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Nota de aplicación

Applying a Software-Assisted Analytical Quality-by-Design Approach for the Analysis of Formoterol, Budesonide, and Related Compounds by UPLC-MS

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Abstract

Analytical method performance is critical to ensure the quality, safety, and efficacy of pharmaceutical products. Two of the most commonly used ones are One Factor at a Time (OFAT) and Analytical Quality by Design (AQbD). A robust method for budesonide, formoterol, and related compounds was developed using a Quality by Design approach on an ACQUITY UPLC H-Class PLUS System running Empower 3 and Fusion Software.

Benefits

- Benefits of using Fusion QbD for method development.
- Straightforward method development capabilities of the ACQUITY UPLC H-Class PLUS System in combination with Empower 3 Chromatographic Data System (CDS) and S-Matrix Fusion QbD Software.
- Benefits of using the ACQUITY QDa Mass Detector for analytical method development
- High performance and robust method development for the analysis of formoterol, budesonide, and its related compounds

Introduction

Analytical method performance is critical to ensure the quality, safety, and efficacy of pharmaceutical products. Currently, there are several approaches for method development in the analytical realm. Two of the most commonly used ones are One Factor at a Time (OFAT) and Analytical Quality by Design (AQbD).[1-4] In the OFAT protocol, only one parameter is varied, and its effect on responses is evaluated whilst others remain constant. When no more improvements are attained from changing this factor, another parameter is then explored.[2] This approach is not very comprehensive, and the separations are often sub-optimal in terms of resolution, peak shape, and robustness.

In the AQbD approach, however, a more comprehensive, systematic, and risk-based strategy that starts with predefined objectives is used for method development. In this approach, multiple parameters and settings are explored to provide a broad knowledge about the impact of the studied factors on the method performance. This knowledge is used to establish the method operable design region (MODR), which corresponds to the multi-dimensional combination of variables that have been verified to meet the method

performance criteria. The outcome of this approach is a fit-for-purpose, well-designed, understood, and robust method that reliably delivers the expected performance throughout its lifecycle.[5,6] Another key advantage for employing the AQbD approach in method development is the potential for regulatory flexibility with regards to changes to the analytical method.[2] As such, AQbD is a desirable approach to be followed in analytical method development.

The primary objective of this study is to employ a software assisted AQbD approach to develop an ultra-performance liquid chromatography-mass spectrometry (UPLC-MS) method for the analysis of formoterol, budesonide, and related compounds. Budesonide (structure shown in Figure 1A) is a corticosteroid used for long-term treatment of asthma by controlling and suppressing inflammation. Agonists, such as formoterol (Figure 1B), also have been widely used in the management of asthma and chronic obstructive pulmonary disease. Inhalation of the two pharmaceutical ingredients as one dose in combination inhalers has proved to be more clinically effective.[7]

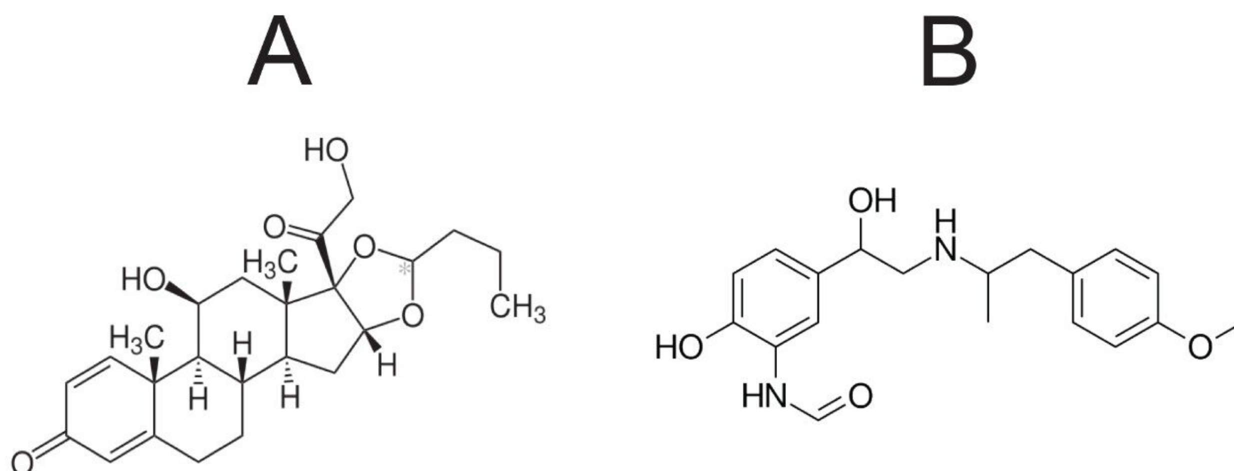


Figure 1. Chemical structures of budesonide (A), which exists as a pair of epimers, and formoterol fumarate (B).

This application note focuses mainly on exploring the analytical potential of the AQbD approach for achieving high-performance separations of formoterol, budesonide, and its related compounds. Several key chromatographic parameters are investigated for their effect on the efficiency of the separations, and the findings are presented and discussed. Fusion QbD will be used as an AQbD software for method development in this application note.

Experimental

Materials and standard preparations

Budesonide and formoterol fumarate reference standards were both purchased from USP (Rockville, USA). Budesonide related compounds G, E, and L were also all purchased from USP (Rockville, USA). Stock solutions of these compounds were prepared by accurately weighing the desired amounts of each standard and dissolving them in acetonitrile as a solvent. The stock solutions were then used to make a test mixture that contains all previously mentioned APIs and impurities. This mixture was prepared by diluting the stock solutions of each standard in 70:30 (v/v) water:acetonitrile as sample solvent. The final concentration of each analyte in the test mixture was approximately: 0.4 mg/mL^{-1} budesonide, 0.15 mg/mL^{-1} formoterol, 0.005 mg/mL^{-1} related compounds E and L, and 0.01 mg/mL^{-1} related compound G.

