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VALIDATION OF MALVERN SPRAYTEC FOR PARTICLE SIZE DISTRIBUTION MEASUREMENT AND SPRAY PATTERNS FOR METAMETASONE FUROATE NASAL SPRAY

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ABSTRACT

In order to understand the interaction between the physical attributes of the nasal formulations and the spray patterns, it was studied if laser diffraction might be utilized to define the droplet-size distribution (DSD) of nasal sprays. With the use of Malvern Spraytec, the effects of actuation force (3–7 kg), rheological characteristics from carbopol 934PNF Avicel RC 591, and actuation distance on the aerosol DSD of nasal sprays were examined. By tracking the released nasal spray that contained a dye or a fluorescent marker, spray-pattern analysis was carried out. Minimum and maximum diameters, ovality, polydispersity, Dv10, Dv50, and Dv90 parameters were all included in the DSD and spray pattern parameters. Nasal-spray products' Dv50 values were lowered by moving the actuation distance from 3 to 6 cm from the laser beam. The surface area and viscosity of Mometasone Furoate formulations using polymer as Avicel RC 591 formulations were found to have a power law connection through spray pattern analysis. In summary, a number of factors, including actuation force, viscosity, rheological characteristics, surface tension, and pump design, affect nasal aerosol generation character.

Keywords: Droplet-Size Distribution (DSD), Actuation, Polydispersity, Etc.

I. INTRODUCTION

Drug distribution within the nose, drug absorption across mucosal barriers to nasal receptors, and rate of clearance from the nose all influence bioavailability, which is defined as the release of the drug substance from the drug product and its availability at the site of action. This makes drug deposition in the nasal cavity of great clinical relevance for medications administered by nose.

Pharmacological absorption and nasal mucosa clearance are affected by the unique anatomical and histologic features of different nasal cavity regions. Nostril residence time is generally longer in the non-ciliated anterior region of the nose. It is a low-permeability area, nevertheless. The ciliated posterior region of the nose, on the other hand, has a higher drug permeability and a shorter residence time when a drug is deposited there.(1) Therefore, depending on how the administered medicines are distributed inside the nasal cavity, their bioavailability may change.

It is a challenging task to measure drug deposition in the human nasal cavity with accuracy. In vivo drug deposition and human nasal spray disposition have been demonstrated using positron emission tomography and gamma scintigraphy (2). The use of radioactive tracers in the formulation and clinical trial execution of these imaging techniques is necessary, even with their high quantitative accuracy and good spatial resolution.

An alternative method involves simulating particle transport and deposition in a three-dimensional, anatomically accurate computer model of the human nasal passages using computational fluid dynamics (3). However, at the lab scale, DSD and Spray Pattern using Malvern Spraytec can be used to study the spray characteristics and expected deposition.

II. MATERIALS AND METHODS

Nasal Formulation Preparation

In the lab, five different nasal formulations were created. Formulation are aqueous-based suspension , where mometasone furoate, the active pharmaceutical ingredient, was dissolved in purified water with different %

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Avicel RC 591. Likewise different concentration from 1 %,1.5%, 2%, 2.5% and 3% of Avicel RC 591 were prepared and named with different batch no respectively. All of the six formulations were filled in identical HDPE bottles and delivered using the same nasal pump (white, high-density, polyethylene bottle fitted with a white metered-dose, manual spray pump, and white cap) with a dosing volume of 100 uL

Spray Pattern and Plume Geometry Characterization

Using the SprayVIEW NSP system (Proveris Scientific Cooperation) with the SprayVIEW NSx automated nasal spray pump actuation system, the spray pattern and plume geometry of each nasal spray formulation were measured. A single test actuation was conducted after each nasal spray sample was primed and shaken four times prior to measurement. The hold time, compression velocity, and stroke length of the nasal spray devices were maintained constant throughout all measurements while they were being operated upward and perpendicular to the laser light.

In order to obtain spray-pattern measurements, the spray pattern was imaged from above using a horizontal laser sheet that was positioned 3 and 6 cm above the device tip. The plume was imaged from the side, directly above the device tip, and the laser sheet was positioned vertically along the nasal spray device's long axis for the purpose of measuring plume geometry. Every photo was taken at several frames per second. For every formulation under ambient conditions, three duplicate measurements were carried out.

