Development of Dual Aerodynamic Particle Sizers Method to Understand Aerosol Plume Dynamics

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Background

- Inhalable medications are highly dependent on size. 0.5-5 µm is considered the optimal size range for drug deposition in the lung [1].
- Current models do not provide an accurate representation of the drug deposition profile.
- Size of the drug particle may change in vivo due to various factors including hygroscopic growth.
- Size distribution is often measured in the bulk phase.
- Change in relative humidity (RH) during actuation.
- Ambient RH ~30%-40%. Deep lung RH ~99%.
- Need to understand the aerosol dynamics at high RH.

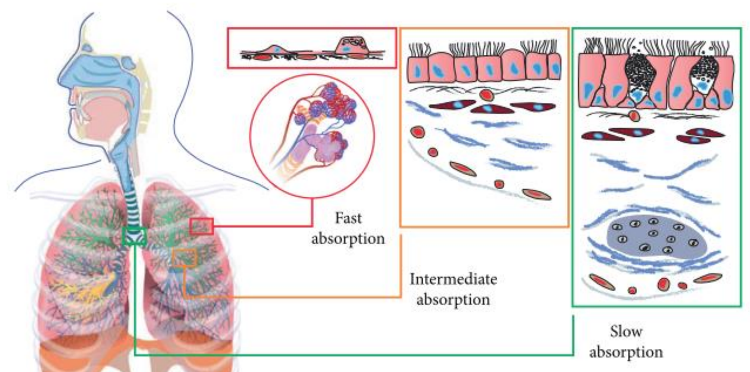

Figure 1 – Schematic diagram illustrating pulmonary absorption kinetics [1]

Aim

- To reconcile the size-changing dynamics of a plume of pharmaceutical aerosol emitted into a controlled environment with single droplet hygroscopic growth and kinetics measurements.

Method

Dual Aerodynamic Particle Sizer (APS)

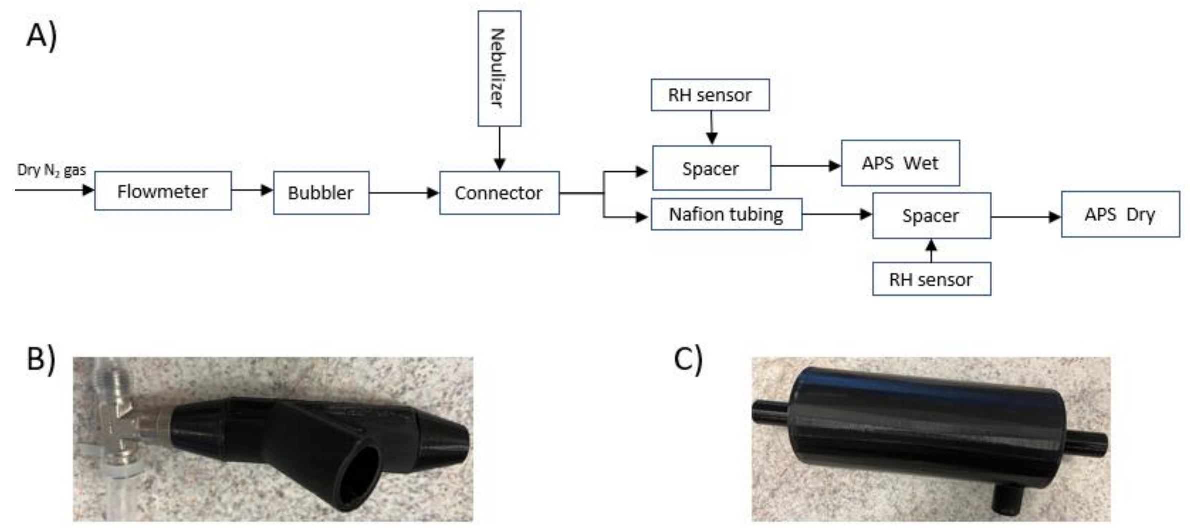

Figure 2 – A) Schematic diagram of the dual APSs set up. B) 3D printed connector and C) spacer.

