Improving Aerosol Drug Delivery in CF therapy

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Introduction

- The eFlow®rapid electronic nebuliser (PARI GmbH) has been adopted from the eFlow® delivery platform and optimized for administration of currently approved medications used in CF. The eFlow®rapid is a compact and silent electronic nebuliser based on a vibrating membrane technology that combines the advantages of nebuliser therapy, i.e. high delivered dose and tolerance to spontaneous breathing, with a reduced treatment time. The core element of this novel type of nebuliser is a membrane that consists of a circular, wafer-thin metal plate perforated with micro holes. A ring-shaped piezo-electric actuator excites the membrane to vibrate, driven by an electronic circuit. Generated by the vibrational motion, sound pressure is built up in the vicinity of the membrane thus ejecting the fluid through the holes as droplets and creating a very fine aerosol [1].
- This study was undertaken to investigate the *in-vitro* aerosol performance of the eFlow®rapid with medications typically used for inhalation therapy in CF patients. The systems were tested for Droplet Size Distribution by cascade impaction and laser diffraction, as well as Delivered Dose, Respirable Dose, Respirable Drug Delivery Rate, and Nebulization Time using breath simulation. Aerosol performance of the eFlow®rapid was compared to data of the PARI LC PLUS® nebuliser powered by a PARI Boy®N compressor.

Materials and Methods

- Ready to use vials of tobramycin (TOBI® 300 mg/5 mL, Chiron Corp.), salbutamol sulfate (Sultanol®, 1500 µg/2.5 mL, GlaxoSmithKline), and rhDNase (Pulmozyme®, 2.5 mg/2.5 mL, Hoffmann LaRoche) were used as drug products.
- A validated Andersen Cascade Impactor (ACI) test set-up at 28.3 l/min was used for salbutamol sulfate and tobramycin to obtain information on the Mass Median Aerodynamic Diameter (MMAD) [2]. A laser diffraction method (LD, Malvern MasterSizerX) was used at 20 l/min to assess the geometric Mass Median Diameter (MMD) for Pulmozyme®, as the Pulmozyme® activity assay is not sensitive enough to conduct cascade impaction measurements. The Respirable Fraction (RF) as well as Geometric Standard Deviation (GSD) were derived from the respective size distributions.
- Delivered Dose (DD) and Drug Delivery Rate (DDR) were investigated using a PARI COMPAS® breath simulator mimicking an adult breathing pattern (15 breaths per minute, tidal volume 500 ml, sinusoidal flow, inhalation/exhalation ratio = 1). The aerosolised drug was sampled on inspiratory and expiratory filters and quantified by HPLC. Enzyme activity was determined by kinetic measurement using a DNA-methyl green substrate and an automated analysis system (Cobas Mira).
- LD and ACI data have been used for calculation of the Respirable Dose (RD_{LD} = DD x RF_{LD} = drug mass below 5 µm; RD_{ACI} = DD x RF_{ACI} = drug mass below 4.7 µm) and Respirable Drug Delivery Rate (RDDR = DDR x RF) [3].

Results

1. Aerosol performance of eFlow®rapid and PARI LC PLUS®

- The aerosol performance of the eFlow®rapid and PARI LC PLUS® with different medications is shown in table 1 and 2:

	eFlow®rapid			PARI LC PLUS®		
	MMAD (µm)	*RF (% < 4.7 µm)*	*GSD*	*MMAD (µm)*	*RF (% < 4.7 µm)*	*GSD*
Salbutamol sulfate	4.29 ± 0.09	60.6 ± 2.6	1.5 ± 0.03	3.00 ± 0.03	76.5 ± 0.8	2.0 ± 0.03
Tobramycin	3.95 ± 0.07	71.3 ± 2.8	1.5 ± 0.02	3.54 ± 0.06	70.1 ± 1.1	2.1 ± 0.01

Table 1: Aerosol performance of eFlow®rapid and PARI LC Plus® with Sultanol® and TOBI® obtained with ACI

	eFlow®rapid			PARI LC PLUS®		
	MMD (µm)	*RF (% < 5 µm)*	*GSD*	*MMD (µm)*	*RF (% < 5 µm)*	*GSD*
rhDNase	3.90 ± 0.11	72.0 ± 3.0	1.6 ± 0.02	4.10 ± 0.10	61.0 ± 2.0	2.1 ± 0.03

Table 2: Aerosol performance of eFlow®rapid and PARI LC Plus® with Pulmozyme® obtained with LD

- Differences between MMD measured by laser diffraction at 20 l/min and MMAD determined by cascade impaction at 28.3 l/min for the LC PLUS® are due to the different flow rates with the two experimental set-ups having an effect on breath enhanced nebulisers. Performance of the eFlow®rapid is not affected by the different flow rates.
- Figure 1 illustrates the droplet size distribution patterns in an ACI obtained upon nebulisation of TOBI® by the eFlow®rapid and the PARI LC PLUS® :

