Applications for Droplet Sizing

Manual versus Automated Actuation of Nasal Sprays

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AUTHORS

Nasal sprays are designed to deliver a precise drug dose to the correct absorption site within the nasal mucosa. The spray pump produces the droplet-size distribution, which must be optimized to increase nasal deposition and minimize lung deposition or absorption via the gastrointestinal tract. In this study, two nasal spray pumps were used to evaluate the effectiveness of manual and automated actuation and the effects of variations in actuation parameters on the resultant droplet-size distributions.

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Drugs delivered through the nasal route alleviate local disorders such as sinus congestion and allergic rhinitis. Currently, researchers are investigating the nasal route for the systemic delivery of vaccines, proteins, and peptides. A typical nasal spray formulation consists of a drug suspended or dissolved in an aqueous medium, which is filled into a bottle equipped with a metered spray pump. Pump actuation by the patient delivers drug-laden droplets into the nasal cavity. The pump is an integral part of the whole assembly and plays a crucial role in atomizing and delivering accurate doses into the nasal cavity. Thus, the emitted droplet size is a key parameter for pump performance and can be a surrogate for *in vivo* bioequivalence. Because droplet sizing for nasal sprays often is measured using laser diffraction, applications and experimental design for these instruments have grown in number and complexity. This article compares manual and automated actuation and describes the effect of variations in automated actuation parameters on droplet-size characterization using model nasal spray pumps.

Motivation for automated actuation of nasal sprays

FDA's 2003 draft guidance, "Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal Sprays for Local Action," has been a key factor in the development of automated testing (1). Typically, the nasal pump spray is actuated manually during product development studies. Manual actuation, however, can create variable actuation forces and inconsistent results, which can lead to speculation about operator-induced variability. Therefore, the FDA guidance document recommends automated actuation stations for "all comparative *in vitro* bioequivalence tests to decrease variability in drug delivery due to operator factors, including removal of potential analyst bias in actuation, and increase the sensitivity for detecting potential differences between products in any of the above tests."

FDA provides further advice about the specification of the actuation station:

> Automated actuation stations may be stand-alone systems or accessories for laser diffraction instruments. Stations may include settings for actuation force, actuation velocity, hold time, return time, delay time between actuations, length of stroke, and number of actuations. Selection of appropri-

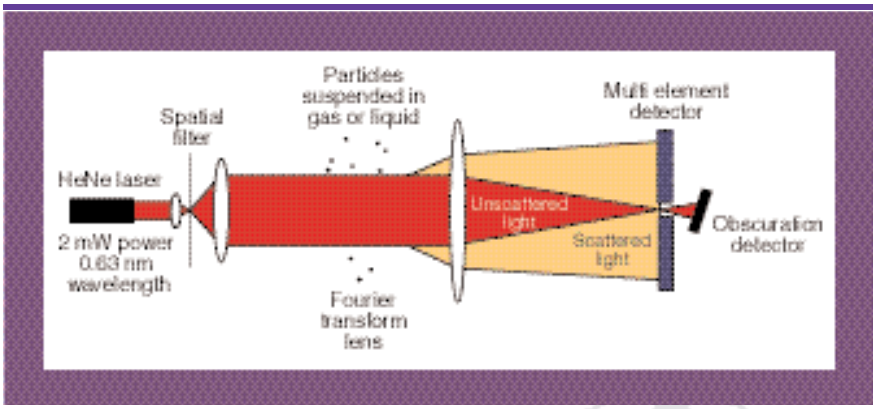

Figure 1: A schematic of a typical laser diffraction instrument.

Table I: Results obtained for the manual actuation of pump A.

	Dv10		Dv50		Dv90		Span	
	Size	Variation	Size	Variation	Size	Variation	Value	Variation
Operator	(μm)	(%)	(μm)	(%)	(μm)	(%)		(%)
1	20.95	4.15	41.65	5.67	88.19	6.39	1.61	1.67
2	18.59	6.65	37.5	7.10	74.02	8.02	1.48	1.54
3	17.31	0.40	34.67	1.03	67.24	4.22	1.44	4.49

Table II: Results obtained for the manual actuation of pump B.