- Aerodynamic diameter
- 0.5 µm -20 µm
- 5 Lmin^{-1} flowrate into the APS
- Controlled Relative Humidity
- Temperature could be changed using water bath
- Omron u100 nebulizer

Comparative Kinetic Electrodynamic Balance (CK-EDB)

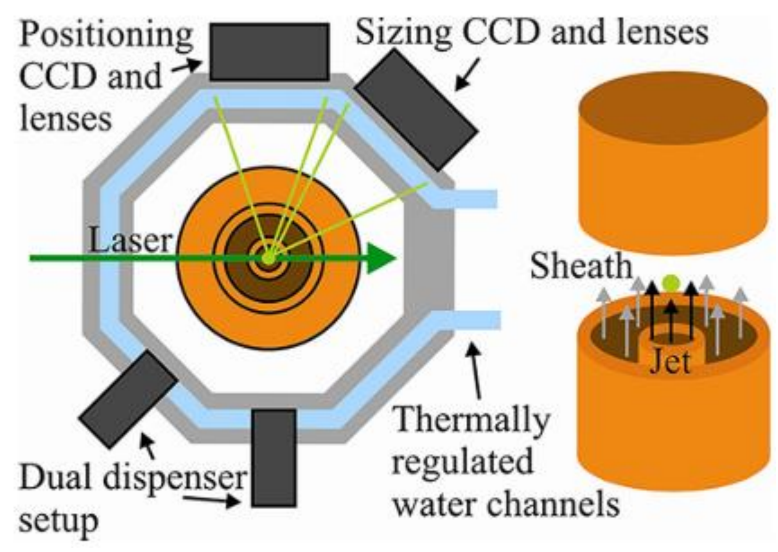

Figure 3 – Schematic of a CK-EDB [2].

- Single droplet levitation
- Controlled temperature and RH
- Laser diffraction
- Phase function
- Change in radius over time for homogeneous droplets

E-AIM Model

- Aerosol thermodynamic model
- Fixed temperature (298.15K)
- Model for common compounds (e.g., NaCl)
- Calculate the radial growth factor from the data

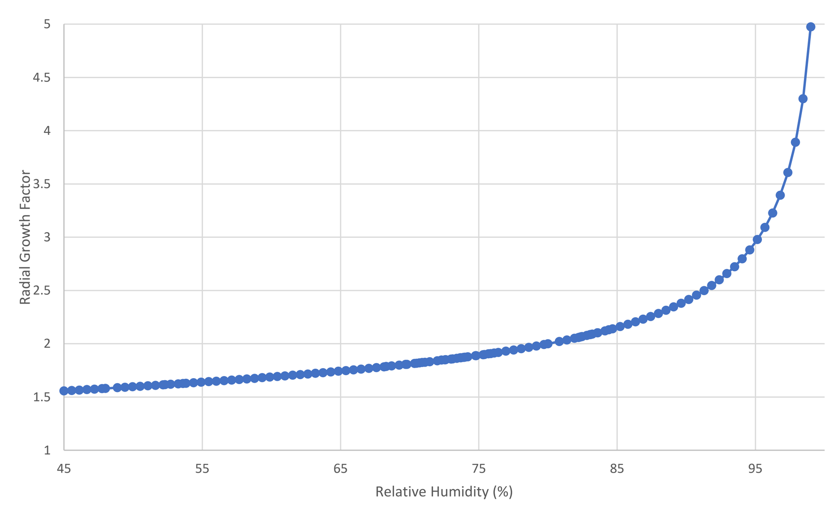

Figure 4 – Radial growth factor curve of salt obtained from E-AIM

SympaTEC

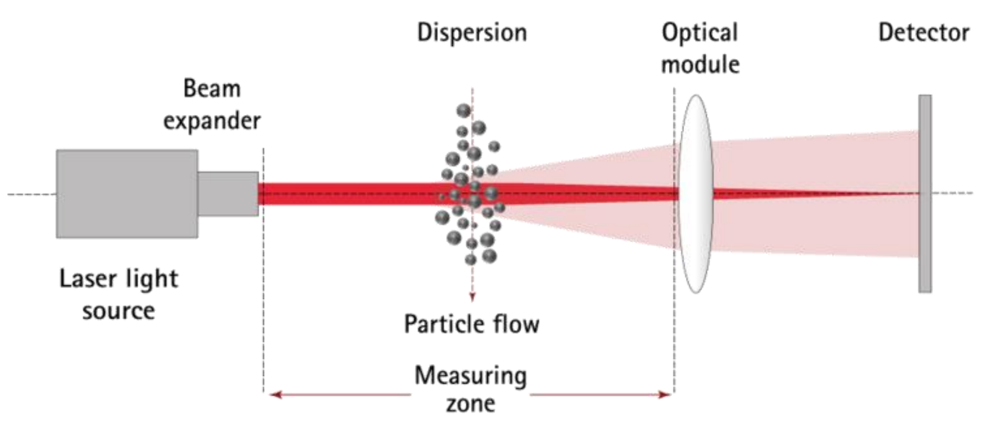

Figure 5 – Optical setup of SympaTEC HELOS unit [3]

