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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%.

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-enanantiomer, 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 process es 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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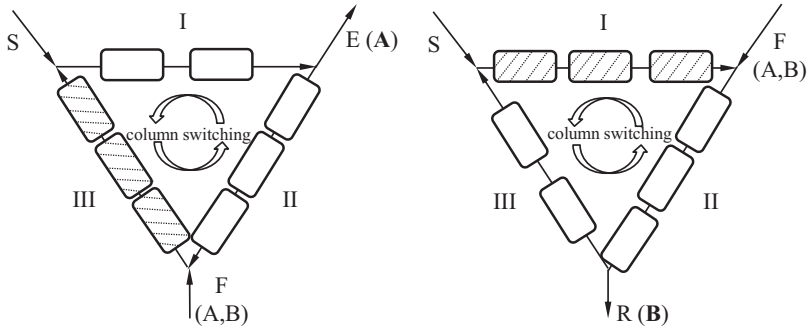

Fig. 1. Integrated 3-zone SMB processes combining chromatographic separation and racemization reaction, as reported in [1]. Hatched columns denote chromatographic reactors. Left – setup for the production of the strongly retained component *A*. Reaction takes place within zone *III*; right – setup for 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 experients 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:

$$\frac{\mathrm{d}c_i^{k,n}}{\mathrm{d}t} + F\frac{\mathrm{d}q_i^{k,n}}{\mathrm{d}t} = \frac{Q^z}{V\varepsilon}\left(c_i^{k-1,n} - c_i^{k,n}\right) + \nu_i\, r^{k,n}, \tag{1}$$

where the indices $i = A, B$ denote the component, $k = 1, \ldots, N_s$ the stage, $n = I, \ldots, N_c$ denote the column, and $z = I, \ldots, N_z$ 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, ε 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 ν_i is the stoichiometric coefficient. The chemical reaction is taking place in the liquid phase. For the reaction rate in Eq. (1) holds:

$$r^{k,n} = k(\mathrm{pH})\left[c_A^{k,n} - c_B^{k,n}\right], \tag{2}$$

with k(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:

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

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(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:

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

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:

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

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

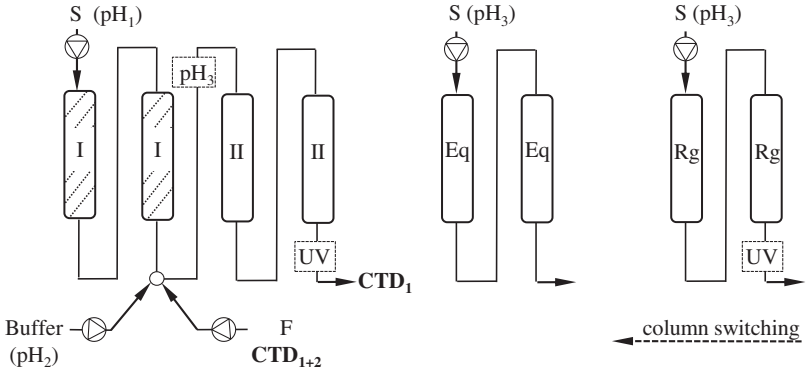

Fig. 2. Open-loop experimetal setup of the 2-zone integrated SMB for producing the less retained enantiomer CTD_1. Zone *I*, at pH_1 performs simultaneous reaction and separation benefiting from the effect of reaction-assisted regeneration [1]. Zone *II*, is responsible for the chiral separation at pH_3. Additional zones are implemented to equilibrate (Eq) and regenerate (Rg) the columns before re-entering zone *II*.

The performance parameters product purity, Pu^R, conversion, X, and recovery yield, Y, are defined as follows:

$$Pu^R = \frac{c_B^R}{c_A^R + c_B^R} \times 100, \quad (5)$$

$$X_A = \frac{c_A^F Q^F - c_A^R Q^R}{c_A^F Q^F} \times 100, \quad (6)$$

$$Y = \frac{(c_B^F + c_A^F)Q^F}{(c_B^R + c_A^R)Q^R} \times 100. \quad (7)$$

The dynamic simulations of the batch and SMB systems were performed using the simulation enviroment DIVA [9,10]. For the SMB unit, the periodic switching of the ports in the direction of the liquid flow was implemented with a Petri net routine. The dynamic simulation reaches a cyclic steady state (CSS) after a certain number of cycles. A stopping criterion based on a Poincaré map [11] was used to identify the CSS in each dynamic simulation.

