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# Impact of adsorption isotherm parameters on the performance of enantioseparation using simulated moving bed chromatography

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## Abstract

Often there are several chromatographic systems, i.e., combinations of mobile and stationary phases, available to solve a certain separation problem. Essential differences of these chromatographic systems are the separation factors and the efficiencies. For preparative applications in addition also the column saturation capacities and solubility limits are of importance. The impact of all these parameters appears to be rather well understood for conventional overloaded elution chromatography using a single column. In the last years the continuous simulated moving bed (SMB) process was increasingly used as a powerful alternative to batch elution since increased productivities and reduced solvent consumptions could be realised. However, the selection of suitable chromatographic systems is more sophisticated for this process. In this paper five different chromatographic systems capable of separating the enantiomers of mandelic acid are compared based on the achievable productivities using SMB chromatography. For these five systems the adsorption isotherms have been determined experimentally. Subsequently, an analysis of the SMB process was performed numerically using a well-established model. © 2002 Elsevier Science B.V. All rights reserved.

**Keywords:** Adsorption isotherms; Enantiomer separation; Simulated moving bed chromatography; Preparative chromatography; Mandelic acid

## 1. Introduction

In the last decades HPLC became one of the most powerful separation techniques in analytical chemistry. This is mainly due to the development of efficient and selective stationary phases in combination with the potential offered by optimising the composition of the mobile phases. Several interactions between the phases of the chromatographic system and the components of the sample can be

utilized and there is usually a certain choice available to realize a concrete separation. As concerns the choice of an appropriate chromatographic system the situation is different in analytical chromatography where small amounts have to be separated and in preparative chromatography where the treatment of larger sample sizes is intended. For analytical applications the selection is based predominantly on the available selectivities and efficiencies. To ease this selection several databases are available (e.g., Ref. [1]) and for certain chromatographic systems useful tools have been developed to predict selectivities based on a minimum of information (e.g., Ref. [2]).

Since in preparative chromatography higher concentrations are of interest additional parameters

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become essential and also decide whether a separation process can be performed economically or not. In particular the course of the distribution equilibria at higher concentrations (including aspects of competition between the components of the feed) and constraints related to restricted solubilities become decisive. Once the specific adsorption isotherms are known there are nowadays well-established theories available to predict and to optimise nonlinear elution chromatography under overloaded conditions [3]. For the batch operation of single columns it is well known that appropriate feed concentrations (loading factors) need to be used in order to maximize productivities. The optimal injection regimes depend specifically on several parameters including the degree of isotherm nonlinearities and the column saturation capacities.

In order to avoid the batch type process of conventional elution chromatography and to increase productivities in the last years the continuous simulated moving bed (SMB) process has been applied increasingly in the pharmaceutical industry and for the purification of fine chemicals. This is mainly due to the facts that reliable hardware is available [4] and the theoretical understanding of this complex process has increased remarkably (e.g., Refs. [5–11]). Since the process essentially splits a feed into two fractions it is in particular attractive to separate racemic mixtures into the corresponding enantiomers. For this reason SMB technology is increasingly applied in the pharmaceutical industry to perform enantio-separations. A comprehensive overview concerning this field was recently given in [12]. Nowadays the development and optimisation of SMB processes usually starts after the choice concerning suitable mobile and stationary phases has been made. Then the established theories [5–11] are adapted to identify attractive operating conditions. Hitherto the selection of the chromatographic system appears to be mostly influenced by criteria useful to identify the best situation for analytical chromatography. Aspects relevant in preparative chromatography as isotherm nonlinearities, competition, column saturation capacities, solubility limits and impacts of the sample concentration on solvent properties are rarely considered during this selection process.

In this paper five different possibilities to separate the two enantiomers of mandelic acid using two

different chiral stationary phases are presented and quantified. As the essential parameters characterising the separations, the adsorption isotherms are determined experimentally using the frontal analysis method. The isotherm parameters are used subsequently to predict the performance of the conventional four-zone SMB process. For this, simulations based on the well-established equilibrium theory and using the equilibrium dispersive model were performed. Besides analysing the process productivities for achieving a complete separation the impact of lowering purity constraints is also discussed quantitatively.

## 2. Theory

An SMB unit consists of several columns interconnected in series. The principle and advantages of the continuous process possible with this arrangement have been explained extensively in the literature (e.g., Refs. [5–11]). In order to design an SMB process at first a reliable model describing the separation in a single column is required. The key information in such a model are usually the adsorption isotherms valid for the system under consideration. To optimise SMB processes suitable flow-rates in the four zones need to be found respecting specific constraints. Below these aspects are shortly summarised.

### 2.1. Column model

Powerful models are available to simulate the development of band profiles in fixed beds [3]. In particular the following mass balance of the equilibrium dispersion model has proven to be useful to describe separation processes in chromatographic columns filled with small particles:

$$\frac{\partial c_i}{\partial t} + \frac{1 - \varepsilon}{\varepsilon} \cdot \frac{\partial q_i(c_j)}{\partial t} + u \cdot \frac{\partial c_i}{\partial z} = D_{\text{app}} \cdot \frac{\partial^2 c_i}{\partial z^2} \quad (1)$$

where  $c_i$  and  $q_i$  are the liquid and the solid-phase concentrations of the  $i$ th component, respectively,  $u$  is the interstitial fluid velocity and  $\varepsilon$  is the total porosity of the packing. This equation considers only convective mass transfer and a permanent equilib-

rium between the two phases is assumed. The apparent dispersion coefficient,  $D_{\text{app}}$ , related to the number of theoretical plates,  $N$ , and the interstitial linear velocity,  $u$ , must be known to quantify band broadening effects:

$$D_{\text{app}} = \frac{uL}{2N} \quad (2)$$

To describe conventional elution processes appropriate initial and boundary conditions have to be provided. Eq. (1) can be solved numerically using standard procedures (e.g., Refs. [3,13]).

The extension to multi-column SMB processes is straightforward. The connection between the columns and the periodic shift can easily be implemented by specifying the appropriate periodic boundary conditions [5–10].

For small dispersion effects (i.e.,  $D_{\text{app}} \rightarrow 0$ ) Eq. (1) is called the equilibrium model. Then for certain adsorption isotherm models (including the Langmuir model) analytical solutions are available as well for single column processes as for the SMB process [7,10,11,14].

The most simple model for the SMB process is based on neglecting dispersion effects and assuming a true countercurrent between the two phases (true moving bed or TMB model). Using this concept, useful estimations of suitable process parameters can be obtained analytically [7,10,11].