Droplet Size Distribution Characterization

An Malvern Spraytec manufactured by Malvern Instruments Ltd. to describe the droplet-size distributions of every nasal spray. Prior to measurement, each nasal spray sample underwent four rounds of priming and shaking, and one test actuation. Using a SprayVIEW NSx automated actuator, the devices were positioned vertically, with the actuator's tip 6 cm below the laser beam. Similar to the plume geometry and spray-pattern measurements, the same actuation parameters were applied. Three duplicate measurements per formulation were performed at room temperature, with a total of 20000 ms. of data collected.

Evaluation of Deposition Pattern

Particle size, polymer concentration, viscosity, surface tension, and osmolality of suspension or solution are some of the formulation-related variables that affect the deposition pattern of a nasal spray. In addition, there are parameters pertaining to the drug delivery device and instrument.

Spray Characteristics of Various Formulations

Table 1 displays the spray properties of all five of the formulations that were looked at in this article, including droplet-size distributions, plume geometries, and spray patterns. The minimum (Dmin) and maximum (Dmax) spray diameters, ovality (Dmax/Dmin), and spray area were used to characterize the spray patterns. The plume width and angle served as characteristics for different plume geometries. The droplet size distributions were identified using the Span value, the 10th (Dv10), 90th (Dv90), and median (Dv50) of the cumulative undersize distribution.

The addition of Avicel RC 591 has a significant effect on formulation viscosity, but it has a negligible effect on spray characteristics. Formulations with an Avicel RC 591 concentration of 1 to 3 % showed the ovality and spray pattern area.

Table 1: Spray pattern area and Ovality

Sr.No	Parameters	F1	F2	F3	F4	F5	F6
1	Osmolarity	325	326	327	326	326	327
2	Spray Pattern (Ovality)	1.259	1.237	1.193	1.082	1.107	1.093
3	Spray content uniformity						
	Min	93.8					
	Max	100.9					
	Avg	96.6					
	% RSD	2.11					

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Similarly, as the concentration of Avicel increases, so do the measurements of the spray's width, angle, and plume geometry. The excipients' effects on droplet size vary once more. The size of the droplets increases when the concentration of Avicel RC 591 is raised from 1 to 3 %.

Table 2: Plume Geometry (Angle)

Sr. No	Parameters	F1	F2	F3	F4	F5	F6
1	Plume Geometry (Angle)	56.1	53.1	52	51.9	51.78	50.3

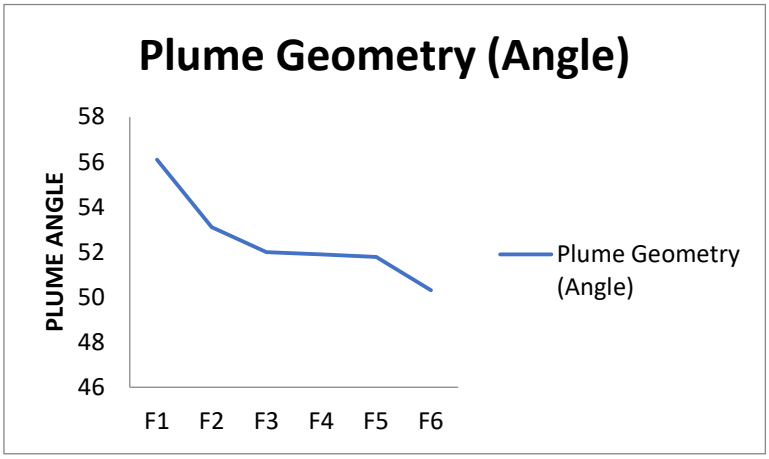

Figure 1: Plume Geometry (Angle)