3. Experimental

3.1. Chemicals

The enantiomers of chlorthalidone (CTD), (*RS*)-2-chloro-5-(1-hydroxy-3-oxo-2,3-dihydro-1*H*-isoindol-1-yl)benzene-1-sulfonamide, were used as model system for the experimental validation of the integrated SMB process. They were purchased from Sigma–Aldrich (Steinheim, Germany) and from Molekula (Gillingham, Dorset, UK). Two buffer systems were used for the different ranges of the pH value applied: Bis-Tris propane (BTP) (Sigma–Aldrich, Munich, Germany) and triethylammonium acetate (TEAA), 1 mol/L (Merck, Darmstadt, Germany). Further, acetic acid (AA), 100%, triethylamine (TEA), and HCl, 32%(v/v) (all from Merck, Germany) were required to prepare solutions at different pH values. Methanol (MeOH) at gradient grade LiChrosolv Reag. Ph Eur (Merck, Darmstadt, Germany) was used as a non-retained tracer compound. All aqueous solutions were prepared with ultrapure water prepared in-house using a Millipore Milli-Q gradient system (Molsheim, France).

3.2. Sample analysis by HPLC

The analysis of samples was carried out by HPLC using a Ultimate 3000 series chromatograph from Dionex (Idstein, Germany) controlled by the software Chromeleon. UV detection was set to 260 nm. A 200 mm × 4 mm Nucelodex-β-OH (Macherey-Nagel, Düren, Germany) column with an average particle size of 5 μm was used for the analysis, which was performed at 10 °C, a flow rate of 0.75 mL/min and an injection volume of 100 μL using TEAA at pH 5.0. MeOH/TEAA (aq.) (40/60, v/v) was used as solvent.

3.3. Racemization kinetics

The kinetic constant k of the racemization reaction in Eq. (2) had to be determined as a function of the pH. As already found by Lamparter et al. [13], the rate of the racemization reaction of CTD depends significantly on the pH value between pH = 2 and 6. They observed a minimum for the rate constant k at pH ≈ 3 and suggested a change in the reaction mechanism for acidic and basic enviroments as origin of this behavior. Here, we extend this range further by performing measurements between pH = 3.0 and 9.0 in order to increase the potential of a pH gradient to be applied in the investigated process.

Samples of pure CTD enantiomer were required for the batch experiments performed. For this purpose, a chromatographic column, Nucleodex-β-OH with 10 mm diameter and 125 mm length, was connected to the HPLC. Relatively large injections (2000 μL) of racemic CTD 0.4 g/L were injected and the fractions of highly purified S-enantiomeric form of CTD (Pu > 98 %) were recovered. The obtained S-enantiomer ic solutions were diluted in two different buffer systems (50 mM) to cover the whole pH-range of interest. TEAA was used for solutions at pH = 3.00, 4.05, 5.00, and 5.80, while BTP was used for mixtures at pH = 5.30, 5.95, 6.90, 8.10, and 9.00. Afterwards, these solutions were prepared to racemize at ambient temperature.

The experiments were performed in batch mode, using vials of approximately 15 mL volume. Samples were taken at different times and immediately frozen and stored at −18 °C. Each sample was analyzed later by HPLC to determine the extent of the racemization reaction. The time during which the samples were handled in liquid form was minimized in order to minimize possible errors due to spontaneous racemization. This attempt was successful, as indicated by negligible deviations between the purities of the fractionated original solutions and the samples taken at the beginning of the racemization experiments.

3.4. Adsorption behavior

Semi-preparative columns (16 mm × 65 mm) were used for the isotherm parameter determination as well as for the SMB experiments. The columns provided from Macherey-Nagel are packed with the same chiral stationary phase as the analytical column (same batch).

Classical methods to determine isotherm parameters experimentally are not suitable under reactive conditions. Therefore, an

Table 1
System parameters of the reactive 2-zone SMB process.

L (mm)	d_c (mm)	ε (−)	c^F (g/L)	t_s (min)	T (°C)
65	16	0.681	0.5	7.0	25

inverse method ('peak fitting') was applied accounting also for the injection profile [12].

