



## Experimental validation of a new integrated simulated moving bed process for the production of single enantiomers

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### ABSTRACT

A new integrated 3-zone simulated moving bed (SMB) concept with internal racemization reaction was suggested recently for the production of single enantiomers from racemic mixtures [1,2]. The process utilizes an internal gradient to trigger the racemization within a single zone. It can deliver the pure enantiomer and outperforms conventional technologies. In this contribution, the concept is validated experimentally for the separation of a model system compound. The results demonstrate that the new concept is capable of producing a single enantiomer with purity, yield and conversion of 100%.

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### 1. Introduction

Enantiomers constitute pairs of stereoisomers that are mirror images of each other. As regards their physiological impact, often only one enantiomer exhibits the desired effect while the other is ineffective or even harmful. Producing directly the desired enantiomer by chemical methods [3] as enantioselective catalysis, biocatalysis, or from enantiopure building blocks is, although desirable, frequently expensive due to long-lasting development efforts or expensive raw materials. Often developed syntheses are not fully enantioselective, and sometimes they are infeasible. Hence the alternative of obtaining single enantiomers from racemic mixtures plays a major role for companies that produce pharmaceuticals, fine chemicals, nutrition additives, or fragrances. The drawback of producing the racemate, which is the 50/50 mixture of both enantiomers, is that it necessitates a subsequent separation. Several techniques are available for this, for example, crystallization of diastereomeric salts, dynamic kinetic resolution, or chromatography. In particular continuous simulated moving bed (SMB) chromatography has been established in recent years for many enantioseparations on the industrial scale [4]. However, without a simultaneous interconversion of the counter-enantiomer, the recovery yield

of separation-based approaches is inherently limited to 50% only.

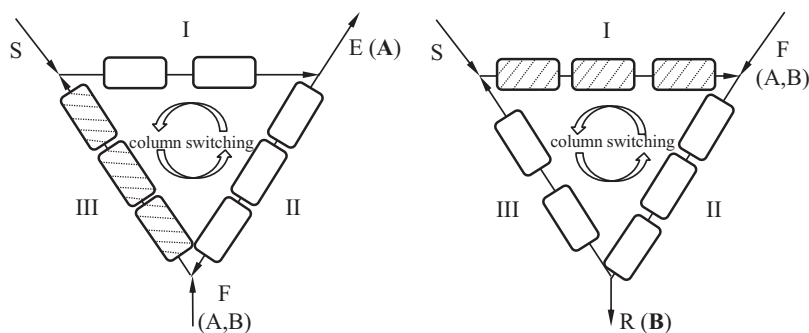
Recently, investigations of several new integrated process concepts combining racemization reaction and continuous chromatography were reported [1,2]. Theoretically, these processes can produce single enantiomers with yield and conversion of 100%. They can outperform the conventional engineering concept of flowsheet integrated processes (reactor-separator-recycle) and processes with side reactors due to an effect denoted as reaction-assisted regeneration. An integrated closed-loop 3-zone SMB unit was identified as a particularly attractive process idea. This scheme combines good performance with a relatively simple setup. It contains no external solvent removal devices or recycle streams. The racemization reaction is optimally performed within the regeneration zone. Fig. 1 shows schematically the suggested 3-zone processes for the production of the more (*A*) and less adsorbed component (*B*), respectively.

In order to fully exploit the potential of the scheme the racemization reaction needs to be performed only in a single specific zone of the SMB. This corresponds to zone *III* for the production of the stronger retained component *A*, and zone *I* for the production of the weakly adsorbing enantiomer *B* (see Fig. 1). In practice, the reaction could be controlled by gradients of, for example, temperature, pH, modifiers or additives, depending on the specific chemical system under consideration [1].

In this work, the new integrated process is validated experimentally for the production of the pure less retained enantiomer *B*

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**Fig. 1.** Integrated 3-zone SMB processes combining chromatographic separation and racemization reaction, as reported in [1]. Hatched columns denote chromatographic reactors. Left – setup for the production of the strongly retained component A. Reaction takes place within zone III; right – setup for the production of the weakly retained component B. Reaction takes place within zone I. F – feed, S – solvent, E – extract, R – raffinate.

(Fig. 1, right). It should be noted that this is a particularly interesting case. The only concept that is comparable to this setup is the partially integrated Hashimoto process [5], which utilizes side reactors. To the authors' best knowledge, Hashimoto processes or similar concepts have never been applied to interconvert an isomeric mixture into the weaker adsorbing component only. As demonstrated in [2] this would in principle be possible, but requires a large number of columns and reactors. The schemes in Fig. 1 provided a better performance than the Hashimoto concept regardless of the target component, in particular for high product purity.

