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Research Article

Determination of Spray Pattern and Plume Geometry of Combined Budesonide and Formoterol Fumarate pressurized Metered Dose Inhalation Aerosol

Ravindra K Kotak[1*], Chintan V. Pandya[1], Aditee C. Pandya[2], Avnish Rajput[3], Brajesh Kumar Thakur[3]

[1]*Kadi Sarva Vishwavidyalaya, Nr. Kh-5 Circle, Sector-15, Gandhinagar-382015, Gujarat, India*
[2]*School of Sciences, PP Savani University, Surat-394125, Gujarat, India*
[3]*Zydus Cadila Healthcare Limited, Moraiya, Ahmedabad-382210, Gujarat, India*

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ABSTRACT

Budesonide and formoterol fumarate pressurized metered-dose inhaler (pMDI) is combined aerosol dosage form. The label claim of this combined dosage form is 100 mcg of Budesonide and 6 mcg of Formoterol Fumarate per actuation. It is prescribed for the treatment of asthma and chronic obstructive pulmonary disease (COPD). Formoterol fumarate is an anti-asthmatic drug (Bronchodilator), and Budesonide is Anti Inflammatory drug (Glucocortico steroid).

The objective of plume geometry and spray pattern study is to monitor the consistency and quality of a device when actuated. The plume and pattern study aims to develop a formulation with robust device which can deliver an accurate amount of drug directly to the lungs of a patient. The chemistry manufacturing and controls (CMC) guideline outlined the basic data required for spray pattern and plume geometry measurement for different pMDI devices. In 2013, draft guidance on bioavailability and bioequivalence (BABE) of pMDI published, which provides details on plume geometry and spray pattern, image collection and evaluation.

In the present study, the spray patterns were collected at 2 distances 3 and 6 cm from the actuator device's exit. The spray pattern Ovality results at 3 cm show 2.52% variation and at 6 cm results show 4.31% variation. Method precision, ruggedness and robustness study for Spray pattern also performed at 6 cm distance from actuator orifice. The plume geometry was collected at 6 cm distance from the exit of an actuator device. Plume geometry results show that Plume height is found in the range 16.20 cm to 18.98 cm, Plume angle is found from 17.7–24.9°, and Plume width is found between 3.68 to 4.57 cm.

Introduction

Pressurised metered-dose inhaler (pMDI) is prescribed for asthma COPD. The performance evaluation and dosing accuracy is must in these types of dosage forms. This provides surety of proper dosing to patients' lungs, leading to quick relief from symptoms of COPD, asthma and other respiratory diseases. Here In the present study, spray pattern and Plume geometry study are evaluated for combined budesonide and formoterol fumarate pressurized metered dose inhaler, consisting of 120 metered doses.

*C*haracterization of spray pattern and plume geometry is important for evaluating the performance of the actuator. An actuator is a device which that delivers a specific amount of medication to the lungs, in the form of aerosolized medicine that is inhaled by the patient. Various factors can affect the spray pattern and plume geometry, including the size and shape of the nozzle, the design

***Corresponding Author:** Ravindra K Kotak
Address: Kadi Sarva Vishwavidyalaya, Nr. Kh-5 Circle, Sector-15, Gandhinagar-382015, Gujarat, India.
Email ✉**:** kotakravindrak@gmail.com
Tel.: +91-9998991984

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of the pump, the size of the metering chamber, and the formulation's characteristics. Spray pattern testing should be performed on a routine basis as quality control for release of the drug product. However, the characterization of plume geometry typically should be established during the characterization of the product and is not necessarily tested routinely thereafter.[1-3]

Materials and Methods

Chemicals and Reagents

Budesonide and formoterol fumarate pressurized metered-dose inhaler (MDI) manufactured by Zydus Cadila healthcare limited. The equipment used to evaluate spray pattern and Plume geometry study are aerosol drug spray analyzer (ADSA) instrument of make Innova systems and automated metered-dose inhaler actuation station (MDIAS). These equipment and inhaler Samples along with its actuators are provided by Zydus Cadila Healthcare Limited, Ahmedabad, India, and study performed at the pharmaceutical technology center, Analytical Development Laboratory of Zydus Cadila Healthcare Limited.

