeisen – Landahl formalism [1].
- Fraction of intact mRNA after nebulisation extracted from [2]. Where mRNA length pre- and post-nebulisation was compared for the different delivery systems, using the COVID vaccines from Moderna and Pfizer/Biontech.
- Total delivery efficiency of full-length mRNA to the lung η_{tot} is calculated as $\eta_{tot} = \eta_{neb} \cdot \eta_{mRNA} \cdot \eta_{lung}$, where η_{neb} is the nebuliser output efficiency as percentage of fill volume as given by the manufacturer (Table 3), η_{mRNA} the fraction of intact mRNA after nebulisation (Table 2) and η_{lung} the fraction of lung depositions as determined by the deposition model (Figure 1).
- To compare the delivery of mRNA to the lungs, the amount of fill volume needed to reach equivalent delivery of intact mRNA to the lung was calculated. Based on aerosol output and aerosol output rate for the three devices, total nebulisation time to achieve equivalent dose was also determined.

Table 1: *Inhalation parameters used during deposition modelling. Parameters set to closely mimic flows attained by users.*

Parameter	Pulmospray™	eFlow rapid	Solo
Model	Weibel A	Weibel A	Weibel A
Tidal breath	1000 mL	500 mL	500 mL
Inspiratory flow rate	15 L/min	15 L/min	15 L/min
Flow pattern	rectangular	sinus	sinus
Breath hold	1 sec	0 sec	0 sec
I/E ratio	1:1	1:1.5	1:1.5
Bolus volume	950 mL	500	500
Delay volume	50 mL	50	50
Breathing frequency	N/A	15/min	15/min

Table 2: *Approximate fraction of intact mRNA after nebulisation [2]*

Parameter	Pulmospray™	eFlow rapid	Solo
mRNA 1	0.88*	0.12	0.64*
mRNA 2	0.73	0.19*	0.64

* Fractions used for subsequent calculations

Results

Table 3: *Device performance data according to ISO 27427 or EN 13544-1*

	Pulmospray™	eFlow rapid	Solo
MMAD (μm)	5.90	4.70	3.10
GSD (-)	1.50	1.70	2.20
Aerosol output (% of fill volume)	84.1	26.8*	51.0**
Aerosol output rate (mg formulation / min)	238***	430	300

* Calculated based on an aerosol output of 0.67g and a fill volume of 2.5 mL
** Calculated based on an aerosol output of 1.02 mL emitted of 2.0 mL dose
*** Calculated based on aerosol output rate of salbutamol and a formulation concentration of 0.1% w/w

