Spray pattern as a screening tool during early development of nasal sprays

Using spray pattern to select an optimum device/formulation combination

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Introduction

Nasal sprays are commonly used in treating allergies and are an emerging, non-invasive route of administration for emergency treatment of opioid overdose as well as treatment of depression[1] and central nervous system diseases and administration of vaccines.[2]

The performance of a nasal spray device is influenced by three factors: device, formulation and human usage factors (which for testing purposes, translate into actuation parameters). Studies have been presented on the effect of formulation properties on spray characteristics. However, less focus has been placed on the impact of formulation as a function of device design. In most cases, spray performance evaluation occurs later in the development cycle and, depending on the results, may lead to delays in product introduction.

Evaluation of device/formulation compatibility during early development is key to producing a successful nasal spray product. However, traditional tests (such as shot weight) may provide limited information by focusing mainly on spray pump performance. Further, droplet size distribution testing may fail to provide accurate measurements for certain formulations, such as those based on ethanol. In contrast, spray pattern and plume geometry can offer comprehensive insight into overall spray characteristics via flow visualization and are highly sensitive to changes in critical parameters such as device design and formulation. This article will focus on the influence of formulation viscosity on device selection and the ways spray pattern can be used as a screening tool to select an optimum device/formulation combination.

Methods

Multidose nasal spray plastic bottles were filled with 15 mL of deionized water or simulated formulations and fitted with 93 µL screw-cap pumps. To ensure complete dose delivery, auto-characterization was performed to determine stroke length for each bottle and all the devices were well primed prior to testing. Low-viscosity-grade carboxymethylcellulose (CMC) (Spectrum Chemical, New Brunswick, NJ, US) was used as a gelling agent to increase solution viscosity. Three different formulations were used: water, 1% CMC and 2% CMC. Three actuators (Aptar, La Vaudreuil, France) were used and labeled as A, B and C. Spray pattern, plume geometry and shot weight were determined.

Spray pattern and plume geometry were measured at 30 mm and 60 mm from the nozzle orifice using a SprayView® measurement system (Proveris Scientific, Hudson, MA). This non-impaction measurement system uses a laser-light sheet and high-speed digital camera to collect images. Its Viota® software quantifies the images and analyzes the data. Optimized method settings (camera and laser) were used for the devices while actuation parameters (velocity, hold time and acceleration) were kept identical across the study. For spray pattern, ovality and area were evaluated for qualitative and quantitative purposes, respectively. Metered shot weights were measured by weighing the devices before and after each actuation using an analytical balance (Mettler Toledo, Columbus, OH, US). For each formulation, testing was performed on all three actuator types. Five bottles were tested per actuator type and five replicate measurements were collected. The results were analyzed using JMP® software (SAS Institute, Cary, NC, US).

Figure 1

Shot weight for devices with a consistent spray pump and three different actuators (A, B and C) tested with water (n = 25).

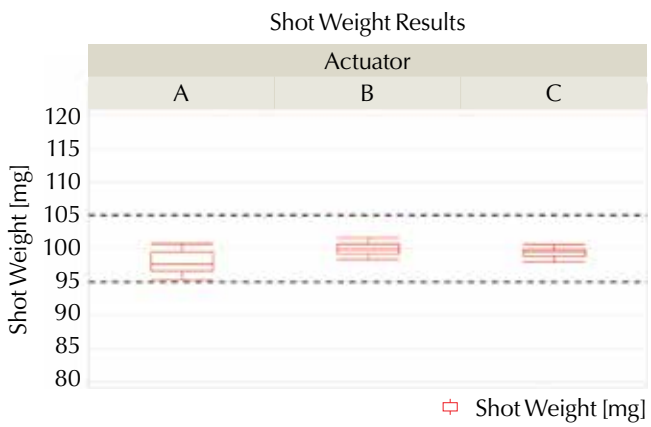
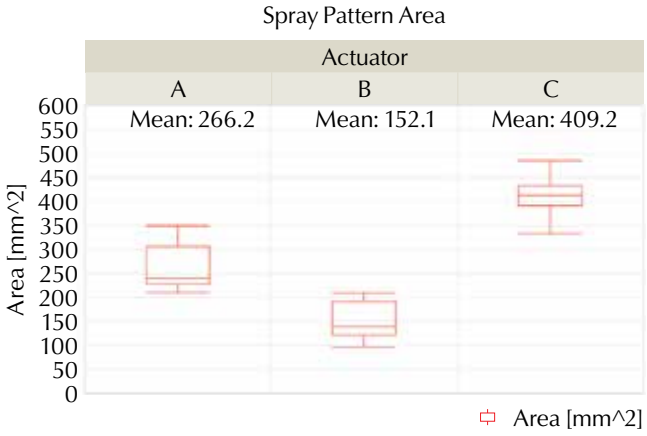