Instrumentation system

Fig. 1 shows the image of the ADSA instrument. It is very advanced system which automates the evaluation of spray pattern and plume geometry characteristics of pressurized MDI. It is a non-intrusive measurement system designed to meet these requirements for complete characterization of actuated sprays when the spray is in flight within mili seconds using laser beam and high-speed camera including spray pattern and plume geometry visualization and measurement, data analysis, archiving and reporting.[4]

General information of ADSA components is described to understand the technology used for this study. The laser supplied with the ADSA emits a continuous beam of light at a nominal wavelength of 660 nm (red). The power rating of the laser diode is 50 mill watts. The laser light passes through an optical assembly forms a light sheet. The camera interface to the ADSA computer by a circuit board that is installed in an available peripheral component interconnect (PCI) card slot. The frame grabber board stores the video images and controls the camera recording operations and signals the computer when various events have occurred. The video camera can record 640 by 480-pixel images at a maximum speed of 250 frames per second (fps). When frame size is reduced to a smaller window, rates up to 2000 fps can be achieved. The image processing software is used to analyze acquired images and video sequences. The laser light plane that is optically formed from the narrow beam emitted by the laser is called a light sheet. The bar that is mounted below the camera is called a light dump. It is used to align the laser light sheet with respect to the camera.

The metered-dose inhaler actuation station (MDIAS) shown in Fig. 2 is the instrument used along with ADSA instrument for automated actuation of pressurized MDI.

This statement is used for precise, accurate and counting error free actuation of each spray from the device. The different parameters like actuation force, force compress time, hold time, force release time, spray delay, agitate cycle and agitate speed can be optimized during method development and used thereafter for desired precise actuation.[5]

What is Spray Pattern?

The image formed by the interaction of a spray plume and a light sheet that are perpendicular to each other is defined as spray pattern. Fig. 3 shows image of spray pattern. Different Food and Drug Administration authorities