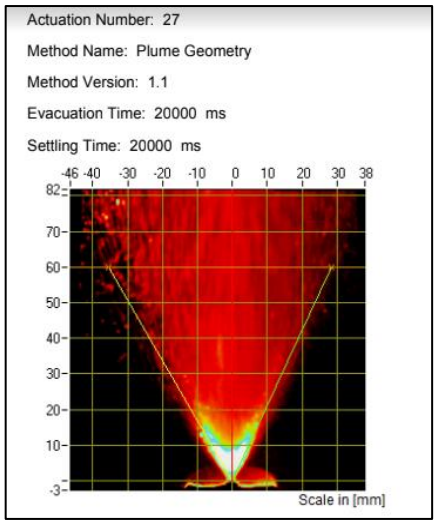

Figure 2: Plume Geometry Pattern for F1 Batch

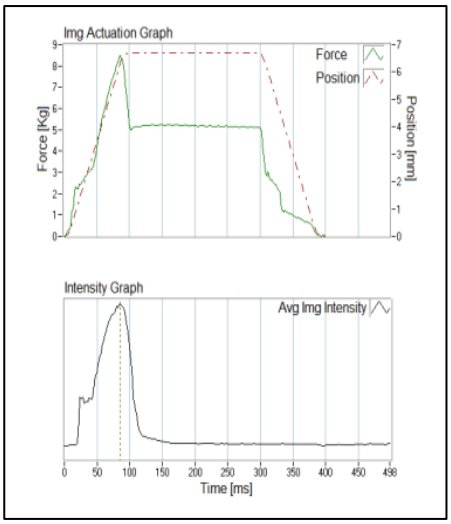

Figure 3: Plume Geometry graph for F1 Batch

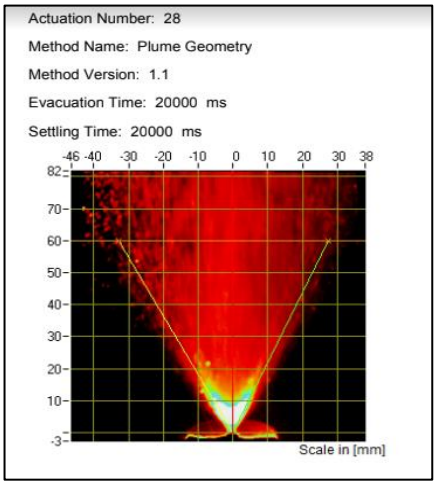

Figure 4: Plume Geometry Pattern for F2 Batch

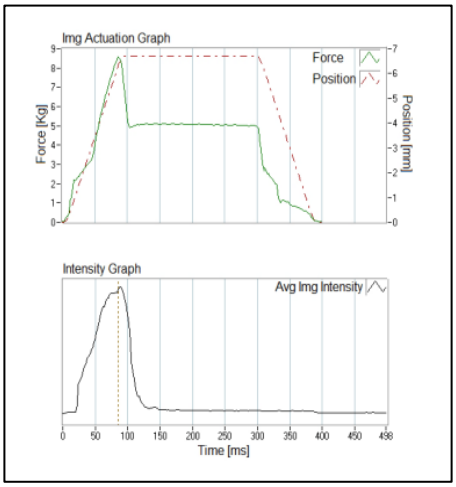

Figure 5: Plume Geometry graph for F2 Batch

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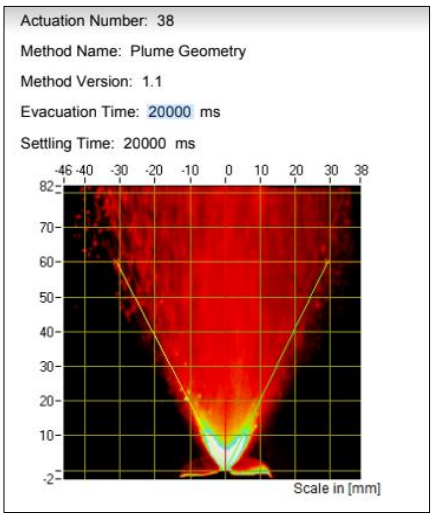

