

# Comparative Analysis of Manual Versus Automated Actuation Parameters for Droplet Size Determination by Laser Diffraction for Spray Devices

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## INTRODUCTION

To ensure reproducibility during in-vitro dose collection, the FDA guidance for Nasal Sprays<sup>1</sup> suggests controlling actuation parameters such as actuation force, stroke length, and force rise and fall time. This is typically achieved by the use of an automatic actuation device. In this study it is described how the same criteria that apply to the optimization of automated actuation parameters for nasal sprays can be applied to novel spray devices that spray on the horizontal plane.

When developing methods for Droplet Size Distribution by Laser Diffraction for nasal sprays, automatic actuation parameters are determined by comparison of automatic droplet size data versus that obtained by manual actuations. The D50 values are typically the most consistent and comparable values between the two actuation methods and typical criterion is that the average value for the automated actuations fall within the range of 85 to 115% of the average manual value. The D10 and D90 values are considered, although a somewhat wider variance may be expected. The criteria is typically that the average value for the automated actuations fall within the range 75 to 125% of manual. Shot weight values and plume duration may also be evaluated for consistency between the two actuation methods.

In this study, Device 1 is a typical nasal spray and Devices 2 and 3 are novel devices which spray on the horizontal plane and have other differences in actuation design. Device 2 is a single-dose spray device that does not contain a spring requiring consistent force to initiate actuation and deliver the drug. Instead, a threshold force is required to actuate the device. Device 3 contains a spring and a metering chamber to deliver the dose and, additionally, has a secondary packaging with a spray orifice. The secondary packaging does not affect the spray mechanics or spray characteristics of the device.

## INSTRUMENTATION

Malvern™ Spraytec Laser Diffraction Spray Particle Sizing System v. 5.41 equipped with a 200 mm lens  
 Innova™ MightyRunt Automated Actuation System  
 Mettler Toledo™ AG-204 Analytical Balance

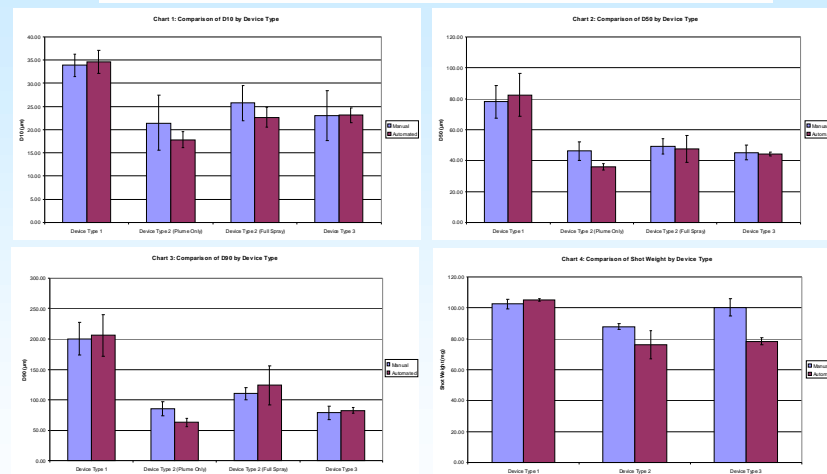
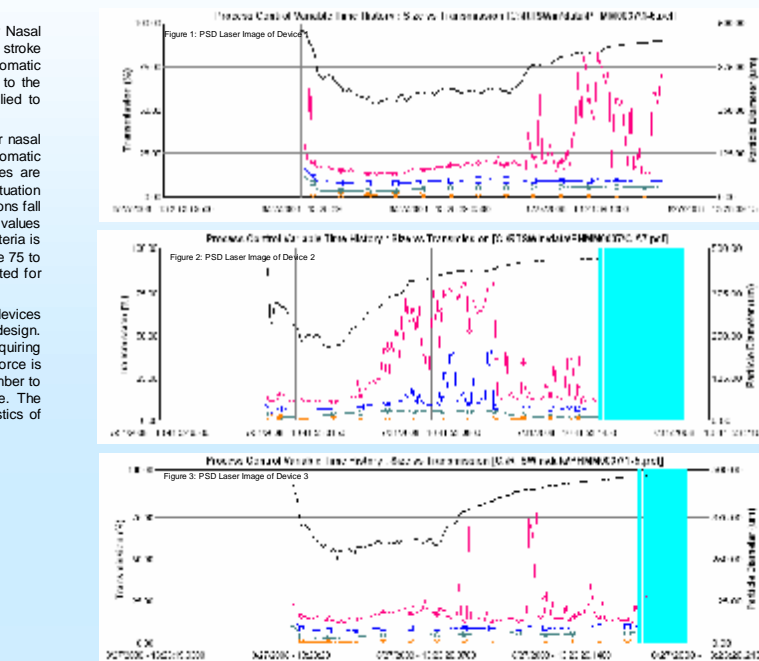
## METHODOLOGY

Droplet Size Distribution by Laser Diffraction was determined for each of three spray devices. Samples of each device were introduced into the laser path by both manual actuations and by automated actuation using the InnovaSystems MightyRunt Actuation Station. Optimized actuation parameters for each device are listed in Table 1. Three samples of Devices 1 and 3 were analyzed (n=6) by each actuation method. Similarly, eighteen samples (single dose) of Device 2 were analyzed by each actuation method. The parameters used for the droplet size distribution determination with the Spraytec in Flash mode for plume capture are listed in Table 2. The D10, D50, D90 and shot weight were evaluated for each spray.