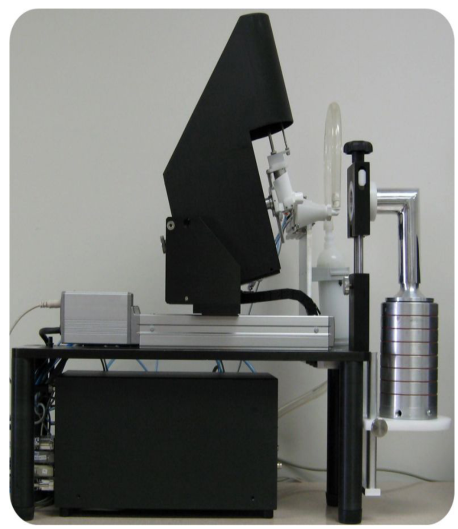

Fig. 2: Image of MDIAS Instrument

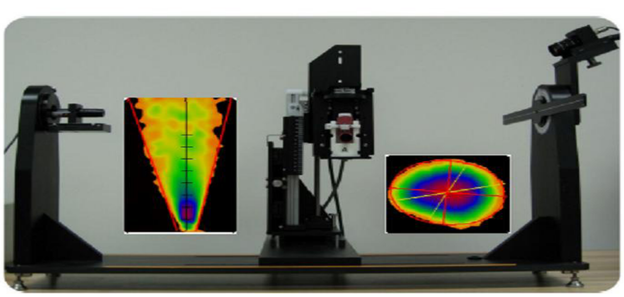

Fig. 1: Image of Aerosol drug spray analyzer (ADSA) Instrument

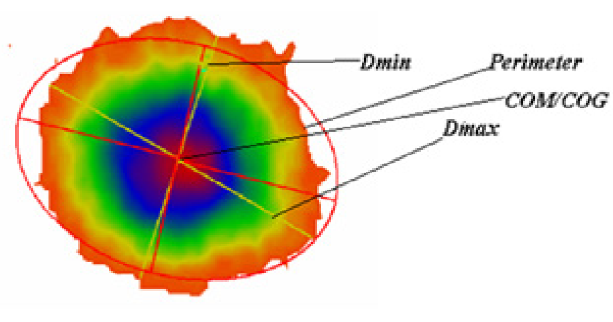

Fig. 3: Image of spray pattern

recommend spray patterns be determined by using single actuation non-impaction systems such as ADSA, or single actuation impaction systems such as thin-layer chromatography (TLC). It is performed for beginning of life stage only and at two distances from the actuator orifice, which allows discriminatory capability between individual pump units. For pMDI's, these distances are recommended to be at least 3 cm apart within the range of 2–7 cm.

Some important terminologies used for understanding of spray pattern are described here. The longest diameter that passes through the center of gravity (COG) and extends to the perimeter of the true shape can be defined as D max. The shortest diameter that passes through the COG and extends to the perimeter of the true shape is known as D min. The ratio of D max to D min is known as the Ovality ratio. The total length of true shape of spray pattern in centimeter is called perimeter. The total area of true shape of spray pattern is presented in square centimeter. The percentage value used to determine the spray pattern contour is called the outline threshold. The ratio of the non-overlapping area between the true shape spray pattern and the fitted eclipse is known as Inclusion ratio. Numerical field that allows the user to note the tip offset provides by the current actuator position are recommended distance at least 3 cm apart within the range of 2–7 cm.

"The evaluation of the spray pattern, the spray distance between the nozzle and the collection surface, number of sprays per spray pattern, position and orientation of the collection surface relative to the nozzle, and visualization procedure should be specified. The acceptance criteria for spray pattern should include the shape (e.g., ellipsoid of relative uniform density) as well as the size of the pattern (e.g., no axis is greater than x millimeters and the ratio of the longest to the shortest axes (Ovality ratio) should lie in a specified range, for example, 1.00–1.30) Data should be provided to demonstrate that the collection distance selected for the spray pattern test will provide the optimal discriminatory capability. Variability in the test can be reduced by the development of a sensitive detection procedure and by providing procedure-specific training to the analyst." The acceptance criteria for the spray pattern should be included in the drug product specification."[6-12]

What is Plume Geometry?

The image formed by the interaction of a spray plume & a light sheet that are parallel to each other is defined as plume geometry. Fig. 4 shows the image of Plume geometry. It describes a side view of the aerosol cloud parallel to the axis of the plume. Quantitation of plume images can be manual analysis or automated image analysis. During the very early life of a pressurized metered-dose inhaler, plume formulation may exit the actuator orifice as a narrow stream that subsequently forms a relatively stable, fully developed, conical plume prior to separating from the orifice. The applicant would provide documentation for the plume is fully developed at the single selected delay time.

Some important terminologies used for the understanding of spray plume are described here. Width measured at selected tip offset is defined as plume width, and it is measured in centimeters. The distance from the actuator orifice to the leading edge of plume is known as Plume length. The angle would be based on the conical region of the plume extending from a vertex that occurs at or near actuator tip is described as Spray angle, and it is measured in degrees. The frame of interest displayed the start of the actuation is known as the start frame. The frame of interest displayed a fully developed plume is known as the analysis frame. The value used to determine the plume boundary is known as the angle threshold. It should be adjusted so that the rays are parallel to the blue-green borders of the output image. The distance along the X-axis between the origins of the two rays outlining the plume is known as tip width. The recommended tip offset would be the distance equal to the greater of the two distances selected for characterization of the spray pattern.

