A Scientific Approach to the Quality Control Enhancement Concept

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Summary

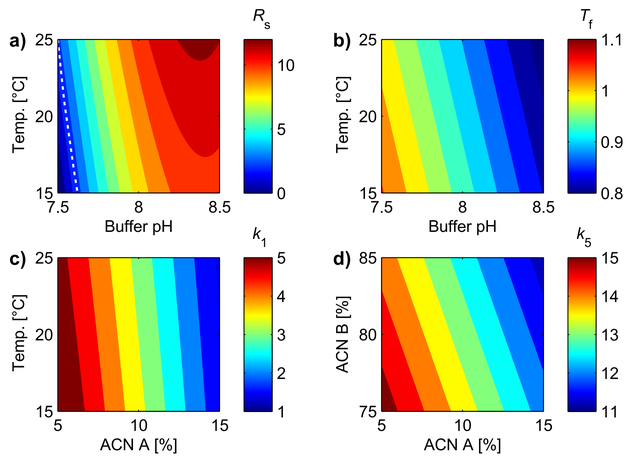
- To get more flexibility for post-approval variations to already aproved quality control methods, Quality by Design (QbD) can be used.
- With QbD, all variations in the validated design space are acceptable.
- The aim of this project was to investigate if switching from HPLC to UHPLC would be possible with a QbD method.
- A quality control method for Nexium was developed for HPLC using QbD and switching to UHPLC was seen as a continuous improvement.
- We found that a clear scientific understanding of the differences between HPLC and UHPLC was essential for a successful method transfer.

Method Development in QbD

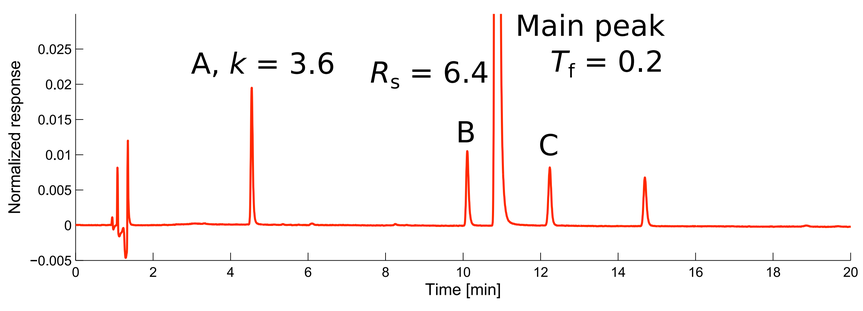
1. Definition of method goals and selection of technique
The method goal was to analyze the purity of Nexium capsules. This is done with HPLC and the method must fullfill the method Analytical Target Profile:

Method Attribute	Acceptance criteria
Specificity	No interference with API
Linearity	≥0.999
Relative response	≥0.7
Limit of quantification (LOQ)	≤0.05% of relative peak area
Accuracy	Mean recovery of 90-110%
Precision	≤3% between operators

2. Method development with risk assessment
i) Find a working point and confirm that it meets the mATP
ii) Identify critical operating parameters
iii) Robustness testing with design of experiments



3. Control Strategy
The control strategy assures that the method is performing as intended. It is described in the system suitability test.



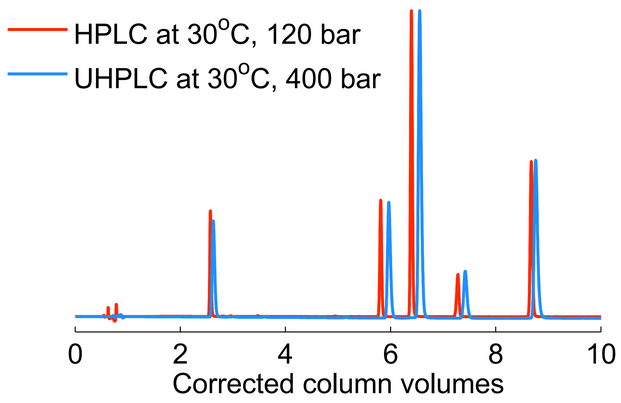
Chromatogram from final HPLC method.

Switching to UHPLC

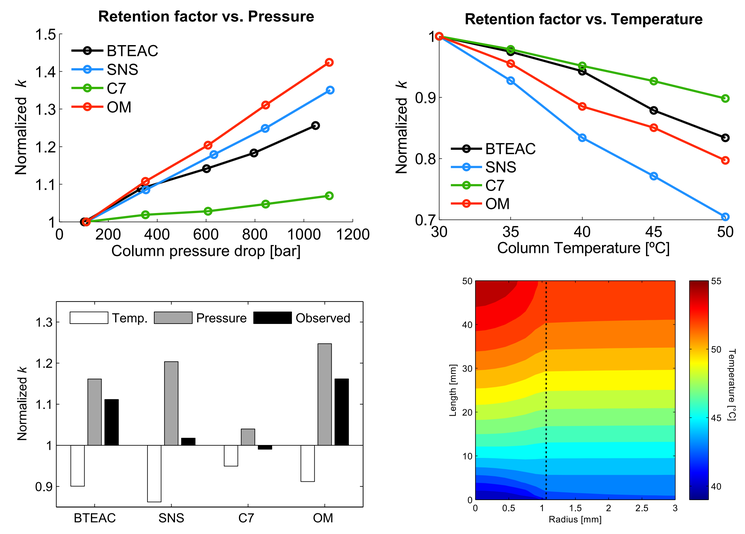
Switching from HPLC to UHPLC was done by changing the column from 4.6 x 100 mm, 3.5 µm to 2.1 x 50 mm, 1.7 µm and switching to a Waters UPLC system which could handle higher pressures. This resulted in that the following factors needed to be scaled:

- Injection volume: 20 µL to 2 µL
- Flow rate: 1.0 mL/min to 0.43 mL/min
- Gradient time: 30 min to 7.15 min
- Gradient delay: 1.0 min to 0.25 min

After scaling, the HPLC and UHPLC methods should give identical result when the elution time is converted to "column volumes". However, this was not the case:



Such differences have to be explained in order to show that we understand the change we want to do to the method. Using three model compounds and omeprazole (OM), the effects of increased pressure and temperature gradients due to frictional heating was studied. Pressure was the dominating effect and increased pressure gave increased retention times.



Above: Individual contributions from pressure (left) and temperature (right) gradients on the retention factor.
Below: Comparison of the individual contributions with the obsreved results (left) and temperature profile in the column for 800 bar pressure drop (right).

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