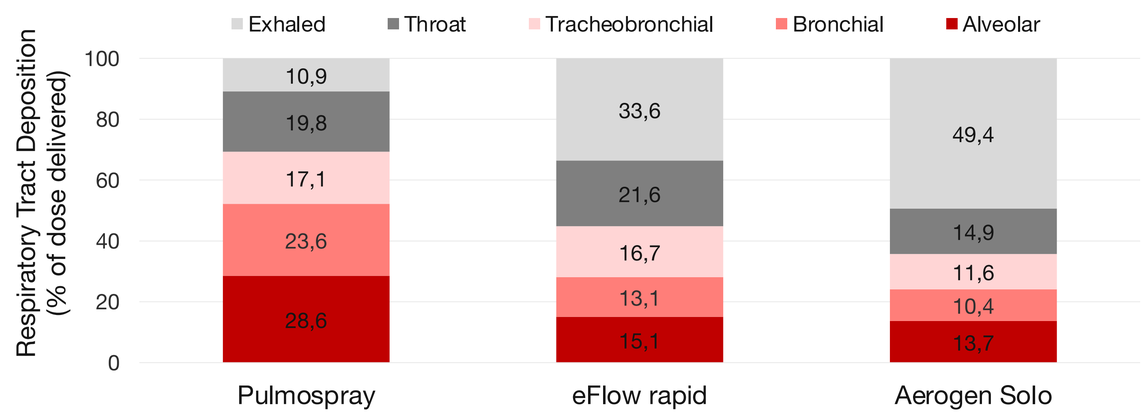

Figure 1: *Regional lung deposition in percentage of delivered dose*

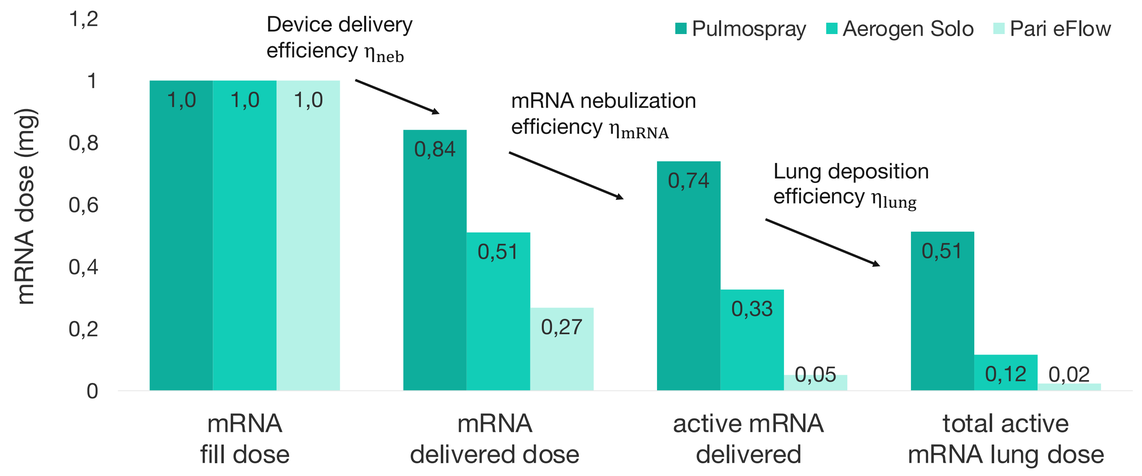

Figure 2: *Quantities of intact mRNA at each prediction stage*

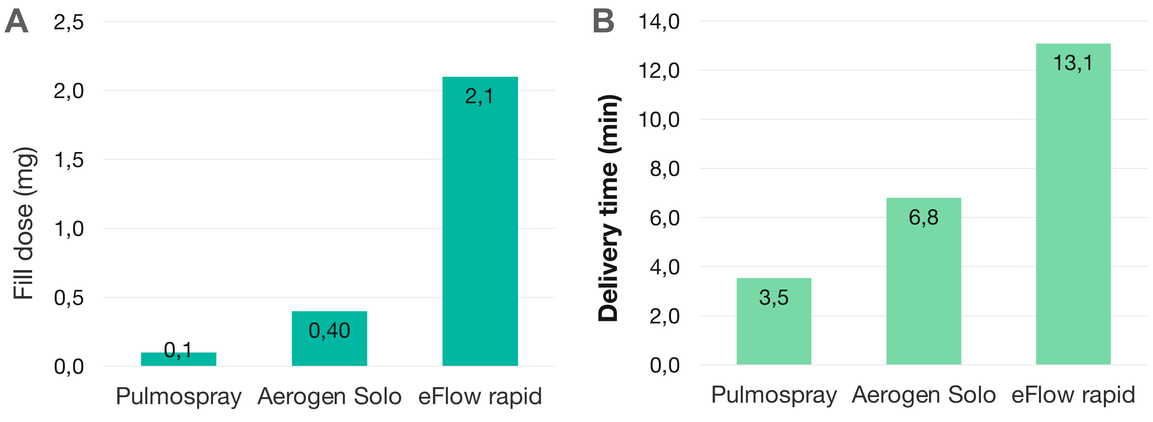

Figure 3: *(A) The calculated fill dose required to achieve a dose of 0.05 mg intact mRNA to the lungs. (B) The calculated time required to deliver an identical full-length mRNA dose of 0.05 mg to the lungs.*

Conclusion

The delivery of full-length mRNA is important, as only full-length mRNA results in the translation of the wanted biological active protein. When selecting a drug delivery device for the inhalation of sensitive biologics, such as mRNA formulations, the device specific drug delivery characteristics must be considered. Based on nebuliser fill volume, large differences in active mRNA delivery efficiently may exist and careful selection of the device is recommended. Particularly for biological compounds that carry high costs, substantial cost savings may be realised when selecting an efficient delivery device. The Resyca Pulmospray™ device is such an efficient device that may provide up to 50% of the filled mRNA to the deep lung intact.

1. B. Olsson and S. C. Kassinos. On the Validation of Generational Lung Deposition Computer Models Using Planar Scintigraphic Images: The Case of Mimetikos Preludium, *J. of Aerosol Medicine and Pulmonary Drug Delivery* 202134:2
2. Cees J. M. van Rijn, Killian E. Vlaming, Reinout A. Bem, Rob J. Dekker, Albert Poortinga, Timo Breit, Selina van Leeuwen, Wim A. Ensink, Kelly van Wijnbergen, John L. van Hamme, Daniel Bonn, Teunis B. H. Geijtenbeek. Low energy nebulization preserves integrity of SARS-CoV-2 mRNA vaccines for respiratory delivery. *Sci Rep* 2023 13:8851