"Plume geometry does not distinguish between drug substance particles and formulation droplets in the spray or indicate any density gradient for the drug substance, but determines the shape of the entire plume. Therefore, this test is complementary to the spray pattern test. The plume geometry characteristics can be used as a baseline to compare similar pMDI drug products by different manufacturers or when certain changes are introduced to an already approved drug product."[13-18]

Analysis of Budesonide and Formoterol Fumarate Pressurized Metered Dose Inhaler

Spray Pattern analysis

Place the canister with actuator in the Metered dose inhaler actuation station (MDIAS), select the proper method and product method as per given test method and prime the valve of the canister with 4 actuations to

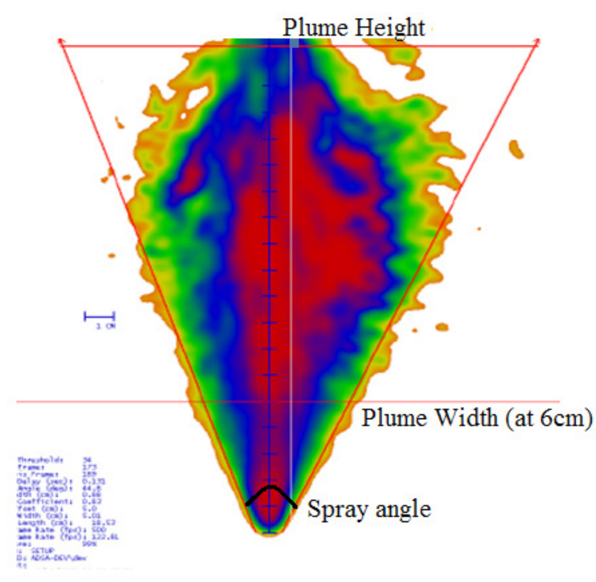

Fig. 4: Image of spray Plume

be tested. Set the distance of actuator tip from laser slit as per requirements (3 cm or 6 cm).

Starts the ADSA software go to setup, camera setup, and select mdi pattern in test parameter, adjust frame rate 30 frames per second and exposure at 100%. Save setup and exit. Click on process pattern, select MDI pattern. Select auto threshold on from the mode and set inclusion ratio 98 percent. Click on acquire sequence option, and select 'OK' from the display window. Now to get the spray to actuate through MDIAS. And pattern gets recorded automatically.

Observe the video of the pattern carefully then analyze the sequence. Fill the appropriate tip off set, run ID and comments then press ok. Drag the right and left line for plume Analysis and press analyze sequences. The software automatically gives the image of spray pattern, click on save output then exports the result in excel format and saves it with the proper definition.

Acceptance criteria: Report individual and mean value of D max, D min, Ovality ratio, Perimeter, and Area for both distances. Relative standard deviation (%RSD) for multiple analysis for both tip offset 3 cm and 6 cm for D max, D min, ovality ratio, perimeter, and area should be not more than 20.

Plume Geometry analysis

Place the canister with actuator in the meter dose inhaler actuation station (MDIAS), select the proper method and product method as per given test method and prime the valve of the canister with 4 actuations to be tested. The laser light sheet should be aligned with the center of the plume by adjusting the laser light sheet and actuator position. Make a point marker to track the position where the light sheet intersects the orifice of the actuator.

Starts the ADSA software go to setup, camera setup, and select MDI plume in test parameter, Adjust frame rate 30 frames per second and Exposure at 100%. Save setup and exit.

Click on process plume, select MDI plume. Select live cameras from source, then click on the acquire sequence option. And select 'OK' from the display window. Now to get the spray to actuate through MDIAS. And plume gets recorded automatically.

Observe the video of the plume carefully, if required, set start frame and end frame. Set angle threshold as per requirement and then analyze sequence. Fill the appropriate tip off set, run ID and comments then press ok. Drag the right and left line for plume Analysis and press analyze sequences. Software automatically gives the Geometry of the plume, click on save output then export the result in excel format and save it with proper definition.