Figure 6: Plume Geometry Pattern for F3 Batch

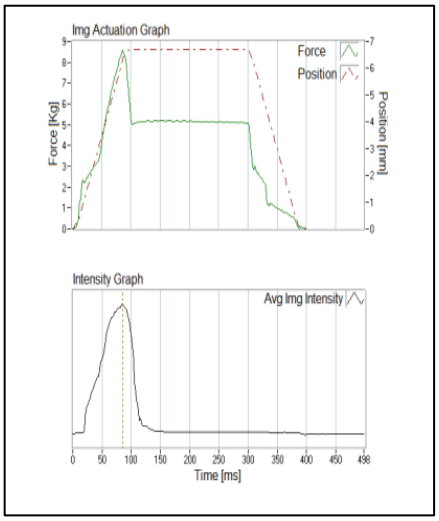

Figure 7: Plume Geometry graph for F3 Batch

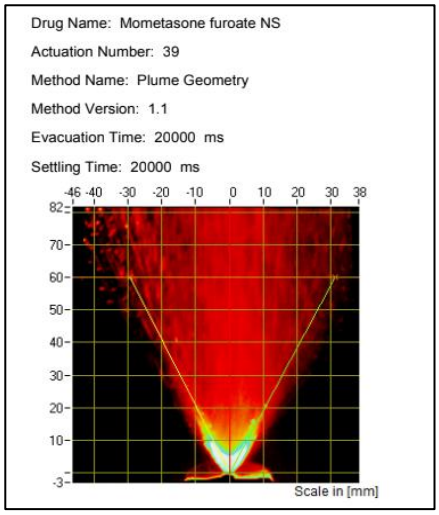

Figure 8: Plume Geometry Pattern for F4 Batch

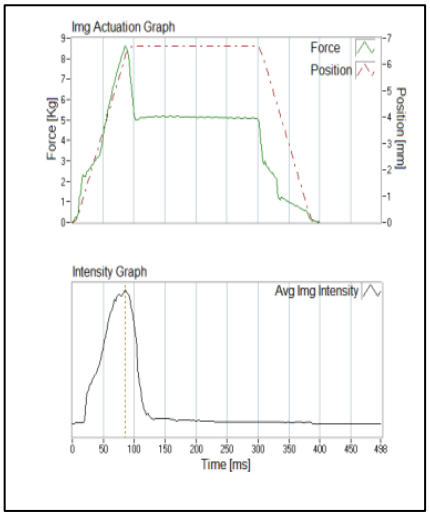

Figure 9: Plume Geometry graph for F4 Batch

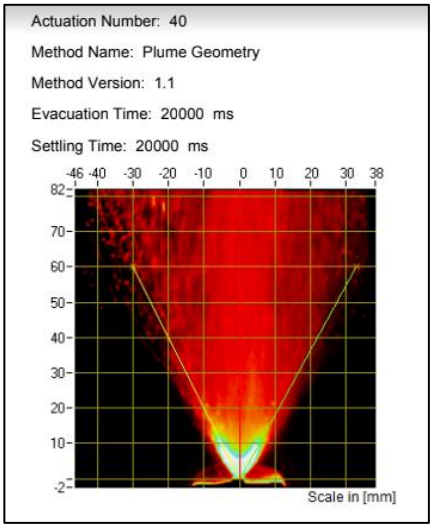

Figure 10: Plume Geometry Pattern for F5 Batch

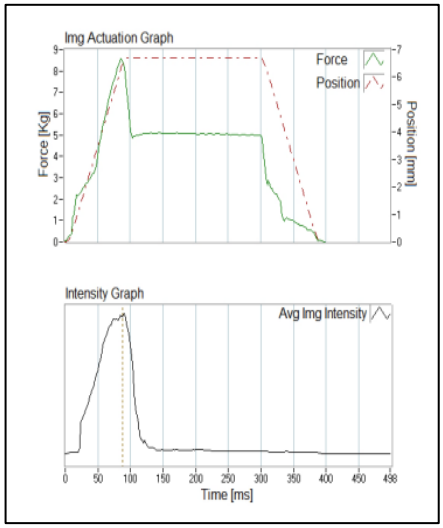

Figure 11: Plume Geometry graph for F5 Batch

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Table 3: Droplet Size Distribution

Sr. No	Parameters	F1	F2	F3	F4	F5	F6
	DSD						
1	D (10)	13.86	14.34	14.42	14.5	14.58	14.63
2	D (50)	33.17	33.58	33.88	34.03	34.1	35.21
3	D (90)	76.52	76.66	76.98	77.46	79.11	80.35