LC conditions

System:	ACQUITY UPLC H-Class PLUS System with Quaternary Solvent Manager (QSM), Sample Manager (FTN), Column Manager (CM with two Auxiliary Column Managers), PDA Detector, ACQUITY QDa Mass Detector
Detectors:	eλ PDA and ACQUITY Qda
Columns:	Five 2.1 × 50 mm columns: ▪ BEH C_{18}, 1.7 µm (column volume fully porous[CVFP] = 114 µL); pH range: 1–12 ▪ BEH Shield RP18, 1.7 µm (CVFP = 114 µL); pH range: 1–11 ▪ CORTECS T3, 1.6 µm (Column volume superficially porous [CVSP] = 85 µL); pH range: 2–8 ▪ CORTECS Phenyl 1.7 µm (CVSP = 85 µL) pH range: 2–8

	▪ HSS PFP, 1.7 µm (CVFP = 114 µL); pH range: 2–8
Flow rate:	0.5 mL/min
Mobile phase A:	First screening (trifluoroacetic acid 0.1%) Second screening (ammonium hydroxide 0.1%)
Mobile phase B:	Acetonitrile (strong solvent [SS])
Mobile phase D:	Solvent-select valve that was used to select between several solvents at different stages of the method development Screening: D1 20 mM ammonium acetate Optimization: D1 (20 mM ammonium acetate/ ammonium hydroxide buffer pH = 8.0), D2 (20 mM ammonium acetate/ ammonium hydroxide buffer pH = 8.5), D3 (20 mM ammonium acetate/ ammonium hydroxide buffer pH = 9.0)
Profile:	Equilibrate at 10% organic for 3.0 min (13.2 CVFP and 17.64 CVSP) Isocratic at 10% organic for 1.0 min (4.4 CVFP and 5.88 CVSP) Gradient from 10% to 60% organic for gradient times ranging from 5–12 minutes Isocratic at 60% SS for 1.0 min (4.27 CVFP and 5.88 CVSP)

	Ramp down from 60% to 5% SS for 0.1 min
	Isocratic at 10% SS for 3.0 min (13.2 CVFP and 17.64 CVSP)
	Note: Percent Strong Solvent plus % Weak Solvents equals 100%
Column temp.:	Constant 40 °C
Detection (UV):	244 nm
Injection volume:	3 µL working solution

MS conditions

System:	ACQUITY QDa Mass Detector
Ionization mode:	ESI+
Capillary voltage:	0.8 kV
Con voltage:	15 V
Source temp.:	600 °C
Data management:	Empower 3 Chromatographic Data System (Empower CDS) and S-Matrix Fusion QbD

Results and Discussion

In the process of LC method development, several factors are normally varied to achieve the desired separation goals. Some of these factors, such as the column stationary phase, the strong solvent, and the pH, have strong effects on separations while others, like gradient steepness and separation temperature, have

weaker effects. The success of any method development is generally evaluated based on the responses obtained from varying these factors. Examples of these responses include retention factor, resolution, tailing, number of peaks in a chromatogram, and the number of peaks with a specific desirable result. The more parameters being screened, the more knowledge is obtained about the method. However, screening several chromatographic parameters can be very time consuming, especially if multiple data points for each parameter are set to be screened. The advantage for using Fusion QbD as an AQbD software platform is that it uses statistical sampling approaches to create comprehensive and representative experimental designs that significantly reduce the number of experiments required for method development. This is because it covers the same design space as a generalized "Full Factorial" design by generating and modeling a much smaller but representative subset of all possible factor combinations. For example, given a "Full Factorial" study for two variables at five different study levels, running all possible combinations would require 25 experiments. However, if Fusion QbD is used to model a comprehensive study to represent all these factors, only 13 experiments will be needed. This significant reduction in the number of experiments is due to the fact the statistical sampling design of Fusion QbD does not run all the combination points, but rather runs some points and predicts others. This gives a comprehensive understanding of all significant factor effects across the entire chromatographic space with fewer actual experiments. Figure 2A shows a generic schematic of a "Full Factorial" design where all elements of the design space are sampled; and Figure 2B shows a "Fractional Factorial" of the same design space, but with fewer points due to proper sampling.

