

# Comparison of two methods to prevent evaporation of aqueous droplets in the Andersen Cascade Impactor

Thomas Hubrath, Jürgen Kumb

Boehringer Ingelheim Pharma GmbH & Co. KG, Ingelheim, Germany

## Summary

The measurement of the particle size distribution by means of cascade impaction is a common and important method to characterize medical aerosols. However, particle size distributions of aqueous droplets (e.g. generated by nebulizers or the Respimat® Soft Mist™ Inhaler) are difficult to determine because of evaporation of water after aerosolization. The aim of this study was to compare two different methods which reduce droplet shrinkage between the points of aerosol generation and droplet impaction. A method based on impactor refrigeration was compared against a method using humidified air. It was shown that both methods are capable of preventing evaporation of aqueous droplets after aerosolization and that they are suitable to measure reproducible particle size distributions of aqueous medical aerosols.

## Introduction

The measurement of the particle size distribution by means of cascade impaction is a common and important method to characterize medical aerosols. However, particle size distributions of aqueous droplets (e.g. generated by nebulizers or the Respimat® Soft Mist™ Inhaler) are difficult to determine because of evaporation of water after aerosolization. The aim of this study was to compare two different methods which reduce droplet shrinkage between the points of aerosol generation and droplet impaction.

## Experimental setup

Doses of an medical aerosol were delivered by using the Respimat® Soft Mist™ inhaler. The doses were collected according to the standard procedures of the USP [1] using Apparatus 1 (Figure 1). Two methods to prevent droplet shrinkage due to evaporation were compared in a cross over study (Table 1). During impaction the measurements of temperature and relative humidity (RH) were performed at the air outlet of the Andersen cascade impactor (ACI) and the laboratory. The ACI conditions were determined at the beginning and end of impaction.

Table 1: Study design for method comparison

Quantity	Test Sequence		
5 devices	priming	Method A (cooling)	Method B (100 % RH)
5 devices	priming	Method B (100 % RH)	Method A (cooling)

The two methods are described below:

### Method A (cooling method)

An alternative method was proposed for nebulizers and described in a draft monograph 2.9.44, "Preparations for Nebulisation" of the Pharm. Eur.

The method based on impactor refrigeration [2] was used to adjust the relative humidity (RH) to nearly 100% within the impactor. The following procedure was applied:

1. The ACI was dry and not warmer room temperature.
2. Allowed range for room conditions were  $T = 23 \pm 3^{\circ}\text{C}$  and  $\text{RH} = 50 \pm 25\%$ .
3. Assembled ACIs were refrigerated at  $\leq 5^{\circ}\text{C}$  for at least 90 minutes.
4. An air flow adjustment to 28.3 L/min and test for impactor tightness was done immediately after refrigeration.
5. Impaction was done within 5 minutes after removal from the refrigerator.
6. After completed sampling the ACI was dismantled and the amount of active ingredient in mouthpiece, throat, plates and filter was determined.



Figure 1: USP Apparatus 1 with fitted Respimat® Soft Mist™ inhaler

## Method B (100 % RH method)

Air saturated with water was generated by a humidifier (Figure 2) and used during impaction. The generated air was delivered via flexible tubing to the ACI. In front of the ACI inlet the Respimat® Soft Mist™ inhaler was enclosed by a special chamber. In the chamber the humidified air flowed around the inhaler before it was pulled into the ACI.

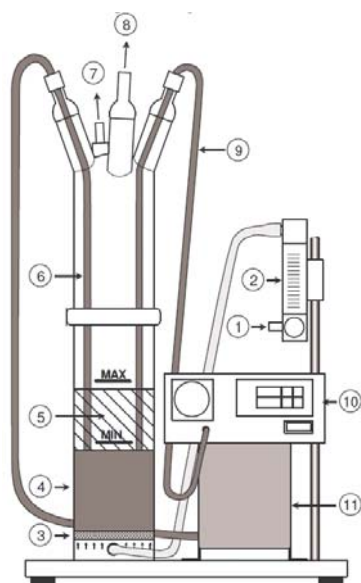


Figure 2: Humidifier for ACI measurements

- 1) Compressed air supply connection
- 2) Flow indicator flow meter
- 3) Sintered glass disc
- 4) Heating element
- 5) Water
- 6) Electrical supply for the heating element
- 7) Positive pressure vent
- 8) Connection to ACI
- 9) Lead temperature sensor on the heating element
- 10) Controller for adjustment of temperature
- 11) Transformer

The following procedure was applied:

1. On the assembled ACI an air flow adjustment to 28.3 L/min and a test for impactor tightness was performed.
2. The Respimat® Soft Mist™ inhaler was attached to the ACI (Figure 3).
3. The humidified air supply was connected and the ACI equilibrated for approx. 30 minutes.
4. Impaction was performed.
5. After completed sampling the ACI was dismantled and the amount of active ingredient in mouthpiece, throat, plates and filter was determined.