- R1 lens: 0.1 µm - 35 µm
- Time slices – 100 ms
- Fraunhofer diffraction scattered light measured
- Does not require knowledge optical properties

Results

Calibration

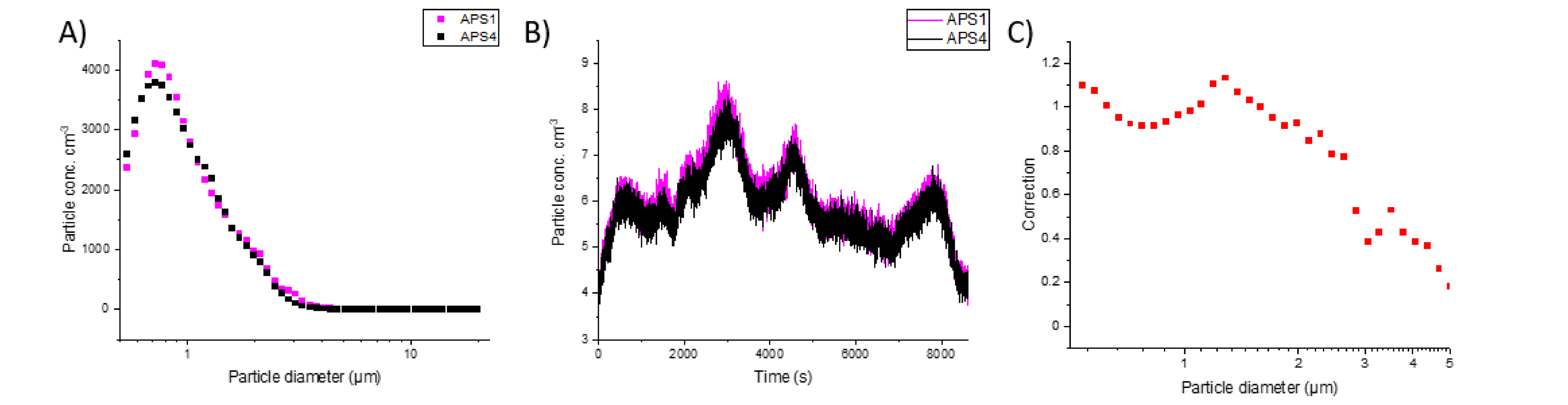

Figure 6 – Both APSs taking in room air through the connector inlet over 24 hours at ambient RH and room temperature. A) Particle concentration at each size bin from 0.5 µm to 20 µm, B) Particle concentration over 24 h and C) Correction factors calculated by dividing the particle concentration of APS 4 over that of APS 1 at each size bin.