Acceptance criteria: Report individual and mean value of Spray angle, Plume width and Plume length at tip off set 6 cm. Percentage relative standard deviation (%RSD) for multiple analyses of spray angle, Plume width, and Plume length should be no more than 20.

Instrumental Parameters

Tables 1 and 2 represents MDIAS instrument parameters and ADSA instrument parameters respectively. Spray pattern analysis is performed at 3 and 6 cm tip offset. Method precision study for Spray pattern performed at 6 cm tip off set and Robustness study also performed at 6 cm tip offset by the varying distance between spray plume and camera by ± 20mm (355 and 395 mm). Plume geometry analysis is performed for 6 cm tip offset.

Results and Discussion

Figs. 5 and 6 represents the Spray pattern analysis output at 3 and 6 cm, respectively. Table 3 represents spray pattern test results at 3 cm tip offset for two different pMDI canisters. Table 4 represents spray pattern test results at 6 cm tip offset for six different pMDI canisters, which is considered as method precision study. Table 5 represents the test results for the ruggedness study at 6 cm tip offset for two different additional pMDI canisters.

Table 1: MDIAS instrument parameters

MDIAS system parameter	*For spray pattern/ plume geometry*
Priming	5 actuations
Actuation force	4.5 kg
Force compress time	0.5 sec
Hold time	0.5 sec
Force release time	0.5 sec
Spray delay	1.0 sec
Current speed	2.0 cps
Previous spray	0.0
Minimum travel distance	1.0 mm

Step	*Agitate*	*Agitate delay*	*Sprays*	*Step delay*	*Replicates*	*Count*
1	5	0	1	0	1	1

Table 2: ADSA instrument parameters

ADSA system parameter	*For Spray pattern*	*For Plume Geometry*
Laser position	Vertical	Horizontal
Frame rate	30 fps	30 fps
Exposure	100 %	100 %
Threshold	Auto	Auto
Tip offset	3 cm and 6 cm	6 cm
Camera position (With respect to scale)	90°	0°
Device position (With respect to laser)	0°	90°
Position of actuation bench centre (From camera support)	375 mm	375mm
Inclusion ratio	98%	Not applicable
Frame delay	Not applicable	4

Fig. 5: Analysis Output at 3 cm tip offset

Fig. 6: Analysis Output at 6 cm tip offset

Table 3: Spray pattern results at 3 cm tip offset

Spray pattern results (Distance: at 3 cm tip offset)					
Sr. No.	*D max (cm)*	*D min (cm)*	*Ovality (D max/D min)*	*Perimeter (cm)*	*Area (Sq. cm)*
1	3.0	2.6	1.17	9.5	6.2
2	3.3	2.7	1.21	10.2	7.1
Mean	3.2	2.7	1.19	9.9	6.7
SD	0.21	0.07	0.03	0.49	0.64
%RSD	6.56	2.59	2.52	4.95	9.55

Table 4: Spray pattern results for method precision

Spray pattern results (Distance: at 6 cm tip offset)					
Sr. No.	*D max (cm)*	*D min (cm)*	*Ovality (D max/D min)*	*Perimeter (cm)*	*Area (Sq. cm)*
1	3.8	3.2	1.18	11.8	9.4
2	3.6	3.1	1.17	11.1	8.6
3	3.8	3.2	2.00	11.9	9.3
4	4.0	3.3	1.19	12.5	10.4
5	3.7	3.1	1.18	11.6	9.1
6	3.6	3.5	1.06	11.9	9.9
Mean	3.8	3.2	1.16	11.8	9.5
SD	0.15	0.15	0.05	0.46	0.63
%RSD	3.95	4.69	4.31	3.9	6.63

Table 5: Spray pattern results for ruggedness

Spray pattern results (Distance: at 6 cm tip offset)					
Sr. No.	*D max (cm)*	*D min (cm)*	*Ovality (D max/D min)*	*Perimeter (cm)*	*Area (Sq. cm)*
1	3.7	3.3	1.12	11.7	9.7
2	3.9	3.3	1.18	12.0	9.8
Mean	3.8	3.3	1.15	11.9	9.8
SD	0.14	0.00	0.04	0.21	0.07
%RSD	3.7	0.0	3.7	1.8	0.7

