The Influence of Sample Size on the Accuracy of Particle Size Distribution Measurements

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INTRODUCTION

Particle size distribution (PSD) measurements are key quality control tests for characterizing inhalers. Typically, cascade impactor (CI) testing is utilized for the characterization of the PSD of inhalation aerosols such as metered dose inhalers (MDIs) or dry powder inhalers (DPIs). Cascade impactor tests have a number of advantages: they characterize the entire aerosol, classify particles according to aerodynamic diameter, and they provide drug-specific analysis. However, CI tests are very labor intensive. Other techniques, such as laser diffraction, time-of-flight (TOF) aerosol spectroscopy, and microscopic analysis can be used to characterize the PSD. Each technique has advantages and disadvantages. This evaluation focuses on the issue of sampling only a portion of the aerosol. In particular, the number of particle size measurements needed in order to obtain accurate particle size distribution (PSD) estimates was assessed using computer simulations.

METHODS

Microsoft Excel spreadsheets were used to simulate the particle measurements. The Excel equation, Equation 1, was used to calculate particle size for each simulated particle measurement, where CMD and GSD were the count median diameter and geometric standard deviation, respectively, of the simulated PSD.

"=LogInv(rand(),Ln(CMD),Ln(GSD))" Equation 1

The CMD was calculated using Equation 2 derived elsewhere (1), below:

CMD = MMAD*EXP(-3*(LN(GSD))^2) Equation 2

The density of the particles was assumed to be 1.0 g/cc.

Using Equations 1 and 2, individual particle measurements were simulated. Once the desired number of particle measurements was obtained, DISTFIT software (Chimera Technologies, Inc.) was used to estimate the PSD from these simulated particle measurements. The number of particle measurements used to estimate the PSD ranged from 100 to 10,000 particles.

RESULTS

Simulated particle size distributions were generated as described previously. The aerosol was assumed to be from a perfectly lognormal distribution (MMAD = 2.5 µm, GSD = 1.6). Simulated size distributions were generated with varying numbers of particles (100 to 10,000) in the simulation. Twenty simulations were generated (i.e. twenty size distribution simulations were generated using 100 particles, twenty were generated using 200 particles, etc.). The calculated MMAD and GSD for each of the simulations are summarized in Figure 1 and 2, respectively.

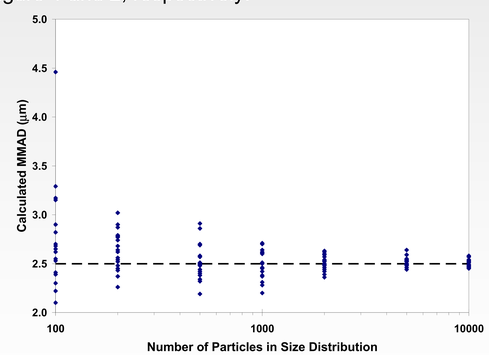


Figure 1. Estimated MMAD versus the number of particles randomly sampled from a theoretical size distribution with an MMAD of 2.5 µm and a GSD of 1.6. The dashed line represents the nominal MMAD value. There were twenty simulations per sample size.

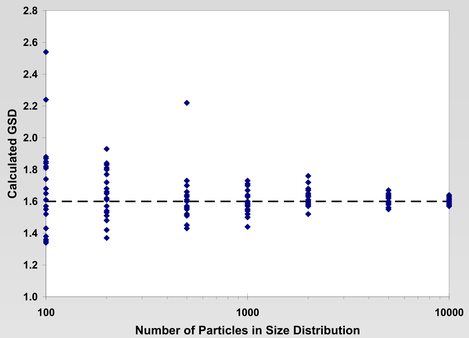
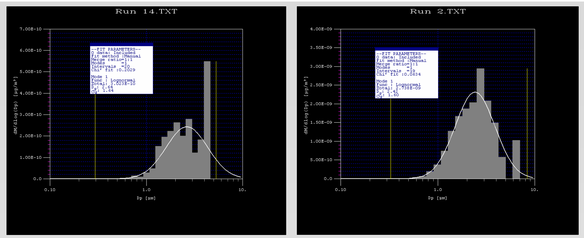


Figure 2. Estimated GSD versus the number of particles randomly sampled from a theoretical size distribution with an MMAD of 2.5 µm and a GSD of 1.6.

When 10,000 particle measurements were used to estimate the PSD, the estimated MMAD and GSD were consistently very close to the target values of 2.5µm and 1.6, respectively. As fewer number of particles were used in the simulation, the estimated MMAD and GSD were more variable and deviated from the target values.

Description of Simulation Configuration	MMAD (Ave±SD)	GSD (Ave±SD)	Chi-Squared of Fit
Calculated from 100 Particles	2.77 +/- 0.52	1.70 +/- 0.30	0.18 +/- 0.07
Calculated from 200 Particles	2.64 +/- 0.22	1.64 +/- 0.16	0.14 +/- 0.04
Calculated from 500 Particles	2.52 +/- 0.17	1.63 +/- 0.16	0.09 +/- 0.04
Calculated from 1000 Particles	2.49 +/- 0.14	1.60 +/- 0.08	0.07 +/- 0.02
Calculated from 2000 Particles	2.51 +/- 0.07	1.62 +/- 0.06	0.05 +/- 0.02
Calculated from 5000 Particles	2.52 +/- 0.05	1.61 +/- 0.03	0.03 +/- 0.01
Calculated from 10,000 Particles	2.50 +/- 0.04	1.60 +/- 0.02	0.02 +/- 0.01

Table 1. Summary of twenty simulated particle size distributions generated by randomly selecting a given number of particles from a theoretical particle size distribution with an MMAD of 2.5 µm and GSD of 1.6.



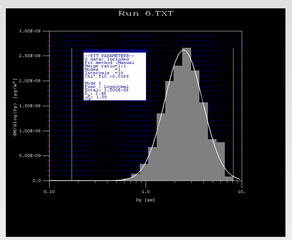


Figure 3. One typical size distributions from the twenty simulations using 100 particles (figure on top left), 1000 particles (figure on top right), and 10,000 particles (figure on right).

CONCLUSION

Accurate PSD estimates were obtained when at least 2000 particles were sampled. The best results were obtained when at least 5000 particles were included. Very poor PSD estimates were obtained when less than 1000 particle measurements were included. This may limit the precision with which some microscopic techniques are able to estimate PSDs. Other techniques that measure a portion of the aerosol can provide accurate and precise PSD estimates provided the sample sizes is at least 5000 particles and is representative of the rest of the aerosol.

REFERENCES

Hinds, W.C. (1999). "Aerosol Technology: Properties, Behavior, and Measurement of Airborne Particles". John Wiley & Sons, New York.