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Separation of stereoisomers in a simulated moving bed-supercritical fluid chromatography plant

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Abstract

The combination of two techniques, simulated moving bed (SMB) and supercritical fluid chromatography (SFC), leads to an apparatus with unique features. Besides the known advantages of the SMB process, like reduced solvent consumption and its continuity, the use of supercritical carbon dioxide as the mobile phase offers an easy product recovery by depressurizing the supercritical fluid. Details of a SMB-SFC plant are presented for the first time. Due to the large number of process parameters a simulation of the SMB process is necessary to achieve optimal operating conditions. The most important thermodynamic information for a SMB process is the adsorption isotherms. Therefore, isotherms for two phytol isomers are measured and correlated. A fast dynamic model for the simulation of SMB is used to calculate the region of complete separation taking different column configurations and the compressibility of the mobile phase into account.

Keywords: Simulated moving bed chromatography; Preparative chromatography; Adsorption isotherms; Supercritical fluid chromatography; Positional isomers; Phytol; Toluene

1. Introduction

The increasing trend towards drugs of highest purity promotes preparative-scale chromatographic techniques. Most of these separations are performed using preparative liquid elution chromatography on a single column. The well known disadvantages of this concept are the dilution of products, the high solvent consumption and its discontinuity. The simulated moving bed (SMB) concept can overcome two of these drawbacks: it is a continuous counter-current process with reduced solvent consumption [1,2].

The SMB concept is derived from the true counter-current movement bed process (TMB, Fig. 1) of the fluid (a liquid, gas or supercritical fluid) and the solid phase (e.g. silica). The TMB and SMB units are divided into four sections, each of them playing a specific role in the process. Due to enormous techni-

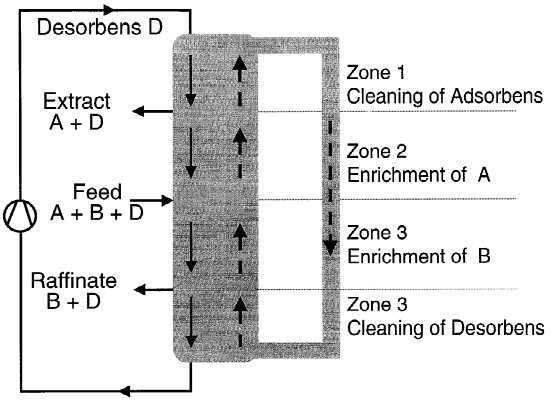

Fig. 1. Scheme of the TMB process.

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cal problems of moving a solid, the counter-current movement of the solid is simulated by moving the inlet and outlet ports in direction of the fluid flow. Fig. 2 shows the functional scheme of the SMB process with a resulting internal concentration profile for the separated components A and B. If for the SMB process a supercritical fluid is used as the solvent the product recovery can easily be achieved by depressurizing the gas. Another unique feature of the SMB-supercritical fluid chromatography (SFC) process is the opportunity to change the elution strength of the mobile phase by density in order to optimise the separation performance.

The SMB technique was originally developed in the 1960s by UOP [3] for the separation of hydrocarbons. In the last decade this technique has been applied for a number of other separations such as sugars [4,5], racemic drugs [6–14], isomers [15] and enzymes [16,17]. All these studies have been carried out using liquid solvents. Up to now only one group is known who have published results of an SMB separation using supercritical carbon dioxide [18], however, without describing details of their work and equipment.

The aim of this project is to develop this technique for the separation of pharmaceutical or fine chemical products with phytol as an example.

The separation of phytol isomers (3,7,11,15-tetramethyl-2-hexadecen-1-ol, $C_{20}H_{40}O$) has been published by Jusforgues et al. [19] using single-column

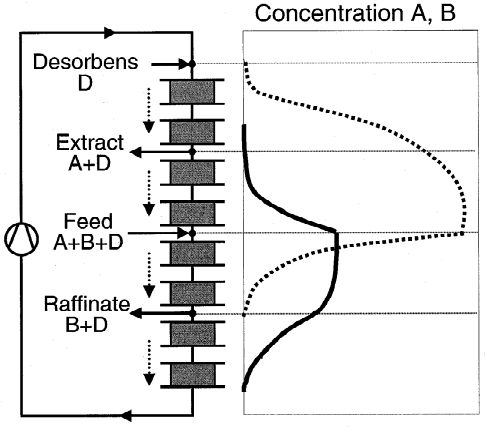

Fig. 2. Functional scheme of the SMB process with internal concentration profile for the components A (dotted line) and B (solid line).