## 2.2. Isotherm model

Obviously the knowledge of the adsorption isotherms, i.e., the functions  $q_i(c_j)$  in Eq. (1), is the most important requirement for process simulation. Several thermodynamic concepts (e.g., the IAS and the RAS theories [15–17]) are available. However, the simple Langmuir equation is frequently a reliable and simple model to quantify nonlinear equilibria:

$$q_i = q_{s,i} \cdot \frac{b_i c_i}{1 + b_i c_i} \quad (3)$$

In this equation,  $q_{s,i}$  is the saturation loading capacity and  $b_i$  is a constant quantifying the adsorption energy. For infinite dilution of the solutes the equation converges into the linear adsorption isotherm:

$$q_i = H_i c_i \quad \text{with} \quad H_i = q_{s,i} b_i \quad (4)$$

Competition effects between the components can often be described adequately with the following multi-component Langmuir model:

$$q_i = q_{s,i} \cdot \frac{b_i c_i}{1 + \sum_{j=1}^n b_j c_j} \quad (5)$$

From the parameters of the isotherm equation selectivities under dilute conditions can be estimated according to:

$$\alpha = \frac{q_{s,2} b_2}{q_{s,1} b_1} = \frac{H_2}{H_1} \quad (6)$$

This isotherm model is thermodynamically consistent only if the saturation capacities,  $q_{s,i}$ , are equal for all components [3,18]. Thus for a binary mixture should hold:

$$q_{s,1} = q_{s,2} = q_s \quad (7)$$

Under this condition the separation factor, Eq. (6), depends only on the equilibrium constants of the two solutes. Using this parameter,  $b_2$  can be expressed as:

$$b_2 = \alpha b_1 \quad (8)$$

If only separations of 1:1 mixtures are considered (like in the case of separating racemic mixtures), i.e., if  $c_1 = c_2 = c_F$ , for the two loadings hold:

$$q_1 = q_s \cdot \frac{b_1 c_F}{1 + (\alpha + 1) b_1 c_F} \quad (9a)$$

$$q_2 = q_s \cdot \frac{\alpha b_1 c_F}{1 + (\alpha + 1) b_1 c_F} \quad (9b)$$

Thus, the equilibrium loadings depend exclusively on the four parameters  $\alpha$ ,  $q_s$ ,  $b_1$ ,  $c_F$ .

## 2.3. Maximum flow-rates

It is well known that the optimum of chromatographic separations with preparative purpose is often achieved at the highest flow-rate possible [3]. Thus, usually constraints related to pressure drops and limits of the pump performances are essential. Pres-

sure drops,  $\Delta p$ , can be roughly estimated as a function of flow-rate,  $Q$ , according to the relation [3]:

$$\Delta p = \frac{uL\eta}{k_0 d_p^2} \quad \text{with} \quad u = \frac{4Q}{\varepsilon\pi D^2} \quad (10)$$

where  $k_0$  is the permeability,  $\eta$  is the viscosity,  $d_p$  is the particle diameter and  $L$  and  $D$  are the length and the diameter of the column, respectively.

#### 2.4. SMB design

Analytical solutions of the equilibrium theory for the TMB process have been derived in order to specify optimum operational parameters allowing for 100% pure products at both outlets [7,10]. The essential parameters in these solutions are four dimensionless flow-rate ratios,  $m_j$ , characterizing the ratios between the liquid and solid-phase flow-rates in the four zones of the multicolumn arrangement. In the case of linear adsorption isotherms the following values of the  $m_j$  characterise the optimal operating point:

$$m_I^{\text{opt}} = m_{\text{III}}^{\text{opt}} = H_2 \quad (11)$$

$$m_{\text{II}}^{\text{opt}} = m_{\text{IV}}^{\text{opt}} = H_1 \quad (12)$$

The subscripts correspond to the established notation for the single zones ( $j=I, II, III, IV$ ) of SMB units (for details see, e.g., Refs. [7,10]). For the competitive Langmuir model optimum values for the  $m_j$  have been also derived [7,10]. Under the simplifying assumptions made above, for the optimum holds:

$$m_I^{\text{opt}} = \alpha q_s b_1 \quad (13)$$

$$m_{\text{II}}^{\text{opt}} = \frac{\omega_G}{\alpha} \quad (14)$$

$$m_{\text{III}}^{\text{opt}} = \frac{\omega_G[\omega_F(\alpha - 2) + q_s b_1]}{\alpha q_s b_1 - \omega_F} \quad (15)$$

$$m_{\text{IV}}^{\text{opt}} = \frac{1}{2} \cdot [q_s b_1 + m_{\text{III}} + b_1 c_F (m_{\text{III}} - m_{\text{II}})] - \frac{1}{2} \sqrt{[q_s b_1 + m_{\text{III}} + b_1 c_F (m_{\text{III}} - m_{\text{II}})]^2 - 4q_s b_1 m_{\text{III}}} \quad (16)$$

where  $\omega_F$  and  $\omega_G$  represent the solutions of the following quadratic equation:

$$(1 + b_1 c_F + \alpha b_1 c_F) \omega^2 - [q_s b_1 (1 + \alpha b_1 c_F) + q_s \alpha b_1 (1 + b_1 c_F)] \omega + \alpha b_1^2 q_s^2 = 0 \quad (17)$$

In real systems dispersion effects and mass transfer resistances will lead to incomplete separation when the optimal conditions given above are used. Obviously, the differences between the optimal performance parameters predicted from the equilibrium theory and the corresponding parameters required for less efficient (real) systems increase with decreasing numbers of theoretical plates. A simple way to account for finite efficiencies is based on the introduction of safety factors,  $\beta_j$  (with  $\beta_j > 1$ ), that can be used to correct the flow-rate ratios,  $m_j$ , in the required direction [6]:

$$m_I = \beta_I m_I^{\text{opt}} \quad \text{and} \quad m_{\text{II}} = \beta_{\text{II}} m_{\text{II}}^{\text{opt}} \quad (18)$$

$$m_{\text{III}} = m_{\text{III}}^{\text{opt}} / \beta_{\text{III}} \quad \text{and} \quad m_{\text{IV}} = m_{\text{IV}}^{\text{opt}} / \beta_{\text{IV}}$$

The expressions given above could be applied directly to analyse TMB processes. A corresponding SMB process achieves similar results if the well-known conversions rules are respected [7,10]. The four relevant flow-rates in an SMB unit need to be expressed as follows:

$$Q_j^{\text{SMB}} = \frac{m_j V (1 - \varepsilon) + V \varepsilon}{t_s} \quad (19)$$

In this equation,  $Q_j^{\text{SMB}}$  is the fluid flow-rate in zone  $j$  of an equivalent SMB apparatus,  $t_s$  is the switching time (adjusted to the solid flow-rate in the corresponding TMB unit) and  $V$  is the volume of a single column.