	Dv10		Dv50		Dv90		Span	
	Size	Variation	Size	Variation	Size	Variation	Value	Variation
Operator	(μm)	(%)	(μm)	(%)	(μm)	(%)		(%)
1	23.69	9.28	44	11.13	75.69	17.83	1.17	10.28
2	20.06	6.30	37.41	4.74	59.89	5.28	1.06	1.45
3	19.16	2.64	35.8	0.60	58.34	1.32	1.09	2.93

ate settings should be relevant to proper usage of the nasal aerosol or nasal spray by the trained patient and should be documented on the basis of exploratory studies in which actuation force, actuation time, and other relevant parameters are varied. These studies should accompany the validation data. Selected settings used for the comparative *in vitro* study should be specified in the SOP for each test for which the automatic device is employed.

Documenting bioequivalence requires that the actuation parameters be representative of the patient population who use the device. For product quality studies, control of actuation parameters is essential for reproducible results. Automated actuation helps ensure quality (*e.g.*, ISO 9001) and the standardization and comparability of results from nasal spray pump suppliers and their customers.

Droplet-size measurement using laser diffraction

Historically, cascade impaction has been used for sizing droplets or particles in nasal sprays and other pharmaceutical aerosols (2). This technique measures aerodynamic diameters on the basis of inertial impaction and allows researchers to directly quantify the sampled mass without artificial processing and without dependence on statistically manipulated data. A downside of cascade impactors is the need to operate the device being tested many times to minimize experimental error associated with the drug assay's limit of quantification. Cascade impactors therefore can only provide time-averaged data and do not allow assessment of the dynamics of aerosol formation. The analysis of the impactor plates also is time-consuming.

The laser-diffraction technique for particle sizing has existed since the late 1970s (3). It is applicable to a variety of particulate systems, is fast, and can be automated. The ISO standard "Particle Size Analysis—Laser Diffraction Measurements" was published in 1999 to "provide a methodology for adequate quality control in particle size analysis" (4). It provides a clear description of the general principles of laser-diffraction particle sizing, with all the terms formally defined, and guides the user in what to expect from an instrument of this type.

The laser-diffraction measurement principle is based on the fact that a particle passing through a collimated laser beam will scatter light at an angle that is inversely proportional to the particle's size. Figure 1 shows a typical experimental setup. The particles being measured are passed through a parallel laser beam. A Fourier transform lens focuses any scattered light onto a radial array of silicon diode detectors. This lens images the scatter from particles of the same size to the same part of the detector array, regardless of their position within the laser beam and their speed. Consequently at any given moment, there is a light-energy distribution across the detector that directly corresponds to the particle-size distribution of the droplets present in the laser beam at that moment.

The particle-size distribution relating to a given scattering pattern is obtained by fitting the data to an appropriate scattering model. Before significant computing power became available in the 1980s, researchers used the Fraunhofer approximation to calculate particle-size distributions. This model, however, incorrectly predicts the scattering from particles smaller than 50 μm (5). For this reason, researchers now use the Mie scattering model. The Mie model correctly accounts for the scattering from small and transparent particles and therefore can be used to accurately assess the fine-particle fraction produced by nasal spray delivery systems. This method requires that the the refractive index of the particles, the refractive index of the medium (air), and a parameter relating to the transparency of the particles be known.

Automated nasal spray actuator

The study was conducted using an NSP3000 automated nasal spray actuator (Malvern), a portable device that can be

Table III: Results obtained as a function of pressure for pump A (force rise time = 0.2 s).

	Dv10		Dv50		Dv90		Span	
	Size	Variation	Size	Variation	Size	Variation	Value	Variation
Force/kg	(μm)	(%)	(μm)	(%)	(μm)	(%)		(%)
3	25.36	1.28	50.12	1.61	111.65	1.21	1.72	0.73
4	22.71	1.63	43.90	1.84	93.39	2.80	1.61	1.43
5	21.28	2.63	40.86	1.11	85.31	0.29	1.57	2.30
6	20.65	1.07	39.31	1.76	79.90	2.75	1.51	1.79
7	18.78	1.93	37.37	3.07	77.60	3.08	1.57	2.36
8	18.87	1.17	36.66	2.37	73.42	1.78	1.49	1.84

Table IV: Results obtained as a function of pressure for pump B (force rise time = 0.2 s).