Column porosity was determined by a 20 μL injection of MeOH as a non-retained tracer compound. The flow rate was 2 mL/min. The column void volume was determined equal to 8.9 mL and the porosity $\varepsilon = 0.681$. The number of theoretical stages N_s in Eq. (1) was determined at a flow rate of 6 mL/min. From 20 μL injections of racemic CTD with a concentration of 0.05 g/L (rac.) an average value of $N_s = 750$ was obtained calculating the first and the second moments of the peaks. No significant influence of pH on N_s was observed.

For the isotherm determination MeOH/BTP (aq.) 50 mmol/L (40/60, v/v) was used as solvent. 2000 μL samples of racemic CTD in the aqueous BTP solution were injected at five different pH values (5.3, 6.0, 7.0, 8.0 and 9.0) adjusted using HCl. The flow rate was adjusted to 6 mL/min and the temperature was set to 25 °C. The concentration of racemic CTD was equal to 0.5 g/L corresponding to the maximum solubility in the used mobile phase composition.

3.5. SMB experiments

For the experimental validation of the new concept, the setup in Fig. 2 was equipped with eight columns. The SMB unit used is a CSEP C916 64 port SMB unit (Knauer, Berlin, Germany). This valve is designed for up to 16 column slots. Thus, the number of columns needs to be a divisor of 16 to perform symmetric switching conditions. It should be noted that, in principle, only three columns would be sufficient for the implementation of this process: one for the separation, one for the reaction and one for the equilibration/regeneration.

Five HPLC pumps (Knauer, Berlin) equipped with two 10 mL and three 50 mL pump heads, were used. Further, two UV detectors, model K-2600 (Knauer) were used at 1 Hz and 260 nm. The data from the UV detectors were monitored using the software EuroChrom2000 (Knauer). An Amersham Biosciences (now GE Healthcare, Freiburg, Germany) UPC-900 pH detector was used for inline pH measurement. Other parameters relevant for the experiments are summarized in Table 1.

The experiments were carried out at ambient temperature (25 °C). The product samples collected were cooled down rapidly by collecting them in an ice bath to stop racemization and analyzed inmediately by HPLC.

4. Results and discussion

4.1. Model parameters

In this section, the racemization kinetics and the adsorption isotherms are investigated as functions of the pH value. Appropiate simple models are suggested to describe the corresponding parameter dependencies.

4.1.1. Racemization kinetics

The reaction rate of the racemization of CTD enantiomers is influenced strongly by the temperature [7]. Thus, in principle, the integrated SMB process could be realized by temperature gradient since the kinetic constant changes by approximately a factor of 500 between 10 °C and 60 °C. However, for CTD, pH gradients are more attractive since they can provide an even stronger modulation of the racemization rate constant. To be able of fully exploiting

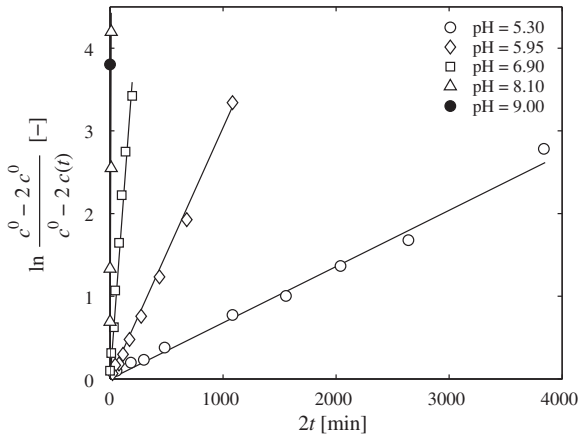

Fig. 3. Experimental results for the racemization kinetics of CTD_1 at different pH values. Lines are obtained by fitting the reaction racte constant k to Eq. (10).

the potential of such pH gradient, a large range of the pH value, between pH = 3.0 and pH = 9.0, was investigated.

The values of the kinetic constant k(pH) were obtained based on the material balance for the batch experiments:

$$\frac{dc_{CTD_1}}{dt} = k(\text{pH})[c_{CTD_1} - c_{CTD_2}] = 2k(\text{pH})c_{CTD_1} - k(\text{pH})c^0, \quad (8)$$

where the indices 1 and 2 mark the S- and the R-enantiomer, and c^0 is the initial concentration of CTD (rac.) in the mixture. After integration and linearization: re-arranging we obtain the relation

$$k(\text{pH}) = \frac{1}{2t}\text{Ln}\ \frac{c^0 - 2c^0_{CTD_1}}{c^0 - 2c_{CTD_1}(t)}. \quad (9)$$

Fig. 3 shows the concentration profiles obtained by racemizing S-CTD solutions at five different pH values (5.30, 5.95, 6.90, 8.10, and 9.00) plotted according to the terms in Eq. (10).