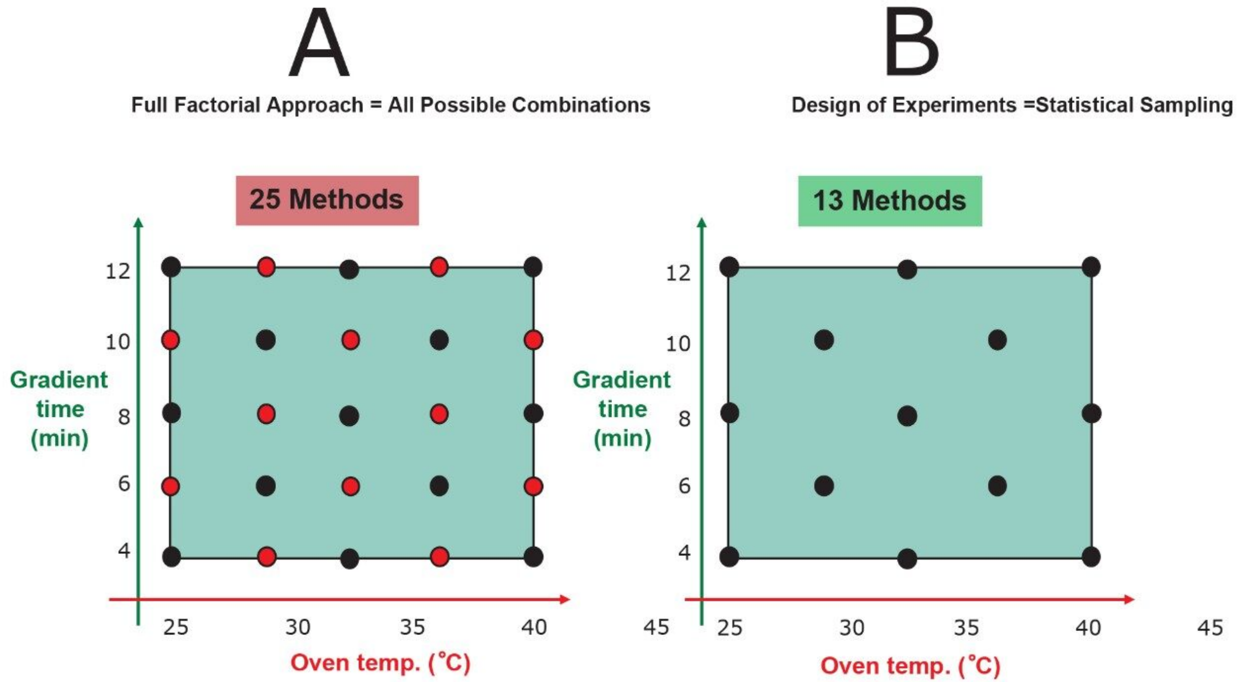


Figure 2. Generic schematic example for a Full Factorial design where all elements (experiments) of the matrix are sampled (A), and a statistical sampling design where only balanced and representative experiments of the matrix are sampled (B).

Design of Experiment (DOE) is defined by the ICH as "a structured, organized method for determining the relationship between factors affecting a process and the output of that process." Fusion QbD is a software that uses the DOE approach to develop robust LC methods. Figure 3 shows the general steps that are normally performed in Fusion QbD method development.

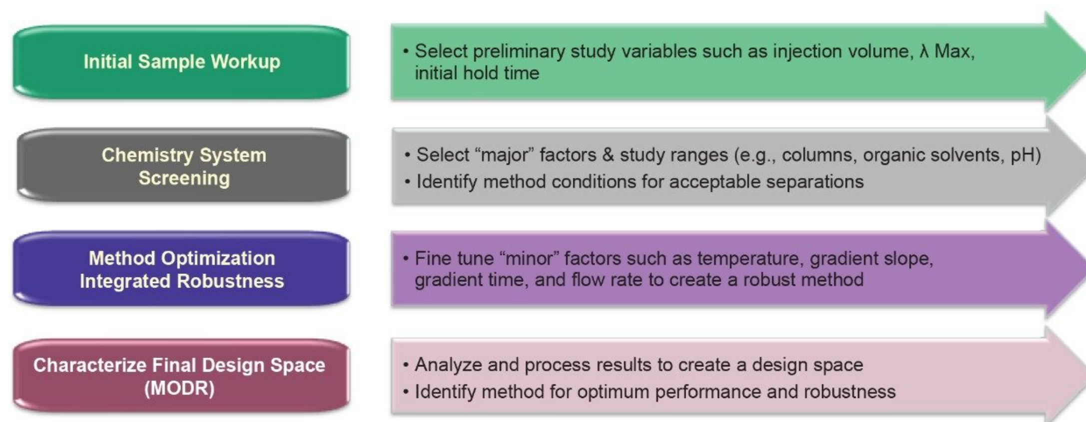


Figure 3. A schematic diagram of the general method development steps in Fusion QbD.

Initial Sample Workup

The main purpose of this step is to find initial chromatographic conditions that can be used as a starting point for the chemistry system screening step. These conditions should in general ensure that the analytes of interest are initially retained, elute beforethe end of the run, and are on scale using an appropriate wavelength. It should be noted here that the peaks are not expected to be well-separated and with good shape at this point, they only need to be retained and integrable.

To do this, we created a small screening experiment using the "General Screening" template in Fusion QbD. In this experiment, a limited number of variables were set to be studied. These variables included: injection volume (1–3 µL), wavelength, initial hold time (1–2 min), and two different column chemistries (BEH C_{18}, CORTECS T3). Results have shown that all compounds of interest can be retained at a starting organic composition of 10.0% and a one-minute initial hold time. It was also found that a wavelength of 244 nm is an appropriate 2-D channel enabling all the analytes to be seen without significant interference from the mobile phase.