Figure 3: Connection between ACI and humidifier

## Data Evaluation

The amount of active ingredient was analyzed by HPLC for both methods. The mass median aerodynamic diameter (MMAD) and the geometric standard deviation (GSD) of the aerosol droplet distributions were calculated on the basis of log-probability plots with distributions assumed to be log-normal. A statistical evaluation [3] was used to determine whether differences of MMAD and GSD were significant (from ten replicate tests) with different humidification methods. A p value of < 0.05 was considered significant.

## Results and Discussion

The room conditions at the time of impaction were  $T = 22 \pm 1^\circ\text{C}$  and  $\text{RH} = 45 \pm 5\%$  for all measurements and, hence, within the allowed range. The average values (measured at the outlet of the ACI) at the beginning and end of impaction were compared (Figure 4). It was shown that for both methods the conditions were maintained during the time of impaction. However, the standard deviations of the measurements for method A (cooling method) were approximately 5 to 8-fold higher than for method B (100 % RH method).

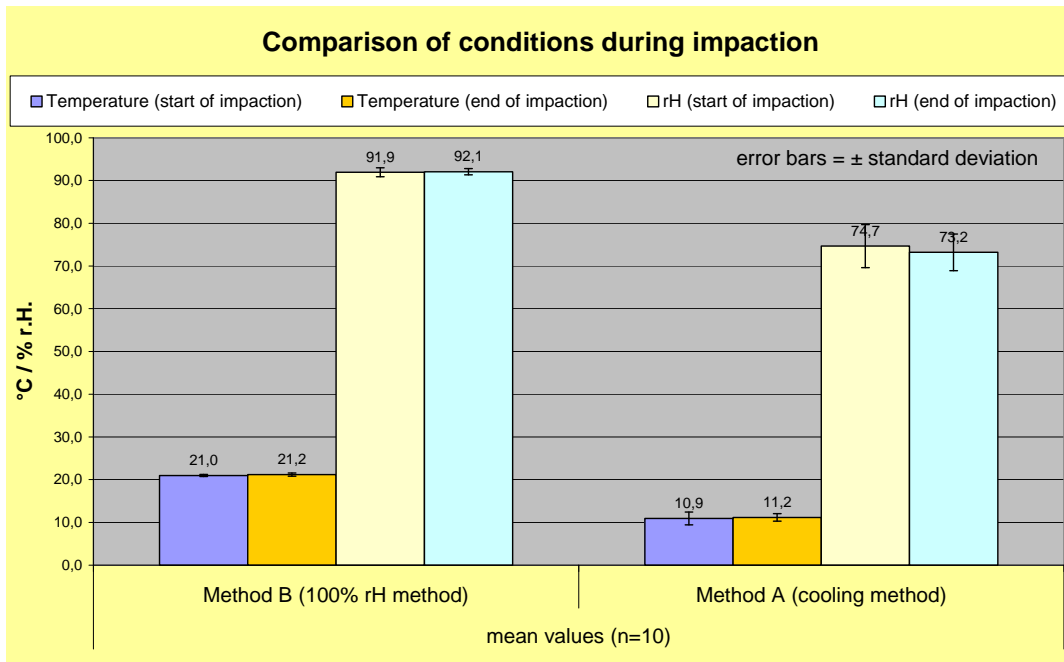


Figure 4: Air conditions measured at the outlet of the ACI

Both methods were able to prevent droplet shrinkage after aerosolization with the Respimat® Soft Mist™ Inhaler. The particle size distributions (Figure 5) were very similar for the two methods but very different from the size distribution measured using an uncooled impactor at room conditions (22°C, 45% RH for ACI and laboratory) for which severe evaporation of the droplets occurred. However, a slight evaporation occurred with method A (cooling) (indicated with an apparent increase in the amount of particles < 1 μm).