Table 6: Spray pattern results for robustness (at camera position 355 and 395 mm)

Spray pattern results (Distance: at 6 cm tip offset)(Camera distance: 355 mm)					
Sr. No.	*D max (cm)*	*D min (cm)*	*Ovality (D max/D min)*	*Perimeter (cm)*	*Area (Sq. cm)*
1	3.7	3.3	1.12	11.7	9.7
Spray pattern Results (Distance : at 6 cm tip offset)(Camera distance: 395 mm)					
Sr. No.	*D max (cm)*	*D min (cm)*	*Ovality (D max/D min)*	*Perimeter (cm)*	*Area (Sq. cm)*
1	3.9	3.3	1.18	12.0	9.8

Table 7: Plume geometry results at 6 cm tip offset

Sr. No.	*Spray angle (deg)*	*Plume width (cm)*	*Plume height (cm)*
1	22.7	3.98	17.94
2	20.5	3.76	17.42
3	24.9	4.57	17.02
4	19.9	3.79	18.98
5	20.7	3.88	18.56
6	18.8	3.68	16.20
Mean	21.3	3.94	17.69
SD	2.2	0.3	1.0
RSD	10.3	7.6	5.7

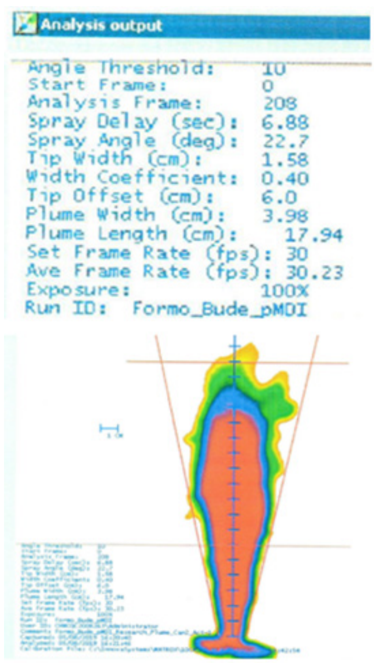

Fig. 7: Analysis output of Plume geometry at 6 cm tip offset

The Mean ovality ratio achieved for method precision study is 1.19 and 1.16 for ruggedness study is a clear indication of a reproducible pattern of spray coming out of pMDI canister. The very less percentage %RSD values achieved for D max, D min, perimeter and area for method precision and ruggedness study indicates precision and accuracy of method. Table 6 represents the test results performed at different camera distances using a pMDI canister is also producing similar data for all parameters, which shows the above method for determination of Spray pattern is Robust.

Fig. 7 represents the plume geometry analysis out put at 6 cm tip offset. Table 7 represents data achieved for spray angle, plume width and plume height for six different pMDI canisters. The mean Spray angle achieved is 21.3°, Plume width is 3.94 cm, and the Plume height is 17.69 cm for plume geometry analysis is an indication of fully developed plume. The achieved results for plume geometry as well as spray pattern study clearly shows consistency and quality of budesonide and formoterol fumarate pMDI device when actuated.

Conclusion

The above Spray pattern and Plume geometry study performed on MDIAS and ADSA instruments using optimized method parameters is validated as per present International Council for Harmonization (ICH) guidelines for pharmaceuticals' technical requirements for human use. The results of the study found well within the acceptance criteria. This shows that the developed method is simple, precise, robust, and rugged within the performed range and is very much suitable for its intended purpose.

The well explained terminologies and methodology for Spray pattern and plume geometry technique using combined Budesonide and Formoterol Fumarate pressurized metered-dose inhaler will be useful for industrial applications as well as academic scientists.

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