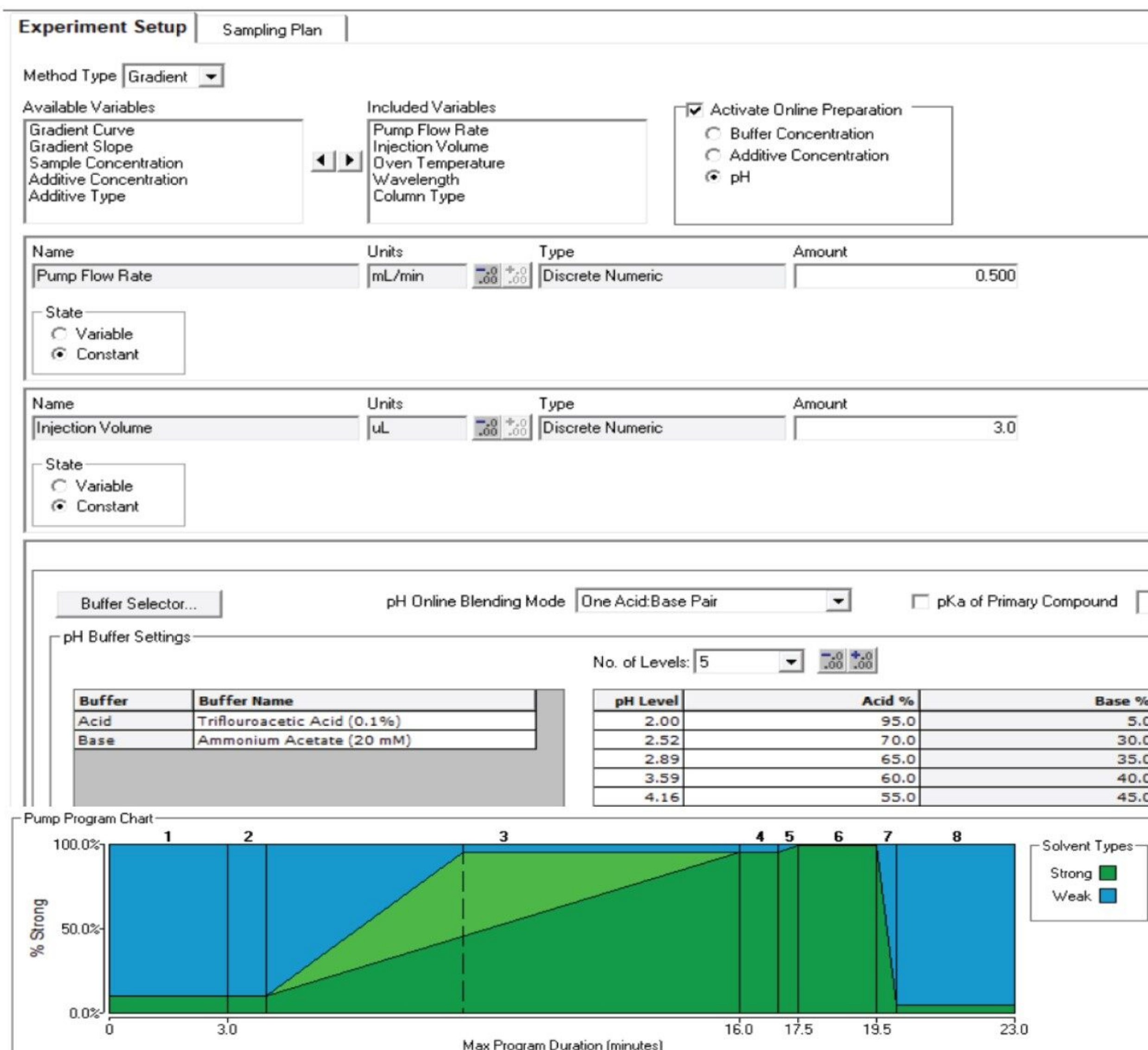
Chemistry System Screening

1: Creating the experimental design

At this stage of the study, the goal was to perform a comprehensive screening experiment, which includes the chemistry system parameters expected to have the largest effects on method performance. Therefore, in this experiment, the pH and the stationary phase chemistries were the two major chromatographic parameters explored. pH values between 2.0–4.2 were explored in half-pH-unit increments. For the stationary phase chemistries, the intention was to select columns that provided a wide range of selectivity, while increasing the chances of success. Five stationary phases were selected for study, in this stage. The first

column was a BEH C_{18}, which is one of the most popular LC columns available with a wide pH range (1–14). The second column was a BEH Shield RP18, as it offers alternative selectivity compared to BEH C_{18} due to embedded polar groups, and supports a wide pH range. The third column was a CORTECS T3 which is a superficially porous C_{18} column that gives increased retention for polar analytes. The fourth column that was chosen for this study was a CORTECS Phenyl which is another superficially porous column and offers alternative selectivity with acetonitrile and methanol due to potential pi-pi interactions. The last column we selected was an HSS PFP due to its unique selectivity. It should be noted here that the appropriate column geometries that match the instrument capabilities were taken into consideration in this experiment. For example, as an ACQUITY UPLC H-Class PLUS System was used, the appropriate geometry choice was 2.1 mm with 1.x µm particle size for the columns. Also, a short column length is desirable for the creation of rapid and high flow rate methods and this led us to use 50-mm-long columns.

The last chromatographic parameter that was varied in this experiment was the gradient time (5–12 min). All other chromatographic parameters, including flow rate, temperature, and injection volume, were set to be constant. An image of the Fusion QbD Software's Experiment Setup window for some of the variables and constants included in this experiment is shown in Figure 4.



All columns used are 5 cm × 2.1 mm × 1.x µm

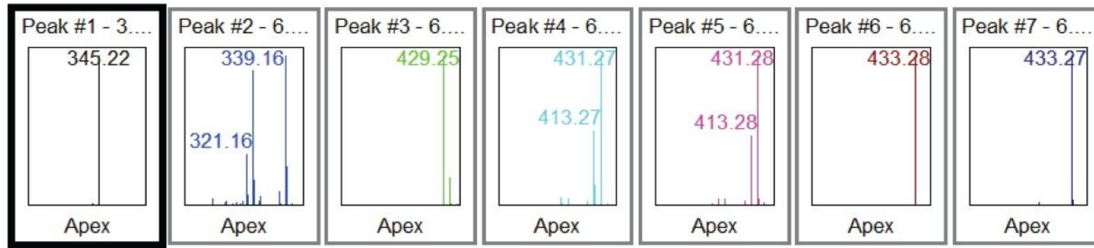
Figure 4. A Fusion QbD screen image showing the selection of the pH and the gradient times in the first screening experiment.

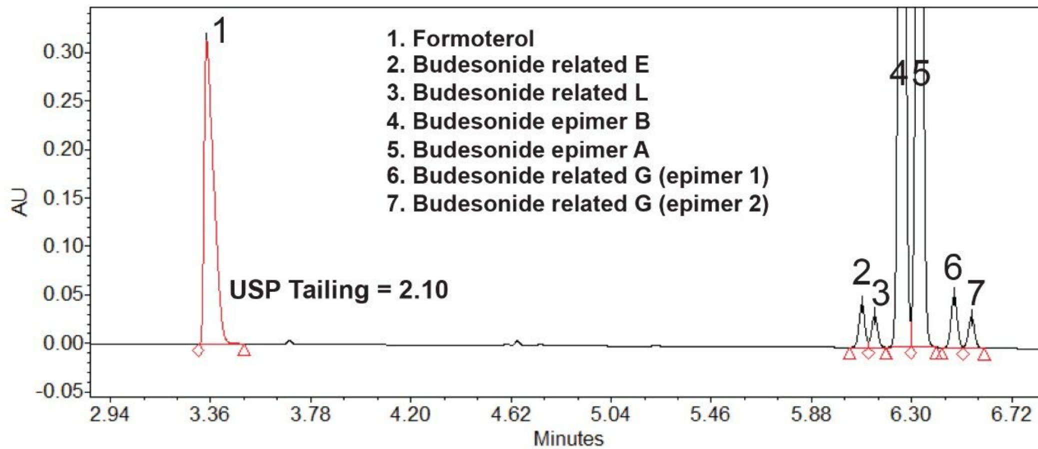
After selecting all the variables and constants for the experiment in Fusion QbD, the software created an experimental design for all required screening experiments using statistical sampling, as previously mentioned. The total number of runs that the software created for this screening experiment was 44. When the experimental design was created, it was exported to Empower to create all the methods and method sets that are needed for these runs. It also created and exported all the necessary conditioning/equilibration methods and method sets. This is particularly important, as it significantly shortens the method development

time by eliminating the time needed to manually generate methods and method sets for such large numbers of experiments. Note that this DOE design is highly efficient, since 125 methods would be required for all possible combinations (five levels of tG × five levels of pH × five columns).