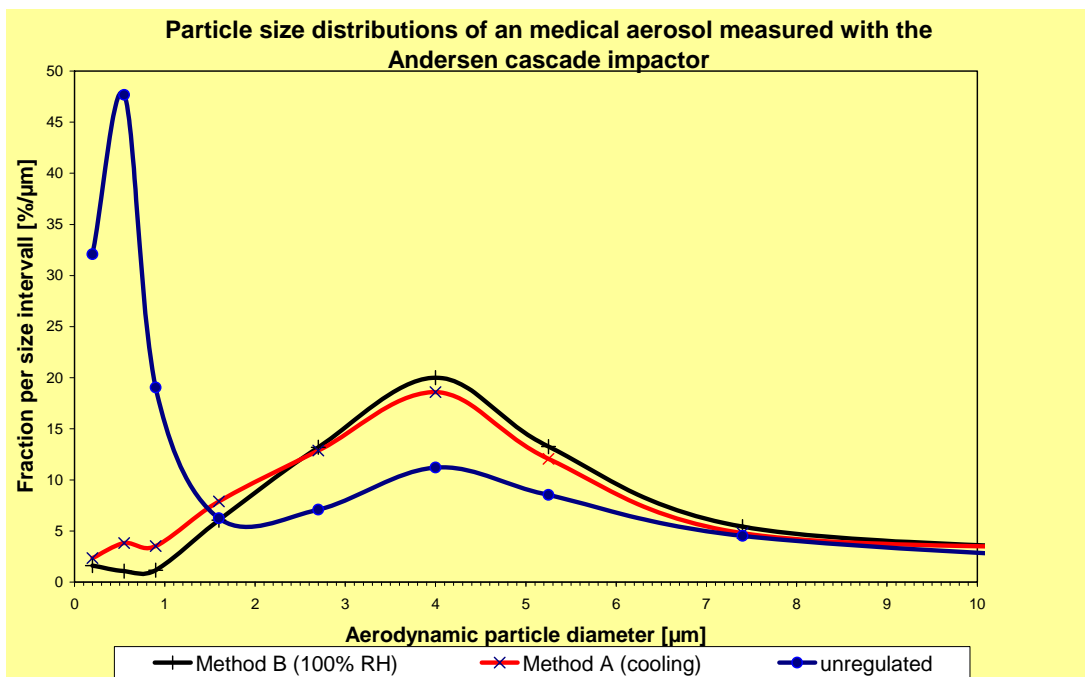


Figure 5: Particle size distributions of a medical aerosol measured with ACI

The statistical evaluation for MMAD and GSD revealed a significant difference between the two methods. The results were summarized in Table 2. The small decrease of MMAD for method A (cooling) can be explained as due to the slight evaporation that occurred.

Table 2: MMAD and GSD of Particle size distributions with significance levels

<b>Method / description</b>	<b>MMAD (<math>\pm</math>SD) [<math>\mu</math>m]</b>	<b>GSD (<math>\pm</math>SD)</b>
Method A (cooling)	4,21 ( $\pm$ 0,15)	1,85 ( $\pm$ 0,08)
Method B (100%RH)	4,42 ( $\pm$ 0,18)	1,70 ( $\pm$ 0,07)
significance level of difference between Method A and B <sup>1)</sup>	0,01	0,001
Uncooled impactor (ACI at room conditions)	3,06 ( $\pm$ 0,16)	3,52 ( $\pm$ 0,01)

<sup>1)</sup> value < 0.05 indicates significant difference

## Conclusion

Both methods were capable of preventing evaporation of aqueous droplets after aerosolization. They are suitable to measure reproducible particle size distributions of aqueous medical aerosols. The advantages of both methods are compared in Table 3.

Table 3: Advantages of methods

<b>Method A (cooling)</b>	<b>Method B (100 % RH)</b>
<ul style="list-style-type: none"> <li>• Ease of use</li> <li>• Humidifier not necessary (less expensive)</li> </ul>	<ul style="list-style-type: none"> <li>• Prevent slight evaporation as occurred with method A (cooling)</li> <li>• Controlled constant conditions during time of measurement (even at measuring times &gt; 5 minutes)</li> <li>• Independent of prevalent room conditions</li> <li>• Higher throughput due to less equilibration times (30 vs. 90 minutes)</li> <li>• Suitable for automation</li> </ul>

## References

- (1) USP 31 NF 26 General Chapters: <601> AEROSOLS, NASAL SPRAYS, METERED-DOSE INHALERS, AND DRY POWDER INHALERS - METERED-DOSE INHALERS AND DRY POWDER INHALERS, 2008
- (2) Berg, E., Svensson, J.O., Asking, L., 2007. Determination of nebulizer droplet size distribution: A method based on impactor refrigeration J. Aerosol Med.: 20 (2), pp. 97-104
- (3) Lothar Sachs, angewandte Statistik (ISBN 3-540-40555-0), 11. Auflage 2003, page 340