Figure 2

Spray pattern area at 30 mm from the nasal tip for actuators A, B and C tested with 1% CMC formulation (n = 25).



Results and discussion

Impact of actuators on product performance

1. Pump determines shot weight of the device

As described in the methods section, metered shot weight was determined for each sample by weighing the device before and after the actuation. For all three combinations, the same pump type was used but the actuators were changed (i.e., for A, B and C). Figure 1 indicates that if the same pump is used, the weight remains consistent, as seen by the mean shot weight values for actuator A (98.02 mg), B (99.81 mg) and C (99.26 mg) when tested with water. Similar results were observed across all actuators when tested with 1% CMC and 2% CMC. All values were within 5% of the target weight, i.e., 100 mg, irrespective of the actuator used. The results confirm previous findings[3] that the pump component of the device is responsible for the shot weight and the spray characteristics of the product are influenced by the actuator.

2. Influence of actuator on spray performance

Figure 2 shows spray pattern area results for the 1% CMC formulation across three different actuators 30 mm from the nasal tip. The results indicate differential spray performance of the same pump/formulation when the actuator is changed. Similar differences in ovality were observed across the three actuator types, indicating differences in spray pattern uniformity.

This underlines the challenge that pharmaceutical companies face when developing a generic product, where the performance must be comparable to the reference product in order to achieve *in vitro* equivalence. Selecting the optimum device component compatible with a given formulation is crucial to successful spray performance.

The results presented in Figure 2 can be visually confirmed using plume geometry measurements (Figure 3). These highlight differences in plume angle and width across actuators, as viewed from a direction parallel to the flow direction of the spray. The width of the

Figure 3

Representative single-time delay plume geometry images for actuators A (left), B (middle) and C (right) tested with 1% CMC formulation.