2: Importing data to Fusion QbD and developing a knowledge space

Next, after all the experiments were run, data was processed in Empower before they were imported to the Fusion QbD software. Processing in Empower involved integrating only all the peaks of interest in the resulting chromatograms and calculating some relevant chromatographic parameters, such as resolution, tailing, and symmetry for these peaks. This was done by viewing all resulting chromatograms to find the "best looking" chromatogram and creating the processing method based on it. This chromatogram is normally the one with the most visible peaks corresponding to actual analytes, and most baseline resolved peaks. Results have shown that the separations obtained from this screening experiment were not optimum and further experiments are still needed to explore other chromatographic parameters. For example, as can be seen in Figure 5, the formoterol peak has very high tailing factor (2.10) and the budesonide related compounds are not all baseline resolved. It should be mentioned here that in this part of the method development process the use of the QDa mass detector was very beneficial. This was because it allowed us to identify and track our peaks of interest despite the changes in their retention times and/or order of elution over the different runs.





Mobile phase:	**A**: Acetonitrile **D**: Ammonium acetate/trifluoroacetic acid buffer
pH:	4.16
Column:	BEH C_{18}, 1.7 µm, 2.1 × 50 mm
Flow rate:	0.350 mL/min
Temp.:	40 °C
Gradient:	**0–1.0 min**: 5% A and 95% D isocratic **1.0–12 min**: 5–60% A linear gradient

Figure 5. A "best looking" chromatogram from the chemistry screening experiment, which corresponds to run 33.

After processing the data in Empower they were next imported into Fusion QbD where mathematical models were automatically built and combined to predict the "Best Overall Answer (BOA)." The performance goals selected in this screening stage included both peak count-based and peak result-based trend responses The peak count-based trend responses used in this analysis were (1) total number of peaks, and (2) number of peaks with a USP resolution of ≥1.50 in each chromatogram. For peak result-based properties, we used Max Peak #2 USP resolution and Max Peak #3 USP tailing. In Fusion QbD, Max Peak #1 is the peak with the largest area, Max Peak #2 is the peak with the second largest area, and so on. In our case we had three

major peaks as we have two active pharmaceutical ingredients – one of which is a pair of epimers (budesonide). Figure 6 shows an image of the Fusion QbD Import Responses dialog configured with the desired Trend Response settings, which are then automatically derived from the experiment chromatograms and imported for analysis.

Select Responses

Channel:

PDA Ch1 244nm@4.8nm

☑ Import Chromatogram Trace Data

☑ Import Prediction Chromatogram Data

Trend Responses

Add | Delete | Undo Changes | Restore Defaults

		Operator	Value	Response
1	☑	No. of Peaks		
2	☑	No. of Peaks >=	1.50	USPResolution
3	☑	No. of Peaks >=	2.00	USPResolution
4	☐	No. of Peaks <=	1.20	USPTailing
5	☑	Max Peak	3	USPTailing
6	☑	Max Peak	2	USPResolution

Select All | Select None

I = Incomplete
D = Duplicate

Figure 6. Fusion QbD screen image showing the performance goals (target responses) that were configured

for automatic import from the chemistry screening experiment.

The next step was "Executing Search" in Fusion QbD. In this step, the software uses the measured responses to calculate models for each chromatographic result. These models calculated a "Cumulative Desirability Result," which is a numerical value that ranges from zero-to-one and represents the probability that the chromatographic conditions will meet the user-specified performance goals. In this study, it was found that the best combination of conditions to achieve the set performance goals are: BEH C_{18} Column, acetonitrile solvent, pH 4.2, and a gradient time of 12 minutes.

Fusion QbD models also provide performance maps that show Acceptable Performance Region (APR) – the unshaded region around the BOA where the method meets or exceeds the predefined screening performance goals. Note that the APR is the region of the graph that remains unshaded after applying all the performance goals on the plot (the white space). This unshaded region shows the setting combinations that meet or exceed the limits of acceptability of all included performance goals. For example, as can be seen in Figure 7A, the whole space is unshaded because no performance goals (responses) are applied yet. However, as performance goals are applied, more shaded region will be seen until all goals are applied (Figures 7B–7C).

