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Integration of simulated moving bed chromatography and enzymatic racemization for the production of single enantiomers

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HIGHLIGHTS

- Proof of concept: Integrated operation of enzymatic racemization and chiral SMB.
- "From racemate to single enantiomer" process with theoretically 100% yield.
- Thorough process analysis conducted by model-based optimization.
- Different optimal operating points identified depending on costs of auxiliaries.
- Cost analysis identified SMB separation as bottleneck for more efficient production.

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ABSTRACT

Integration of enantioseparation by simulated moving bed (SMB) and mild enzymatic racemization enables the production of single enantiomers from a racemic mixture in theoretically 100% yield and hence overcomes the 50% yield limitation of conventional SMB processes. We implemented such a process consisting of a Chirobiotic TAG column-SMB, an amino acid racemase-containing enzyme membrane reactor, and a nanofiltration unit for concentration of the distomer-enriched SMB raffinate prior to racemization on lab-scale for the production of enantiopure D-methionine. The integrated process scheme was operated continuously for over 30 h without significant variations in product concentration and purity and with a yield of 93.5%, demonstrating the feasibility of this integrated process concept. Furthermore, a rational analysis of the integrated process on the basis of a short-cut model was conducted. The process model consists of a true moving bed equilibrium stage model to represent the SMB, a continuous stirred tank reactor model with reversible Michaelis–Menten kinetics to represent the enzyme membrane reactor, a nanofiltration model and feed node mass balances, and enabled the identification of optimal operating points (flow rate ratios, enzyme concentration) at a variety of process specifications and objectives. Optimal operating points were calculated for different cost distributions between the applied materials such as stationary phase, enzyme, solvent, and nanofiltration membrane. By assigning plausible pricing data and lifetimes to the respective materials, variable costs for the specific process considered in this work were estimated.

1. Introduction

As the biological activity of chemical compounds can be drastically different depending on their stereoconfiguration, methods to obtain such molecules in enantiopure form are of high importance. The preferred method to obtain enantiopure preparations largely depends on the specific molecule to be synthesized. Efficient synthesis routes starting from cheap enantiopure precursors are often not readily available, and, despite the rapid progress in the field (Ager et al., 2012; Trost, 2004), the development of an asymmetric synthesis can be time consuming due to the challenging chemistry and the complexity of the development process (Blaser, 2002; Federsel, 2009). Consequently, a reaction sequence of less complicated non-enantioselective synthesis steps resulting in a racemic precursor and its subsequent enantiospecific resolution constitutes often the preferred synthetic strategy, despite the fact that the theoretical yield is limited to 50%

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Nomenclature

A_{NF}	membrane area (cm^2)
b	Langmuir constant ($L\,g^{-1}$)
c	concentration in fluid phase ($g\,L^{-1}$)
DR	desorbent requirement ($L\,kg^{-1}$)
ER	enzyme requirement ($kg\,day\,kg^{-1}$)
F	objective function ($kg\,day\,kg^{-1}$)
k_{cat}	catalytic constant of racemization (min^{-1})
K_M	Michaelis–Menten constant ($g\,L^{-1}$)
m	flow rate ratio (dimensionless)
M	mass (kg)
MR	membrane requirement ($m^2\,day\,kg^{-1}$)
N	number of stages (dimensionless)
n_c	number of SMB columns (dimensionless)
P	price ($\$\,kg^{-1}$ or $\$\,m^{-2}$)
PC	production cost ($\$\,kg^{-1}$)
PR	specific productivity ($kg\,kg^{-1}\,day^{-1}$)
Pu	purity SMB outlets (%)
Q	volumetric flow rate ($mL\,min^{-1}$)
q	concentration in solid phase ($g\,L^{-1}$)
q_s	saturation capacity ($g\,L^{-1}$)
r	reaction rate ($g\,L^{-1}\,min^{-1}$)
REJ	rejection (dimensionless)
t^*	switch time (min^{-1})
TP	throughput ($kg\,day^{-1}$)
V_C	column volume (mL)
VCF	volume concentration factor (dimensionless)
V_D	extra-column dead volume (mL)
w	weight factor (dimensionless)
X	conversion in EMR (dimensionless)
Y	yield (dimensionless)