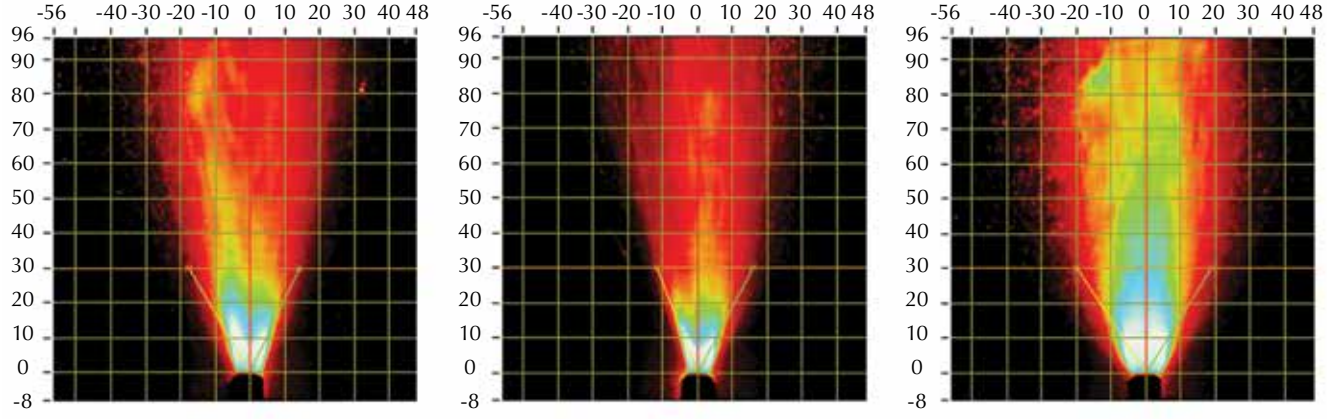


Figure 4

Spray pattern area at 30 mm from the nasal tip for actuator A tested with water, 1% CMC and 2% CMC.

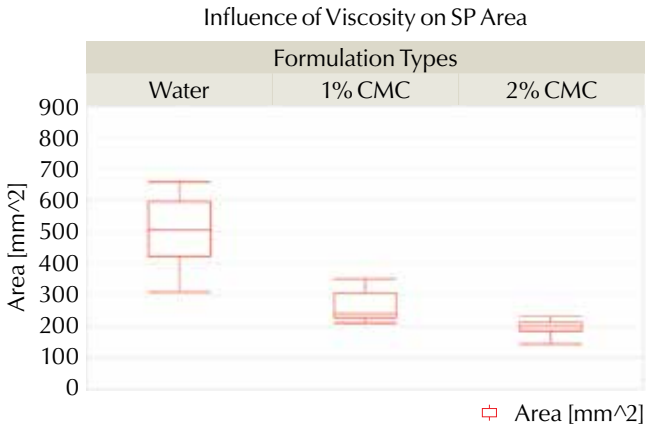
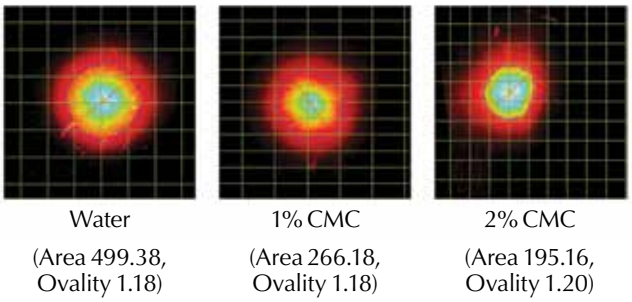


Figure 5

Representative spray pattern images and mean area and ovality results for actuator A tested with water (left), 1% CMC (middle) and 2% CMC (right) at 30 mm from the nasal tip.



Water	1% CMC	2% CMC
(Area 499.38, Ovality 1.18)	(Area 266.18, Ovality 1.18)	(Area 195.16, Ovality 1.20)

spray cone is a complementary measurement to the spray pattern diameter.

Both plume geometry and spray pattern provide macroscopic views of spray aerosolization and insight into the performance of the device. Being highly sensitive, these tests can prove to be efficient during device/formulation screening studies.

Influence of viscosity on spray performance

Viscosity is known to be one of the major influencing factors on spray characteristics. Carboxymethylcellulose is a common thickening agent used in pharmaceutical formulations. For this study, three formulations of different viscosities (water, 1% CMC and 2% CMC) were used. Results indicated a direct influence of viscosity on spray pattern area. A distinct decrease in spray pattern area was seen with an increase in the solution viscosity. Results shown in Figure 4 are for actuator A and the same effect of viscosity on spray pattern area was observed across all three actuators. These results are in line with a previous study by United States Food and Drug Administration (FDA) investigators on the same formulations (1% CMC and 2% CMC).[4]

Figure 5 shows representative spray pattern images illustrating the decrease in spray pattern area with increasing CMC concentration. The same trend was observed with plume angle and width (Figure 6). The sensitivity of these metrics to viscosity and changes in device design make them excellent tools for formulation screening for new product development.

Evaluation of device/formulation compatibility

1. Device selection

Generic drug manufacturers must meet strict tolerances in matching their test product to a reference product. Moreover, reference product selection is crit-

Figure 6

Plume angle results at 30 mm from the nasal tip for water, 1% CMC and 2% CMC formulations.

