

Performance Characteristics of Colistimethate Sodium Solutions (Colistin) Delivered by Jet Nebulizers compared to the eFlow® SCF Electronic Nebulizer

M. Keller, A. Balcke, A. Bucholski, K. Reul, and M. Knoch

P281 PARI Aerosol Research Institute, Steinerstr. 15C, D-81369 Munich, Germany

Introduction

- Lung deposition and therapeutic efficacy of nebulized drugs depend on the specific nebulizer system used. The interaction of drug formulation and device can affect aerosol performance in terms of the delivered dose (DD), droplet size distribution, respirable dose (RD) and nebulization time. Hence, proper bench testing of the drug product in combination with selected nebulizer systems is necessary to estimate potential lung deposition [2, 3].
- This study was undertaken to assess the *in-vitro* nebulization performance of colistimethate sodium solutions using different jet nebulizers in comparison to the eFlow® SCF electronic nebulizer making use of a perforated vibrating membrane principle [4].
- Inhalation of Colistin, a peptide antibiotic, is popular in some European countries and regarded as beneficial for administration during the off-cycle of TOBI® treatment and, as an alternative choice for treating *Pseudomonas aeruginosa* (PA) infections in CF-patients [1].

Materials and Methods

- "Colistimethate for Injection USP" (Pharma-Tek, Inc., Huntington, NY) contains sterile colistimethate sodium equivalent to 150 mg of Colistin. The physicochemical properties of colistimethate sodium solutions using different volumes and diluents were investigated. The drug solutions were nebulized using two breath enhanced jet nebulizers (PARI LC STAR® and PARI LC PLUS®, PARI Innovative Manufacturers, Richmond, VA) powered by a PARI PRONEB® ULTRA compressor and the eFlow® SCF Electronic Nebulizer (PARI Innovative Manufacturers, Richmond, VA).
- Colistimethate solutions were prepared in concentrations of 150 mg in either 2ml or 3ml of water, 4ml of 0.45% or 0.225% saline and, 8ml of 0.9% or 0.225% saline, respectively. Osmolality, pH, surface tension and viscosity were tested.
- In-vitro* nebulization efficiency was investigated by breath simulation measurements utilizing the PARI COMPAS™ breath simulator mimicking an adult breathing pattern (15 breaths/min, 500 ml tidal volume, inh : exh = 1 : 1). Droplet size distributions were measured by laser diffraction (LD) utilizing a Malvern MasterSizer X [5] for calculation of the Respirable Fraction (RF), Mass Median Diameter (MMD) and Geometric Standard Deviation (GSD). Total Output Rate (TOR) was assessed by gravimetric measurements at a constant inspiratory flow of 20 l/min. All tests were performed with 3 devices in duplicate, each (n=6).
- Sample solutions were assayed by a validated HPLC-method using evaporative light scattering detection (ELSD) developed in PARI's pharma laboratories.

Results

- Table 1 compares the physicochemical properties of four Colistimethate concentrations in water and different saline concentrations in comparison to isotonic saline.

| Product | Saline | Colistimethate for Injection USP, 150 mg/ vial, lot no. 1E4CM, exp. date 01/06 | | | | | |
|----------------------------|--------|--|-----------------------|------------------|-----------------|------------------|----------------|
| Drug concentration [mg/ml] | 9 | 75 | 50 | 37.5 | 18.75 | 18.75 | 18.75 |
| Diluent per vial | | 2 ml H ₂ O | 3 ml H ₂ O | 4 ml NaCl 0.225% | 4 ml NaCl 0.45% | 8 ml NaCl 0.225% | 8 ml NaCl 0.9% |
| Osmolality [mosmol/kg] | 291 | 644 | 426 | 392 | 458 | 239 | 443 |
| pH | 5.20 | 6.47 | 6.61 | 6.82 | 6.72 | 7.36 | 7.19 |
| Surface Tension [mN/m] | 72.9 | 39.46 | 42.02 | 42.70 | 42.68 | 47.52 | 47.04 |
| Viscosity [mPa·s] | 1.0 | 2.04 | 1.65 | 1.44 | 1.41 | 1.19 | 1.20 |

Table 1: Physicochemical properties of colistimethate solutions in comparison to isotonic saline

- Figure 1 illustrates the Delivered Dose over time based on a sinusoidal breathing pattern.

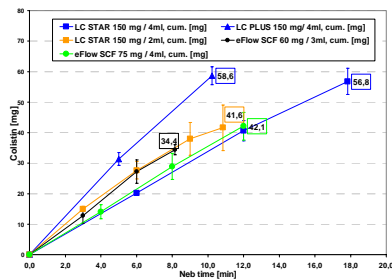


Figure 1: Delivered Dose as a function of nebulization time

- Figure 2 illustrates the Respirable Dose delivered over time:

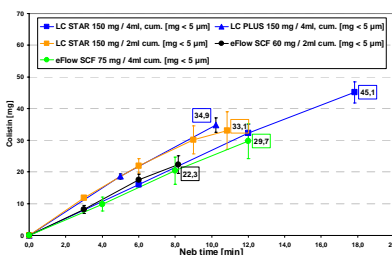


Figure 2: Respirable dose as a function of time

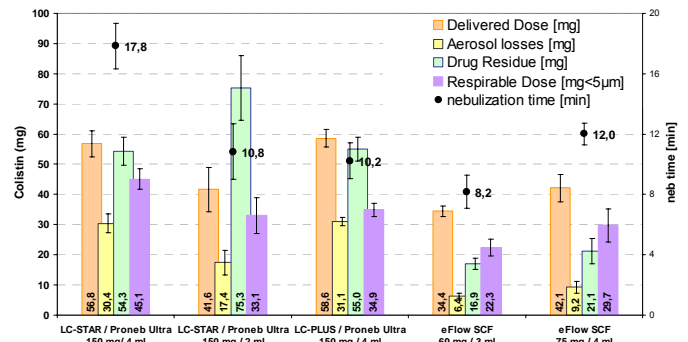


Figure 3: Colistin distribution upon nebulization during breath simulation

| Nebulizer Type | PARI LC STAR® | | | | LC PLUS® | | eFlow® SCF | |
|----------------------------|---------------|-------|---------------|-------|---------------|------|--------------|-------|
| | 150 mg / 2 ml | | 150 mg / 4 ml | | 150 mg / 4 ml | | 60 mg / 3 ml | |
| Drug concentration | mean | SD | mean | SD | mean | SD | mean | SD |
| Delivered Dose [%]* | 28.9 | 5.26 | 37.5 | 2.87 | 38.5 | 1.7 | 58.6 | 2.86 |
| Drug Residue [%]* | 52.2 | 7.22 | 35.9 | 2.98 | 36.2 | 2.8 | 28.8 | 3.22 |
| Aerosol losses [%]* | 12.1 | 2.81 | 20.1 | 2.14 | 20.4 | 1.0 | 10.9 | 1.31 |
| Recovery [%]* | 93.1 | 1.23 | 93.4 | 2.50 | 95.1 | 2.1 | 98.3 | 1.18 |
| Respirable Dose [% <5µm] | 22.9 | 4.21 | 29.8 | 2.25 | 22.9 | 1.35 | 38.0 | 4.71 |
| Drug Delivery Rate [%/min] | 2.7 | 0.10 | 2.1 | 0.19 | 3.3 | 0.79 | 7.3 | 1.06 |
| RDDR [% <5µm/min] | 2.1 | 0.08 | 1.7 | 0.15 | 1.9 | 0.46 | 4.7 | 0.60 |
| Nebulization time [min] | 10.8 | 1.83 | 17.8 | 1.53 | 10.2 | 1.2 | 8.2 | 1.10 |
| MMD [µm] | 3.1 | 0.03 | 3.0 | 0.01 | 4.18 | 0.13 | 4.1 | 0.29 |
| GSD | 2.2 | 0.10 | 2.1 | 0.03 | 2.2 | 0.01 | 1.8 | 0.03 |
| FPF [% droplets <5µm] | 75.9 | 0.50 | 79.4 | 0.20 | 59.5 | 1.64 | 64.7 | 5.19 |
| TOR [mg/min] | 316.5 | 11.50 | 411.4 | 14.91 | 564 | 12.9 | 273.0 | 54.64 |

Table 2: Summary of results from breath simulation and laser diffraction tests

Summary

- The physicochemical properties of the formulation and nebulizer output characteristics are affected by the type and volume of diluents used to dissolve colistimethate sodium.
- Drug Delivery Rate is lower and nebulization time longer with eFlow® SCF than has been observed with other antibiotic solutions. This is most likely attributable to foaming with colistimethate solutions.
- Delivered Doses (DD) range from 28.9% to 58.6% of the loaded dose and were higher for eFlow® SCF than for the jet nebulizers.
- Respirable doses (RD = drug in droplets < 5 µm) ranged from 22.9% to 41.2% and was higher for eFlow® SCF than for the jet nebulizers.
- Little difference was seen in the time required to deliver the 'target' RD (≈ 30 - 35 mg) with the devices tested.
- eFlow® SCF delivered a comparable RD to the PARI LC PLUS® and required approximately 12 minutes using a colistimethate concentration of 18.75 mg/ml vs. 37.5 mg/ml.

Conclusions

- Higher colistimethate doses are used in the U.S. than in Germany. The aerosol delivery efficiency of colistimethate is affected by drug concentration, fill volume and nebulizer type.
- eFlow® SCF allows a 'dose split' for colistimethate (Pharma-Tek, Huntington, NY) when dissolving a 150 mg vial in 8 ml 0.45% or 0.9% saline, compared to 4 ml of a 0.225% saline recommended for jet-nebs.
- eFlow® SCF offers potential economic benefits to patients and payors.
- Testing of a specific drug/device combination is essential to properly characterize nebulizer products. Surrogate solutions (NaCl, NaF) as described in the CEN Nebulizer Standard [6] do not reflect important drug/device interactions.
- The *in-vitro* equivalence of a drug/device configuration must be verified by *in-vivo* studies to demonstrate comparable therapeutic efficacy and safety.

References

- Beringer: The clinical use of colistin in patients with cystic fibrosis. Current Opinion in Pulmonary Medicine 2001, 7, p. 434-440
- Katz et al.: Nebulizer Choice for Inhaled Colistin Treatment in Cystic Fibrosis. Chest 2001, 119, p. 250-255.
- Keller et al.: Using Infant Deposition Models to Improve Inhaler System Design. Proceedings Respiratory Drug Delivery IX, Palm Springs, USA, April 25-29, 2004, p. 221-231.
- Stangl et al.: Quality Control of Inhalers for Clinical Studies. Proceedings Drug Delivery to the Lungs, 14, London, UK, Dec. 11&12, 2003, p. 168-171.
- Schuschnig et al.: Customisation of the eFlow™ Electronic Inhaler to Target Pulmonary Delivery of Aztreonam Formulations for the Treatment of Lung Infections. Proceedings Drug Delivery to the Lungs 13, London, UK, Dec. 12&13, 2002, p. 252-255.
- CEN-Nebulizer Standard EN 13544-1: Respiratory therapy equipment - Part 1: Nebulizing systems and their components. Released 2002.