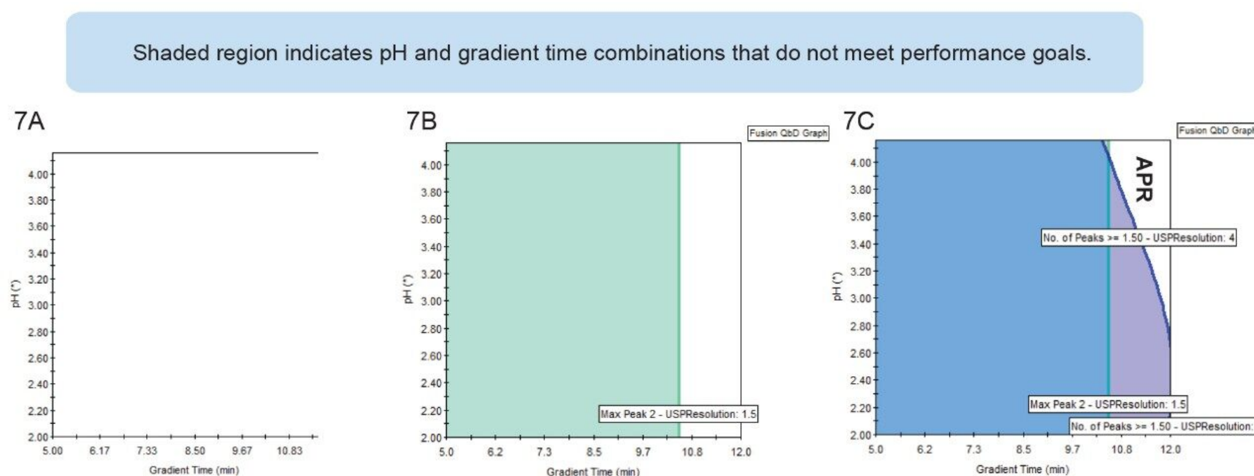


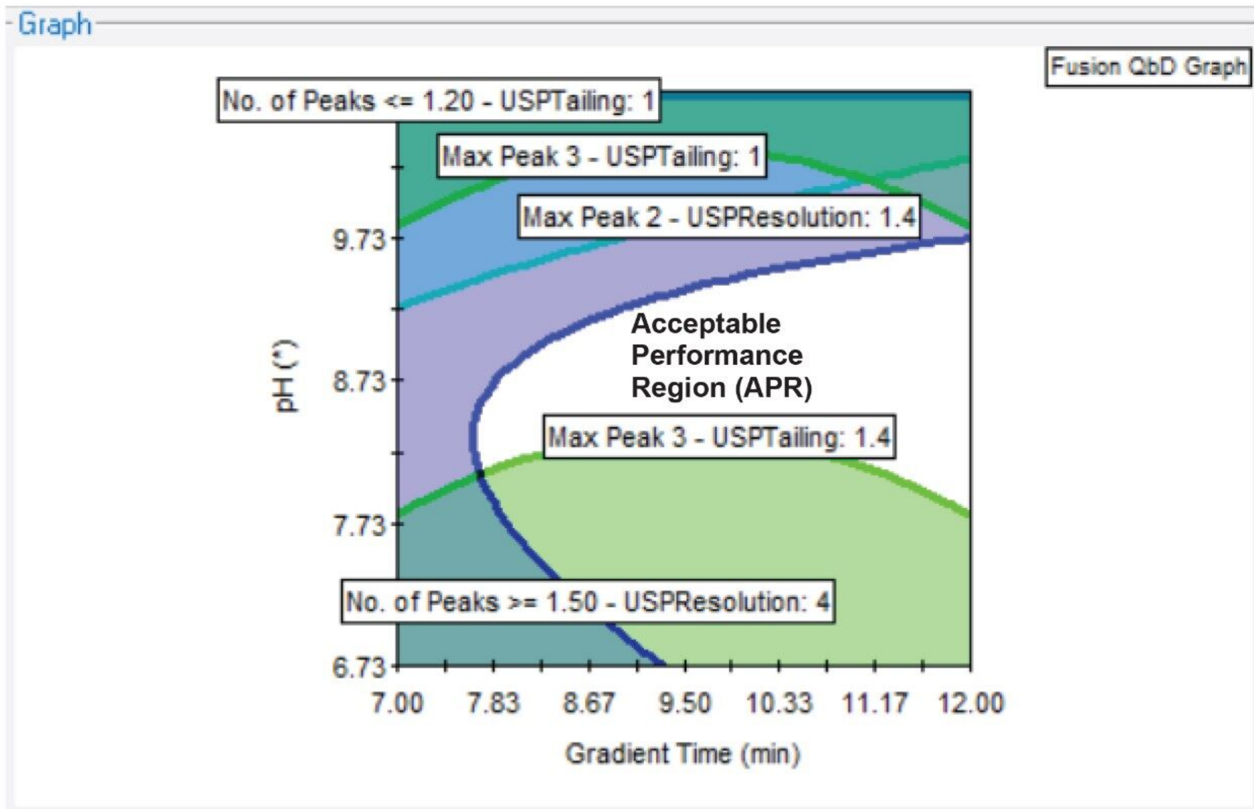
Figure 7. Fusion QbD screening design images, showing the construction of the workable region within the screening experimental design region.

Second Screening (High pH)

Our first chemistry screening experiment was reasonably successful in separating some of the analytes of

interest, however, it was not able to achieve all the desired performance goals. For example, as shown earlier, some analytes were not baseline resolved and the formoterol peak was unsymmetrical with tailing factor values between 1.44 to 2.88. Therefore, it was necessary to perform a second screening experiment to see if further improvements can be attained under different chromatographic conditions. As stated earlier, pH is a primary chromatographic parameter that has a major influence on the separations. As such, a second screening experiment under different pH conditions was pursued. This was done by using the best column that was found in the previous experiment and screening it under high pH conditions. In this experiment, pH values ranging from 6.7 to 10.7 were screened using the BEH C_{18} Column. All other variables and constants were maintained at the settings used in the first screening experiment. Results of this experiment showed that the formoterol peak shape significantly improved when high pH mobile phases were used. For example, the tailing for the formoterol peak was less than 1.3 for 10 of the 15 high pH screening runs.

The results of these screening runs were next processed in Fusion QbD to find the BOA and the APR. The major performance goals that were set in this search included baseline resolution for at least four peaks and a target tailing of 1.2 for the formoterol peak. It was found, as can be seen in Figure 8, that the tailing of formoterol decreases as the pH increases. The BOA search identified that, using the BEH C_{18} Column, a pH of 8.76 and a 12-minute run time were the best conditions for the next optimization experiment.