SFC. The *trans* isomer is used as a fixer in perfume industry. Blehaut et al. [20] published on HPLC-SMB large-scale separation.

2. Experimental

2.1. Materials

Carbon dioxide with a purity of more than 99.95% was obtained from KWD (Bad Hönningen, Germany). Toluene and isopropanol were purchased from Merck (Darmstadt, Germany) with a purity of more than 99.95 and 99.95%, respectively. Phytol was obtained from Merck–Schuchardt (Hohenbrunn, Germany). The material is a 1:2 mixture of the isomers with impurities of $<5\%$.

2.2. Supercritical fluid chromatography

Besides the well known physical states of pure substances (liquid, gas and solid) the supercritical (or fluid) state exists. Substances are in that state if both the pressure and the temperature are higher than the critical values. Because of its low critical temperature (304.2 K) carbon dioxide is a preferred supercritical fluid which is available in purified form at low cost. Food and health industries greatly appreciate carbon dioxide because it is inert, non-toxic and has a natural character. Unfortunately, carbon dioxide is a relatively non-polar component and has negligible solvating power for even slightly polar compounds. One possible method of increasing its solubility, is to add several percent of modifier such as low molecular weight alcohols. The elution strength of the fluid is highly dependent on pressure and temperature. So by variation of these parameters the separation performance can be optimised

After Klesper [21] developed the chromatography with supercritical eluents in 1962, this technique has been applied for analytical separations only. During that time technical problems avoided the usage of SFC at a preparative scale. In 1980, Perrut and Berger [22] first described a preparative SFC plant. An overview about SFC applications in the years between 1962 and 1989 is given by Berger et al. [23]. The addition of a modifier to the carbon dioxide lead to shorter retention times and an

improvement of peak shapes for many solutes [24,25]. In the last decade, SFC has become a consolidated technique used for several analytical and preparative applications. Williams and Sandler [26] give an overview about analytical SFC separations of enantiomers.

Lembke [27,28] described the isolation of ethyl esters from fish oil with preparative batch-SFC using an aminopropyl stationary phase. Perrut et al. and Doguet et al. [29,30] studied also the separation of fish oil ethyl esters by chain length and used several stationary phases. Reichmann [31] separated the ethyl esters of the unsaturated fish oil components, docosahexaenoic acid (DHA) and docosapentaenoic acid (DPA), on modified alumina. Perrut et al. [32] separated enantiomers on a preparative scale. Aaltonen et al. [33] replaced the traditional LC separation step for the separation of cyclosporin A from the fermentation broth by a preparative two-step batch SFC. By using carbon dioxide as mobile phase the needed amount of toluene, hexene and methanol of more than 1000 kg per kg of product was reduced to several kg per kg of product with the usage of ethanol and methanol as the modifier. Jusforgues et al. [19] separated the stereoisomers of phytol as well as the racemic mixture of guaifenisin using batch-SFC.

Preparative chiral separations of phosphine oxides on a Pirkle phase were carried out by Fuchs et al. [34] under SubFC (subcritical fluid chromatography: the mobile phase is a compressed fluid, but the temperature is lower than the critical temperature of the fluid) conditions in a dynamical axial-compressible column with an inner diameter of 60 mm. The obtained selectivity was 1.15–1.35, while product purity was over 95% with a flow of up to 100 mg/h. Also under SubFC conditions Blum et al. [35] separated some chirally and pharmaceutically interesting substances in a column with an inner diameter of 25.4 mm. The stationary phase was Whelk-O 1(Merck).