	Dv10		Dv50		Dv90		Span	
	Size	Variation	Size	Variation	Size	Variation	Value	Variation
Force/kg	(μm)	(%)	(μm)	(%)	(μm)	(%)		(%)
3	31.39	1.29	81.71	3.20	190.21	5.67	1.94	5.71
4	24.60	2.35	43.89	0.70	81.44	3.17	1.29	4.54
5	21.82	1.26	38.65	1.73	64.05	1.18	1.09	0.99
6	20.75	0.72	38.21	0.69	62.84	1.16	1.10	0.99
7	20.22	3.96	37.24	1.09	60.47	1.50	1.08	4.74
8	19.13	2.18	35.67	0.63	58.12	1.63	1.09	2.29

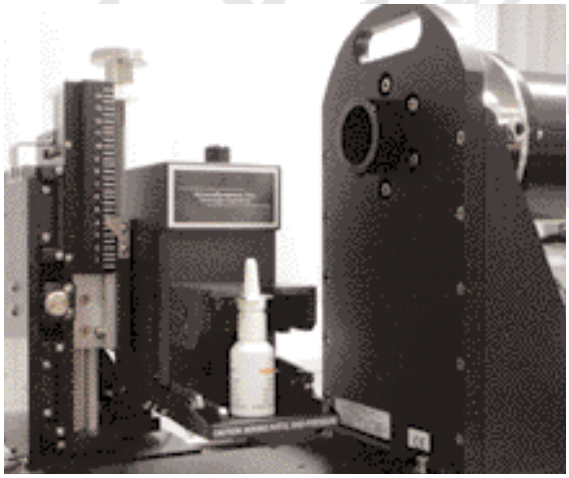

Figure 2: Nasal spray actuator mounted on the Spraytec optical bench.

used either as a stand-alone unit or mounted onto a suitable optical bench such as the Spraytec bench (Malvern) (see Figure 2). This actuator automates the actuation of spray bottles to reduce analyst-induced variances. Operation is via a graphical user interface. The NSP3000 actuator system can store and recall user-settable actuation parameters and can monitor and store force and displacement profiles during actuation. User-defined actuation parameters include the number of actuations, the maximum spray force, the force rise time (*i.e.*, the time taken to reach the user-specified actuation force) and force fall time (*i.e.*, the time taken to release the applied force), the hold time, the delay between actuations, the minimum actuation distance, and the maximum actuation time. The distance traveled during actuation and the applied force can be calibrated and are recorded for each actuation profile. By adjusting the applied force and the rise time, one can mimic a human actuation profile.

Experimental setup

FDA requirements. The draft FDA bioequivalence guidance document suggests that the following measurements be carried out to completely characterize the particle size produced by a nasal pump spray (2):

- Spray dynamics should be measured during the actuation of the pump, including the average particle size produced during the formation, stable (fully developed), and dissipation phases of the actuation process.
- Data analysis should be performed from the stable phase of the plume. The stable phase is defined either on a specific time period after the beginning of the actuation cycle or according to the measured laser-light transmission.
- Measurements should be taken at the start and end of the unit life.
- Measurements should be taken at two distances between the laser diffraction measurement zone and the tip of the pump. These distances must be between 2 and 7 cm, with a difference of at least 3 cm between points.

Multiple measurements are required for each measurement point to assess the measurement precision. The 10th, 50th, and 90th percentiles (Dv10, Dv50, and Dv90) must be reported for the size distributions measured during each stage. The span of the size distribution must also be reported as follows:

$$\text{Span} = \frac{\text{Dv90} - \text{Dv10}}{\text{Dv50}}$$

In this study, we evaluated the output of two pumps at 5 cm for the beginning of the unit's lifetime. The effects of automatic and manual actuation on the variability of the results and the dependence of the particle size on the actuation force and the actuation profile were evaluated.

Instrument settings. The Spraytec and nasal spray actuator were installed with an extraction system 300 mm from the nozzle tip to prevent droplets from falling back and being remeasured. The 200-mm Fourier lens, the most commonly used lens for this application, allows measurements over a 1–440 μm range. The data acquisition rate was set at 2500 Hz (*i.e.*, one measurement every 0.4 ms), thereby allowing the dynamics of spray production to be assessed in line with FDA's guidelines. Measurements were synchronized with the appearance of the spray droplets in the measurement zone by monitoring the drop in laser-light transmission caused by droplet scattering.

In all cases, isotonic saline solution was the test medium. Distance and force were calibrated on the nasal spray actuator before each batch of samples was measured.