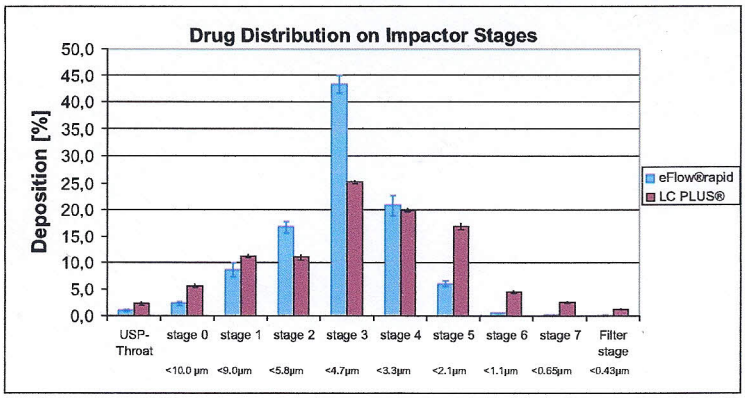

Fig. 1: Droplet size distribution upon nebulization of TOBI® using eFlow®rapid and PARI LC PLUS®

- The narrow size distribution of droplets generated by eFlow®rapid helps to carve out smaller (< 2.1 µm) and larger droplets (> 5.8 µm) as apparent from Figure 1. Using TOBI®/eFlow®rapid a higher percentage of drug is deposited on ACI-stages reflecting a more favourable respirable size range compared to the TOBI®/LC PLUS® combination since the percentage of both, large and very small droplets (< 2.1 µm) is reduced. The more advantageous droplet size distribution pattern is reflected by a smaller GSD (1.5 vs. 2.1) compared to TOBI® nebulised by the PARI LC PLUS®.

2. Comparison of Delivered Dose (DD), Respirable Dose (RD), Respirable Drug Delivery Rate (RDDR) and Nebulization Time of eFlow®rapid and LC PLUS®

- The DD, RD, RDDR and the nebulization time of the eFlow®rapid and PARI LC PLUS® with the different medications was determined by breath simulation and compared in Table 3.

	Salbutamol sulfate				*Tobramycin*				*rhDNase*			
	eFlow®rapid		LC PLUS®		eFlow®rapid		LC PLUS®		eFlow®rapid		LC PLUS®	
	mean	SD	mean	SD	mean	SD	mean	SD	mean	SD	mean	SD
Delivered Dose [mg]	0.82	0.03	0.61	0.03	131.1	9.6	114.2	6.2	0.67	0.16	0.69	0.06
Nebulisation time [min]	2.1	0.3	3.0	0.18	6.8	0.8	13.3	0.9	2.3	0.20	5.8	0.10
Delivered Dose [% of nominal]	31.1	1.3	24.4	1.2	43.8	3.1	38.4	2.6	26.8	6.5	27.7	2.3
Respirable Dose [mg]	0.50	0.02	0.47	0.02	95.2	5.6	80.1	2.8	0.48	0.13	0.42	0.03
Respirable Dose [% of nominal]	20.0	1.0	18.7	0.9	32.2	1.8	26.7	0.9	19.3	5.0	16.9	1.4
Respirable Drug Delivery Rate [mg/min]	0.14	0.02	0.12	0.01	13.8	1.0	6.0	0.3	0.22	0.05	0.07	0.01

Table 3: Summary table; results of breath simulation measurements

- The DD of eFlow® rapid is 34% higher with salbutamol sulfate and 15% higher with tobramycin compared to the PARI LC PLUS®. With rhDNase the delivered dose is the same for the eFlow®rapid and the PARI LC PLUS®. The RD is only slightly increased with eFlow®rapid. The in-vitro nebulization time of eFlow®rapid is significantly shorter for all medications tested. The nebulization time with eFlow®rapid is reduced by a factor of 1.5 with salbutamol sulfate, by a factor of 2 with tobramycin and by a factor of 2.5 with rhDNase compared to the PARI LC PLUS®. Both, Drug Delivery Rate (DDR) and Respirable Drug Delivery Rate (RDDR) are significantly higher for eFlow®rapid allowing for a much faster drug delivery to the lungs.

Summary and Conclusions

- The Delivered and Respirable Dose using the eFlow®rapid are comparable *in-vitro* to the therapy using the PARI LC PLUS® .
- The eFlow®rapid electronic nebulizer shows a high RDDR and significantly reduced treatment time for all tested medications which is essential for an effective and convenient inhalation therapy. This is important with respect to patient compliance and, thereby, may improve therapeutic efficacy.

References

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