Bartle et al. [36] determined the separation of milbemycin α from a fermentation extract. This study was conducted in HPLC columns with inner diameters of 20 mm and pressure jackets. The SFC unit that was used had five fraction samplers in which the fluid-cooled products were collected. There have been only few studies with countercurrent separations under supercritical conditions. Yu et al. [37,38] used supercritical carbon dioxide in a fluid–liquid chromatography unit for the separation of synthetic phenon mixtures. Clavier [18] described the separation of a synthetic mixture of γ-linoleic acid ethyl ester (GLA) and docosahexaen-acid ethyl ester (DHA) in a SMB plant using pure supercritical carbon dioxide as the fluid phase. He worked with eight columns of 33 mm I.D. packed with C_{18} reversed-phase silica. The obtained purities for the raffinate (GLA) and the extract (DHA) fractions were 97.7 and 97.8%, respectively. A total productivity of 33.1 g per day in the isocratic mode was reported. By the implementation of a pressure gradient in the system, a four-fold higher productivity was reached. Mazzotti et al. [39] used the results of Clavier as a basis for simulations.

2.3. The SMB-SFC plant

The SMB-SFC plant (Fig. 3) consists of up to eight custom-made columns (inner diameter 30 mm) with dynamic axial compression and variable bed length (Fig. 4). The columns are designed for pressures up to 40 MPa and temperatures up to 470 K. Between two columns six valves are needed (Fig. 5) to allow the removal of the raffinate (less retained), extract (more retained) and the recycling streams and the input of feed and eluent. The five in- and outgoing streams (feed, desorbens, raffinate, extract and recycling) are guided by five 8+1-way valves (SD8UW, Valco, Switzerland). Between two columns shut-off valves (Labor-Ventil Typ 1, Nova Swiss, Switzerland) are located. All these valves are operated with air actuators. The raffinate and extract fractions are collected in high-pressure fluid cyclones made at the Technical University Hamburg-Harburg (TUHH). The cyclones have an inner diameter of 20 mm and an integrated product storage tank. Both columns and cyclones are electrically heated with heating tapes (type HS/030, Hillesheim, Waghäusel, Germany). Temperatures are measured with PT 100 resistors (type GR2105, Hartmann and Braun, Alzenau, Germany). They were fixed into holes of the columns using a silicone adhesive (Elastosil E14, Wacker-Chemie, Burghausen, Germany) The carbon dioxide is pumped by an air driven pump (type G60 L, Maximator, Zorge, Germany), which pumps up to