Response Settings

	Name	Goal	Lower Bound	Upper Bound	Pointer Predictions
☑	No. of Peaks	Maximize	6.0		7.016
☑	No. of Peaks >= 1.50 - USPResolution	Maximize	4.0		4.83
☑	Max Peak 3 - USPTailing	Target	1.00	1.40	1.387
☐	Max Peak 1 - USPResolution	---	---	---	---
☑	Max Peak 2 - USPResolution	Maximize	1.40		1.664
☐	No. of Peaks >= 2.00 - USPResolution	---	---	---	---
☐	No. of Peaks >= 1.20 - USPTailing	---	---	---	---
☑	No. of Peaks <= 1.20 - USPTailing	Maximize	1.0		4.16

Figure 8. A Fusion QbD screen image showing the workable region within the experimental region for the high-pH-screening experiment.

Optimization

Optimization in LC method development is normally done by fine tuning some of the less important parameters such as the temperature, gradient slopes, gradient times, and flow rates. In this experiment the flow rate and the temperature were varied.

Two flow rates of 0.35 and 0.5 mL/min^{-1} and temperatures ranging from 30–50 °C were included in this study. Three buffers at pH levels of 8.0, 8.5, and 9.0 were also studied. As the BEH C_{18} stationary phase has shown to be efficient at separating the analytes of interest, it was selected as the stationary phase in this optimization experiment. It should be noted here that a 10 cm BEH C_{18} (2.1 mm × 1.7 µm) Column was used instead of the 5 cm (2.1 mm × 1.7 µm) that was used in the screening experiments. This was done to achieve better separations for all analytes given that a longer column will have a higher number of theoretical plates and therefore a higher efficiency.

The gradient times were adjusted from the 5 cm column to the 10 cm column using the "Column Calculator" tool in Empower. The experimental design was created again using the Fusion QbD Software and the results were also processed using the software to find the APR and the BOA. Results have shown that the desired performance goals can be achieved under wide ranges of experimental conditions.

For example, as shown in Figure 9, all analytes of interest (seven peaks) can be separated with a minimum resolution of 2.3 and with a tailing factor of less than 1.2 over a wide range of temperatures (32.2–38.6 °C) and a wide range of gradient times (13–25 min). The graph in Figure 9 also shows the location of the final method within the design space – the point designated as "T," for target method.

The rectangle within the final design space illustrates the joint "Proven Acceptable Ranges (PARs)" – the subset of the design space within which the graphed parameters can be independently adjusted post approval without requiring full re-validation of the method. These findings indicate that a robust method that achieves all the desired performance goals can be created in the middle of the APR space. It should be noted here that the models obtained from the optimization experiment are more precise than those obtained from the screening, which enable the APR to now be considered a final design space. The analysis results identified the design space shown in Figure 9, which encompasses wide ranges of the experimental factors within which the desired performance goals can be achieved.

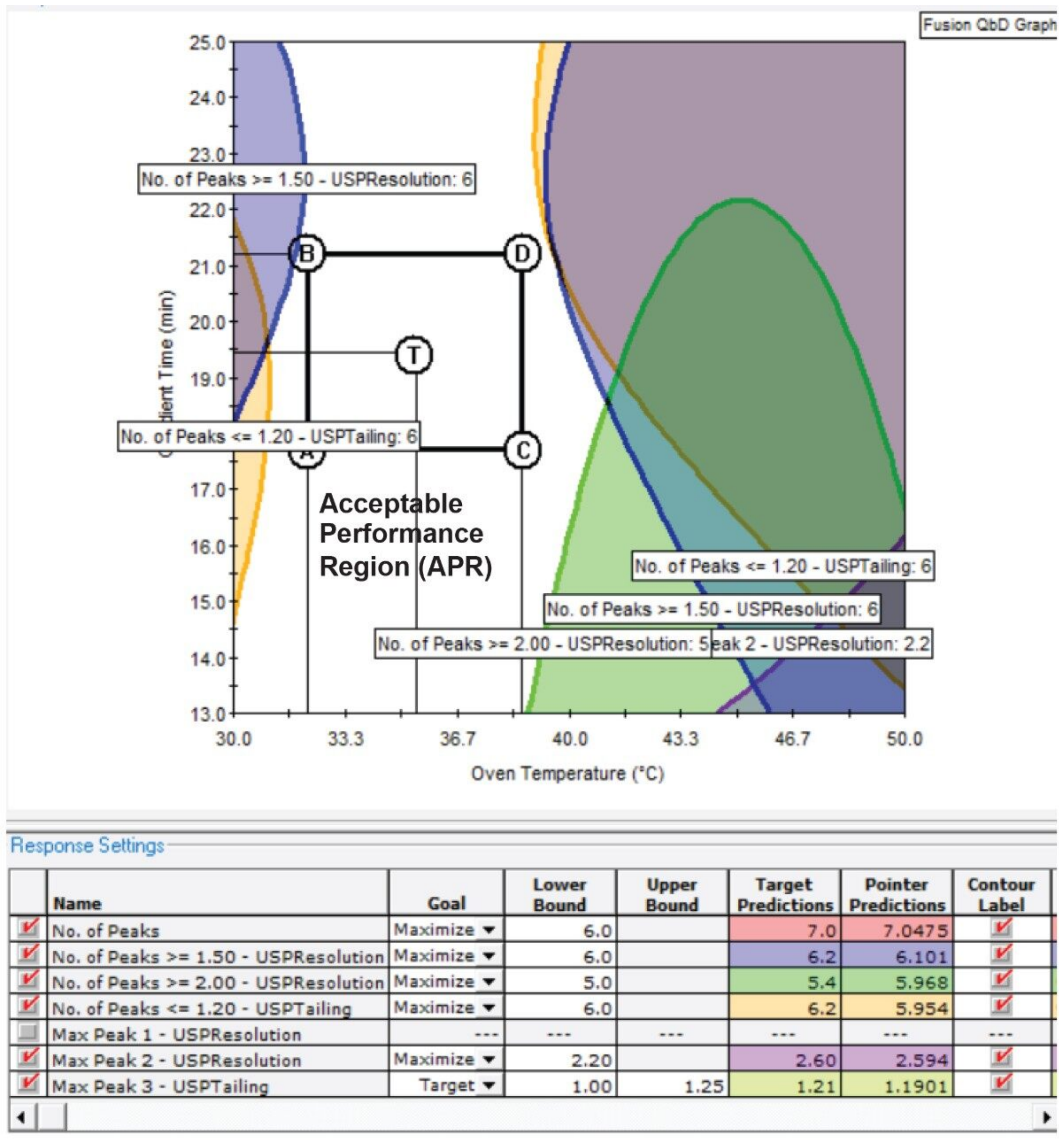


Figure 9. Fusion QbD graph of the design space and the PARs obtained from the optimization experiment. The table under the graph shows the user specified performance goals that were achieved in this design.

