

Spraytec Real Time Droplet Sizing System (Spraytec RTSizer) - A Robust Method for Rapid Screening of Nebulized Formulations

Lei Mao, Kristie Hamby, David Wilcox

Catalent Pharma Solutions, 160 N Pharma Drive, Morrisville, North Carolina, 27560, USA

Summary

Spraytec Real Time Droplet Sizing System (Spraytec RTSizer) has been assessed for determination of particle size distribution of aerosols of two liquid formulations delivered from three commercial nebulizers and the results compared to the aerodynamic particle size distribution determined by the Next Generation Pharmaceutical Impactor (NGI). Both techniques gave comparable fine particle dose (FPD, < 5µm), fine particle fraction (FPF, < 5µm) and cumulative particle size in the range between 3µm to 8µm. The cumulative particle size was slightly higher for the results generated by the Spraytec RTSizer compared to those from the NGI. However, this does not compromise Spraytec RTSizer as an efficient tool for rapid screening of the nebulized formulations, especially when FPD and FPF of less than 5 µm are the main screening criteria.

Introduction

Aerosolization efficiency is one of the key formulation performance measures to be considered in developing nebulized formulations. Historically, impaction methods using either Andersen Cascade Impactor or Next Generation Pharmaceutical Impactor are used in formulation screening. The process can be labor intensive and time consuming.

In a recent program, we assessed the feasibility of using the Spraytec Real Time Droplet Sizing System (Spraytec RTSizer, Malvern Instruments, USA), a laser diffraction method for the formulation screening. Nebulized solution formulations A (125 mg/mL) and B (100 mg/mL) prepared with the same active ingredient and excipient were used in the study. Particle size distribution (PSD) of the formulations delivered from three commercial nebulizers: Omron NE-C30 (Omron Healthcare, Inc. USA), Technoneb Model 3003, Technology & Health LLC, USA) and Pari Proneb Ultra (Pari Innovative Manufacturers, Inc, USA) was measured using the Spraytec RTSizer and aerodynamic particle size distribution (APSD) by the Next Generation Pharmaceutical Impactor (NGI). The Spraytec RTSizer and NGI results were analyzed to assess comparability of the data generated by two methods.

Methods

Two formulations were assessed in the study.

For both NGI and Spraytec tests, an air flow rate of 15 L/min was used when testing Omron NE-C30 and Pari Proneb Ultra nebulizers to simulate the low air flow pattern typically used by the patients. However, for the Technoneb nebulizer, an air flow rate of 30 L/min was used to prevent “escape” of the aerosol from the inlet of the nebulizer for both NGI and Spraytec tests.

For the Spraytec RTSizer testing, an Andersen Cascade Impactor (ACI) induction port was connected to the inlet and an ACI connected to the outlet of the sample cell (Figure 1) for the purpose of collecting the aerosol waste only. The airflow rate was set at the required value prior to testing and the nebulizer was attached to the inlet of the induction port through an elastic adaptor. PSD of the aerosols was measured using the following conditions: test duration = 60,000 ms, data acquisition rate = 100 Hz, single scan, triggering transmission = 98.0 %.

For the NGI testing, nebulizers were attached to the inlet of the NGI induction port through an elastic adaptor. No pre-separator was used. The airflow rate was set to the required value prior to testing. Doses were collected over 5 minutes for all tests. Following collection, drug deposited on induction port, NGI stages and filters was recovered with the diluent and assayed by HPLC. APSD of the aerosols was calculated using the Copley CITDAS software (Version 2.0) for the NGI tests performed at 30 L/min. For the NGI tests performed at 15 L/min, the cut off diameters were corrected in accordance with the figures published by Marple et al¹ when calculated using the CITDAS software.

Results and Discussion

Spraytec RTSizer Results

Triplicate measurements were then taken for both formulations A and B delivered from three nebulizers. The results are presented in Table 1.

NGI Results

NGI results were presented in Table 2.

Comparison of the Spraytec RTSizer and NGI Results

Comparison of the Spraytec RTSizer and NGI results is presented in Table 3. No evidence of significant difference was detected in the FPF (< 5 µm) between the methods.