The largest flow-rate occurs usually in zone I where desorbent and recycle stream are introduced. To increase the overall process productivity it is attractive to use in this zone the highest tolerable flow-rate,  $Q_{\text{max}}$ . This flow-rate can be estimated from a pressure drop correlation, e.g. from Eq. (10). If  $m_I$  and  $Q_{\text{max}}$  are specified from Eq. (19) follows the switching time:

$$t_s = \frac{V[m_I(1 - \varepsilon) + \varepsilon]}{Q_{\text{max}}(\Delta p)} \quad (20)$$

Subsequently, from the remaining  $m_j$  also the three other internal and thus all external flow-rates can be calculated using Eq. (19).

Note that for an extended optimisation of the process in terms of column geometry and particle size it would be useful to substitute the pressure drop correlation, Eq. (10), directly into Eq. (20). This approach has been applied already in SMB optimisations [6,19]. Below we will mainly discuss the productivity of an SMB process for different thermodynamic properties of the chromatographic systems.

### 2.5. Productivity

In this work we define the productivity belonging to a certain successful operating point as the corresponding mass of component  $i$  that is introduced in the SMB per time and per volume of applied stationary phase. Successful operation means that an a priori specified purity requirement (PUR) is met by the corresponding outlet streams:

$$PR_{i,PUR} = \frac{Q_F c_{F,i}}{V^{SP}} = \frac{Q_F c_{F,i}}{nV(1-\varepsilon)} \quad i = 1,2 \quad (21)$$

In this equation,  $n$  is the number of columns in the SMB unit. If for both components 100% purity are required the introduced mass streams of the two feed components are identical to the corresponding outlet streams ( $Q_F c_{F,1} = Q_{Raff} c_{Raff,1}$ ,  $Q_F c_{F,2} = Q_{Extr} c_{Extr,2}$ ). For reduced purity requirements the outlet mass streams will be lower. Although in principle different purity requirements for the two individual outlet streams might be of practical interest, below it is assumed:

$$PR_{1,PUR} = PR_{2,PUR} = PR_{PUR} \quad (22)$$

The feed flow-rate appearing in Eq. (21) corresponds to the difference of the flow-rates in zones III and II, respectively, which are adjacent to the feed port:

$$Q_F = Q_{III} - Q_{II} \quad (23)$$

With Eqs. (19) and (20) and the assumption of a 1:1 feed mixture follows for the productivity:

$$PR_{PUR} = \frac{Q_{max} c_F}{nV} \frac{m_{III} - m_{II}}{m_I(1-\varepsilon) + \varepsilon} \quad (24)$$

The highest productivity corresponds to the highest possible difference between  $m_{III}$  and  $m_{II}$ . Considering PUR=100% and an infinite efficiency this difference is related to the optimum values for the  $m_j$  given with Eqs. (11)–(17). Thus, for this special case analytical expressions can be used to study the influence of the isotherm parameters on the productivity of SMB units. For this purpose the expressions for the optimal  $m_I^{opt}$ ,  $m_{II}^{opt}$  and  $m_{III}^{opt}$  can be substituted into Eq. (24). From Eqs. (11), (12) and (24) follows for the maximal productivity under linear conditions:

$$PR_{100}^{opt} = \frac{Q_{max} c_F}{nV} \cdot \frac{H_1(\alpha - 1)}{H_1 \alpha(1 - \varepsilon) + \varepsilon} \quad (25)$$

Analogously follows for the productivity in case of the nonlinear Langmuir isotherm from Eqs. (13)–(17) and (24):

$$PR_{100}^{opt} = \frac{Q_{max} c_F}{nV[\alpha q_s b_1(1 - \varepsilon) + \varepsilon]} \cdot \left\{ \frac{\omega_G[\omega_F(\alpha - 2) + q_s b_1]}{\alpha q_s b_1 - \omega_F} - \frac{\omega_G}{\alpha} \right\} \quad (26)$$

From these expressions the maximum productivity achievable in an SMB unit for complete separation under ideal conditions can be explicitly calculated.

For real systems the dependence of the productivity on the isotherm parameters and on the feed concentrations can be studied based on numerical solutions of Eq. (1). In such a study also purity values below 100% can be considered.

Below an analysis of the productivity of an SMB process will be presented based on experimentally determined adsorption isotherm parameters characterizing the chiral separation of a racemic mixture.

### 3. Experimental

To exemplify the fact that frequently the same separation can be performed applying different chromatographic systems the separation of the two enantiomers of mandelic acid is discussed here. A detailed study of this separation using the glycopeptide teicoplanin covalently bonded on the surface of silica gel and different mobile phases was published recently [20]. Selected data from Ref. [20] in

addition with results of new measurements carried out in this work using a second cyclodextrin-based chiral stationary phase will be analysed. The characteristics of the considered chromatographic systems as well as the applied experimental procedures are summarized below.

### 3.1. Sample

S(+)-Mandelic acid (99+) was purchased from Sigma-Aldrich (Steinheim, Germany) and R(-)-mandelic acid (99+) from Merck-Schuchardt (Hohenbrunn, Germany).

### 3.2. Columns

The following two commercially available chiral stationary phases (CSPs) were applied:

*CSP1*: teicoplanin (Chirobiotic T, ASTEC, USA), 150×4.6 mm I.D., 5- $\mu$ m particles.

*CSP2*: nucleodex  $\beta$ -OH (Macherey-Nagel, Germany), 200×4 mm I.D., 5- $\mu$ m particles.

### 3.3. Mobile phases

For the separation of mandelic acid using *CSP1* the following four different mobile phases (MP) have been considered (more options are discussed in Refs. [20]):

*MP1*: ethanol–water (50:50, v/v), unbuffered

*MP2*: ethanol–water (50:50, v/v), 0.36 mol/l triethylammoniumacetate, pH 6.56

*MP3*: methanol–acetonitrile–triethylammoniumacetate–acetic acid (54.5:45:0.25:0.25, v/v), pH 6.5

*MP4*: methanol–water (20:80, v/v), 0.3 mol/l triethylammoniumacetate, pH 4.02

*CSP2* was used together with the following mobile phase:

*MP5*: water–acetic acid–acetonitrile (86.4:9.1:4.5, v/v), 0.05 mol/l ammoniumacetate, pH 3.0.

Purified water was obtained from a Milli-Q gradient system (Millipore, Molsheim, France). Acetonitrile (gradient grade) and acetic acid (100%, GR for analysis grade) were purchased from Merck (Darmstadt, Germany). Ammonium acetate (98%) was delivered by Sigma-Aldrich.