Fig. 4 contains all experimental results obtained for the kinetic constant k as function of the pH value for the two different buffer systems. In analogy to [13], the logarithm of k (which has unit s^{-1}) is plotted in order to cope with the scale of the values. Also, the results at different temperatures as reported in [7] are plotted for comparison. The influence of the pH on the reaction kinetics is greater than that of the temperature. Changes in the kinetic constant of factor

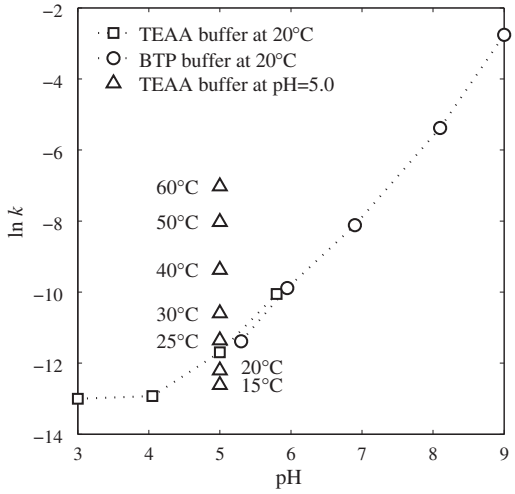

Fig. 4. Racemization kinetics for the model system chlorthalidone (CTD). Results for the thermal and pH-dependent racemization are depicted for two different buffer systems: triethylammonium acetate (□) and bis-tris propane (○). Lines are guide to the eye.

Table 2
Adsorption isotherm parameters for the enantiomers of CTD as a function of pH (as described in Eqs. (3) and (11)).

q_1^s(pH = 5.3) (g/L)	C_2 (−)	C_3 (−)	b_1 (L/g)	$q_{A,2}^s$ (g/L)	$q_{B,2}^s$ (g/L)	$b_{A,2}$ (L/g)	$b_{B,2}$ (L/g)
82.2888	10.2999	0.8034	0.0753	0.4337	3.2088	0.3554	0.6198

5600 are possible in the pH range between 5.3 and 9.0. Therefore, a pH gradient between 5.3 and 9.0 can provide an 'on and off' switching behavior of the reaction within the SMB unit. For this range, only BTP as buffer compound is required.

An exponential function can be used to describe k(pH) in Eq. (2) within this pH range:

$$k(\mathrm{pH}) = k_0 \cdot e^{C_1 \cdot \mathrm{pH}}, \tag{10}$$

where $k_0 = 5.67 \times 10^{-11}\ \mathrm{s}^{-1}$ and $C_1 = 2.28$. The coefficient of correlation was $R_c = 0.997$.

It should be emphasized that the strong influence of the pH on the racemization rate of CTD enantiomers is not an isolated scenario. More examples can be found where the pH influences significantly the kinetics of racemization [14], epimerization [15] or isomerization [16].

4.1.2. Adsorption behavior

The adsorption isotherm model in Eq. (3) contains six parameters that need to be determined experimentally. Further, the saturation capacity of the achiral sites q_1^s(pH) is considered a function of the pH value. Since classical methods for isotherm determination are not applicable under reactive conditions, the isotherm parameters were estimated numerically by applying the inverse method (for details see, e.g., [17]).

First, the injection profile of the HPLC pump needs to be characterized. Fig. 5 shows a corresponding example. The profile deviates strongly from an ideal rectangular pulse. As shown in Fig. 5, it can be modelled with sufficient accuracy by fitting it piecewise to three sigmoidal functions.

Afterwards, five samples of racemic CTD were injected at pH values equal to 5.3, 6.0, 7.0, 8.0 and 9.0. The column model was solved using the previously obtained function for the kinetic constant in Eq. (10) and the injection profile as boundary condition. An evolutionary algorithm in DIVA [10] was used to estimate the isotherm parameters minimizing the differences between calculated and experimental chromatograms. The following sigmoidal function was assumed for q_1^s(pH):

$$q_1^s(\mathrm{pH}) = \frac{q_1^s(\mathrm{pH} = 5.3)}{1 + e^{(\mathrm{pH} - C_2)/C_3}}, \tag{11}$$

with the two additional free parameters C_2 and C_3.

