Control of simulated moving beds and advanced multi-column processes for chiral separations

Author(s):
Langel, Christian

Publication Date:
2010

Permanent Link:
https://doi.org/10.3929/ethz-a-006103267

Rights / License:
In Copyright - Non-Commercial Use Permitted
CONTROL OF SIMULATED MOVING BEDS
AND ADVANCED MULTI-COLUMN PROCESSES
FOR CHIRAL SEPARATIONS

Dissertation submitted to the
ETH ZURICH

for the degree of
DOCTOR OF SCIENCES

presented by
Christian Langel
Chemical Engineer, TU Munich

born on November 16\textsuperscript{th}, 1979
Citizen of Germany

Accepted on the recommendation of
Prof. Dr. Marco Mazzotti (ETH Zurich), examiner
Prof. Dr. Massimo Morbidelli (Politecnico di Milano), co-examiner
Dr. Stefanie Abel (Carbogen-Amcis), co-examiner

Zurich 2010
Abstract

The production of single enatiomer drugs requires advanced separation tech-
niques to meet the strict regulations on the purity requirements dictated by
regulatory agencies such as the Food and Drug Administration (FDA) and
the European Medicines Agency (EMEA). Over the last years multi-column
chromatographic processes, like simulated moving bed (SMB), have become
a well established technique for the separation of fine chemicals and produc-
tion of single enantiomer drugs. This is especially true for the purification of
species characterized by low selectivities, i.e. difficult to separate, such as chi-
ral molecules for single enantiomer drug development. There are two striking
advantages of the SMB technology. Firstly, compared to batch chromatogra-
phy, it has a higher productivity and lower solvent consumption, which results
in lower production costs. Secondly, and even more important in pharmaceu-
tical industry, SMB separation processes can be rapidly and reliably scaled
up from drug development to industrial production scale, a very important
feature in an industry where time to market is very crucial. However, when
operating small scale SMB units the extra-column dead volume might become
comparable to the column volume and one has to consider its effect on the
separation performance of the unit.

This thesis presents guidelines and rules to calculate the extra-column dead
volume for the different sections of an SMB unit and it is demonstrated how
to account for it in the calculation of the operating parameters. The rules are
validated through detailed simulations and experiments, separating a racemic
mixture of an Allene into its pure enantiomers.

In production scale SMB units the effect of extra-column dead volume can be
neglected. Nevertheless, the full exploitation of the economic advantages of
SMB units is still an open issue due to the uncertainties about the physical
properties of the mixture to be separated. Therefore, in operational practice,
SMB units are most often operated conservatively to guarantee the purity
specifications enforced by the regulatory agencies.
To address this issue different control schemes have been proposed in literature but in general the presented concepts depend on the availability of accurate physical data about the mixture to be separated, i.e. the complete adsorption isotherm. Obtaining these data can be a time consuming task which is in conflict with realizing a short time to market. This limitation was overcome by the ‘cycle to cycle’ control concept developed at ETH Zurich, which requires only minimal information about the system to be separated, namely the Henry constants of the compound to be separated and the average overall void fraction of the columns installed in the SMB unit. The proposed control concept is based on linear model predictive control (MPC) and was implemented experimentally for the separation of guaifenesin enantiomers making use of optical detectors, i.e. polarimeter, UV detector, to determine the feedback information required by the controller. The performance of the controller depends directly on the accuracy of the feedback information from the plant and it was found that the measurements of the polarimeter are greatly affected by pressure fluctuations in the measuring cell and by impurities in the system.