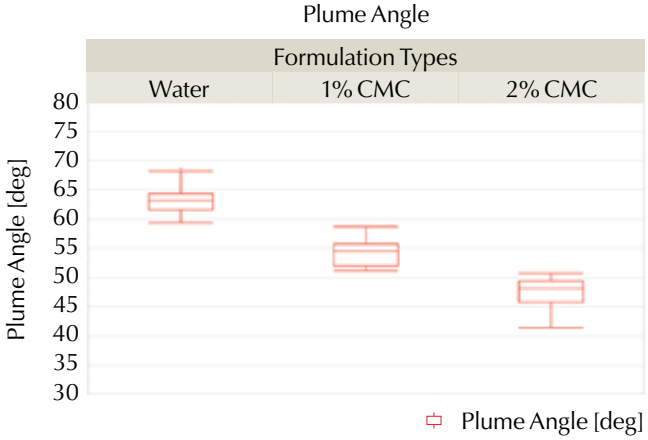


Figure 7

Spray pattern area to screen nine different formulation/device combination candidates. Performance of candidate F2C falls within the desired target range.

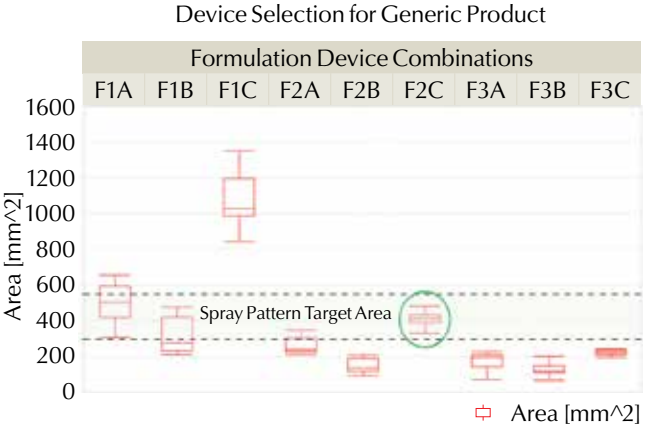


Table 1

Summary of mean values for spray characteristics for the actuator/formulation combinations used in this study.

30 mm distance				60 mm distance					
Formulation	Actuator	Spray Pattern		Formulation	Actuator	Spray Pattern		Plume Geometry	
		Area (mm²)	Ovality			Area (mm²)	Ovality	Angle (deg)	Width (mm)
Water	A	499.38	1.18	Water	A	2089.93	1.19	55.80	63.81
Water	B	325.89	1.16	Water	B	1292.48	1.21	48.34	53.98
Water	C	1074.67	1.24	Water	C	5747.48	1.34	73.16	89.23
1% CMC	A	266.18	1.18	1% CMC	A	578.10	1.25	41.99	46.12
1% CMC	B	152.14	1.18	1% CMC	B	428.76	1.23	31.51	33.93
1% CMC	C	409.20	1.35	1% CMC	C	838.68	1.62	44.56	49.43
2% CMC	A	195.16	1.20	2% CMC	A	473.64	1.34	35.80	38.85
2% CMC	B	115.20	1.24	2% CMC	B	325.03	1.27	25.83	27.61
2% CMC	C	222.24	1.29	2% CMC	C	602.02	1.45	32.39	34.95

ical when establishing the design space for a test product so, ideally, multiple lots of the reference product should be selected.

Among spray characteristics, spray pattern is a critical measure. Investigating spray pattern performance early can save time and resources and may prevent problems later, which could cause delays in bringing a product to market. Figure 7 illustrates the use of spray pattern as a quick and efficient screening tool to evaluate available device/formulation candidates and determine which combination gives the most consistent performance.