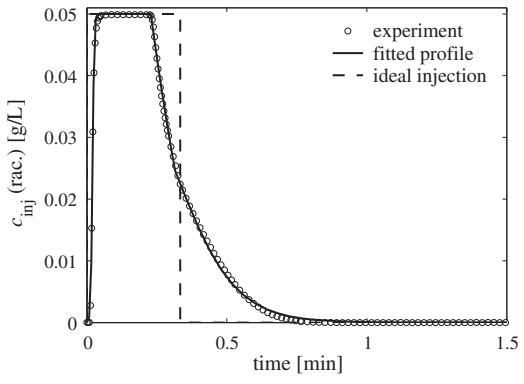

Fig. 5. Injection profile obtained experimentally (symbols) and fitting results (solid line) for a 2 mL injection of of 0.5 g/L racemic CTD at a flow rate of 6 mL/min. The three sigmoidal functions are connected at $t = 0.23$ and $t = 0.32$ min, respectively. Ideal rectangular profile (- - - dashed line) plotted for comparison.

A total of seven free parameters in Eqs. (3) and (11) are used to describe the adsorption behavior. The experimentally determined isotherm parameters reported in [7] were used here as initial guess. The results of the parameter estimation are summarized in Table 2.

Fig. 6 shows the experimental chromatograms together with the numerical results. A good agreement is observed between them. Note that a simpler isotherm model might be applied requiring less parameters to be fitted. However, the bi-Langmuir model is most frequently suggested for enantiomers.

In the chromatograms, almost baseline separation can be observed at pH = 5.3. At pH = 8.0, an intermediate plateau is formed. Further, at pH = 9.0 a single peak is obtained due to the fast racemization kinetics. These are typical effects observed in 'on column' racemization [18–20]. The retention time decreases with increasing pH value. This is not only an effect of the reaction-assisted regeneration, but also due to a change of the adsorption strength. The effect of the pH on the retention time increases if the pH is in the proximity of the pK_a value of CTD, pK_a = 11.1 [21]. This effect has been observed also for other compounds [22–24].

4.2. Validation of the integrated SMB concept

For conventional non-reactive SMB processes so-called triangle theory is used as a powerful design tool [25,26]. Based on this method, a region of complete separation can be plotted on the m^{II}–m^{III} plane. Analogously, such complete separation region can be shown for the new integrated SMB system. In these considered here, where the weaker adsorbed enantiomer is produced, the corresponding reagion is defined in the parameter space m^{I}–m^{II}. In order to demonstrate this, the mathematical model was solved using the determined kinetic constant of the racemization and the adsorption isotherm parameters. A step gradient of the pH was assumed that gives maximum performance in the frame of the investigated parameter range. In the reactive zone *I* pH was set to 9.0, while in the non-reactive zone *II* a pH of 5.3 was used. Fig. 7 shows the simulation results where triangular regions are plotted for different purity requirements. Note that for processes producing the stronger adsorbed enantiomer, the corresponding separation regions are found in the m^{II}–m^{III} plane.

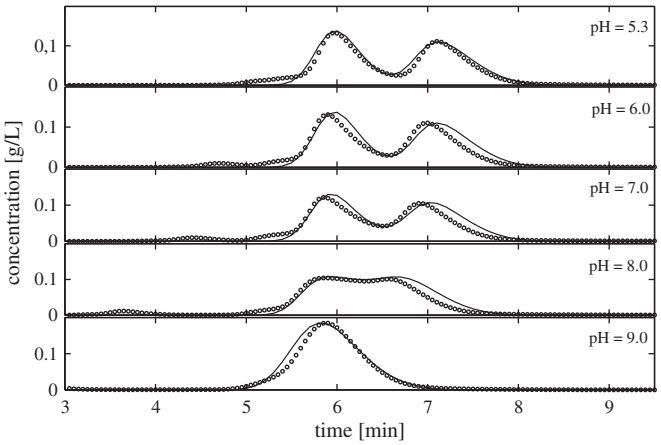

Fig. 6. Experimental chromatograms (symbols) and fitting results (lines) of CTD enantiomers at different pH values.

