# Assessment of Mass Fraction Less than 10 micron in Nasal Products – Method Considerations

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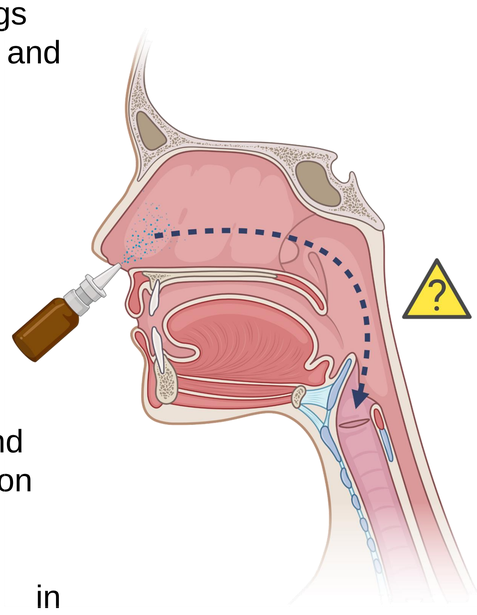
## Introduction and Aim

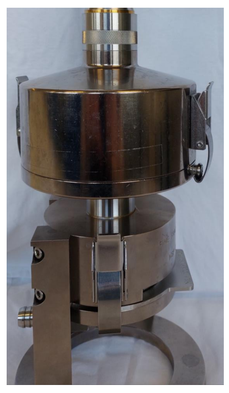
- Rising interest in nasal administration of drugs
  - Versatile application site: local, systemic and CNS targeted treatment
  - High vascularisation
  - Easily accessible
  - Patient friendly
- Nasal sprays exhibit broad droplet spectrum
- ➢ How is a nasal formulation distributed in the nasal cavity and beyond?
- Particles and droplets below 10 µm possibly reach the lungs and may cause side effects
- European Medicines Agency & U.S. Food and Drug Administration recommend determination of mass fraction below 10 µm
  - No further information on the method
  - No method currently described in Pharmacopeia




The **aim of this study** was to **assess different aerodynamic setups** in the search for a robust method to precisely determine the **mass fraction less than 10 micron** of droplets in nasal products to assess how much **API could potentially reach the patients' lungs.**

## Experimental Methods

Pollicrom® nasal spray (20 mg/mL solution of Na cromoglycate)


FSI

Aerodynamic assessment

- Automatised actuation (dose time = 0.2 s; force-to-actuate 5 kg; hold-time 2 s)
- Impactors, all tested at 30 L/min flow rate
  - Fast Screening Impactor (FSI) with 10 µm cut off plate
  - Next Generation Pharmaceutical Impactor (NGI)
  - Reduced variant of the NGI (rNGI)

In one nozzle of the NGI (left) a filter holder (middle) and a filter (right) are inserted to obtain the reduced NGI. This way, all remaining droplets or particles are collected on the filter.

HPLC analysis

- RP-18 250-4 mm column with pre-column, 50 °C
- 40% methanol, 60% 10 mM phosphate buffer (pH 2.4)
- Internal standard: salicylic acid (5 µg/mL)
- Double injection

## Results and Discussion

**Method considerations: Mass fraction < 10 µm**

- Mass fraction below 10 µm is expected to be below 1% of emitted dose
- High recovery needed
- Experimental setup with high reproducibility
  - automatic actuation with predefined parameters
  - suitable administration of the nasal product into the impactor (inlet)
- Validated analytical method with low limits of quantification and detection
  - internal standard

**Inlets for nasal product characterization (Fig. 1)**

- Must enable use of nasal product as described in patient information
- Easy to handle and recover product from
- No need for anatomical correctness

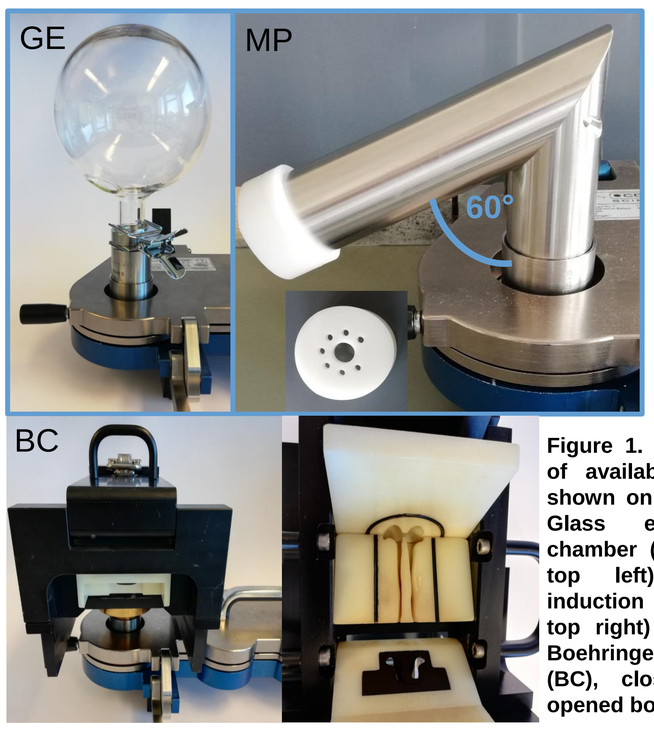



**Figure 1. Selection of available inlets shown on the NGI. Glass expansion chamber (GE, 1 L, top left), metal induction port (MP, top right) and the Boehringer cast (BC), closed and opened bottom).**