In addition, spray pattern can be an efficient way of determining at the outset which test candidate best matches the performance of the reference product. In the current study, if the target spray pattern area was between 300-550 mm², the candidate labeled "F2C" (circled in Figure 7) would be the preferred choice. While the majority of test results for candidate F1A are within the target range, part of those results are outside of the target range. It must be noted that if the sample size is inadequate during an initial evaluation, variation of product performance will not be assessed. This will lead to greater risk of difficulties later, during *in vitro* bioequivalence studies or product release testing. This same approach can be carried out for other spray pattern metrics, such as ovality and D_{max}.

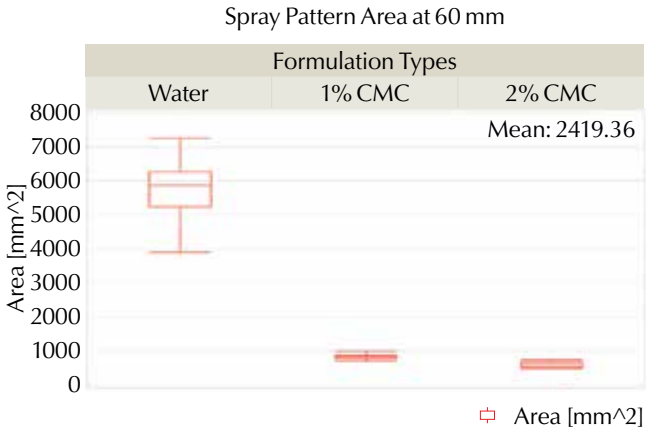
It should be noted that, along with a compatible device, optimum testing methods using human achievable/appropriate actuation parameters are also important to the accurate and consistent performance of the final product.

2. Spray pattern to predict device/formulation compatibility

For an innovator product, it is critical to ensure that the formulation used is compatible with the final device selected, as shown by reproducible results. For this purpose, it is important to perform initial testing with the actual formulation, rather than with water. Table 1 provides a summary of mean values of spray characteristics for the various actuator/formulation combinations studied. Also, Figure 8 shows the spray pattern area for actuator C across three formulations. The results indicate that water does not adequately predict the performance of the drug/device combination. In fact, the results obtained by testing the device with water could be misleading. Based on these findings, the results from actuator C are more consistent for the 2% CMC solution (a viscous solution) compared to a low viscosity liquid (water). Therefore, if the device screening was performed only using water, a device candidate with the desired consistent performance might be overlooked. Or worse, a device selected based on the results with water might not achieve consistent results with the formulation due to incompatibility between the device and formulation.

Figure 8

Spray pattern area for three different formulations at 60 mm from the nozzle tip.



Conclusion

It is important to evaluate the performance of a drug/device combination early in the development process. In nasal spray product development, spray pattern can be employed as a sensitive analytical tool to understand spray performance and facilitate changes in formulation and/or device design to obtain tighter control of product performance.

This study highlights various factors that should be considered during nasal spray product development. The results show that regardless of the actuator used, the shot weight was within the specification and that the spray pump was the dominant factor controlling the shot weight. In addition, the actuator drives the spray characteristics such as spray pattern and plume geometry. Also, the formulation viscosity directly influences spray pattern area as well as plume angle and width.

Depending on the device/formulation combination and other factors, such as shaking parameters, specific actuation parameters based on human profiles may also need to be evaluated for successful product development.

References

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3. Chauhan H, Liu-Cordero S, Liao L, Werbeck J. Impact of actuator design on multi-dose nasal spray characteristics. Respiratory Drug Delivery 2018. 2018. 2:497-502.

4. Guo C, Stine KJ, Kauffman JF, Doub WH. Assessment of the influence factors on *in vitro* testing of nasal sprays using Box-Behnken experimental design. European Journal of Pharmaceutical Sciences. 2018. 35: 417-426.

Suggested reading

United States Food and Drug Administration. Guidance for Industry Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal Sprays for Local Action. https://www.fda.gov/downloads/Drugs/.../Guidances/ucm070111.pdf.

United States Food and Drug Administration. Guidance for Industry Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products—Chemistry, Manufacturing, and Controls Documentation. https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm070575.pdf.

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