SMB Online Detection with Spectral Deconvolution for Achiral Separations

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Introduction

Simulated Moving Bed (SMB) is an established tool for enantiomeric separations and has recently gained traction as an important tool for binary separation of achiral mixtures. Typically, SMB separations are optimized based on internal profiles from offline analysis. It is a time-consuming and tedious process. We will demonstrate an online FiberDAD™ spectrophotometer along with a custom-made flow cell and deconvolution software (AutoSMB) for near real-time monitoring of SMB profile. The software can deconvolve multiple peaks, as long as peaks have sufficiently different spectra. Our main goal is a convenient, effective and efficient approach for SMB achiral purification, in areas of impurity isolations and low-level impurities removal.

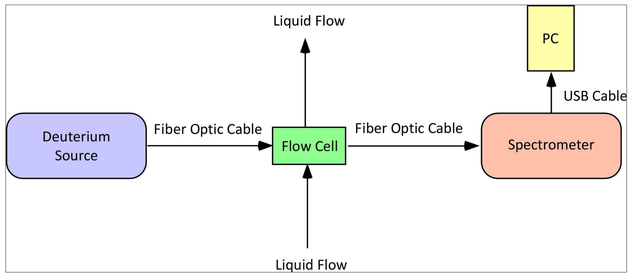

Figure 1. FiberDAD™ spectrometer configuration

Experimental

- A Micro SMB system (NovaSep, Nancy, France) with five pumps (Raffinate, Extract, Feed, Eluent, and Recycle).
- A FiberDAD™ miniature fiber optic spectrometer with inline flow cell (0.5 mm path length) was installed before the recycling pump in the loop.
- AutoSMB, a custom deconvolution software (written in Java and developed by Necmi Bugdayci) was used for data processing, display, and deconvolution.
- Six SMB70-20 columns (10 mm ID x 100 mm, 20 um, Fuji Silysia) were connected in series (1:2:2:1 configuration). Initial conditions were generated from Novasep Help software and refined with a few adjustment runs for purity and yield recovery optimization.
- For the proof-of-concept, the mobile phase was 75/25 (v/v) acetonitrile/methanol. The feed concentration was 50mg/L of 1:1 (w:w) biphenyl and caffeine in the mobile phase. The five flow rates: Qrecycle: 13.98 ml/min; Qfeed: 0.5 ml/min; Qeluent: 8.0 ml/min; Qraffinate: 4.0 ml/min; Qextract: 4.5 ml/min; with a switch time DT: 0.71 min.
- For the case study, the mobile phase was 35/65 (v/v) ethanol/heptane. The feed concentration was 0.5 mg/ml of the crude sample in the mobile phase. The five flow rates: Qrecycle: 8.52 ml/min; Qfeed: 1.64 ml/min; Qeluent: 2.68 ml/min; Qraffinate: 2.01 ml/min; Qextract: 2.31 ml/min; with a switch time DT: 1.21 min.

Results and Discussion

Proof-of-Concept

A mixture of caffeine and biphenyl was used as feed solution for the proof-of-concept study. Individual spectra of each compound were collected from a single HPLC injection and imported to the AutoSMB. SMB process data was collected from the inline FiberDAD™ spectrometer and deconvolved by AutoSMB. We developed a new chemometric algorithm as the commonly used principal component analysis (PCA) provided marginal success. Figure 2 shows calculated (deconvolved) internal profiles (left) compared with the internal profiles generated from offline analysis (right). Both profiles agree well, therefore, a case study was initiated to further refine our system.

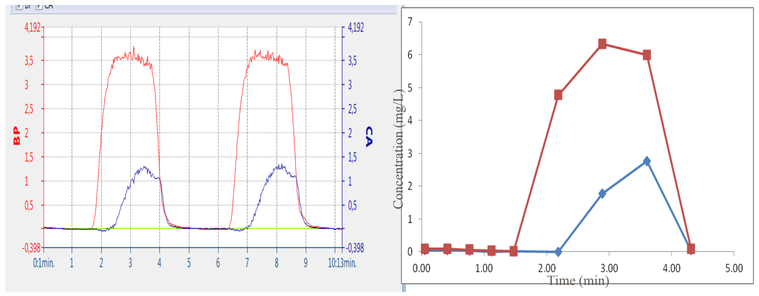

Figure 2. Comparison of deconvolved spectra and the internal profile. Red lines denote biphenyl and blue lines represent caffeine.