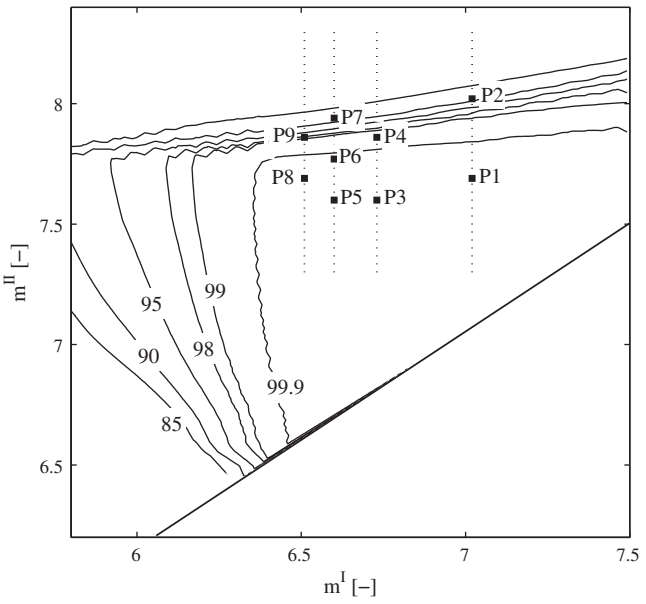

Fig. 7. Simulation results corresponding to the scanning of the m^I vs. m^{II} region for the model substance CTD. Surfaces denote the achievable product purity. Points *P*1 to *P*9 represent the operating conditions for the 9 experimental runs.

To validate the process experimentally, nine operating points are selected inside and outside of the region of complete separation (*P*1 to *P*9). No points are chosen left from the boundary of the 99.9% purity region since we are interested in achieving complete regeneration. These nine points were applied in nine different experimental runs using the setup in Fig. 2. The eluent used was methanol/50 mM BTP (40/60, v/v). The same pH gradient was used as in the simulations above. For this purpose, the pH of the desorbent *S* (pure eluent) was adjusted to $pH_1 = 9.0$, for the regeneration streams (pure eluent) to $pH_3 = 5.3$, and that of the additional buffer to $pH_2 \approx 1.0$ (cf. Fig. 2). The latter was in each case prepared such that, after mixing it with the effluent of zone *I* and the actual feed (0.5 g/L racemic CTD in pure methanol), the fluid entering zone *II* had the desired composition (methanol/50 mM BTP, 40/60, v/v) and pH value of 5.3. The switching time of $t_s = 7$ min was chosen as a compromise between throughput and pressure drop. All individual flow rates can be calculated from the parameters given in Table 1 and the *m*-values in Table 3.

For the sake of brevity, only the results for one operating point, *P*8, will be discussed in detail. *P*8 corresponds to the highest throughput among the operating points contained in the complete separation region. As indicated in Fig. 2, online measurement was carried out with two UV detectors: one at the product outlet of the 2-zone SMB, and the other at the outlet stream of the regeneration zone. In Fig. 8 the UV-signal is shown for the start-up of the experimental run of *P*8. The CSS is reached approximately after 150 min. That corresponds to 21 column switches, i.e., 5 cycles of the 2-zone SMB. After the CSS is reached, deviations from peak to peak can be observed for the product port. This is due to the different packing quality observed among the columns. However, this is a minor problem since SMB units can be operated successfully with columns giving significantly different retention times for the two compounds involved [27]. Further, perturbations are observed in the product port after every switching event. These perturbations can be observed in Fig. 8 after approximately 125 min. The peaks reach a considerable height in the cyclic steady state. However, their peak area is negligible and they are categorized as system peaks, since a detrimental effect on product quality was not observed.

Table 3
Simulated and experimental results for the integrated 2-zone SMB process. *P*1 to *P*9 correspond to nine different operating points on the m^I–m^{II} plane.

Operating point	m^I (–)	m^{II} (–)	Simulation		Experiment		
			Pu^R (%)	X_{CTD_2} (%)	Pu^R (%)	X_{CTD_2} (%)	Y (%)
*P*1	7.02	7.69	99.9	99.9	>98	95.1	95.3
*P*2	7.02	8.02	87.6	75.3	71.2	42.1	94.3
*P*3	6.73	7.60	99.9	99.9	>98	95.1	98.7
*P*4	6.73	7.86	99.7	99.4	97.1	93.3	98.0
*P*5	6.60	7.60	99.9	99.9	>98	95.6	95.4
*P*6	6.60	7.77	99.9	99.9	>98	96.8	98.1
*P*7	6.60	7.94	86.9	73.8	91.1	79.5	97.0
*P*8	6.51	7.69	99.9	99.9	>98	96.1	98.0
*P*9	6.51	7.86	99.1	98.0	92.9	85.1	97.1