Figure 2 presents a comparison of the cumulative particle size distribution measured by Spraytec RTSizer and NGI. It can be observed that the PSD results measured by two methods were consistent and comparable at the particle size above 2 µm. The cumulative percentage of the particles < 2 µm was higher when measured by the Spraytec RTSizer compared to the NGI. Why Spraytec RTSizer gave a higher cumulative percentage of particles less than 2 µm was, at this point, unknown. Difference in the principles of PSD measurement between two methods could be one of the reasons and further investigation will be required. This, however, does not compromise Spraytec RTSizer as an efficient tool for rapid screening of the nebulized formulations when the overall aerosolization performance and FPD/FPF of less than 5 µm are the main selection criteria.

Consistency in the overall PSD results was considered attributable to the nature of the nebulized aerosols. Nebulization tends to produce fine droplets of spherical shape at a unit density, resulting in negligible difference between geometric and aerodynamic particle size distributions.

Conclusions

Both Spraytec RTSizer and NGI were used in determination of PSD of aerosols of two nebulized formulations delivered from three nebulizers. The PSD results from both measurement techniques were comparable with exception of the cumulative percentage of the particles less than 2 µm.

For the purpose of formulation screening, Spraytec RTSizer was considered to be a robust and efficient tool for assessing the aerosolization performance of nebulized formulations.

REFERENCES

1. Virgil A Marple, Bernard A Olson, Kumaragovindhan Santhanakrishnan, Daryl L Roberts, Jolyon P Mitchell and Buffy L Hudson-Curtis (2004), "Next Generation Pharmaceutical Impactor: A New Impactor for Pharmaceutical Inhaler Testing. Part III. Extension of Archival Calibration to 15 L/min," J Aerosol Medicine Vol. 17, No 4, p335-343 2004

Table 1 Particle Size Distribution of Formulations A (125 mg/mL) and B (100 mg/mL) Delivered from Three Nebulizers Measured by Spraytec RTSizer

| Nebulizer | Formulation A | | | | | Formulation B | | | |
|----------------------|---------------|----------|----------|----------|-------|---------------|----------|----------|-------|
| | Test | D10 (µm) | D50 (µm) | D90 (µm) | %<5µm | D10 (µm) | D50 (µm) | D90 (µm) | %<5µm |
| Technoneb Model 3003 | 1 | 0.6 | 3.1 | 8.9 | 70.8 | 0.6 | 3.3 | 9.4 | 68.5 |
| | 2 | 0.6 | 3.4 | 9.8 | 66.5 | 0.6 | 3.3 | 9.8 | 67.4 |
| | 3 | 0.6 | 3.3 | 9.1 | 69.1 | 0.6 | 3.3 | 9.0 | 69.8 |
| | Average | 0.6 | 3.3 | 9.3 | 68.8 | 0.6 | 3.3 | 9.4 | 68.5 |
| | %RSD | 2.5 | 4.3 | 5.1 | 3.2 | 1.0 | 1.2 | 4.0 | 1.8 |
| | Min | 0.6 | 3.1 | 8.9 | 66.5 | 0.6 | 3.3 | 9.0 | 67.4 |
| | Max | 0.6 | 3.4 | 9.8 | 70.8 | 0.6 | 3.3 | 9.8 | 69.8 |
| Omron NE C30 | 1 | 0.6 | 3.4 | 10.3 | 66.8 | 0.6 | 2.9 | 10.6 | 71.9 |
| | 2 | 0.6 | 3.5 | 11.4 | 66.8 | 0.6 | 2.8 | 8.4 | 74.9 |
| | 3 | 0.6 | 3.4 | 9.8 | 66.6 | 0.6 | 3.4 | 11.7 | 69.5 |
| | Average | 0.6 | 3.4 | 10.5 | 66.7 | 0.6 | 3.0 | 10.2 | 72.1 |
| | %RSD | 2.4 | 1.6 | 7.6 | 0.1 | 3.0 | 10.8 | 16.5 | 3.7 |
| | Min | 0.6 | 3.4 | 9.8 | 66.6 | 0.6 | 2.8 | 8.4 | 69.5 |
| | Max | 0.6 | 3.5 | 11.4 | 66.8 | 0.6 | 3.4 | 11.7 | 74.9 |
| Pari ProNeb Ultra | 1 | 0.9 | 6.2 | 17.8 | 43.1 | 0.8 | 5.4 | 16.5 | 47.6 |
| | 2 | 0.9 | 5.8 | 17.0 | 45.1 | 0.8 | 5.3 | 16.1 | 48.0 |
| | 3 | 0.9 | 5.8 | 15.9 | 45.1 | 0.8 | 5.3 | 16.0 | 48.2 |
| | Average | 0.9 | 5.9 | 16.9 | 44.4 | 0.8 | 5.3 | 16.2 | 48.0 |
| | %RSD | 2.8 | 3.6 | 5.9 | 2.6 | 0.7 | 1.0 | 1.6 | 0.6 |
| | Min | 0.9 | 5.8 | 15.9 | 43.1 | 0.8 | 5.3 | 16.0 | 47.6 |
| | Max | 0.9 | 6.2 | 17.8 | 45.1 | 0.8 | 5.4 | 16.5 | 48.2 |