### 3.4. Instrumentation

The performed measurements with *CSP1* were described extensively in [20]. For the measurements with *CSP2* and *MP5* an HP1100 system (Hewlett-Packard, Waldbronn, Germany) was used consisting of a quaternary pump, a vacuum degasser, an autosampler, a thermostated column compartment, a diode array UV detector and a workstation with software (Chemstation for LC 3D).

### 3.5. Porosities and efficiencies

The column porosities,  $\varepsilon$ , were measured conventionally from tracer injections with nonadsorbing components. Column efficiencies,  $N$ , were estimated from the retention times and peak widths of small sample sizes using standard procedures (e.g., Ref. [3]).

### 3.6. Determination of adsorption isotherms

For the determination of the single component isotherms frontal analysis experiments [3,21] were performed. The gradient delivery system was used to mix a solvent stream and a concentrated solution containing a pure enantiomer of mandelic acid. The resulting breakthrough curves were recorded. After equilibration the proportion of the stream containing the sample was increased stepwise. This was done in steps of 5–10% up to the highest sample concentration, i.e., the concentration in the sample flask. The pH was adjusted to the same value in both feed flasks. To calculate isotherm data the loading of the stationary phase,  $q_i$ , was determined for each step solving the integral mass balance [3]:

$$q_i = q_{i-1} + \frac{(c_i - c_{i-1})Qt_R}{V(1 - \varepsilon)} \quad (27)$$

In this equation,  $q_i$  and  $q_{i-1}$  are the equilibrium loadings for the  $i$ th and  $(i - 1)$ th step,  $c_i$  and  $c_{i-1}$  are the equilibrium mobile phase concentrations.  $Q$  is the volumetric flow-rate,  $V$  is the column volume and  $t_R$  is the retention time characterising the step. The latter was determined as the time of the inflection point of the breakthrough curve minus the time delay

caused by the volume of the connecting tubing and the retention time of a nonretained solute.

### 3.7. Maximum sample concentrations

In order to increase the productivity of preparative chromatography it is well known that the usage of large concentrations is usually advantageous [3]. Thus, in general the maximum possible concentrations are most attractive. However, there are two principal constraints. The first one is connected with solubility restrictions. For the given systems the solubility of the mandelic acid enantiomers was relatively high (larger than 50 g/l in all five mobile phases). The second constraint is set by the fact that often the pH has to be stabilized. To avoid changes of the acid–base equilibria for some of the systems considered here buffers were used. If the specific buffer capacities were exceeded by using high mandelic acid concentrations, the pH changed and the chromatographic retention behaviour was altered, which resulted in a significant decrease of enantiomeric selectivity at higher column loads [20]. A detailed analysis of the interactions between the mandelic acid enantiomers, the components of the solvent and the multiple adsorption sites of CSP1 is very difficult and outside the scope of this paper. Thus, in this work maximum concentrations of

mandelic acid were estimated as the concentrations at which the pH started to change for the given specific buffer concentrations.

## 4. Results and discussion

### 4.1. Obtained parameters of the chromatographic systems

#### 4.1.1. Porosities and efficiencies

The following values were obtained for the two columns:

CSP1:  $\varepsilon=0.683$ ,  $N \approx 1000$  (averaged value for all mobile phases at a flow-rate of 1 ml/min)

CSP2:  $\varepsilon=0.756$ ,  $N \approx 1000$  (at a flow-rate of 1 ml/min)

#### 4.1.2. Adsorption isotherms

All determined isotherms exhibited the typical behaviour of Langmuirian systems. For this reason the Langmuir isotherm (Eq. (3)) was used for processing the equilibrium data for both enantiomers.

The isotherms were estimated by matching the parameters of Eq. (3) and the loadings,  $q_i$ , calculated with Eq. (27). The results are summarised in Table 1. Obviously there are large differences between the parameters for the five systems. While the separation

Table 1  
Langmuir isotherm parameters for *R*(–)- and *S*(+)-mandelic acid and different chromatographic systems

No.	System	Solute	<i>T</i> (°C)	$q_{s,i}$	$b_i$ (l/g)	$q_{s,i} b_i$	$\alpha$	$c_{\max}$ (g/l)
1	CSP1 <sup>a</sup> /MP1	<i>R</i> (–)	40	1.28	0.6336	0.81	4.26	15
		<i>S</i> (+)		3.29	0.0565	0.19		
2	CSP1 <sup>a</sup> /MP2	<i>R</i> (–)	40	181.8	0.0064	1.16	1.14	50
		<i>S</i> (+)		178.3	0.0057	1.02		
3	CSP1 <sup>a</sup> /MP3	<i>R</i> (–)	40	155.7	0.0085	1.33	1.22	38
		<i>S</i> (+)		278.4	0.0039	1.08		
4	CSP1 <sup>a</sup> /MP4	<i>R</i> (–)	40	77.8	0.0207	1.61	1.40	15
		<i>S</i> (+)		261.4	0.0044	1.15		
5	CSP2 <sup>b</sup> /MP5	<i>R</i> (–)	20	70.6	0.1222	8.62	1.07	5
		<i>S</i> (+)		72.5	0.1111	8.06		
2* <sup>c</sup>	Fictive reference system	<i>R</i> (–)		<u>180</u>	0.0065	1.17	<u>1.14</u>	<u>50</u>
		<i>S</i> (+)			<u>0.0057</u>	1.03		

<sup>a</sup> Chirobiotic T.

<sup>b</sup> Nucleodex  $\beta$ -OH.

<sup>c</sup> Derived from data for system 2 (CSP1/MP2) assuming constant saturation capacities, (underlined: reference parameters used in parametric calculations).

factors under dilute conditions for CSP1 (Eq. (6)) range from 1.14 to higher than 4, for CSP2 a relatively low value of 1.07 was found. The saturation capacities for CSP1 vary over a wide range depending on the solvent composition. However, the product of  $q_s$  and  $b_1$  (i.e., the slope of the isotherm at infinite dilution,  $H_1$ ) is about 1 for all isotherms on CSP1. This value is considerably higher for the isotherm on CSP2 (about 8).

In Fig. 1 are plotted all single component isotherms described by Eq. (3). For four out of the five systems investigated the  $R(-)$ -enantiomer was in the whole covered concentration range stronger adsorbed than the  $S(+)$ -enantiomer. For the unbuffered system CSP1/MP1 at higher concentrations a selectivity reversal was observed and the loadings of  $S(+)$ -mandelic acid exceeded the loadings of the  $R(-)$ -enantiomer. Due to this complex behaviour and due to the rather low capacities this system was not considered further in the study presented here. The three isotherms of CSP1 with MP2, MP3 and MP4 look quite similar with respect to their selectivity and their slope at infinite dilution. In contrast the isotherms for CSP2/MP5 reveal a steep slope at infinite dilution but a lower selectivity.