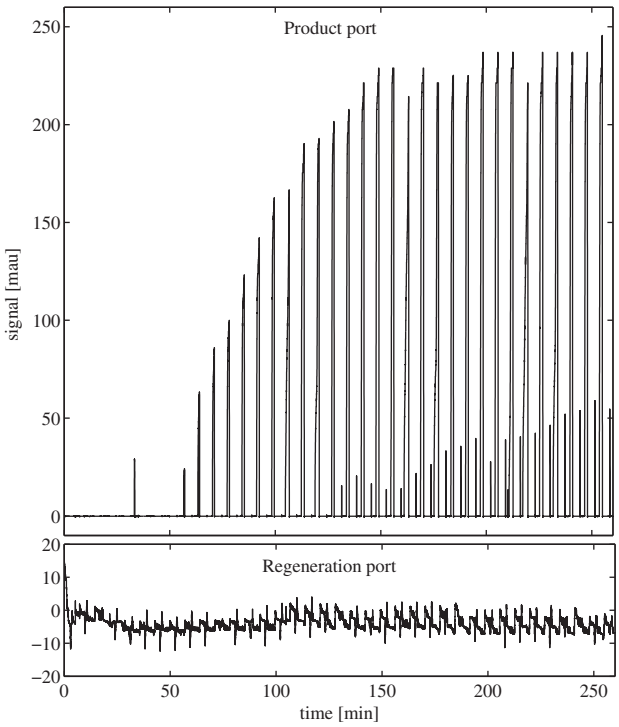

Fig. 8. Start-up behavior of the 2-zone SMB unit obtained for *P*8 (see Fig. 7). Signals of the UV online measurements for the product and the regeneration ports (see Fig. 2).

Online pH-measurent was carried out after the feed port (as indicated in Fig. 2). The results indicated that during the operation in CSS regime lower pH values than adjusted in the buffer solutions occured temporarily in zone *II*. These lower pH values were observed inmediately after the switching of the columns. At this point in time, the pH of the liquid contained in the void volume of the column placed left to the feed port (coming from zone *II*) is equal to 5.3. Mixing this liquid with the feed stock and the acidic buffer leads to momentary low pH values (between 1.5 and 3.0). In the present case, this transient effect causes the formation of small amounts of side products (always <5% of the total feed). To avoid this, advanced feeding strategies could be implemented modulating the pH of the buffer periodically.

Once the unit reached the CSS, the product, regeneration and equilibration streams were collected and analyzed by HPLC. In Fig. 9, the analysis results are plotted for the three outlet streams. The analysis of the product stream shows a single peak eluting at the retention time of the less retained enantiomer CTD_1. The purity of CTD_1 is close to 100%. The detection limit of HPLC analysis with respect to enantiomeric purity was estimated to be 98% because a baseline separation could not be achieved. It could not be clarified

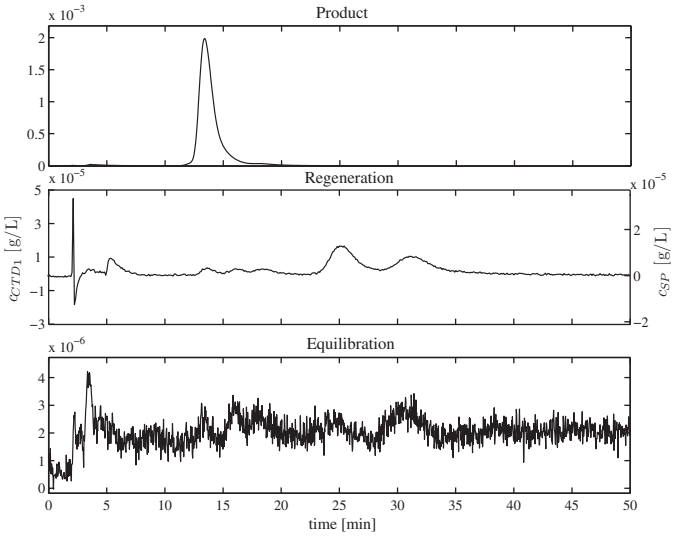

Fig. 9. Experimental results obtained for *P*8 (see Fig. 7). HPLC analysis of the product stream, regeneration and equilibration streams after reaching the cyclic steady state. c_{sp} denotes the concentration of the side products.

whether this is due to on-column racemization or other separation difficulty.