Plume (3% w/v NaCl) vs Single Droplet

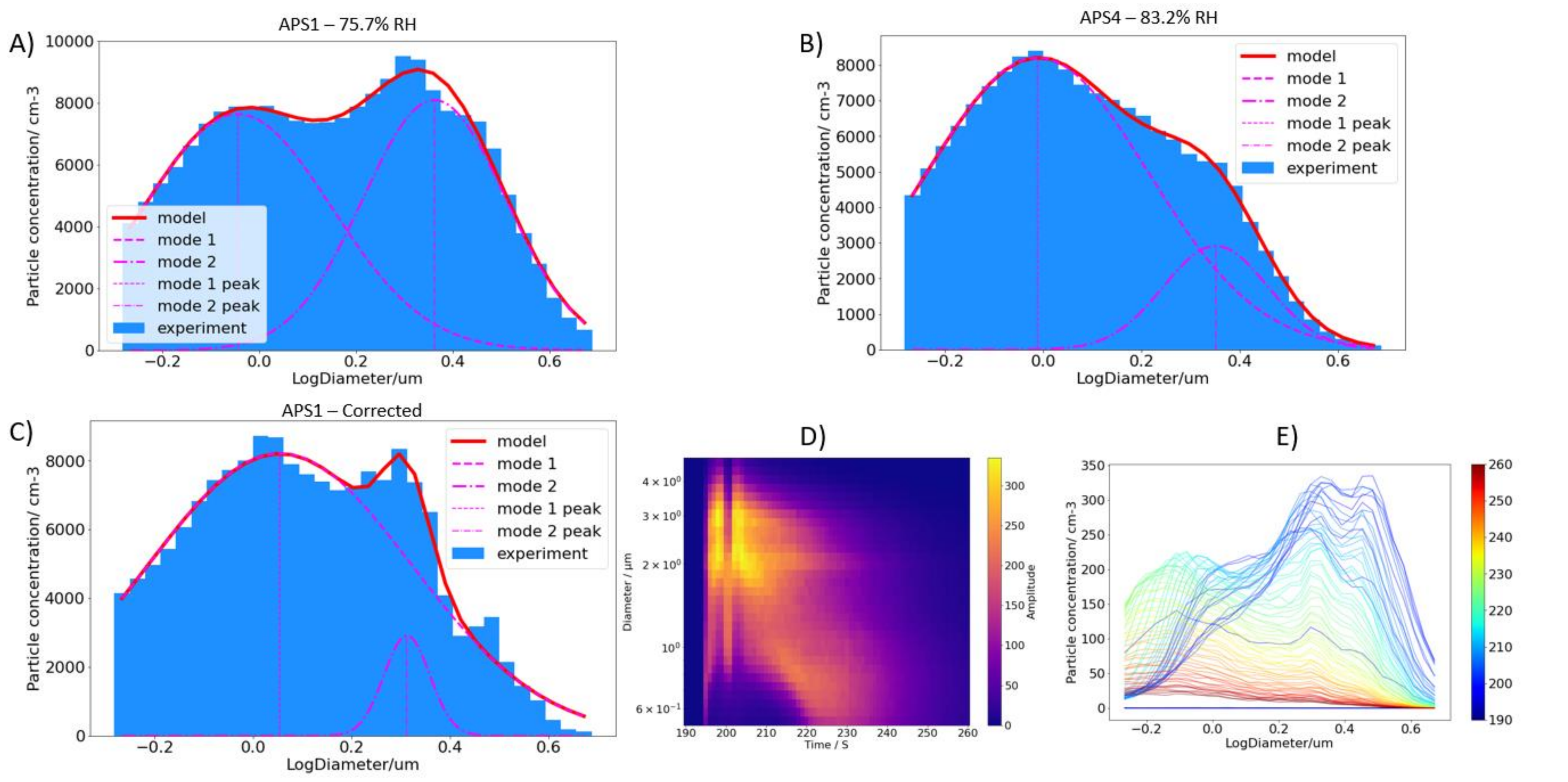

Figure 7 – Processing APS data using Python. **A)** Bimodal distribution fitted for the total size distribution obtained from APS1 at 24.6 °C, 75.7% RH (Mode 2 = 2.3011 µm); **B)** bimodal distribution fitted for APS4 data at 24.6 °C, 83.2% RH (Mode 2 = 2.2437 µm); **C)** Bimodal distribution fitted for the corrected APS1 size distribution using the correction factors in Figure 5 (Mode 2 = 2.0536 µm); **D)** Time frame selected for data processing to minimize background noise. **E)** Size distribution for each sample point throughout the actuation (1 sample per second).

- From the E-AIM model, the expected ratio of the radial growth factor (rGF) between 83.2% and 75.7% RH can be calculated by rGF (APS4) / rGF (APS1) = 2.090 / 1.905 = **1.097**
- From the experimental data, a ratio can be obtained by dividing mode 2 of the APS4 data by that of the APS1 data (2.2437 µm / 2.3011 µm = **0.975**)
- A corrected ratio can be obtained by the same approach (2.2437 µm / 2.0536 µm = **1.093**)