#### 4.1.3. Maximum sample concentrations

The following maximum concentrations of man-

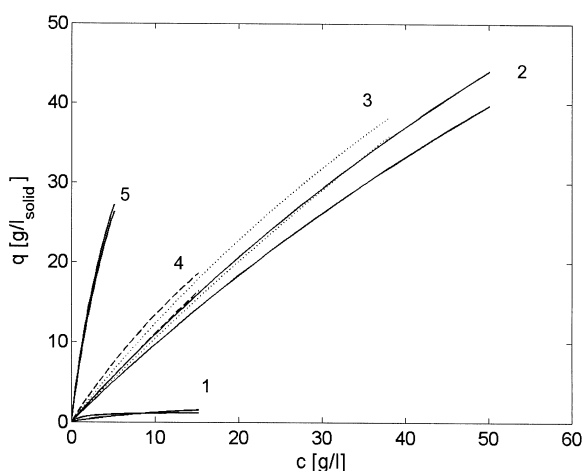


Fig. 1. Experimental isotherms for mandelic acid. The numbers refer to the data in Table 1.

delic acid were estimated allowing for stable pH-conditions:

$$\text{CSP1/MP2: } c_{\max} = 50 \text{ g/l;}$$

$$\text{CSP1/MP3: } c_{\max} = 38 \text{ g/l;}$$

$$\text{CSP1/MP4: } c_{\max} = 15 \text{ g/l;}$$

$$\text{CSP2/MP5: } c_{\max} = 5 \text{ g/l;}$$

Only up to these concentrations the adsorption isotherms are shown in Fig. 1

#### 4.1.4. Maximum flow-rates

A maximum flow-rate,  $Q_{\max}$ , was estimated from the pressure drop correlation, Eq. (10), assuming for the column size and equipment applied an acceptable maximum pressure drop of about 100 bar. A value of  $k_0 \approx 10^{-3}$  (valid for water) was applied. In relative agreement with experimental observations the resulting maximum flow-rates were 1.135 ml/min for the CSP1 column and 0.71 ml/min for the CSP2 column, respectively. To simplify the discussion, for both columns a maximum flow-rate of 1.0 ml/min was set as a constraint in the calculations presented below.

#### 4.2. Impact of isotherm parameters on SMB performance

In the first part of the study the analytical solutions have been used to analyse the impact of the isotherm parameters for the ideal situation on  $PR_{100}^{\text{opt}}$ . For this only the parameters of one isotherm model have been used. Subsequently, based on extensive numerical calculations the influence of feed concentrations and purity requirements was studied for several isotherm describing the separation of the enantiomers of mandelic acid with different chromatographic systems.

##### 4.2.1. Analysis based on equilibrium theory (infinite efficiency, pure products)

For the limiting case where an infinite efficiency of the chromatographic system can be assumed, the equilibrium theory allows for the derivation of analytical expressions for the productivity as a function of isotherm parameters (Eqs. (25) and (26)). These solutions are valid only for the case of 100% pure products. For studying the SMB productivity based on Eqs. (25) and (26) a modified parameter set of system 2 (CSP1/MP2) was applied. The isotherm



data shown in Table 1 reveal that for this system the saturation capacities are most similar and the assumptions that underlie Eqs. (13)–(17) and thus (26) are most closely fulfilled. To have exactly the same saturation capacities for the two enantiomers the primary data have been reanalysed and a slightly modified parameter set was determined which is also shown in Table 1 and designated as system 2\*. Since in the analysis presented in this paragraph the isotherm parameters are altered systematically around these values, the following two isotherms for system 2\* can be considered as reference isotherms:

$$q_{1,\text{ref}} = q_{s,\text{ref}} \cdot \frac{b_{1,\text{ref}} c_F}{1 + (\alpha_{\text{ref}} + 1) b_{1,\text{ref}} c_F} = \frac{1.026 c_F}{1 + 0.0122 c_F} \quad (28)$$

$$q_{2,\text{ref}} = q_{s,\text{ref}} \cdot \frac{\alpha_{\text{ref}} b_{1,\text{ref}} c_F}{1 + (\alpha_{\text{ref}} + 1) b_{1,\text{ref}} c_F} = \frac{1.1696 c_F}{1 + 0.0122 c_F} \quad (29)$$

Assuming the hypothetical situation that the initial slopes of the isotherms given with Eqs. (28) and (29) continue to hold also at higher concentration the following linear reference isotherm equations result:

$$q_{1,\text{ref}} = H_{1,\text{ref}} = 1.026 c_F \quad (30)$$

$$q_{2,\text{ref}} = \alpha_{\text{ref}} H_{1,\text{ref}} = 1.1696 c_F \quad (31)$$

The geometrical extensions and porosities of the CSP1 columns used for measuring the adsorption isotherms were applied to estimate productivities. As mentioned before the maximum flow-rate in zone I was set to be  $Q_{\text{max}} = 1.0$  ml/min. As the maximum feed concentration leading to maximal values for the productivities was set  $c_{\text{max}} = 50$  g/l.

For the hypothetical linear reference isotherms (Eqs. (30) and (31)) from Eq. (25) results:  $\text{PR}_{100}^{\text{opt,ref(lin)}} = 984.2 \text{ g l}^{-1} \text{ day}^{-1}$ . This value represents the maximum productivity for an ideal (i.e., infinitely efficient) SMB unit. Fig. 2 illustrates the influence of the separation factor,  $\alpha$ , and the Henry constant,  $H_1$ , on this productivity. The abscissa shows the ratio of the actual parameter ( $\alpha$  or  $H_1$ ), to the respective reference parameter ( $\alpha_{\text{ref}}$  or  $H_{1,\text{ref}}$ ), the

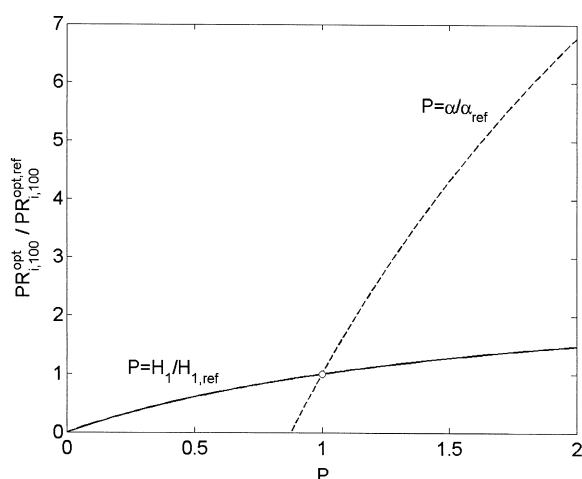


Fig. 2. Influence of the separation factor,  $\alpha$ , and the Henry constant,  $H_1$ , on the productivity of the SMB process under linear conditions.  $P$  is the ratio of the actual parameter to the respective reference parameter according to Eqs. (30) and (31).  $\text{PR}_{100}^{\text{opt,ref}}$  is the theoretical productivity for the reference parameters ( $984.2 \text{ g l}^{-1} \text{ day}^{-1}$ ).