The acceptance criteria for equivalence of the manual versus automated actuations were: Individual shot weight results for the automated actuations should all fall within the range of 75 to 125% of the average shot weight for the manual actuations. Average D10 and D90 results of the automated actuations should be within 75 to 125% of the average D10 and D90 results for the manual actuations. Average D50 results of the automated actuations should be within 85 to 115% of the average D50 results for the manual actuations.

Parameter	Device 1	Device 2	Device 3
Actuation Force, kg	6.0	4.0	6.0
Force Rise Time, s	1.0	0.2	0.5
Hold time, s	0.5	1.0	1.0
Force fall time, s	0.1	1.0	0.5
Spray delay, s	1.0	1.0	1.0
Minimum travel distances, mm	5.0	10.0	5.0
Maximum travel time, s	1.0	4.0	2.0
Trigger signal delay, s	0.0	0.0	0.0

Parameter	Device 1	Device 2	Device 3
Test duration, ms	600	200	200
Data acquisition rate, Hz	2000	1000	1000
Acquisition Duty Cycle	0% single scan	0% single scan	0% single scan
Experimental Trigger	Transmission	Transmission	Transmission
Transmittance, %	98.0%	98.0%	98.0%



## REFERENCE

<sup>1</sup>Food and Drug Administration (July 2002) "Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products- Chemistry, Manufacturing, and Controls documentation," Guidance for Industry, U.S. Food and Drug Administration, Washington D.C.

## ACKNOWLEDGEMENTS

Malvern is a trademark of Malvern Instruments Ltd, Innova is a trademark of InnovaSystems, Inc., Mettler Toledo is a registered trademark of Mettler Toledo, Inc.

Device Type	Actuation Type	D10 (µm)	D50 (µm)	D90 (µm)	Shot Weight (mg)
Device Type 1	Manual	34	78	200	102
	Automated	35	82	206	105
Device Type 2 (Plume Only)	Manual	21	46	86	88
	Automated	18	36	63	76
Device Type 2 (Full Spray)	Manual	26	49	111	88
	Automated	23	48	124	76
Device Type 3	Manual	23	45	79	100
	Automated	23	44	82	78

Device Type	D10 (µm)	D50 (µm)	D90 (µm)	Shot Weight (mg)
Device Type 1	102	106	103	102
Device Type 2 (Plume Only)	74	78	74	87
Device Type 2 (Full Spray)	88	97	112	87
Device Type 3	100	98	104	78

## RESULTS AND DISCUSSION

The average D10 and D90 for automated actuations for each of the three devices met the acceptance criteria of 75 to 125% of the average for manual actuations. The average D50 for automated actuations for each of the three devices met the acceptance criteria of 85 to 115% of the average D50 for manual actuations. The individual shot weight results for the automated actuations fell within the range of 75 to 125% of the average shot weight for the manual actuations, meeting the acceptance criteria. Reference Tables 3 and 4 and Charts 1-4 for results.

Typically, comparisons of droplet size distribution use the stable stage of the plume. All spray plumes have three stages. The first stage, development, is characterized by variable droplets and decreasing transmission of the laser. The second stage, stable, is characterized by a stable droplet distribution and transmission. Variable droplets and increasing transmission characterize the final stage, dissipation. Reference Figures 1-3 for the laser images of each device's full spray.

In this study, the stable stage of the plume was used for analysis of devices 1 and 3, and the full spray was used for analysis of device 2. Because this device does not contain a spring requiring a consistent force to initiate actuation and deliver the drug, there is variability in the amount of force required to actuate the device and deliver the drug once the initial resistance mechanism has been broken. This variability in force causes an inconsistent transmission from the laser creating difficulty in identifying the stable stage of the plume. Reference Figure 2 for the illustration of the transmission for device 2, demonstrating the small duration and fluctuation of the second stage of plume development.

While the results for the D10, D50, and D90 met the acceptance criteria for all devices, the data for device 2 demonstrates more inter-device variance than the results for devices 1 and 3. As device 2 is a single-dose unit, this variability could be the result of performing data collection using different bottles, while devices 1 and 3 had multiple collections from the same bottles. It is also possible that the intra-device variance is the result of the lack of a spring or metered chamber providing consistent force for actuation and drug delivery.

## CONCLUSION

Automatic actuation parameters were optimized and qualified for a nasal spray device and two novel spray devices that spray on the horizontal plane for the MightyRunt Actuation Station for determination of droplet size distribution by laser diffraction. All devices met the acceptance criteria demonstrating the comparability with manual actuations necessary to meet the requirements for reproducibility during in-vitro dose collection per the FDA guidance for Nasal Sprays<sup>1</sup>.

It was demonstrated that the same criteria that are used to evaluate nasal sprays also have the potential to be applied to other novel devices, however there are device considerations that must be taken into account in order to establish appropriate parameters for the automated actuation apparatus. The actuation mechanism and components for the devices should be considered in the selection of the method parameters. Also, it may be necessary to evaluate the consistency of transmission from the laser in order to determine if the full spray instead of or in addition to the stable stage of the plume should be analyzed.