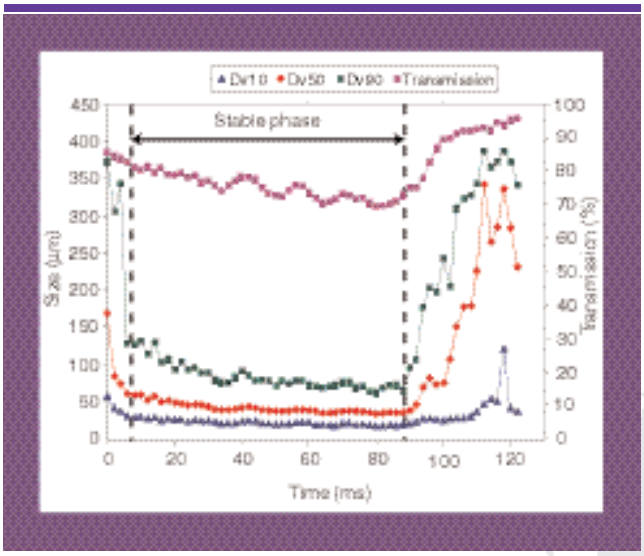

Figure 3: Time history plot obtained for the development of a nasal spray for a typical actuation profile.

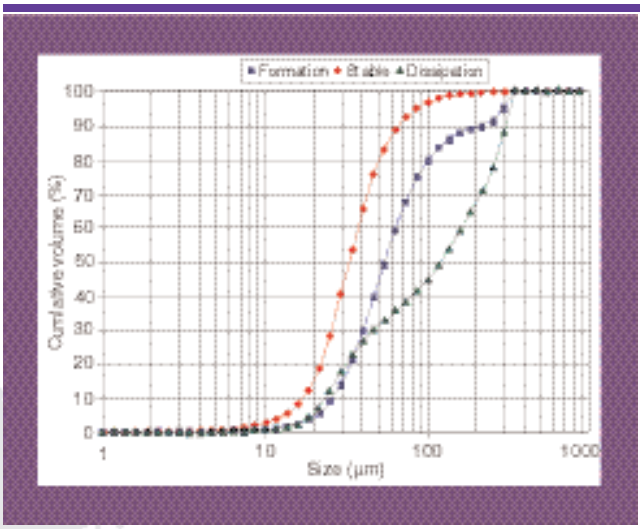

Figure 4: Particle-size distribution measured during the formation, stabilization, and dissipation phases of the nasal spray.

All reported particle-size distribution data were calculated as the average of three separate measurements. Result variations were calculated by expressing the standard deviation of the reported parameters as a percentage of the mean values.

Results

Spray dynamics. Figure 3 shows a typical time history obtained for the actuation of a nasal pump spray. The time history view allows the three phases of spray production to be assessed. Passage of the spray through the measurement zone occurs in less than 130 ms, which is typical for most nasal sprays. An initial formation phase occurs in this case (0–8 ms) where the full atomization pressure has not been reached, resulting in the formation of large droplets. Afterward, in the stable phase, the device delivers a relatively constant droplet size and concentration. This stable phase should be used in the analysis. Finally, an increase in droplet size appears toward the end of the actuation process (90–125 ms) as the atomization pressure and flow rate through the pump begins to decrease.

The Spraytec software allows regions of the time history display to be selected for calculating the average droplet size delivered during each phase of the spray. Results confirm that the droplet size delivered during the stable phase is associated with smaller droplets than during the formation and dissipation phases (see Figure 4). The highest concentration of material is delivered during the stable phase. All pump comparisons were carried out by taking only the stable phase into account.

Manual pump actuation

Droplet sizes measured for two nasal spray pumps, A and B, during the stable phase were recorded for manual pump operation by three operators (see Tables I and II). Operators 1 and 2 were inexperienced in measuring nasal pump sprays but were trained in the use of the pumps before taking the measurements. Operator 3 was an experienced operator.

Results from this section indicate that the operators were

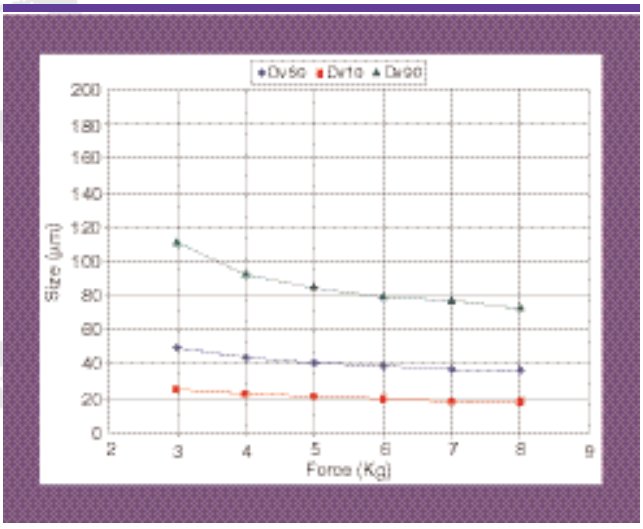

Figure 5: Force dependence of the Dv10, Dv50, and Dv90 reported for pump A.

