EXPLORATION OF ALTERNATIVE METHODOLOGIES FOR SPRAY PATTERN EVALUATION IN A BUDESONIDE / FORMOTEROL FUMARATE DIHYDRATE PMDI

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CHALLENGE STATEMENT

- Spray pattern must be assessed for pMDI generics as part of FDA IVBE guidance.
- Suitable agreement between test and reference products is required to establish equivalence.
- A laser light sheet technology-based system evaluates spray pattern of the plume in-flight and can produce poor spray pattern reproducibility, depending on environmental factors.
- A manual impaction method was investigated to try and overcome these limitations.

KEY SUMMARY

This study aimed to provide an alternative approach for the determination of spray pattern, with an impaction technique investigated to overcome the challenges posed by the laser light sheet method. These included the use of Thin-Layer Chromatography (TLC) plates and the application of staining techniques to develop an API-specific impaction method.

The following steps were developed to provide a functional impaction method:

1. Spray pMDI onto TLC plates at two fixed distances in accordance with FDA guidelines.
2. Selective staining of Budesonide within the impacted spray using a steroid-specific staining agent.
3. Illumination and imaging of stains using a Camag TLC visualizer
4. Calculation of spray pattern diameter (Dmin and Dmax) and ovality using ImageJ software.

The study demonstrated a notable enhancement in produced spray quality, with greater sensitivity and reproducibility achieved. Overall, the manual impaction method was demonstrated to be a viable alternative to laser light sheet technology for the determination of spray pattern.

METHOD DEVELOPMENT

While laser light sheet technology (LLS) has become the industrial standard for the determination of spray pattern, manual impaction methods remain an acceptable alternative for FDA submissions.

Due to poor spray pattern reproducibility seen with LLS technology, a manual impaction method was devised with the objective of reproducible spray pattern determination at two distances (3cm and 6cm) following spray impaction from a single device actuation.

- A significant challenge was posed by the small quantities of drug material delivered from a single actuation (80/4.5 and 160/4.5 µg/actuation Budesonide/Formoterol).
- Initially use of TLC plates coated with an F254 indicator produced sprays that could be imaged under UV light at 254nm at a 3cm distance. However, insufficient sensitivity was achieved at a 6cm spray distance.
- Use of phosphoric acid as a specific staining reagent for steroids was explored. Phosphoric acid's high viscosity made it difficult to apply and so was mixed with methanol (50:50) to enhance spray-ability.
- Reaction of the phosphoric acid with impacted Budesonide led to a bright yellow fluorescence when exposed to UV light at 254nm, allowing an API-specific spray pattern method to be established with greatly enhanced method sensitivity.
- APSD determination of the test product demonstrated good agreement between stage deposition of Budesonide and Formoterol, supporting the use of Budesonide-specific staining as an accurate representation of overall product spray performance.

RESULTS AND DISCUSSION

- Spray pattern measurements obtained using the developed method are provided in Tables 1 and 2. Determination of the test and reference products was performed at both high and low strengths. Unlike the LLS technique, good agreement between the attributes of Dmax and ovality was found.

Low strength test vs reference ratios				
Rep	3cm D_{max}	Ovality	6cm D_{max}	Ovality
T/R 1	1.05	1.01	1.02	0.98
T/R 2	1.01	0.99	0.99	0.96
T/R 3	1.01	1.01	1.02	0.98

Table 1. Low Strength Test vs Reference Product Results

High strength test vs reference ratios				
Rep	3cm D_{max}	Ovality	6cm D_{max}	Ovality
T/R 1	0.94	0.99	0.98	0.98
T/R 2	0.95	0.97	1.04	0.96

Table 2. High Strength Test vs Reference Product Results

- Discrepancy between the two methodologies may be explained by the difference in how the sprays are measured, with impaction methods creating a lateral wall-jet when meeting the perpendicular TLC plate surface in contrast to non-impaction methods relying upon free-jet measurement.
- In accordance with 2015 FDA draft guidance for a budesonide and formoterol suspension pMDI, 95% of the total spray pattern was targeted for encompassment within the perimeter of the derived oval. Given that spray pattern measurement was performed manually, this proved to be time inefficient and risked operator influence on the results.

CONCLUSIONS

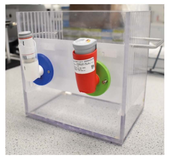
The work conducted as part of this study aimed to develop an impaction-based spray pattern measurement system with the sensitivity required to assess a single actuation at two distances. This was achieved using an API specific staining technique, allowing for a measurable spray pattern.

The spray patterns collected only accounted for the budesonide in the formulation, and a sufficiently sensitive formoterol specific technique may need to be developed to confirm how it contributes to the overall spray pattern.

Challenges associated with measurement of the spray pattern were identified, and in the future an automated approach would be preferable.

METHOD

50:50 MeOH:H3PO4 sprayed onto plate and dried at 120°C for 10 minutes



Sample actuated onto plate at set distances

Plate imaged using CAMAG TLC Visualiser under UV light at 254nm

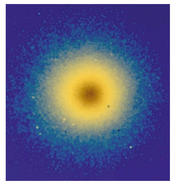


Figure 1. Low strength 3cm test spray pattern captured using impaction method

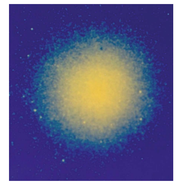


Figure 2. Low strength 6cm test spray pattern captured using impaction method

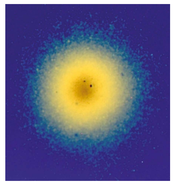


Figure 3. High strength 3cm reference spray pattern captured using impaction method

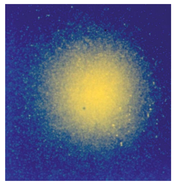


Figure 4. High strength 6cm reference spray pattern captured using impaction method

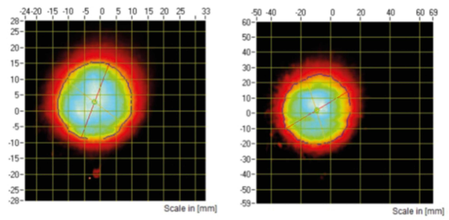


Figure 5. 3 and 6cm spray patterns captured using a LLS measurement system

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