

Determination of Automated Nasal Actuator Parameters Based on a Twenty Volunteer Study

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INTRODUCTION

The Food and Drug Administration (FDA) recommends use of automated nasal spray pump actuation systems for *in vitro* bioequivalence testing of nasal products to decrease variability otherwise introduced by manual actuations (1). The agency asserts that the ‘setting selection should be relevant to proper usage of the product’ (1). Instrument settings allow automated actuators to replicate either the force (pneumatically driven systems) or displacement (servo or electrically driven systems) profiles applied to test articles, but how instrument parameters are derived from hand actuation studies is poorly understood and documented. We report how displacement and force profiles generated by twenty volunteers were converted into actuation station settings.

METHODS

Study Design

Twenty healthy volunteers (10 male, 10 female, ages 23–38) were asked to actuate two, in-date, previously unused but primed, Nostrilla® oxymetazoline HCl USP 0.05% nasal spray bottles (In-sight Pharmaceuticals Corp., Langhorne, PA) three times each, while the bottles were situated in a Hand Actuation Monitor (HAM, Figure 1, InnovaSystems, Inc., Moorestown, NJ). Volunteers were asked to read directions based on instructions located on the bottle and confirm their understanding of them before spraying the units as they saw fit into an absorbent media collector held adjacent to their nose by the study coordinator. Volunteers were not coached in appropriate technique in an effort to simulate the self-selection of their left or right hand and bottle orientation during a normal actuation (Figure 1). They did not see data as it was collected, or receive feedback, to minimize ‘learning’ as the 6 sprays were discharged.

Volunteers fired sprays alternating between target nostrils (but deliberately missing so they inhaled no drug), beginning with the right nostril. The HAM (approximate weight: 187.8g, dimensions: 8.2cm x 7.7cm x 23.3cm) incorporated a load cell with a capacity of ~222N (50lbf)

and Linear Variable Displacement Transducer (LVDT) (approximate range: 67mm) which were calibrated before use, and interfaced to a computer via the InnovaSystems Mighty Runt Actuation software to provide data in 5 millisecond (ms) intervals. Spray weights were recorded (but blinded from the study coordinator) until after parameter determination to allow later comparison to machine actuated sprays .

Parameter Determination

Compression velocity and **release velocity** were calculated from the upward and downward slopes, respectively, of the displacement vs. time regression line between 10% and 90% of the maximum displacement. The **velocity hold time** (the length of time the pump is held in the compressed or fired position), was calculated as the time above 90% of the maximum displacement. The **maximum force** was defined as the single greatest force achieved during the actuation. The **force rise time** is the time it took for the initial force applied to initiate displacement to increase to 90% of the maximum force. The **force hold time** was the time above 90% of the maximum force. Finally, the **force fall time** is the time for the force to decline from 90% of the maximum force to the baseline force (full release of pump). The bolded words are the parameter settings needed to operate InnovaSystems force and velocity-based automated actuators, and values were calculated from the average of 120 profiles collected.

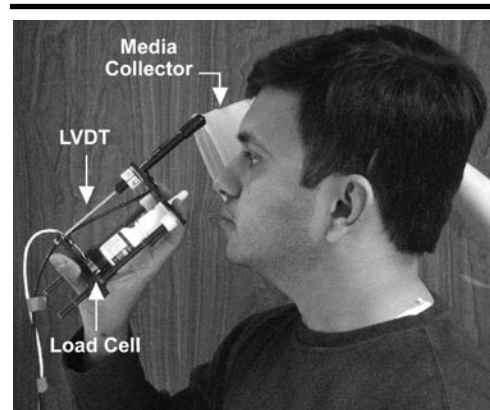


Figure 1. Volunteer spraying Nostrilla in an orientation that mimics labeled instructions for Nostrilla use, but without dosing, while the bottle is held in the Hand Actuation Monitor (HAM).

RESULTS AND DISCUSSION

Relatively constant compression and release velocities were evidenced by linear initial and terminal segments of the displacement vs. time profile for most volunteers (an example profile is shown in Figure 2). Actuation force was always greater than zero initially because the HAM initiates force data capture when displacement begins (by which time a volunteer must be applying force to hold the nasal spray unit in their hand and begin compression). Volunteers tended to increase finger force until they perceived insurmountable resistance, i.e. after the pump is fully compressed, and then they relaxed quickly. Subsequently, the hold time is most apparent in the displacement vs. time profile which portrays specific limits imposed by valve geometry. Force declines before pump displacement begins to return to zero.

The mean **compression velocity** was less than the mean **release velocity** (Table 1), which can be attributed to the need to overcome the valve spring force during compression, and speaks against the practice of using the same value for both parameters. The **velocity hold time**, corresponding to the plateau in the displacement vs. time profiles, is apparent although it demonstrates a moderately high %RSD. The **maximum force** is associated with the smallest %RSD. The **force rise and fall time** demonstrated higher variability and may not reasonably be fixed if the data are to represent a diverse patient population. Inspection of the force vs. time profiles supports the use of a transient **force hold time**, since most volunteers did not maintain the compressed pump at a maximum force.

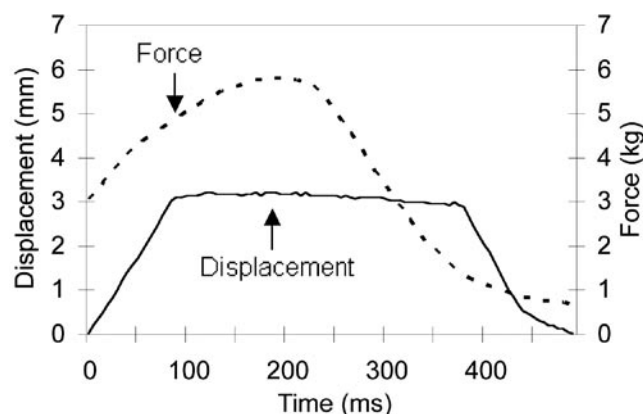


Figure 2. Example of the most common actuation profile shape. Displacement vs. time (solid line) and force vs. time profile (dashed line) were obtained using the Hand Actuation Monitor (HAM).

Table 1

Mean parameters obtained from 120 spray pump actuations – 6 by each of 20 volunteers.

Parameters	Mean	Standard Deviation	% RSD
Compression Velocity (mm/s)	33.0	8.5	25.8
Velocity Hold Time (ms)	323.0	175.7	54.4
Release Velocity (mm/s)	45.5	20.6	45.2
Maximum Force (kg)	6.0	1.3	9.8
Force Rise Time (ms)	179.6	265.0	145.6
Force Hold Time (ms)	163.1	94.8	58.1
Force Fall Time (ms)	300.5	660.2	220.0

CONCLUSIONS

Average calculated parameters necessary for the operation of velocity-controlled and force-controlled automated nasal spray pump actuation stations were determined using data from twenty healthy volunteers. We did not find it necessary nor desirable to prescribe modes of nasal spray use during HAM studies or to include outcome measures such as spray weight in the parameter setting process. The variability we saw was patient-related; and we assert that regulators should be willing to accept data generated using a wide range of machine settings, and the variability this may impose (2). Notwithstanding this assertion, the global mean hand-actuated spray weight was 0.0970 ± 0.0049 g, which represent a quite small RSD of 5.0%. Subsequent studies will report the spray weight (and other performance metrics) that result from use of these parameters in automated systems, and compare them to the results in this volunteer study.

ACKNOWLEDGEMENTS

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