Table 2 Particle Size Distribution of Formulations A (125 mg/mL) and B (100 mg/mL) Delivered from Three Nebulizers Measured by NGI

| Nebulizer | Omron NE C30 | | Technoneb Model 3003 | | Pari Proneb Ultra | |
|--|--------------|-----------|----------------------|-----------|-------------------|-----------|
| | 15 L/min | | 30 L/min | | 15 L/min | |
| Test flow rate (L/min) | 125 mg/mL | 100 mg/mL | 125 mg/mL | 100 mg/mL | 125 mg/mL | 100 mg/mL |
| Formulation strength | mg/mL | mg/mL | mg/mL | mg/mL | mg/mL | mg/mL |
| Mean residual in the vial (mg) | 12.3 | 10.3 | 12.5 | 9.4 | 12.2 | 9.5 |
| Mean residual in the nebulizer (mg) | 503.3 | 395.3 | 357.5 | 275.7 | 374.6 | 223.2 |
| Mean deposition on induction port (mg) | 4.2 | 2.3 | 12.3 | 13.1 | 8.4 | 11.2 |
| Mean deposition on stage 1 (mg) | 1.7 | 1.4 | 5.5 | 4.6 | 13.0 | 17.9 |
| Mean deposition on stage 2 (mg) | 2.9 | 2.5 | 22.7 | 20.4 | 30.7 | 40.9 |
| Mean deposition on stage 3 (mg) | 7.8 | 5.7 | 38.0 | 35.9 | 36.3 | 44.9 |
| Mean deposition on stage 4 (mg) | 18.2 | 14.6 | 59.0 | 49.1 | 39.9 | 43.2 |
| Mean deposition on stage 5 (mg) | 19.2 | 17.5 | 42.0 | 35.2 | 31.8 | 32.3 |
| Mean deposition on stage 6 (mg) | 10.6 | 11.2 | 18.1 | 15.1 | 18.3 | 16.8 |
| Mean deposition on stage 7 (mg) | 5.1 | 5.2 | 6.6 | 5.8 | 8.6 | 7.8 |
| Mean deposition on the Micro Orifice filter (mg) | 2.3 | 1.8 | 3.0 | 2.5 | 4.5 | 3.7 |
| Mean deposition on the glass fiber filter (mg) | 1.8 | 2.1 | 0.9 | 0.8 | 4.3 | 4.1 |
| Mean total delivered dose (mg) | 73.9 | 64.2 | 208.2 | 182.5 | 195.8 | 222.7 |
| RSD (%) | 9.6 | 1.8 | 2.9 | 1.4 | 35.7 | 20.8 |
| Mean FPD < 5 µm (mg) | 54.7 | 50.4 | 150.0 | 127.9 | 101.5 | 101.0 |
| RSD (%) | 4.9 | 1.6 | 0.3 | 0.4 | 23.2 | 18.3 |
| Mean FPF < 5 µm (%) | 74.3 | 78.5 | 72.1 | 70.1 | 54.0 | 45.5 |
| RSD (%) | 4.4 | 2.6 | 2.8 | 1.1 | 16.3 | 3.1 |
| Mean MMAD (µm) | 3.0 | 2.8 | 3.0 | 3.0 | 4.4 | 5.2 |
| RSD (%) | 5.8 | 2.1 | 5.1 | 1.9 | 23.4 | 2.2 |
| Mean GSD | 1.9 | 1.9 | 2.1 | 2.0 | 2.3 | 2.1 |
| RSD (%) | 3.0 | 3.0 | 2.8 | 2.8 | 9.2 | 2.7 |