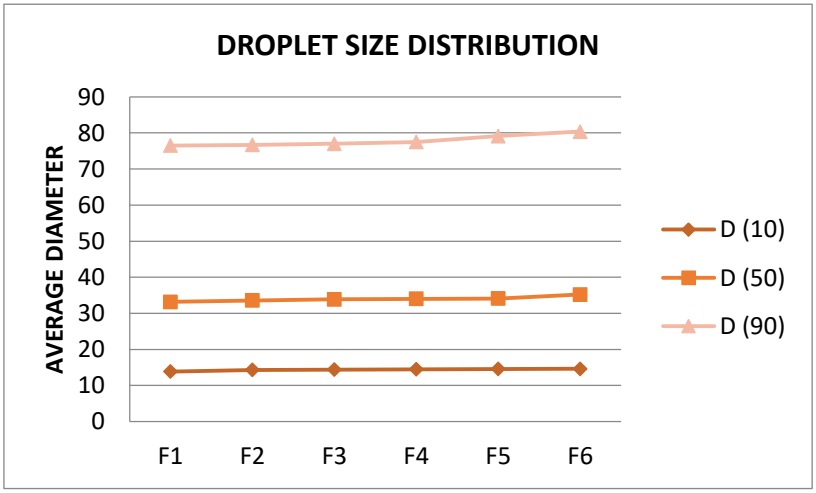

Figure 12: Droplet Size Distribution

Although the in vitro characterization tests perform well in the quality control setting, it is unclear how the nasal cast's deposition pattern will be determined. Larger droplets and wider spray angles were found to increase deposition in the anterior region. Theoretically, deposition in the nasal cavity should be dominated by impaction of droplets (and/or particles) of the nasal spray (5), which in turn should be governed primarily by droplet size and plume geometry (6). In a similar vein, (7) discovered that sprays with small plume angles deposited more posteriorly while relying less on the size or viscosity of droplets. Not all literature reports, though, support this theory. As an illustration, (8) found that sprays with larger plume angles had more posterior deposition. In the meantime, no effect of plume angle on deposition was observed in the computational simulations of (3).

The droplet size and regional deposition, however, do not appear to be significantly correlated in this instance.

While droplet sizes, particularly Dv90, tend to increase in tandem with decreases in anterior deposition, it is hypothesized that this is due to the Visualized deposition patterns of various nasal solution formulations at 70 s after actuation. An excellent illustration of the nasal physiology's anterior (I), posterior (II), and nasopharynx (III) segmentation can be found in (11).

It was discovered that there is an inverse relationship between droplet size and plume angle. The selected excipient affects the correlations between other spray characteristics and regional deposition footprints. Therefore, it is not possible to forecast the deposition pattern using those correlations. This observation has implications that are especially pertinent to formulation development, as it may involve the evaluation of several excipients.

For the purpose of formulation and device development, it is therefore advised to directly visualize the deposition pattern in a nasal cast.

It was investigated whether laser diffraction (Spraytec) (1) could be used to characterize the droplet-size distribution (DSD) from nasal sprays in order to comprehend the connection between the physical characteristics of nasal formulations and their spray characteristics (9) Spray characteristics, including DSD, dosage accuracy, and spray pattern, differ based on the pump design and physicochemical properties of the drug product. The metering chamber, actuator length, orifice design, pump valves, and force of actuation are all part of the pump design. The formulation's physical state (solid or liquid), shape, viscosity, osmolality, and surface tension of the liquid are examples of physicochemical properties.

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A particular combination of drug formulation and device is called a nasal product. When developing new products, plume pattern and DSD studies can be helpful in maximizing the design of nasal devices using formulation blends (10).

The ovality and "effective diameter" of the spray pattern were determined. The ovality was expressed as the maximum diameter divided by the minimum diameter, and "effective diameter" was defined as the average of the maximum and minimum diameters of three actuated sprays. Effect of Polymer Concentration on DSD and Spray Pattern was included to provide a visual representation of the spray pattern and the impact of pump design and viscosity. Table No. The DSD (Dv10, Dv50, and Dv90) changes in a concentration-dependent manner following the addition of Avicel RC 591 are summarized in figure 3.