The enantiomers of chlorthalidone (CTD) will serve as experimental model system. In this particular example, an internal gradient of the pH value is used to control the reaction. Therefore, at first, the effect of the pH on the racemization kinetics and on the adsorption behavior is investigated. The obtained parameters are applied in a detailed mathematical process model used for designing the process. A semi-preparative SMB unit is used under pH-gradient operation to produce the less retained enantiomer in the validation experiments.

The paper is organized as follows. First, the mathematical model is explained. Afterwards, the chemicals, instrumentation and experimental strategy are described. In Section 4 the results of the parameter measurements and SMB experiments are presented and discussed.

## 2. Theory

A conventional equilibrium stage model is applied to simulate the integrated SMB process. The mass balances for the two components in the fluid and solid phases within each stage read as:

$$\frac{dc_i^{k,n}}{dt} + F \frac{dq_i^{k,n}}{dt} = \frac{Q^z}{V\varepsilon} (c_i^{k-1,n} - c_i^{k,n}) + \nu_i r^{k,n}, \quad (1)$$

where the indices  $i=A, B$  denote the component,  $k=1, \dots, N_s$  the stage,  $n=1, \dots, N_c$  denote the column, and  $z=I, \dots, N_z$  the corresponding zone of the SMB unit.  $c_i$  and  $q_i$  are the liquid and solid phase concentrations,  $V$  is the volume of a stage,  $\varepsilon$  the porosity and  $F=(1-\varepsilon)/\varepsilon$  is the phase ratio.  $Q$  is the volumetric flow rate of the fluid phase. The axial dispersion is accounted for by the number of stages,  $N_s$  [6].

The last term in Eq. (1) describes the chemical reaction.  $r$  is the reaction rate and  $\nu_i$  is the stoichiometric coefficient. The chemical reaction is taking place in the liquid phase. For the reaction rate in Eq. (1) holds:

$$r^{k,n} = k(\text{pH}) [c_A^{k,n} - c_B^{k,n}], \quad (2)$$

with  $k(\text{pH})$  the rate constant of the reaction as a function of pH.

The relation between the solid and the liquid phase concentrations in Eq. (1) is given by the adsorption equilibrium. The adsorption behavior of CTD was reported in a previous publication [7] for the same stationary phase using a bi-Langmuir adsorption isotherm model:

$$q_i = \frac{q_1^s(\text{pH})b_1c_i}{1+b_1(c_A+c_B)} + \frac{q_{i,2}^sb_{i,2}c_i}{1+b_{A,2}c_A+b_{B,2}c_B}, \quad i=(A, B). \quad (3)$$

According to the Pasteur principle, Eq. (3) describes competitive adsorption of the two solutes ( $A, B$ ) on two different types of adsorption sites of the solid: type 1 (achiral) and type 2 (chiral);  $q_1^s$  and  $q_{i,2}^s$  are the saturation capacities for the corresponding sites, respectively. Here, the integrated SMB unit is operated using pH gradients. For the model system CTD it was found useful to describe the dependency of the adsorption behavior on the pH value in the term  $q_1^s(\text{pH})$ . This corresponds to cases where the capacity of the achiral sites depends most strongly on the pH [8].

The SMB configuration used for the validation experiments is a four column 2-zone open-loop system for the production of the weakly retained enantiomer (see Fig. 2). Zone I performs the solid phase regeneration and the racemization reaction, while zone II is responsible for the separation. The regeneration of the liquid phase is carried out in two external zones as shown in Fig. 2. In contrast to a 3-zone system with closed loop, in this setup the third zone and the recycle stream are omitted for the sake of simplicity. Furthermore, analyzing the effluents of the external zones allows us to identify possible issues such as incomplete regeneration or side product formation.

For this system, the corresponding boundary conditions are:

$$\begin{aligned} \text{if } n=1: & \quad Q^S c_i^S = Q^I c_i^{0,1}, \\ \text{if } n=3: & \quad Q^I c_i^{N_s, n-1} + Q^F c_i^F = Q^{II} c_i^{0,n}, \\ \text{if } n=2, 4: & \quad c_i^{N_s, n-1} = c_i^{0,n}, \end{aligned}$$

where  $c_i^{0,n}$  corresponds to the concentration of component  $i$  entering column  $n$ .

The dimensionless zone flow rate ratios  $m^z$  are used as design variables for each zone  $z$  of the SMB:

$$m^z = \frac{Q^z t^* - \varepsilon V_c}{(1-\varepsilon)V_c}, \quad (4)$$

where  $V_c$  is the volume of a chromatographic column, and  $t^*$  is the switching time.

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