Table 3 Comparison of NGI and Spraytec Results

| Nebulizer | Test flow rate (L/min) | Formulation | A (125 mg/mL) | | | B (100 mg/mL) | | |
|----------------------|------------------------|---------------------|---------------|-------|-------|---------------|-------|-------|
| | | | 1 | 2 | 3 | 1 | 2 | 3 |
| Omron NE C30 | 15 L/min | % < 5 µm by NGI | 76.22 | 70.50 | 76.23 | 76.54 | 78.32 | 80.63 |
| | | % < 5µm by Spraytec | 71.94 | 74.86 | 69.52 | 66.77 | 66.80 | 66.64 |
| Technoneb Model 3003 | 30 L/min | % < 5 µm by NGI | 73.77 | 72.69 | 69.87 | 69.65 | 69.55 | 70.97 |
| | | % < 5µm by Spraytec | 68.45 | 67.36 | 69.76 | 70.83 | 66.45 | 69.06 |
| Pari Proneb Ultra | 15 L/min | % < 5 µm by NGI | 64.02 | 47.56 | 50.32 | 44.55 | 47.16 | 44.87 |
| | | % < 5µm by Spraytec | 47.62 | 48.03 | 48.22 | 43.09 | 45.12 | 45.09 |

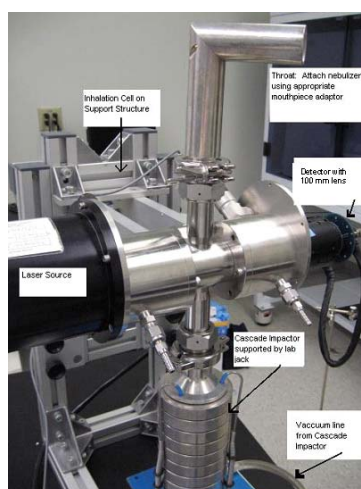
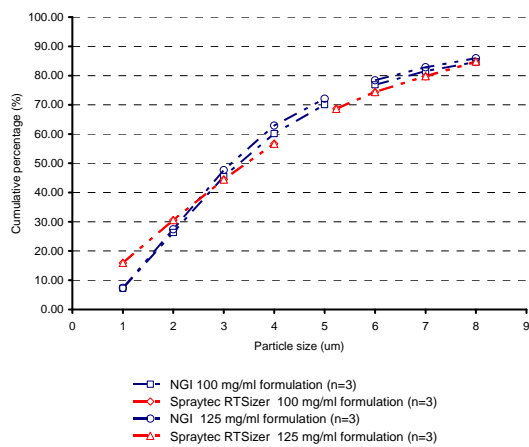
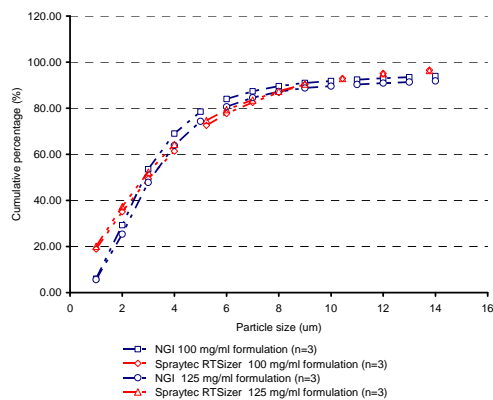


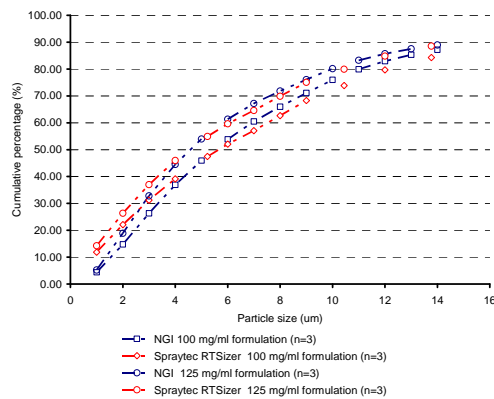
Figure 1. Set Up of Spraytec Real Time Droplet Sizing System for Measurement of Particle Size Distribution of Nebulized Formulations



(a)



(b)



(c)

Figure 2

Comparison of Cumulative Particle Size Distribution of the Formulation A (125 mg/mL) and B (100 mg/mL) Delivered from a) Technoneb Model 3003 Nebulizer, b) Omron NE C30 Nebulizer and c) Pai Proneb Ultra Nebulizer Measured by Next Generation Pharmaceutical Impactor (NGI) and Spraytec Real Time Sizer (Spraytec RTSizer)