likely consistent in their actuation efforts; that is, Operator 1's data set always produced the largest droplet sizes while Operator 3 showed good reproducibility across all of the measurements. Not surprisingly, the reproducibility recorded for the other operators was larger, especially for Operator 1 when actuating pump B. This result may be related to the high yield force required to actuate pump B.

Results revealed a large variation for each pump between each operator. Pump A showed a 7% variation in the measured Dv50, and pump B showed an 11% variation. This suggests that, even with training, variation in results associated with manual actuation may make comparisons between products difficult. The operator variability is related to differences in the actuation force and speed delivered by each operator.

Automatic pump actuation. Force dependence. The droplet size measured for nasal spray pumps A and B during the stable phase

Table V: Results obtained as a function of force rise time for pump A (actuation force = 8 kg).

	Dv10		Dv50		Dv90		Span	
	Size	Variation	Size	Variation	Size	Variation	Value	Variation
Rise time/s	(μm)	(%)	(μm)	(%)	(μm)	(%)		(%)
0.2	18.87	1.17	36.66	2.37	73.42	1.78	1.49	1.84
0.5	21.31	3.07	41.79	2.20	88.12	2.25	1.60	0.80
1	25.51	1.89	49.64	1.33	108.26	1.34	1.67	0.55
1.5	26.26	2.58	53.72	3.59	120.43	3.48	1.75	2.05
2	27.85	4.35	57.39	4.37	136.45	9.74	1.90	13.91

Table V: Results obtained as a function of force rise time for pump B (actuation force = 8 kg).

	Dv10		Dv50		Dv90		Span	
	Size	Variation	Size	Variation	Size	Variation	Value	Variation
Rise time/s	(μm)	(%)	(μm)	(%)	(μm)	(%)		(%)
0.2	19.13	2.18	35.67	0.63	58.12	1.63	1.09	2.29
0.5	21.92	1.53	40.07	2.23	68.25	2.64	1.16	2.28
1	25.10	0.95	46.23	0.79	85.79	1.14	1.31	1.92
1.5	29.84	5.66	55.80	0.40	111.51	1.49	1.46	4.42
2	31.35	1.76	64.71	3.49	142.13	1.35	1.71	4.47

of spray production was determined using the spray actuator. Ranges of various actuation forces between 3 and 8 kg were used with a fixed force rise time of 0.2 s (this defines the time taken to reach the defined actuation force). Tables III and IV list the results.

At low actuation forces both pumps produce large, broad droplet-size distributions. The droplet size then decreases as the actuation force is increased (see Figures 5 and 6). At low actuation forces, pump A produced a much smaller droplet-size distribution than did pump B (see Figure 7). This result may be caused by the difference in operating mechanisms between the two pumps. Pump B is less sensitive to actuation force beyond 5 kg and delivers a more consistent droplet-size distribution. In addition, at low actuation forces, the variation is smaller for pump B when automated actuation is used compared with manual actuation from Operator 1.

The reproducibility of the results at each automated actuation force is excellent compared with that of the manual actuations. This result shows the effectiveness of automatic actuation over manual measurements. Removing the errors associated with manual operation, especially with regard to operator bias, allows for a more accurate assessment of the performance of various pump sprays. This, in turn, improves the likelihood of obtaining bioequivalence between devices.

Force rise time dependence. The effect of changing the force rise time (*i.e.*, the time taken to reach the desired actuation force) was ascertained for pump A and pump B. A range of various force rise times (0.2–2.0 s) were used with a fixed actuation force of 8 kg (see Tables V and VI).

As the force rise time increased, each pump performed similarly. An increase in the droplet size and distribution width was observed in each case. Figure 8 clearly shows the Dv50 recorded for each pump as a function of the force rise time. A significant degradation exists in the reproducibility of the delivered spray at longer force rise times. This is believed to be a real effect rather than an artifact of the actuation process. At the longest force rise times, the actuation cycle was completed before the specified actuation force was achieved. In these situations the actuation occurred under a constantly varying force, which explains the poor reproducibility.