Greek

ε	porosity (dimensionless)
ρ	density ($g\,L^{-1}$)
Π	specific cost per time ($\$\,kg^{-1}\,day^{-1}$)
δ	feed node dilution factor (dimensionless)

Index

C	column
CSP	chiral stationary phase
$D0$	desorbent
E	SMB extract
EMR	enzyme membrane reactor
ENZ	enzyme
F	SMB feed
$F0$	process feed
i	components, 1=L-Met, 2=D-Met
j	SMB section
k	stage index
NFM	nanofiltration membrane
PER	nanofiltration permeate
R	SMB raffinate
RET	NF retentate
X	unit index

(Sheldon, 1996). Resolution can be achieved by a variety of methods including kinetic resolution and physical separation methods such as (diastereomeric or preferential) crystallization and chromatography. In particular, chiral chromatography – typically realized in continuous operating mode, such as through the simulated moving bed (SMB) technology – is widely used today for enantioseparations in the pharmaceutical sector due to the ability to design chromatographic processes rapidly and in conformity with regulations. Next, the use of SMB in chirotechnology is facilitated by an increasing selection of chiral stationary phases (CSP's) that enable the enantioseparation of the majority of racemates (Chankvetadze, 2012; Francotte, 2001).

In recent years a number of integrated process concepts have been proposed in order to increase productivity and to overcome the yield limitation of chromatography-based resolution processes. The optimization potential results from the fact that the throughput in chromatography can be increased when purity requirements are reduced (Blehaut and Nicoud, 1998). This was investigated in more detail by simulations, e.g. for the coupling of chromatography and crystallization with recycling of the residual mother liquor (Amanullah and Mazzotti, 2006; Gedicke et al., 2007), where the eutomer is first enriched to a suitable purity by a chromatographic step, and subsequently crystallized.

The yield limitation can be addressed similar to well established dynamic kinetic resolution processes (Ward, 1995) by racemization of the distomer. This can be realized inside of an SMB unit, e.g. by a pH gradient (Palacios et al., 2011), with side reactors as part of a multi-column chromatography process (Hashimoto et al., 1983), by integration of crystallization and racemization (Würges et al., 2009), or as a combination of chromatographic separations with an external reactor (Nimmig and Kaspereit, 2013).

In fact, a number of process combinations of chromatography, crystallization and racemization can be envisioned (Kaspereit et al., 2012). For selection of the optimal process structure a three step procedure has been proposed. First, a pre-selection of feasible processes based on qualitative criteria such as the availability of a racemization procedure and the type of phase diagram is conducted. In a next step the process variants are evaluated with short-cut models, followed by the process optimization of the most feasible concept (Kaspereit et al., 2012). Recently, the experimental implementation of a process for the production of 2,6-pipecoloxylidide by combining steady state recycling chromatography, crystallization, and racemization induced by an organometallic catalyst was reported (von Langermann et al., 2012). However, the process was operated such that the individual units were not directly coupled to each other for continuous operation.

Here we report the design and implementation of one of the promising process options in continuous operating mode: the integration of chiral SMB, recycle concentration by nanofiltration (NF), and enzymatic racemization for the production of enantiopure compounds in high yield (Fig. 1). As a model problem the production of D-methionine (D-Met) from racemic D,L-Met was chosen, since amino acids represent an important class of intermediates in the fine chemical industry (Leuchtenberger et al., 2005). Please note that such an installation can flexibly produce both enantiomers in high yield, depending only on which of the available ports is used for product removal. In principle, the NF unit can be placed at different positions in the process (Martin et al., 2015; Siitonen et al., 2015). The selected position has distinct advantages for EMR operation as it features the largest concentration difference and residence times.

Due to the direct coupling of units the same solvent needs to be applied in all unit operations. Hence, the design and optimization of a fully integrated production system requires a detailed