ordinate is the ratio of the actual productivity to the corresponding productivity for the reference parameters. It can be estimated that a hypothetical doubling of the Henry constant ( $H_1 = 2H_{1,\text{ref}}$ ) for  $\alpha = \alpha_{\text{ref}}$  leads to a 1.5-times higher productivity. In contrast, it can be seen that the impact of the separation factor is much more significant. For  $\alpha = 2\alpha_{\text{ref}}$  and  $H_1 = H_{1,\text{ref}}$  the productivity is about seven times higher than that for the reference case. This indicates the trivial rule that high selectivities are desirable. The observed impact of the size of the Henry constants on the productivities is in conflict with the claim made in [22] that low  $k'$  values are preferential for SMB applications.

For the nonlinear reference isotherms, Eqs. (28) and (29), a productivity of  $\text{PR}_{100}^{\text{opt,ref(nonlin)}} = 178.3 \text{ g l}^{-1} \text{ day}^{-1}$  was calculated from Eq. (26). This represents less than 20% of the productivity possible for the hypothetical linear case. Obviously, nonlinearities of the isotherms have a strong impact on the process performance.

The influence of the individual Langmuir isotherm parameters,  $q_s$ ,  $\alpha$  and  $b_1$ , on the productivity, was also estimated in a parametric study. For this, one parameter was changed systematically while the others were held at their reference values. The

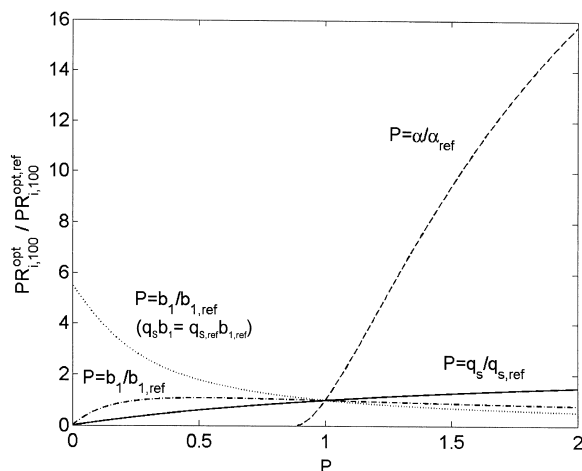


Fig. 3. Productivity of the SMB process as a function of the Langmuir isotherm parameters ( $q_s$ ,  $b_1$  or  $\alpha$ ) relative to the results for the reference parameters according to Eqs. (28) and (29).  $PR_{100}^{opt,ref}$  is the productivity for the reference state ( $178.3 \text{ g l}^{-1} \text{ day}^{-1}$ ).

corresponding productivities were always calculated using Eq. (26). Fig. 3 shows the impact of  $q_s$ ,  $\alpha$  and  $b_1$  on the productivity presented in a similar manner as in Fig. 2 for the linear isotherms. Obviously the dependencies are more complex in the nonlinear case. However, it is evident that again the most significant impact on the process productivity originates from the separation factor  $\alpha$ .

The role of an individual parameters can be better quantified using the partial derivatives of the productivity (Eq. (26)) with respect to this parameter. The partial derivatives can be approximated by the corresponding finite differences. Thus, the following sensitivities  $S_j$  can be estimated for each parameter:

$$S_j = \frac{\text{PAR}}{\text{PR}_{100}^{opt}} \cdot \frac{\Delta \text{PR}_{100}^{opt}}{\Delta \text{PAR}} \quad \text{PAR} = q_s, \alpha \quad \text{and} \quad b_1 \quad (32)$$

For the reference isotherm parameters the following values  $S_{\text{PAR}}$  were calculated from Eq. (32) for shifting each parameter by 1%:  $S_\alpha = 13.6$ ,  $S_{q_s} = 0.65$ ,  $S_{b_1} = -0.24$ ,  $S_{b_1} (q_s b_1 = \text{const.}) = -0.89$ . These values can be understood as the change of the productivity in percent resulting from the corresponding change of the actual isotherm parameter. For the example studied it follows that increasing  $\alpha$  by 1% will lead to an increase of the productivity by 13.6%,

while an increase of  $b_1$  by 1% leads to a 0.24% drop of the productivity.

#### 4.2.2. Analysis based on numerical simulations (finite efficiency, varying purity)

In this section we examine the dependence of the productivity of the SMB process on the feed concentration as well as on the product purity for the experimentally determined isotherms by solving numerically the equilibrium dispersive model (Eq. (1)) in combination with the competitive Langmuir isotherm model (Eq. (5)). In contrast to the analytical solutions analysed above, it is now possible to consider the limited efficiency (plate number) of 'real' systems as well as to study the impact of lowered purity requirements. It is a well known fact that lowering purity requirements usually leads to higher productivities. For enantioseparations studied here, the purity requirements can be, e.g., reduced if the SMB process is used just as an enrichment step for a succeeding separation process, e.g., fractional crystallisation [23].

To solve Eq. (1) it is necessary to specify the number of theoretical plates,  $N$ . As mentioned before  $N$  was found to be about 1000 for both column types used. The application of this number in Eq. (1) requires rather long computation times. However, it is well known that for a sufficiently high number of theoretical plates the SMB process becomes less sensitive to the size of  $N$  (e.g., Ref. [13]). Thus, the application of lower numbers is possible without considerably affecting the accuracy of the results. In our case, we observed satisfactory convergence of the solutions for plate numbers higher than 250 for each column. Hence, for all SMB calculations presented in this work  $N$  was fixed to be 300 per column. A series connection of four identical columns was considered.