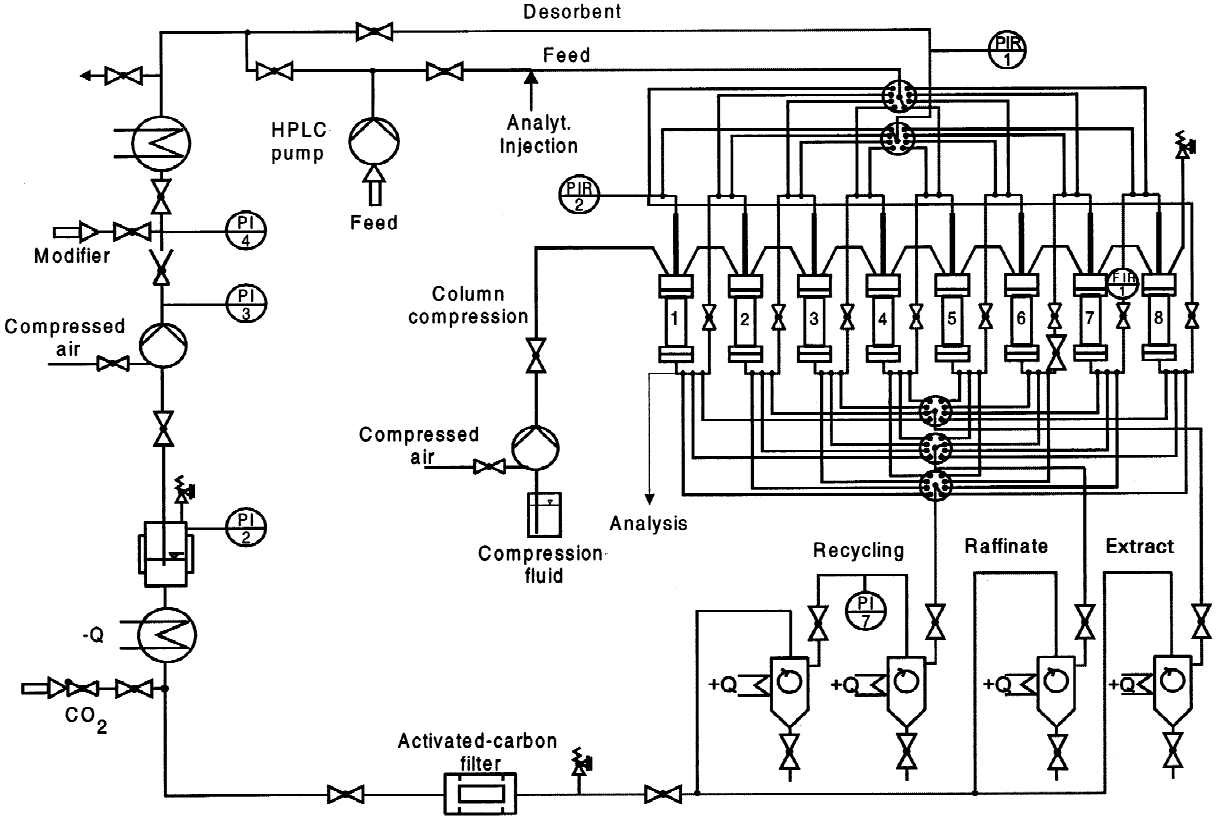

Fig. 3. Scheme of the SMB-SFC plant.

18 kg/h. The pump sucks cooled, liquid carbon dioxide from the bottom of an autoclave (500 ml). Then the carbon dioxide passes a pressure regulating valve (type 44–1100, Dräger Tescom, Lübeck, Germany), which regulates the pressure as desired. The modifier (isopropanol, analytical-grade reagent; Merck, Darmstadt, Germany) is added by a HPLC pump (LC pump 414-T, Kontron Instruments, Neufahrn, Germany). Heating is carried out in a temperature-controlled water bath. The stream is divided into two parts: one for the desorbent and one for the feed. The liquid feed material is pumped with a HPLC pump (LC pump 414-T, Kontron) into the system. All connections are made with 1/8 in. stainless steel tubing (Dockweiler, Oststeinbek, Germany) and fittings from Autoclave Engineers, Valco and Swagelok (1 in.=2.54 cm). Unlike HPLC-SMB, where the flow-rates are controlled by HPLC pumps (in combination with a balance), the flow-rates in this system are controlled by manually actuated metering valves located at the cyclone inlets. The mass flow is measured with a Rheonik mass flow detector (Type RHM GNT 01 P, Schwing, Germany) located between columns 7 and 8. Between columns 6 and 7, a pressure transducer (AO5, STW, Kaufbeuren, Germany) is mounted. A 100 μl sample loop (A6UW, Valco Europe, Schenkon, Switzerland) for the determination of the internal concentration profile is located between columns 1 and 2. The sample device is coupled to an analytical SFC constructed in our laboratories. The analytical separation was carried out using a 250×4 mm column filled with LiChrospher Si 60 from Merck. The SMB system is controlled by a Pentium 233 personal computer in combination with a control cabinet built at our university.

