# In-vitro measurement of the combination of inhalation and respiratory therapy - a clinically relevant laboratory study

Measurement of the particle size distribution using laser diffraction (ISO 13320-2020) with regular nebulizers with and without connecting the RC-Cornet® PLUS

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BACKGROUND:

- A combination of inhalation with oscillating PEP therapy with the RC-Cornet® PLUS offers many advantages in terms of practicability, time savings and simplicity for the patient.
- In addition, a reduced exhalation flow (due to the stenosis in the Exhalation limb) can increase the retention time of the aerosol in the lungs and thus improve the drug deposition.
- As always, it is important to ensure that the effectiveness and mode of action of the original therapy is maintained by the cobination therapy.

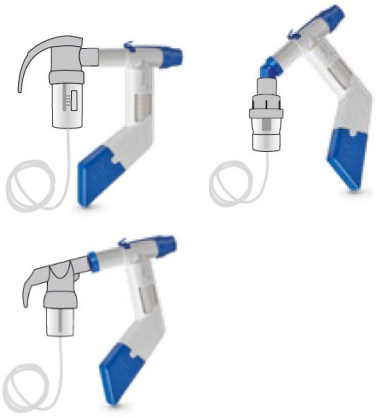

*Figure 1 Combination of the RC-Cornet® PLUS with different types of nebulizers with or without adapters*

In order to assess the influence and effects of simultaneous respiratory therapy with inhalation via different nebulizers, the **particle size distribution** of the active ingredient to be inhaled was measured using **laser diffractometry**[1]. The particle distribution of the different wet **nebulizer heads and their factory-supplied mouthpieces were compared to the nebulization with an RC-Cornet® PLUS** instead of the mouthpiece*. The laser diffractometry measurement method is an ISO standardized [3] alternative to the very complex cascade impactor measurement[2] and is easily comparable with it in the range ≥ 0.5µm.

MATERIALS & METHODS:

- The measurement was carried out by Sympatec, specialist for particle measurement, Clausthal-Zellerfeld, Germany.
- The following nebulizer heads were measured:
  - AeroEclipse2BAN
  - Pari LC Sprint
  - Pari LL
  - Sidestream Plus
  - NebuTech HDN
  - Curaplex_SVN
  - MicroDrop
  - belAir
  - DAR Nebulizer
  - Omron A3
  - Omron C28P
  - Aerogen Solo
  - DeVilbiss, Medeljet Plus Nebulizer Kit



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- The HELOS laser diffraction system + inhaler according to ISO13320-2020 was used; with the following measurement parameters::
    - Focal length 50mm, detected droplet size range 0.25/0.45 - 87.5µm
    - Measuring time of 20s with a resolution of 100ms, after a few seconds warm-up time
    - Aspiration with inhaler volume flow: 30l/min**
    - Nebulization by nebulizer's own system or compressed air of 3.5bar (=51psi), 1.9bar (=27psi) or compressor pressure
    - 5 measurement repetitions per test
    - Evaluation of the measurement data using Mie theory


*Figure 2 Laser diffraction measurement setup, by courtesy of © Sympatec GmbH*

- The active ingredient solutions salbutamol 1.25mg/2.5ml (= albuterol) and budesonide 0.5mg/2ml were nebulized.

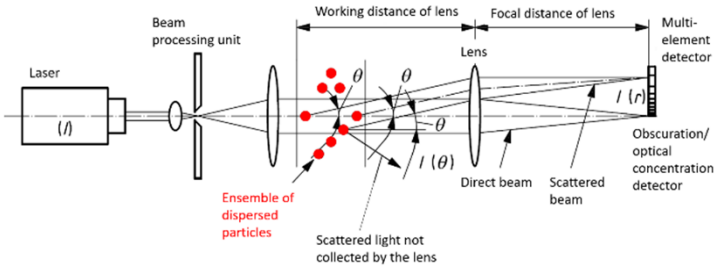


*Figure 3 Measurement setup laserdiffraction, by courtesy of Sympatec*

RESULTS:

In accordance with ISO9276-14, the results of the measurement are the cumulative distribution and the density distribution over the particle size. The distributions using the regular mouthpiece and using the RC-Cornet® PLUS instead of the mouthbpiece can be compared. An example measurement result is shown in Figure 4. The two curves are superimposed in Figure 5.