The analysis of the regeneration stream indicates that four different components are present in the mixture. CTD_1 and CTD_2, as well as the two side products SP_1 and SP_2. These were expected based on the reaction mechanism at low pH values suggested in [13]. Note that the scale of this plot is two orders of magnitude lower than the one for the product stream. This makes the amounts of CTD in the regeneration a 0.8% of the total throughput, while the side product formation makes up only a 1.2%. In the analysis of the equilibration stream only noise can be observed.

Note that in this work the 2-zone open loop concept was implemented for the sake of easier process monitoring and guaranteeing the proper functioning of the regeneration zone. Apart from that, in cases where the side product formation is significant and an accumulation of side products is expected due to their adsorption behavior, the open-loop concept might be preferred over a 3-zone closed-loop. An important aspect of 3-zone closed loop processes is related to the pH gradient. In order to maintain the magnitude of this gradient, the pH of the desorbent and feed streams will have to be adjusted to more "extreme" values.

The numerical and experimental results for the nine operating points are summarized in Table 3. Five operating points were chosen inside the complete separation region: *P*1, *P*3, *P*5, *P*6 and *P*8, where 100% purity, conversion and yield were expected. The other four operating points were chosen outside this triangle to determine the limits of the complete separation region. A good agreement is obtained between experiments and theoretical predictions. For the five operating points inside the complete separation region the detection limit for the product purity of 98% is reached. Conversions and yields above 95% are obtained in these cases from the overall material balances.

High product purity and negligible amounts of CTD enantiomers in the regeneration stream were observed in the experiments designed to produce pure product. This demonstrates that the new integrated SMB concept is capable of producing single enantiomers with purity, conversion and yield close to 100%.

5. Conclusions

A new integrated 3-zone SMB process was identified in previous publications [1,2] as a promising concept to produce single enantiomers. In this work, the process was experimentally validated for the model system chlorthalidone (CTD).

First, the racemization kinetics of CTD were determined as a function of the pH value. Afterwards, the adsorption isotherms were determined applying the inverse method in the pH range of interest. To design the process, a mathematical model was implemented accounting for the experimentally investigated reaction rate and adsorption isotherms.

For the sake of easier controllability, the experimental validation was performed using a 2-zone open-loop configuration. A 3-zone implementation is straightforward if side product formation is negligible. Such side prduct formation can be reduced by a modified feed strategy.

In a semi-preparative open-loop SMB setup several experimental runs were carried out corresponding to different operating points. The results confirm that pure single enantiomers can be produced with the new integrated process achieving conversion and yield values of 100%.

The new integrated process can be applied to enantiomeric systems where the racemization kinetics can be tuned significantly by means of the pH value. The dependency of the racemization kinetics on the pH is reported for other species (e.g., in [14]), as well as for epimerization [15] and isomerization kinetics [16]. Alternatively, other gradients of, for example, temperature, modifiers, additives, homogeneous catalysts or inhibitors could also modulate sufficiently the reaction kinetics, enabling more applications of this concept.

Nomenclature

Symbols

b	adsorption isotherm coefficient (L/g)
c	liquid phase concentration (g/L)
C_1, C_2, C_3	constants
ε	total porosity (−)
F	phase ratio, $F=(1-\varepsilon)/\varepsilon$ (−)
k	reaction rate constant (s^{-1})
m	flow rate ratio (−)
N_c, N_s, N_z	number of columns/stages/zones
ν	stoichiometric coefficient (−)
Pu	purity (%)
q	solid phase loading (g/L)
q^s	saturation capacity (g/L)
Q	volumetric flow rate (mL/min)
r	reaction rate (g/L/s)
t	time (min)
t^*	switching time of SMB process (min)
V	volume of a single stage (mL)
V_c	volume of a single column (mL)
X	conversion (%)
Y	yield (%)

Sub- and superscripts

A	stronger adsorbing component
B	weaker adsorbing component
0	initial or boundary condition
F	feed stream
i	component, $i=(A, B)$
I, II, III	zone of SMB system
k	index of stage, $k=1, \ldots, N_s$
n	Index of column, $n=I, \ldots, N_c$
S	desorbent stream
z	index of zone, $z=1, \ldots, N_z$

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