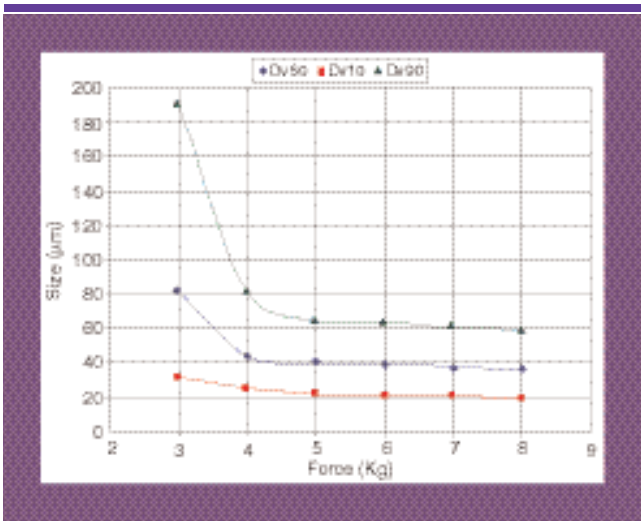

Figure 6: Force dependence of the Dv10, Dv50, and Dv90 reported for pump B.

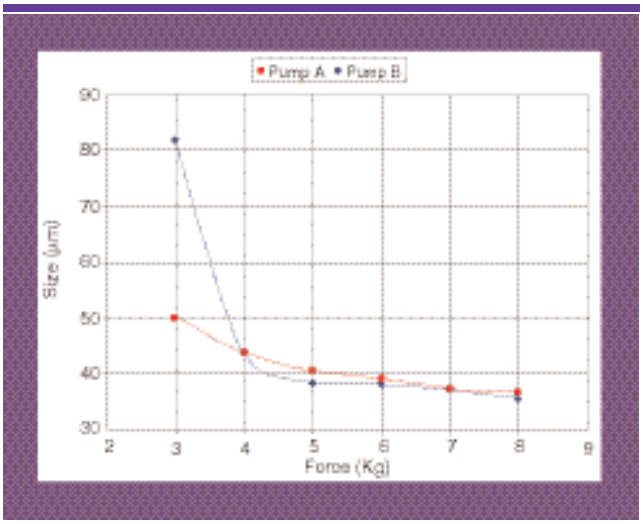

Figure 7: Observed force dependence for pumps A and B based on reported Dv50.

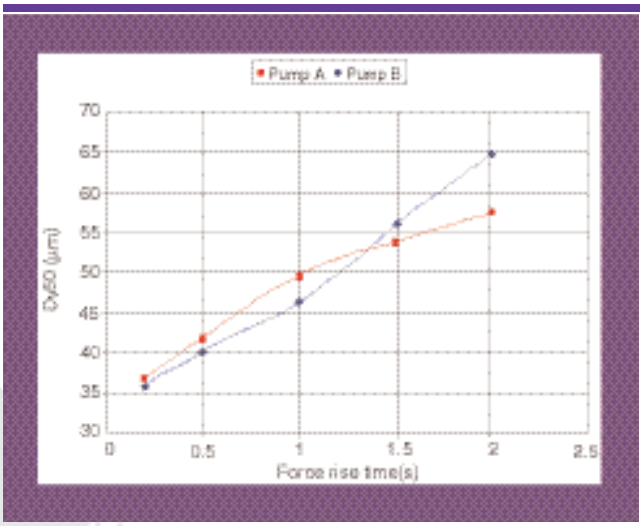

Figure 8: Observed force rise time dependence for pumps A and B based on reported Dv50.

Conclusion

The reproducibility of results for two nasal spray pumps was ascertained for manual and automated actuation. Results show that automated actuation reduces the variability in the results, thus allowing the easy comparison of devices. Standardization of the measurement procedure using automated actuation, therefore, will be important for bioequivalence studies defined in FDA's draft bioequivalence guidance document. To evaluate performance, one should also assess pump quality using a specific actuation force and rise time. This method can help eliminate some variation associated with various batches of drug product. Monitoring the effect of the actuation force and the force rise time also can lead to a better understanding of the variation observed during manual actuation, and can therefore facilitate the development of new nasal pump spray devices and formulations. FDA recommends the use of automated actuation stations, and the results presented in this article demonstrate their usefulness.

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