The Challenges of Developing a Purity Method for the Analysis of a Single Dose DPI Inhaler

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Introduction

The USP albuterol purity method was redeveloped using Fusion QbD to reduce solvent use, improve sensitivity, and enable impurity analysis in a lactose formulation. The original method used a high flow rate, increasing cost and environmental impact, and lacked sensitivity for single-dose testing.

Fusion QbD optimization of gradient, organic content, oven temperature, and flow rate improved robustness and critical pair resolution, enabling impurity analysis from a single-dose DPI inhaler.

Time / mins	MP A / %	MP B / %
0	90	10
35	45	55
45	45	55
45.1	90	10
55	90	10

Mobile Phase A	5mM SDS in Water/ACN (80/20%v/v)
Mobile Phase B	5mM SDS in Water/ACN (60/40%v/v)
Flow Rate	2 mL/min
Injection Volume	50 µL
UV Wavelength	230 nm
Column Temp	30 °C
Column	Pursuit 5 C18, 150 x 4.6mm, 5 µm

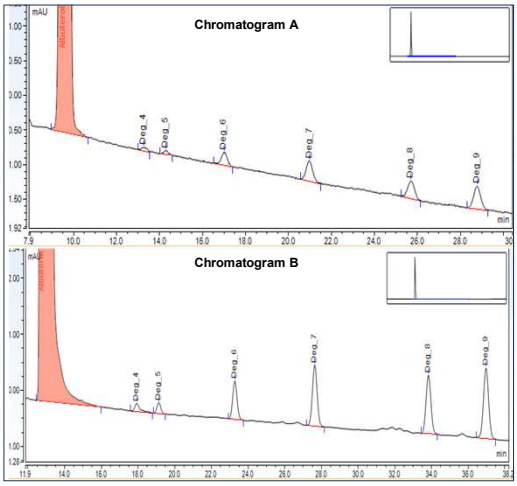
Materials and Methods

- A proprietary blend with 100 µg albuterol and lactose monohydrate was degraded at 70 °C for two weeks in an open beaker to generate degradation products.
- Method development was performed on an Agilent 1100 HPLC with a UV detector.
- Test sequences were designed using Fusion QbD® method development software (S-Matrix Inc.), a data-driven HPLC development tool.
- Fusion QbD® was also used to establish the Method Operable Design Region (MODR) following Analytical Quality by Design (AQbD) principles.
- An online HPLC method transfer calculator (Merck™) provided baseline conditions for a 2.7 µm silica column, 10 cm length (vs. 5 µm, 15 cm in the monograph).

Results and Discussion

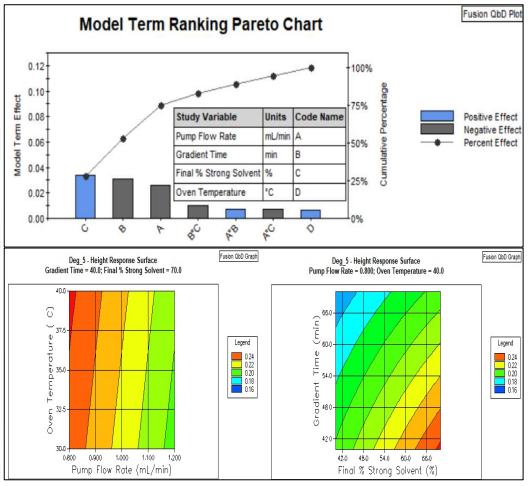
Column Optimisation

Chromatogram A – USP Method
Chromatogram B – Shorter column with smaller particle size.



Fusion QbD

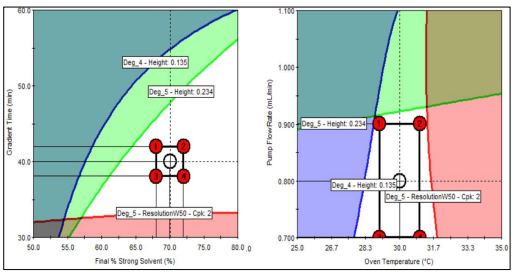
Assessment of gradient time, % organic, oven temperature and flow rate.



Robustness

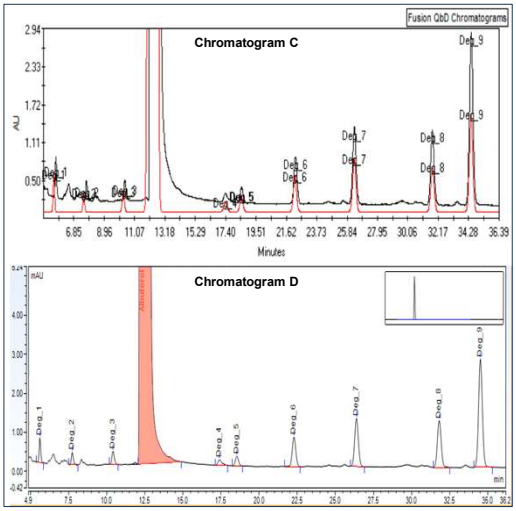
The goal was to identify the steepest gradient while meeting robustness criteria. A simulation generated Deg-5 resolution distributions from virtual robustness experiments. Optimization was then performed to maximize Deg-4 and Deg-5 peak heights and Deg-5 resolution robustness.

The optimal method was located at the corner of the experimental region, with conditions of 30 °C column temperature, 0.8 mL/min flow rate, 40 min gradient time, and 70% final organic content.



Verifying Fusion Best Method Centre Point

Chromatogram C – Fusion Best Method Centre Point.
Chromatogram D – Representative Chromatogram



Final Conditions

Time / mins	MP A / %	MP B / %
0	90	10
40	30	55
40.1	90	55
50	90	10

Mobile Phase A	5mM SDS in Water/ACN (80/20%v/v)
Mobile Phase B	5mM SDS in Water/ACN (60/40%v/v)
Flow Rate	0.8 mL/min
Injection Vol	25 µL
UV Wavelength	225 nm
Column Temp	30 °C
Column	InfinityLab Poroshell 120 EC-C18, 100 x 4.6mm, 2.7 µm

Conclusion

The USP monograph was successfully redeveloped to enhance sensitivity by sevenfold and reduce solvent usage by 70 mL per injection, thereby minimizing environmental impact.

Significant sensitivity improvements were achieved through alternative column technology, use of albuterol's λ max, and optimization of HPLC parameters known to affect sensitivity.

The Fusion QbD software facilitated this optimization while maintaining excellent robustness of the separation under the modified conditions.

The data suggest that further improvements may be possible by extending the experimental region studied, and translating the method to a UPLC column and instrument is expected to provide additional advantages.

References
Pharmacopeial Forum; PF Vol.27, No. 3, page 2505.
https://www.sigmaaldrich.com/GB/en/support/calculators-and-apps/hplc-method-transfer-calculator.
S-Matrix Inc; Fusion QbD Method Development Software.