The dimensionless flow-rate ratios in the two separation zones,  $m_{\text{II}}$  and  $m_{\text{III}}$ , are the most essential operating parameters of the SMB process. According to the equilibrium theory, a complete separation of the two components can be achieved within a triangular region in the  $m_{\text{II}}-m_{\text{III}}$  plane [7,10]. By performing a systematic scan over a sufficiently narrow equidistant grid in the  $m_{\text{II}}-m_{\text{III}}$  plane and calculating always the steady-state solutions of the mathematical model it is possible to find analogous

regions for limited efficiencies and lower product purities. To do this for each operating point ( $m_{II}$ ,  $m_{III}$ ) again  $Q_1$  was fixed to be 1.0 ml/min. The values for  $m_I$  and  $m_{IV}$  were specified from the optimal values according to the equilibrium theory (Eqs. (13) and (16)) in combination with a small safety factor  $\beta = \beta_I = \beta_{IV}$  (Eq. (18)). The value of this safety factor was determined for each chromatographic system in preliminary calculations using the equilibrium dispersive model and checking for selected operating parameters if the regeneration zones I and IV work properly. The lowest acceptable value of  $\beta$  was chosen. The switching time,  $t_S$ , was calculated from Eq. (20) using the determined value for  $m_I$ . All remaining internal and external flow-rates have been finally calculated from Eq. (19).

Typical results of the performed calculations are shown in Fig. 4 for the system CSP1/MP3 and a feed concentration of  $c_F = 10$  g/l. The thick line depicts the region of complete separation from equilibrium theory [7,10] while the thin lines depict regions for lower purities according to the equilibrium dispersive model. It can be seen that the region for 90% purity almost coincides with the theoretical region of complete separation. This means that the theoretical productivity resulting from equilibrium theory, Eq. (26), can be reached only if the purity

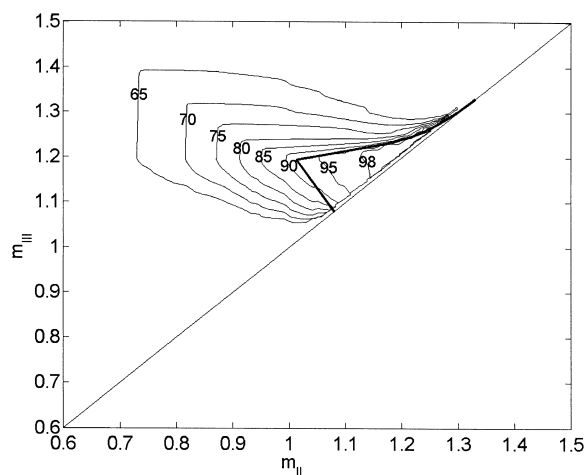


Fig. 4. Example of separation regions calculated for the combination CSP1/MP3 (Table 1),  $c_F = 10$  g/l and  $\beta = 1.2$ . Thick line: region of complete separation from equilibrium theory. Thin lines: numerically calculated separation regions for different values of product purity.

requirements are lowered to about 90%. It should be noted that the shape of the regions and the position of their vertices, i.e., the most productive operating points, depend strongly on the isotherm parameters and the feed concentrations.

In order to identify the operating point delivering the maximum productivity for a desired product purity and feed concentration, the vertex of the respective purity region in the  $m_{II}$ – $m_{III}$  plane has to be found. This can be done either via extensive simulations analysing all intercepts of an equidistant grid as explained above or by implementing some optimisation approach. For the latter option the accessible optimal parameters delivered by the equilibrium theory offer useful initial estimates. Similar to the algorithm described in [19] in our work a heuristic search strategy was applied. Based on the results of neighbouring grid points the direction of search was fixed. Using this approach it was possible to find relatively quickly the operation points that provided the desired product purities and met the requirement of maximal productivity.

Essential design parameters and obtained productivities are summarized in Table 2. In the first two lines are listed for each system the productivities predicted by the equilibrium theory for the ideal case (Eq. 26) using  $\beta = 1$  (first line) or the estimated safety factors as applied in the numerical simulations ( $\beta > 1$ , second line). The difference between the corresponding productivities indicates the effect of the safety factors. The next three lines show for each system and for three different values of the target purity the results obtained from the numerical simulations considering the reduced efficiencies. The strong impact of the required purity on the achievable productivity becomes obvious. Lowering the purity demands from 97.5 to 65% facilitates a multiple of the productivity (3–28-fold). On the other hand, increasing the purity demands from 97.5 to 99% causes a loss of about 60% of the productivity for the system CSP1/MP3 ( $\alpha = 1.22$ ) and of about 11% for CSP1/MP4 ( $\alpha = 1.4$ ). For the systems 2 and 5 a purity of 99% cannot be obtained using four columns with  $N = 300$  each. It is clear in general and was confirmed by the results obtained that predictions based on Eq. (26) are too optimistic. The last line in Table 1 shows the results for the reference isotherms that had been derived from data for the

Table 2

Design parameters and selected predicted productivities of the SMB process for the separation of the enantiomers of mandelic acid using different chromatographic systems

No.	System	$\alpha$	$c_F$ (g/l)	PUR (%)	$\beta$	$m_I$	$m_{II}$	$m_{III}$	$m_{IV}$	$t_S^a$ (min)	$PR_{PUR}^{b,c}$ (g l <sup>-1</sup> day <sup>-1</sup> )
2	CSP1/ MP2	1.14	50	100 <sup>d</sup>	1.0	1.160	0.962	0.987	0.920	2.62	172.7
				100 <sup>e</sup>	1.35	1.566	0.962	0.987	0.682	2.94	153.9
				99.0	–	–	–	–	–	0	
				97.5	1.35	1.566	1.040	1.050	0.682	2.94	57.2
				65.0	1.35	1.566	0.606	0.857	0.682	2.94	990.4
3	CSP1/ MP3	1.22	38	100 <sup>d</sup>	1.0	1.330	0.963	1.046	0.953	2.75	416.3
				100 <sup>e</sup>	1.2	1.596	0.963	1.046	0.794	2.96	386.8
				99.0	1.2	1.596	1.191	1.195	0.794	2.96	130.5
				97.5	1.2	1.596	0.931	1.068	0.794	2.96	329.0
				65.0	1.2	1.596	0.520	1.104	0.794	2.96	1723
4	CSP1/ MP4	1.40	15	100 <sup>d</sup>	1.0	1.610	0.950	1.204	1.041	2.97	467.8
				100 <sup>e</sup>	1.1	1.771	0.950	1.204	0.947	3.10	448.6
				99.0	1.1	1.771	1.031	1.243	0.947	3.10	367.2
				97.5	1.1	1.771	0.983	1.226	0.947	3.10	415.3
				65.0	1.1	1.771	0.432	1.549	0.947	3.10	1272
5	CSP2/ MP5	1.07	5	100 <sup>d</sup>	1.0	8.621	7.787	7.817	7.557	7.19	7.75
				100 <sup>e</sup>	1.5	12.93	7.787	7.816	5.038	9.83	5.67
				99.0	–	–	–	–	–	0	
				97.5	1.5	12.93	8.213	8.221	5.038	9.83	1.39
				65.0	1.5	12.93	6.125	6.473	5.038	9.83	33.1
2* <sup>f</sup>	Ref.	1.14	50	100 <sup>d</sup>	1.0	1.170	0.966	0.992	0.924	2.63	178.3

<sup>a</sup> Eq. (20),  $Q_1 = Q_{max} = 1.0$  ml/min,  $V$  and  $\varepsilon$  as in Section 4.1.