Case Study

A separation with GSK compounds was used to further fine-tune the deconvolution algorithm. The goal was to isolate a minor impurity for structure elucidation and reference material. Peak A in Figure 3 is the desired component in the mixture, which has a quite different spectrum compared to the major component, peak B.

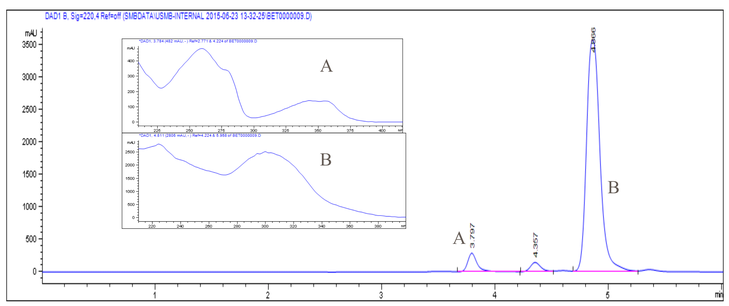

Figure 3. HPLC separation of the crude sample with the spectra of the two main peaks. HPLC conditions: column: SMB 70-5, 5um, 4.6x250mm; mobile phase: 35/65 (v/v) EtOH/Heptane; flow rate: 1 ml/min; detection: 220nm.

Figure 4 is the online profile of the initial operation parameters based on the predictions from NovaSep Help software.

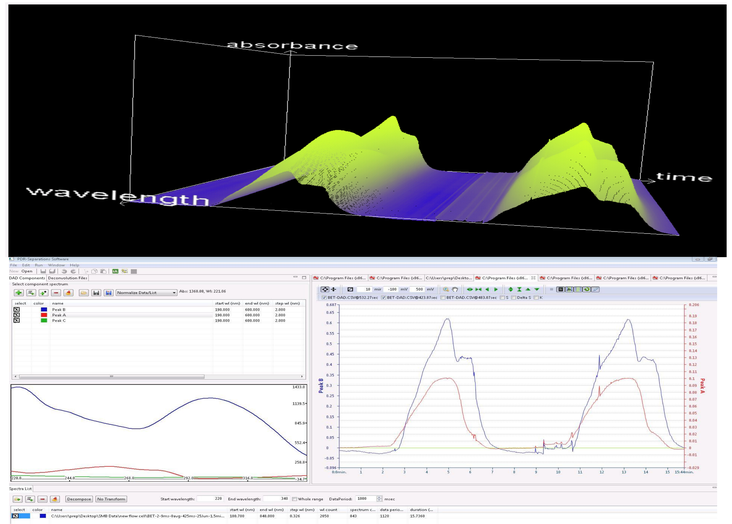

Figure 4. 3D spectra data (top) and deconvolved data (bottom) using initial SMB parameters. Red line represents peak A and blue line is peak B.

We used the deconvolved results to optimize the SMB process further and were able to achieve both raffinate and extract purity over 90%. The internal profile was manually collected and compared to deconvolved data with good agreement (Figure 5).

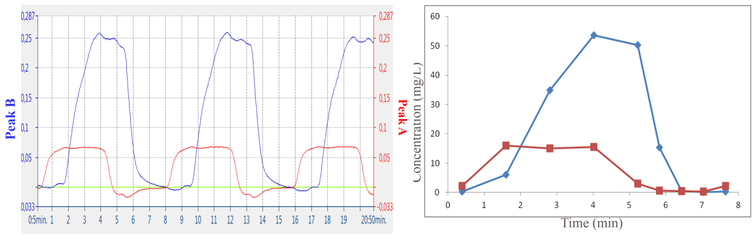

Figure 5. Comparison of deconvolved spectra and the internal profile using optimized SMB parameters. Red line represents peak A and blue line is peak B.

Conclusions

By using the online detection/deconvolution technique we were able to shorten the optimization time of the SMB process and avoiding the tedious manual sample collections. Our future work will include full integration of detection and deconvolution softwares to provide real-time data. We expect that FiberDAD™ with AutoSMB deconvolution software will become an important tool for monitoring and controlling SMB achiral separation processes.

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