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A Dual-Internal Standard LC-UV-MSD Method to Improve Accuracy and Efficiency of Characterizing Mometasone Furoate MDIs

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PURPOSE

The purpose of this study is to improve the efficiency relative to conventional methods (such as USP methods) of aerodynamic particle size distribution (APSD) characterization of mometasone furoate pressurized metered dose inhalers (MDIs) by Next Generation Impactor (NGI) by using a liquid chromatography method with ultraviolet detection and mass spectrometry (LC-UV-MSD) method.

METHODS

NGI Methods: Mometasone furoate delivery from three lots of MDIs was characterized using four MDIs per lot, at the beginning of canister life by NGI operated at 30L/min. The assayed components of the NGI were collected with 10 to 100mL of methanol, approximated by graduations on beakers. Methanol as a collection solvent is known to pose concerns due to its volatility, which leads to increasing variability in results. However, it was used for these collections since mometasone furoate is readily soluble and stable in methanol compared to partially aqueous diluents. Once the samples were collected, a precise volume of stock solution of an internal standard (beclomethasone dipropionate) was added to each sample and to a control sample.The control sample was prepared using class A volumetric flask. This control sample was used to precisely determine the volume of methanol used to collect each NGI component by comparing beclomethasone dipropionateresponse between NGI samples and the control sample, as determined by the analytical method presented.

LC-UV-MSD Methods: The LC-UV-MSD method utilizes two different types of internal standards: beclomethasone dipropionate and deuterated-mometasone furoate. The beclomethasone dipropionate internal standard, assayed by UV, is used to measure the sample volume; the deuterated standard compensates for MSD signal instability and for the phenomenon of ionization suppression. In contrast to the conventional method of analysis that uses a fixed response factor to determine the concentration of samples within the working range, this method extends the working range by using a "floating response factor" (FRF), equivalent to the average response factor (RF) of the two standards that bracket the sample concentration range.

RESULTS

The utility of the FRF method to that of the conventional LC-MS method using a fixed RF is summarized below:

- The fixed RF approach does not have the accuracy necessary for the desired linearity range (see Figure 1).
- FRF method has 1.5% RSD inter-injection precision and 98.0 to 102.0% accuracy (see Figure 1).
- Working range of the FRF method is 20 to 1500 ng/mL, which is significantly extended compared to that seen with conventional, fixed RF method (see Figure 2).
- The run time for this method is 2.5 min (see Figure 3).
- Conventional, fixed RF method requires collecting with < 0.5mL of diluent for the micro-orifice collector (MOC) and > 215mL of diluent for the inlet to ensure that all samples are within working range. In contrast, the use of FRF method allows for collecting the NGI components with more reasonable diluent volumes (i.e., the MOC with 10mL, the inlet with > 130mL).
- FRF method allows for characterization of unit dose NGI samples with a wide range of drug concentrations while minimizing the cost per collection and improving the ease of collection(see Figures 4 and 5).

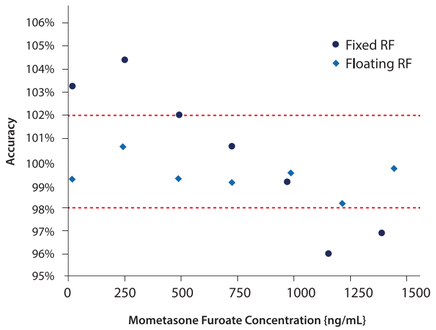


Figure 1: Accuracy of quantifying mometasone furoate using fixed and floating RF approaches for desired concentration range.

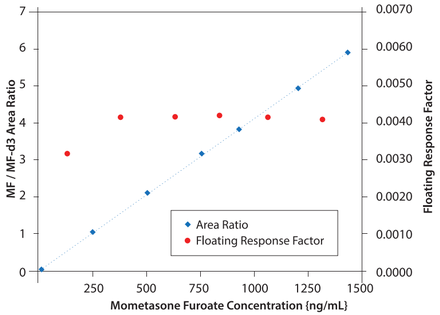


Figure 2: Calibration curve for mometasone furoate and the associated representative floating response factors.