SympaTEC – Size distribution analysis

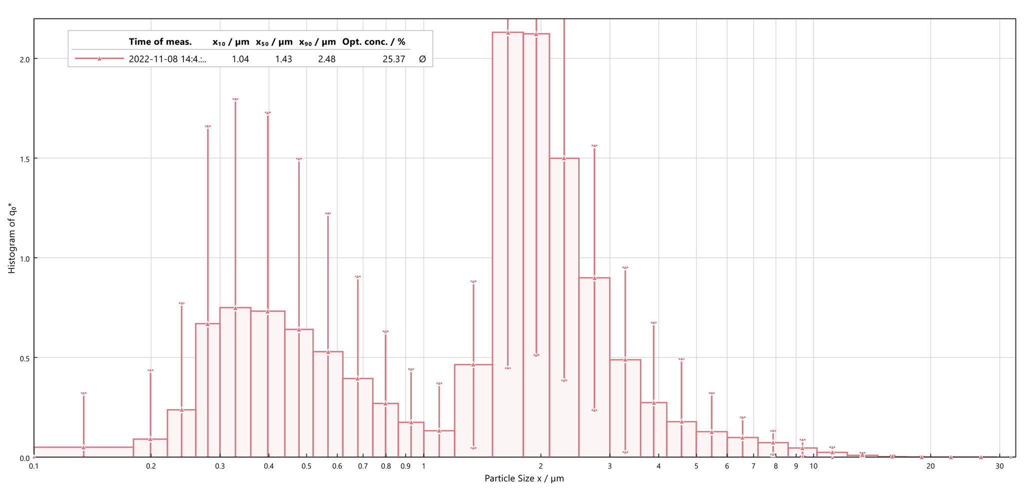

Figure 8 – Sympatec size distribution data of 3% w/v NaCl actuated by Omron u100 for 5 s at 1 mbar ambient RH and temperature using a R1 lens.

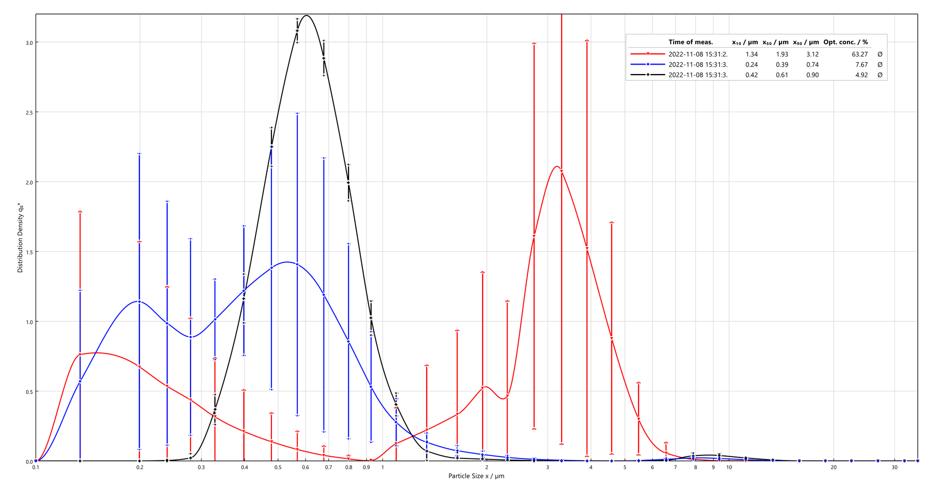

Figure 9 – Example of time slices of 1 s at the beginning (red), middle (blue) and end (black) of an actuation of the Respimat device actuating 3% w/v NaCl over approximately 1.5 s at 1 mbar, ambient RH and temperature using a R1 lens.

Conclusion

- Results from the dual APS method shows agreement with the single droplet data in the shift of radial growth factor at different relative humidities.
- Calibration correction is essential for the dual APS method.
- Sympatec data showed that the formation of the bimodal distribution is likely due to the plume development over time.

Further development

- Mass flow controller – faster RH change
- Unify the length of the actuation
- Minimize inter-dose variation
- Python script for obtaining time slice data
- Next Generation Impactor data comparison
- Different formulations
  - Tiotropium bromide, salbutamol
  - Ethanol based formulations, HFA-152a

Reference

[1]Borghardt, J. M., Kloft, C., & Sharma, A. (2018). Inhaled Therapy in Respiratory Disease: The Complex Interplay of Pulmonary Kinetic Processes. *Canadian Respiratory Journal*. https://doi.org/10.1155/2018/2732017
[2] Davies, J. F., Haddrell, A. E., Rickards, A. M. J., & Reid, J. P. (2013). Simultaneous analysis of the equilibrium hygroscopicity and water transport kinetics of liquid aerosol. *Analytical Chemistry*, *85*(12), 5819–5826. https://doi.org/10.1021/ac4005502
[3] Sympatec GmbH. (n.d.). *Laser Diffraction*. Retrieved November 9, 2022, from https://www.sympatec.com/en/particle-measurement/sensors/laser-diffraction/

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