The results showed that when different polymer concentrations were added, the Dv 10 changed more significantly than the Dv 50 or Dv 90 value. The distributions skewed in favor of the smaller fractions as a result. This pattern was seen with the ovality ratio as well. We found no correlation between changes in droplet size and viscosity increases.

III. RESULTS AND DISCUSSION

Measuring nasal spray accurately is essential for assessing the effectiveness of nasal products. Commercial formulations were utilized to find the best experimental setups and study the dynamics of plumes using laser diffraction .s. In addition, research was done with internal formulations to comprehend and investigate the connection between the physicochemical characteristics of nasal formulations and their spray characteristics using varying polymer concentrations.

In order to assess a product's performance and forecast nasal deposition, DSD and spray-pattern studies are crucial characterization methods (10).

Distance from Commercial Nasal Sprays: Its Effect Reports on how actuation distance affects DSD have been inconsistent (12) have observed significant drops in Dv50 values when the Malvern Spraytec1 actuation distances of 3 and 6 cm are increased. There are no reports that sufficiently describe how the DSD varies with distance.

The DSD must be calculated from two distances, according to a recent FDA draft. The maximum separation from the beam is 7 cm, and the second distance needs to be at least 3 cm apart. A short distance should be selected to characterize the aerosol distribution if the nasal orifice produces droplets instantly. Furthermore, during flight, the amount of droplets lost from the measurement zone is minimal.

Spray Analysis: Importance of Polydispersity (Span)

The density of the droplets (assuming a size-independent density for the droplets) is what links the volume median diameter, which describes the particle/droplet sizes, to the mass median diameter. A tiny span value denotes a narrow DSD since the span gauges the DSD's width from the median droplet range (Dv50). Studies indicate that aerosols will deposit differently if they have different span values but the same primary particle size (13).

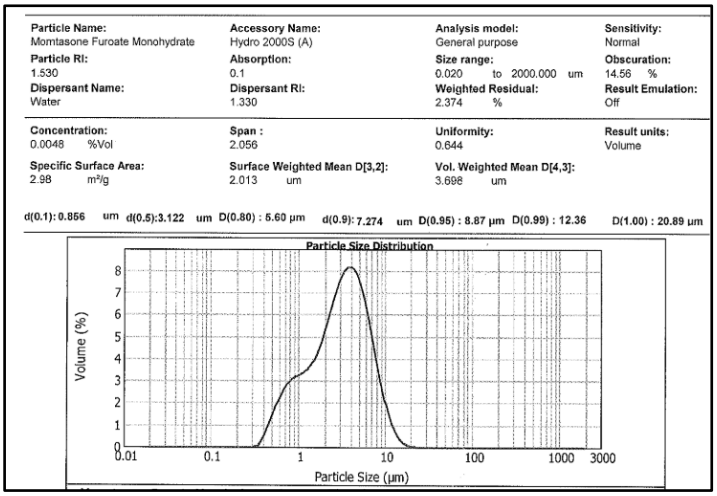

Figure 13: PSD Histogram for Mometasone Furoate Nasal spray

There are no published reports on the effects of span values on nasal deposition and bioavailability for nasal sprays. On the other hand, span values can be utilized to evaluate the spray's quality in in vitro experiments. A higher span value indicates high cohesiveness, high surface tension, and/or relatively low energy available for liquid dispersion (a low dispersion efficiency of the nasal device). Thus, to maximize the aerosol performance of a particular nasal Spray, a lower span should be selected.

IV. CONCLUSION

By using laser diffraction and Malvern spraytec, we have exhibited a variety of testing considerations for the measurement of DSD and spray pattern characterization from nasal sprays. Our research demonstrates the versatility of Spraytec in separating the effects of formulation variables like polymer concentration and actuation distance on DSD.

With nasal sprays with variable polymer concentration, we could show a power-law relationship between spray area and viscosity and a linear correlation between the two.

According to the work presented, actuation force, viscosity, surface tension, and pump design all affect nasal aerosol generation.

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