**Choice of impactor (Fig. 2)**

- Impactors were compared using one inlet (GE); stages below 10 µm of the NGI were washed subsequently with 5 mL of solvent to pool the sample
- ➢ NGI seems unsuitable
  - Too high count of stages → loss of sample, not exceeding LoQ
- ➢ rNGI and FSI
  - Significantly different fractions
  - Comparable recovery and standard deviation
  - rNGI is laborious to operate

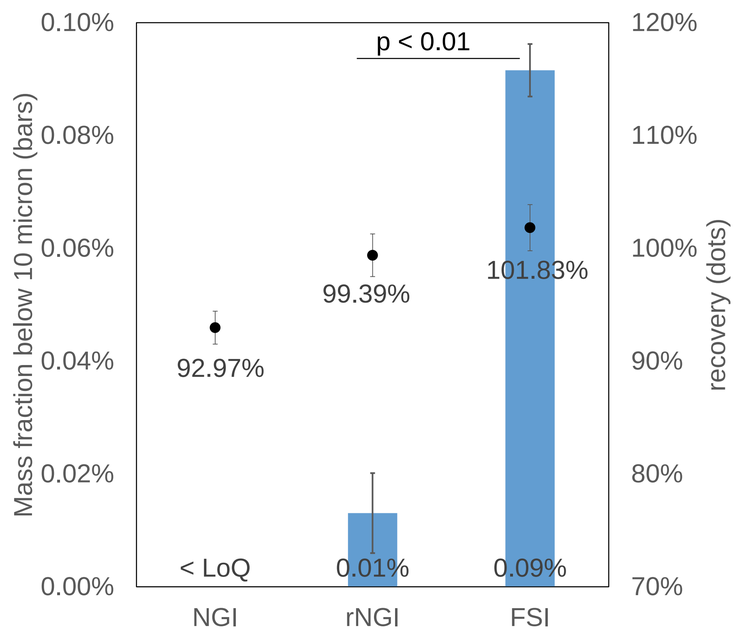



**Figure 2. Comparison of impactors. Fraction and recovery reported as percentage of determined emitted dose. Inlet: glass expansion chamber, one spray shot per assessment. (n=3, error bars=SD)**

FSI seems the most suitable impactor for the assessment of the mass fraction below 10 µm as the fraction can be determined from one filter and is easy to operate

Inlet should be easy to wash and ideally automatable to analyse
→ GE and MP further assessed

**Comparison of inlets (Fig. 3)**

- GE and MP give comparable mass fractions below 10 µm (difference non-significant)
- Recovery of emitted dose similar
- SD higher for MP
  - Administration angle fixed to 60° with the MP although upright position advised in product information
  - Liquid spill to deeper compartments
- GE enables nearly full expansion of the spray cloud
  - Overestimation of the fraction?

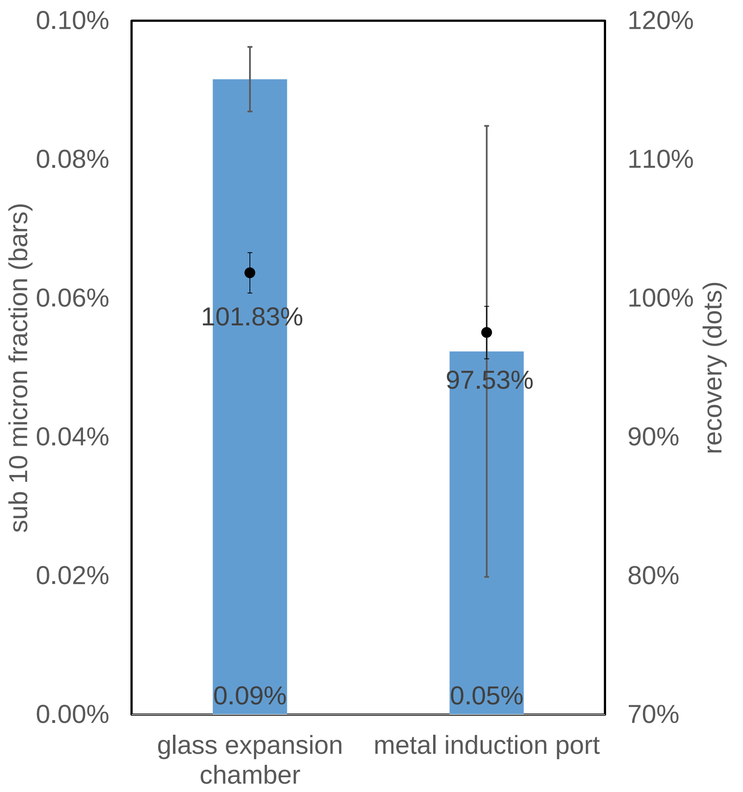



**Figure 3. Comparison of different inlets. Fraction and recovery reported as percentage of determined emitted dose. Fast screening impactor, one spray shot per assessment. (n=3, error bars=SD)**

## Conclusion & Outlook

- Presented FSI method can determine the mass fraction below 10 µm with good reproducibility
  - glass expansion chamber operated with 30 L/min flow rate likely gives the highest possible fraction due to full expansion of the spray cloud
  - metal induction port seems unsuitable for nasal sprays with an administration angle other than 60° and large spray volumes
- Inlet configuration needs optimisation
  - influence of the inlet on determined fraction
- Test with suspension, powder and nMDI formulations
- low drug load products
- replication in other laboratories
- validation of the method with defined particles

**Get in touch** **Full abstract**

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