<sup>b</sup>  $c_F = c_{max}$  (Section 4.1).

<sup>c</sup>  $N = 300$  (Section 4.1).

<sup>d</sup> From equilibrium theory, Eq. (26),  $m_I$  and  $m_{IV}$  for  $\beta = 1$  (PUR = 100%).

<sup>e</sup> From equilibrium theory, Eq. (26),  $m_I$  and  $m_{IV}$  for  $\beta > 1$  (PUR = 100%).

<sup>f</sup> See Table 1.

system CSP1/MP2. Naturally the resulting operation parameters as well as the determined productivity are very close to the values for CSP1/MP2.

From the results summarized in Table 2 it can be recognized that the obtained productivities depend strongly on the chromatographic system applied. Fig. 5 illustrates the observed dependencies of the productivities on the feed concentrations and on the purity requirements in a three-dimensional plot for the four different chromatographic systems considered. Every point in the diagrams corresponds to a vertex found by the optimisation approach as described above. For all systems  $PR_i$  increases with increasing feed concentration. Furthermore  $PR_i$  rises rapidly if the required purity is lowered. In contrast to the situation at higher purities the productivity for lower purities does not reach a maximum for the

concentration range examined here. As expected, the SMB process based on the isotherms exhibiting the highest separation factor of  $\alpha = 1.4$  (CSP1/MP4) is most productive for high purities (Fig. 5c). However, for low purities the highest productivity is obtained for the system CSP1/MP3 (Fig. 5 b). Obviously, in this case the higher applicable feed concentration is advantageous. Such type of isotherms might be of interest if a low purity is required and the feed solution can be introduced very concentrated. Although the feed concentration for the case plotted in Fig. 5a (CSP1/MP2) is the highest, it does not lead to high productivities, since the separation factor is not sufficiently large. Because of the very low separation factor (1.07) and the low maximum feed concentration (5 g/l), the productivity for the isotherms measured on the cyclodextrin column (CSP2/

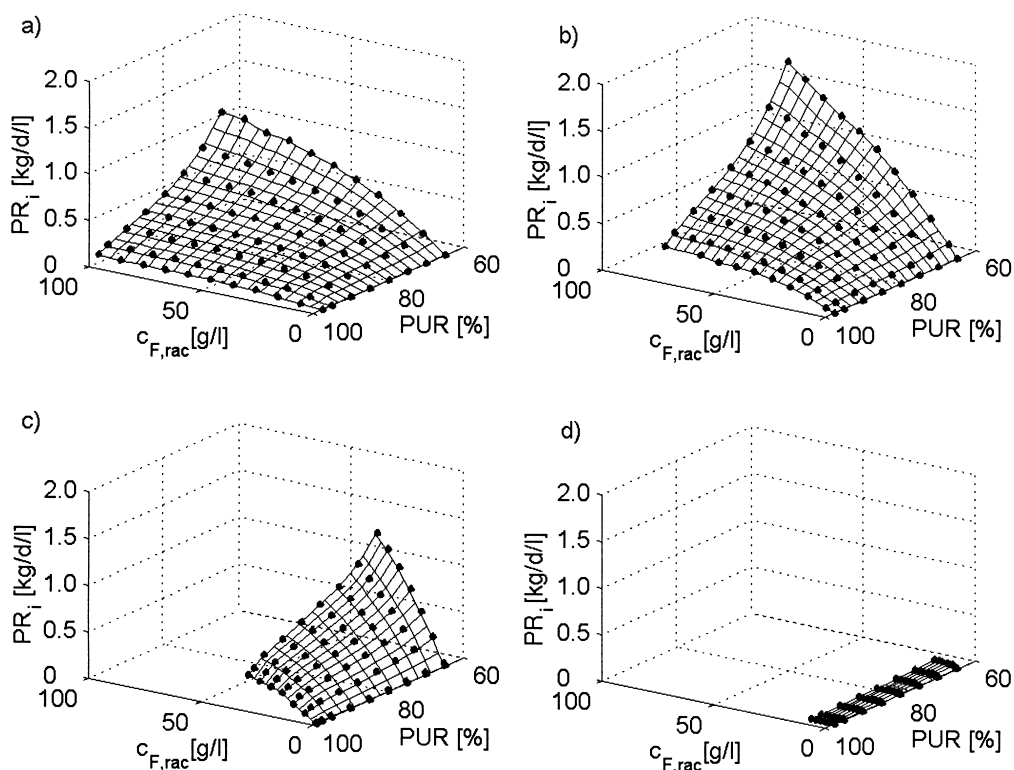


Fig. 5. Simulated productivities of the SMB process as a function of feed concentrations and specified purity requirements. Calculated for the isotherm parameters and operating parameters given in Tables 1 and 2. (a) No. 2, CSP1/MP2; (b) No. 3, CSP1/MP3; (c) No. 4, CSP1/MP4; (d) No. 5, CSP2/MP5.

MP5, Fig. 5d) is negligible compared to the productivities accessible with the teicoplanin (CSP1) systems.

Finally, it should be emphasized that the numerical results presented hold for the considered four-column SMB system which was restricted by a low maximum flow-rate related to the lab scale column dimensions. Changing the number and size of columns might effect the absolute values of the productivity without changing the main tendencies presented in Fig. 5.

## 5. Conclusions

The influence of different sets of adsorption isotherms on the achievable productivities in enantio-separations by SMB chromatography was studied. For this, parameters of the Langmuir model were

measured for the adsorption of the mandelic acid enantiomers on two different chiral stationary phases using different mobile phases. To analyze the productivity of the SMB process, as well analytical solutions based on the equilibrium theory as numerical solutions based on the equilibrium dispersive model were used. Parametric studies revealed the large impact of the selectivity factors on the process productivity. In addition to inspecting the productivity related to collecting pure products also the aspect of lowering the purity requirements was considered. In the latter case higher productivities can be reached and other chromatographic systems might be superior as for the production of very pure products. The selection of the proper chromatographic system for solving a certain separation problem with the SMB process requires a careful analysis. The methodology used in this study appears to be capable to analyze problems of this type.

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