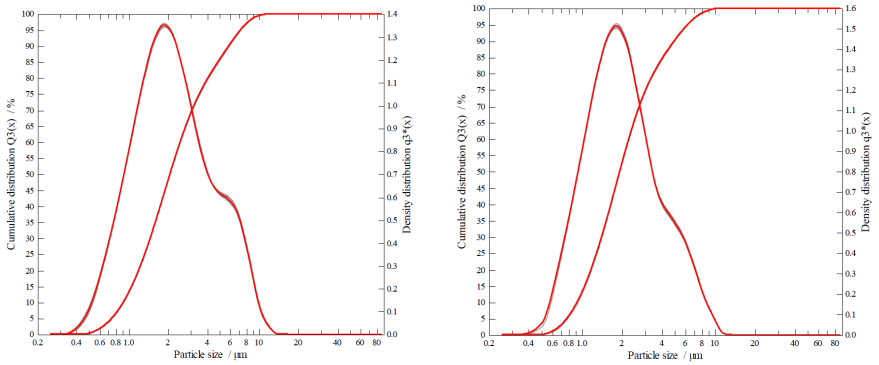


*Figure 4 Example results, left: using the factory-supplied mouthpiece, right: using the RC-Cornet® PLUS*

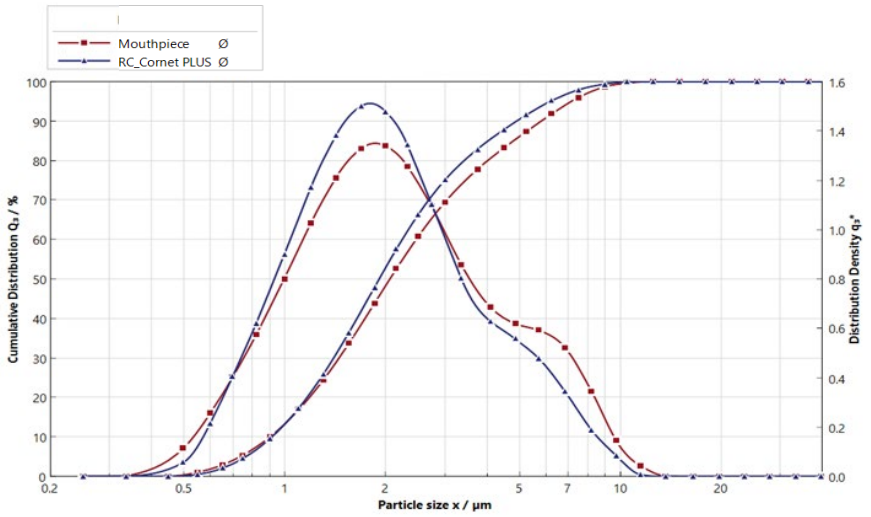


*Figure 5 Example results as per ISO9276-1[1], graphs from Figure 4 superimposed*

All measured particle distribution curves have a similar shape, with a distribution between 0.5 and 10µm and the peak at 1.5- 2.5µm. The distribution is only minimally altered by connecting the RC-Cornet® PLUS to the nebulizer. Almost all particle distribution curves with regular mouthpieces show a "second peak" of varying intensity in the range of 5-8µm. This second peak is flattened (to varying degrees) by using the RC-Cornet® PLUS.

Characteristic values of the measurement are shown as an excerpt of the measurement results in Figure 6. (Further measured values are available on request).