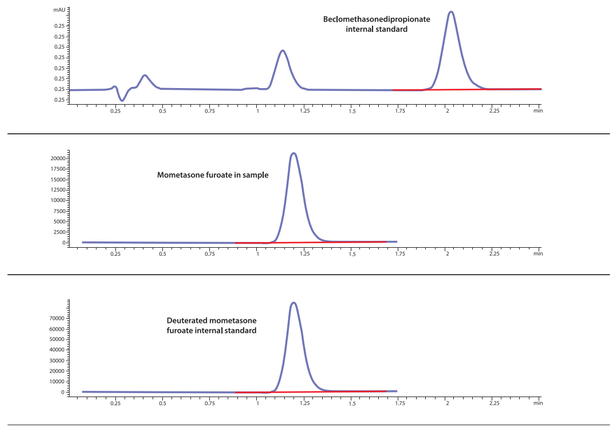
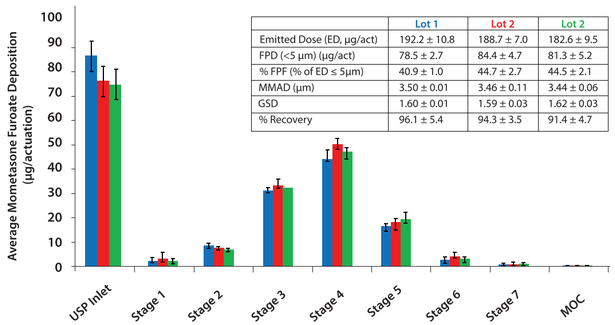


Figure 3: Representative chromatograms from an NGI sample.



	Lot 1	Lot 2	Lot 2
Emitted Dose (ED, µg/act)	192.2 ± 10.8	188.7 ± 7.0	182.6 ± 9.5
FPD (<5 µm) (µg/act)	78.5 ± 2.7	84.4 ± 4.7	81.3 ± 5.2
% FPF (% of ED ≤ 5µm)	40.9 ± 1.0	44.7 ± 2.7	44.5 ± 2.1
MMAD (µm)	3.50 ± 0.01	3.46 ± 0.11	3.44 ± 0.06
GSD	1.60 ± 0.01	1.59 ± 0.03	1.62 ± 0.03
% Recovery	96.1 ± 5.4	94.3 ± 3.5	91.4 ± 4.7

Figure 4: Unit dose lot characterization of mometasone furoate from three MDI lots by NGI (n = 4 per lot).

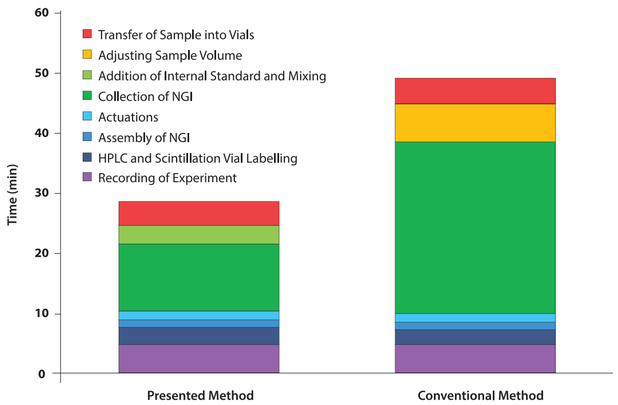


Figure 5: Expected gain in efficiency using presented method compared to conventional methods.

CONCLUSIONS

The use of the FRF and the dual-internal standard for LC-UV-MSD method allows for rapid, accurate, and precise quantification of mometasone furoate aerosol samples.

FUNDING

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ADDITIONAL REFERENCES

1. Menzeleev R, et al. RDD 2004, 453-456.
2. Menzeleev R, et al. RDD 2006, 585-588.
3. Moore C, et al. RDD 2008, 487-490.