Verification

In this part of the study, several verification runs were performed to compare the results that were obtained by Fusion QbD to actual runs. Results have shown that the predicted performance matches the real performance reasonably well. For example, as shown in Figure 10, Fusion QbD predicted that the number of peaks under the BOA conditions (detailed in the graph) will be seven peaks and results of the real

chromatogram (Figure 10) have also shown seven peaks. Further, Fusion QbD predicted that six of these seven peaks will have a USP resolution of ≥2 and the real chromatogram have shown the same thing. Finally, the Fusion QbD Software predicted that all seven peaks will have a tailing factor of equal or less than 1.2 and the real chromatogram has shown six of the seven peaks had a tailing factor of less than 1.2. It is worth noting here that Fusion QbD Software can also successfully predict the performance for specific peaks in the chromatogram. For example, the predicted value of the resolution of budesonide epimer A was within less than 2% difference from the actual value when five different verification runs were performed.

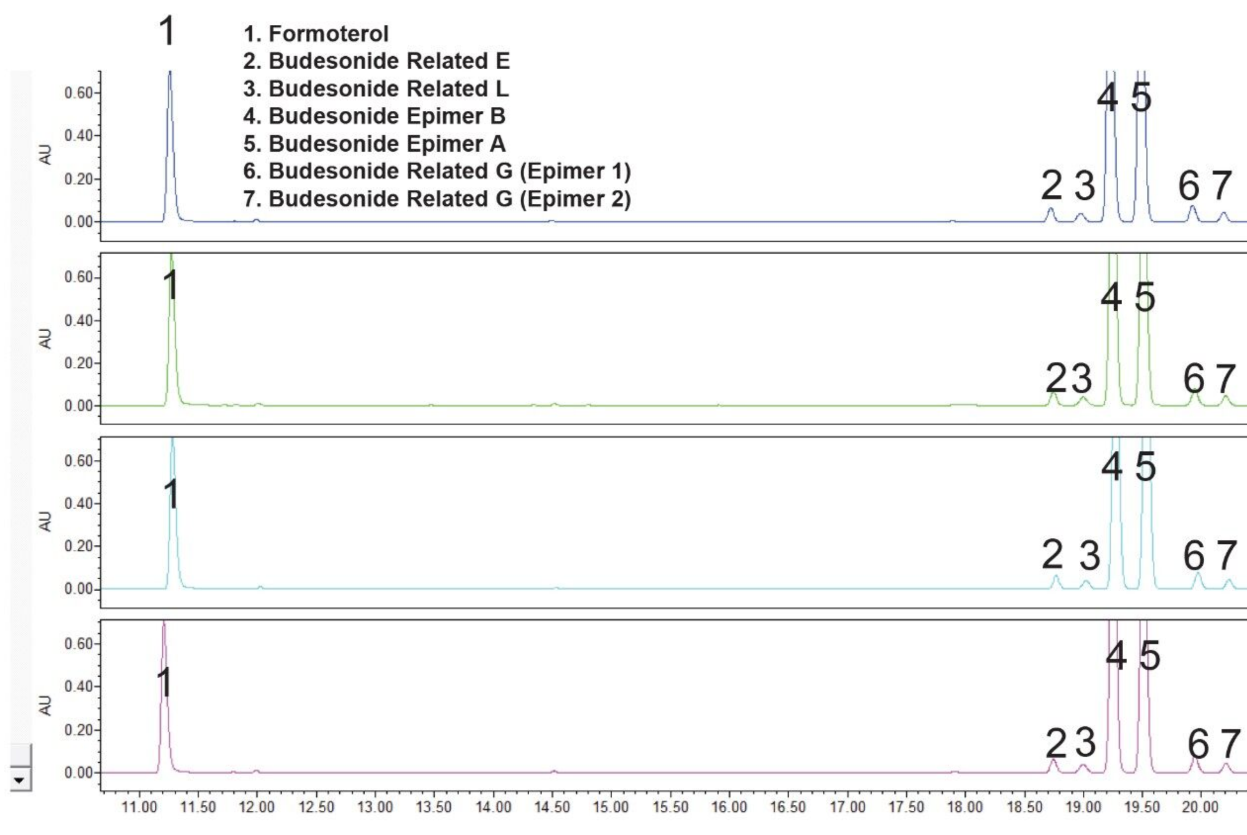


Figure 10. Four replicate injections of formoterol, budesonide, and its related compounds under the BOA conditions that were obtained from the optimization experiment. These conditions are: pH = 8.2, temperature = 33 °C, and flow rate = 0.350 mL/min^{-1}. The gradient profile was: initial hold of two minutes at 5% acetonitrile and 95% ammonium followed by a linear gradient of acetonitrile from 5–60% over 25 minutes.

Conclusion

A robust method for budesonide, formoterol, and related compounds was developed using a Quality by Design approach on an ACQUITY UPLC H-Class PLUS System running Empower 3 and Fusion Software.

- Using Fusion QbD as a tool for developing LC methods can be advantageous as it:
    - Automates the entire method development process
    - Saves time by determining the minimum number of experiments needed for valid results
    - Provides tools to quantify and visualize all important instrument parameter effects on all critical method performance characteristics
- QbD method development software in conjunction with an ACQUITY UPLC H-Class PLUS System allows for rapid screening over a wide variety of chromatographic parameters, such as column chemistries, mobile phases, temperatures, and injection volumes
- Using the ACQUITY QDa Mass Detector in method development is very beneficial as it allows for fast and easy identification of analytes over the different chromatographic conditions.

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