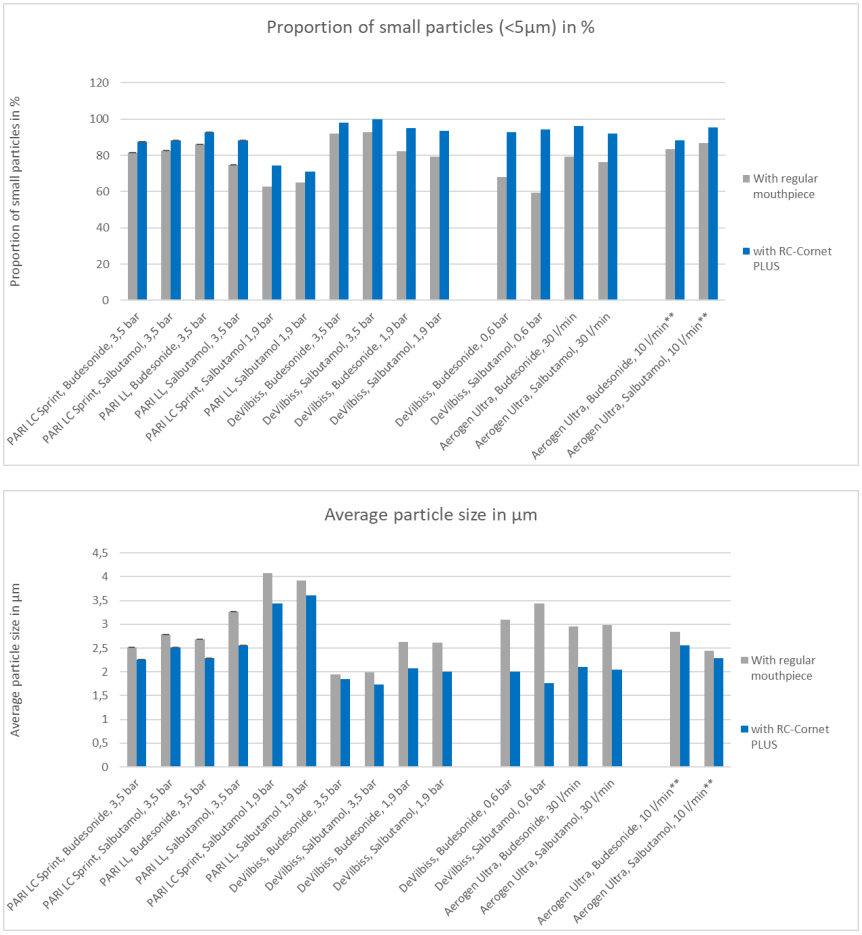


*Figure 6 Characteristic measurement values for different inhalation systems (Excerpt from the results)*

- The RC-Cornet® PLUS shifts the distribution curve (q3) to the left by a few tenths of a micrometer, i.e. the average particle size becomes smaller. In addition, the peak becomes somewhat more pointed, i.e. the particles with the average diameter take up a higher percentage share.
- The second peak in the 5-8µm range is flattened by the RC-Cornet® PLUS.
- In addition, the optical density (not shown, represents an indirect measure of the quantity) decreases slightly.

DISCUSSION & CONCLUSION:

- Looking at the characteristic measurement results as well as the graphical comparison, in which a flattening of the second peak is visible for the larger particles, it can be concluded that some particles are "filtered out" by connecting the RC-Cornet® PLUS to the inhalation device. These are mostly the large particles >5µm; the rest of the distribution curve remains almost identical.
- Particles are only respirable from a size of 4.6µm and smaller. Filtering them out is therefore not disadvantageous for the patient.
- Apart from these changes, the particle distribution curves with and without RC-Cornet® PLUS are almost identical.
- With lower nebulization pressures of the compressed air nebulizer, the proportion of small particles is decreased. Connecting the RC-Cornet® PLUS at these low nebulization pressures results in a larger delta of the characteristic values. This happens because it is the large particles in particular, which are filtered. If, in addition to the lower nebulization pressure, the aspiration volume flow is also reduced and thus changed from the standardized value to a more realistic value, the delta in the characteristic values is reduced again.

→ The combination of inhalation and respiratory therapy can be used to simplify and shorten the therapy for the patient while maintaining the defined distribution of active ingredient particles.

* This measurement only takes inspiration into account. In reality, the oscillating positive pressure during exhalation (OPEP) also causes the medication enriched air to back up in the device. In addition to the reduced exhalation flow caused by the stenosis, this results in a longer retention time of the medication-laden air. Accordingly, deposition can improve further.

** 30 l/min is a standardized value for the volume flow, which is derived from the standard for cascade impactor measurement. However, studies show that inhalation is significantly more effective with slower inhalation (e.g. Alcoforado et al. 20165). For this reason, some additional measurements were carried out at a flow rate of 10 l/min.

References:
1 Sympatec analysis report no. 18-027, DE 230229 and DE 230293
2 ISO 27427:2023-12. Anaesthetic and respiratory equipment
3 ISO 13320:2020-01. Particle size analysis - Laser diffraction
4 ISO 9276-1:1998. Representation of results of particle size analysis. Part 1: Graphical representation
5 Alcoforado L, Ari A, De Melo Barcelar J, Brandao SS, Fink JB and Dornelas De Andrade A. Comparison of Aerosol Deposition with Heated and Unheated High Flow Nasal Cannula (HFNC) in Healthy Adults. Poster presentation at ATS. 2016