**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®) and the 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 COMPASS™ 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 Tor (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.
- Table 2: Summary of results from breath simulation and laser diffraction tests

**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.
- Drug Delivery Rate is lower and nebulization time longer with 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 (TOR) [mg/min] for 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.

**References**


M. Keller, A. Balcke, A. Bucholski, K. Reul, and M. Knoch
PARI Aerosol Research Institute, Steinerstr. 15c, D-81369 Munich, Germany