Therefore, one of the aims of this thesis was to develop a new automated on-line HPLC monitoring system for chiral separations that overcomes the limitations of the old one. The performance of the new monitoring system was successfully tested for the separation of a racemic mixture of guaifenesin enantiomers at low feed concentrations. In a next step for the first time the ‘cycle to cycle’ optimizing controller was experimentally applied for a nonlinear chiral separation of guaifenesin enantiomers, i.e. at high feed concentrations. To benchmark the performance of our controller various case studies were carried out ranging from pump disturbances to changes in the feed mixture during an ongoing separation experiment. The experimental results clearly validate the most valuable asset of the ‘cycle to cycle’ controller: the controller can meet the product specifications and improve the separation performance with the knowledge of the linear adsorption behavior only, even if the separation at stake is governed by an unknown nonlinear adsorption isotherm. This is an important achievement since it is well known that the productivity of an SMB unit increases with the total feed concentration and therefore, this
regime is the most interesting one for industry, particularly for pharmaceutical applications and chiral separations. Moreover, the time consuming task of determining the complete adsorption isotherm for a new separation problem becomes unnecessary which helps to realize a short time to market. The ‘cycle to cycle’ controller together with the new automated on-line HPLC monitoring system offer a fast and reliable way to set up new chiral SMB separation. To demonstrate this important feature of our control concept the separation of a new compound was carried out, namely the separation of Troeger’s Base enantiomers on the stationary phase CHIRALPAK™ AD using pure ethanol as mobile phase. It is shown that the proposed control concept is simple enough to be implemented quickly and reliably for a new separation campaign.

Another direction in the research field of advanced multi-column chromatographic processes aims at developing modified SMB schemes to improve the separation performance yet guaranteeing the specified purity specifications. One of these modifications is presented in this thesis, the intermittent simulated moving bed (I-SMB) process. This process is based on intermittent feed and product withdrawal and was first patented by the Nippon Rensui company under the name improved SMB (ISMB) process. This thesis presents the principle of the I-SMB process, the design criteria in the frame of the triangle theory, and the successful experimental implementation for the separation of the chiral compound (RS,RS)-2-(2,4-difluorophenyl)butane-1,2,3-triol, an important intermediate in the production of different antifungal drugs.
Zusammenfassung


In grösseren SMB-Anlagen, wie sie für die Produktionsphase verwendet werden, kann der Effekt des Totvolumens auf die Trennleistung vernachlässigt werden. Trotzdem ist die volle Ausnutzung der wirtschaftlichen Vorteile welche
die SMB Technologie bietet aufgrund der Unsicherheiten bei der Bestimmung der physikalischen Eigenschaften der zu trennenden Mischung immer noch schwierig. Aus diesem Grund werden SMB-Anlagen in der Regel unter konserativen Betriebsbedingungen gefahren um die Produktspezifikationen, die von den Regulierungsbehörden verlangt werden, zu gewährleisten.


Ein Ziel dieser Arbeit war es, ein neues automatisches online Überwachungssystem zu entwickeln, welches auf Hochleistungsflüssigkeitschromatographie (HPLC) basiert und in der Lage ist, die "feedback information" für den Regler präzise und zuverlässig zu bestimmen und damit die Grenzen des alten Systems überwindet. Die Leistungsfähigkeit des neuen online HPLC Überwachungssystems wurde experimentell getestet indem die Trennung

Eine andere Richtung im Bereich der Forschung über Mehr-Kolonnen chromatographischer Trennprozesse zielt darauf ab, neue Prozesse zu entwickeln,
welche eine höhere Trennleistung erreichen dabei aber immer noch die geforderten Produktspezifikationen erfüllen. Einer dieser modifizierten Prozesse wird in dieser Arbeit vorgestellt, der ”Intermittent Simulated Moving Bed” (I-SMB)-Prozess. Dieser Prozess basiert auf partieller Zufuhr des Feedstromes und Abfuhr der Produktströme und wurde zunächst von der Firma Nippon Rensui unter dem Namen ”Improved SMB” (ISMB)-Prozess patentiert. Die vorliegende Arbeit erläutert das Prinzip des I-SMB-Prozesses, erklärt die Design Kriterien im Rahmen der ”Triangle Theory”, und präsentiert die erste experimentelle Umsetzung für die Trennung der chiralen Verbindung (RS,RS)-2-(2,4-difluorophenyl)butane-1,2,3-triol, ein wichtiges Zwischenprodukt bei der Herstellung von verschiedenen Antimykotika.