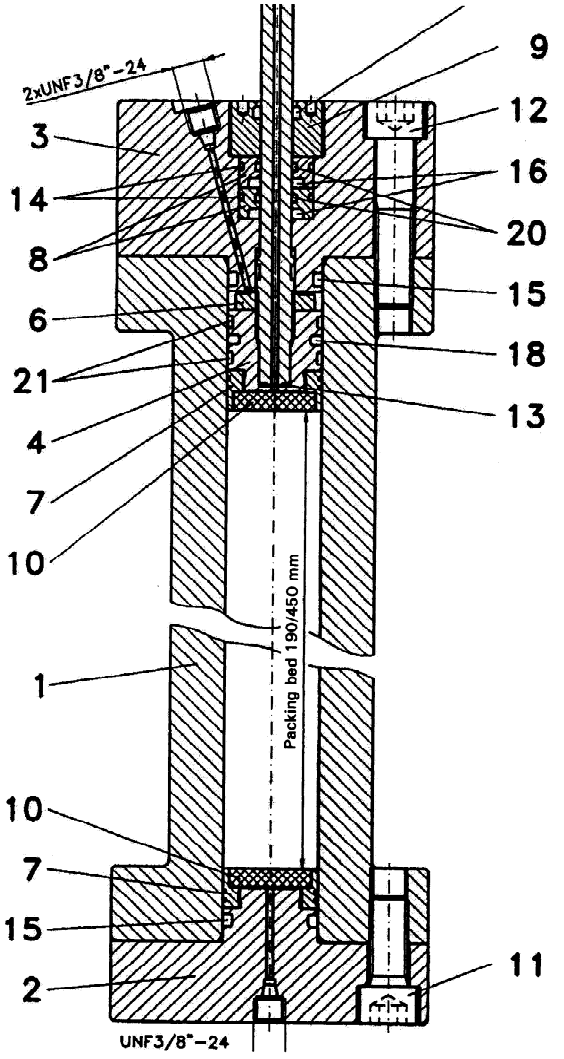

Fig. 4. SMB column (1″=1 in.=2.54 cm).

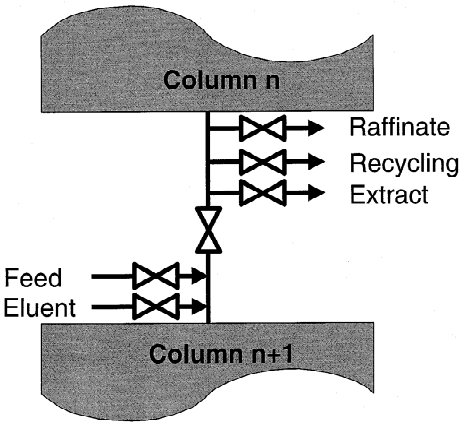

Fig. 5. Connection of SMB-SFC columns.

2.4. Separation development

Before starting a separation with a SMB system the chromatographic separation has to be optimized on an analytical scale. The needed optimization steps in SFC separations are similar to those in HPLC. In addition, the best operating pressure and temperature for SFC separations has to be found. Once this is done, the SMB separation can be carried out. Following the ideas of Nicoud [4] the separation in an SMB plant is conducted in five steps: (1) the packing of the columns, (2) the testing each of the columns by pulse injection, (3) pulse injection into the complete plant, (4) separation of a dilute feed and productivity optimisation by increasing the feed concentration, and for the last step the knowledge of the adsorption isotherms is needed.

In linear chromatography the ratio of the adsorbed and fluid phase concentration for one component is given by the linear adsorption parameter $\bar{K}$. From the measurement of the retention times and the flow rate, the linear adsorption parameter can be calculated using Eq. (1):

$$t_R = \frac{\epsilon_{total} V}{Q} \cdot \left(1 + \frac{1 - \epsilon_{total}}{\epsilon_{total}} \cdot \bar{K}\right) \quad (1)$$

where t_R is the retention time, ϵ_{total} the overall void fraction of the packing, V the volume of the column and Q the volumetric flow rate. In combination with the TMB model published by Ruthven [40] and Storti [41], the flow rates in the four zones can be calculated on the basis of the linear adsorption parameters, described by Mazzotti et al. [42].

2.5. Column packing and testing

The columns were packed with a slurry method: 50 g of stationary phase (LiChrospher Si 60, 15 μm, Merck) was slurried in 200 ml isopropanol (IPA) and filled into the columns. By using a vacuum pump the IPA is sucked out of the columns. After mounting the

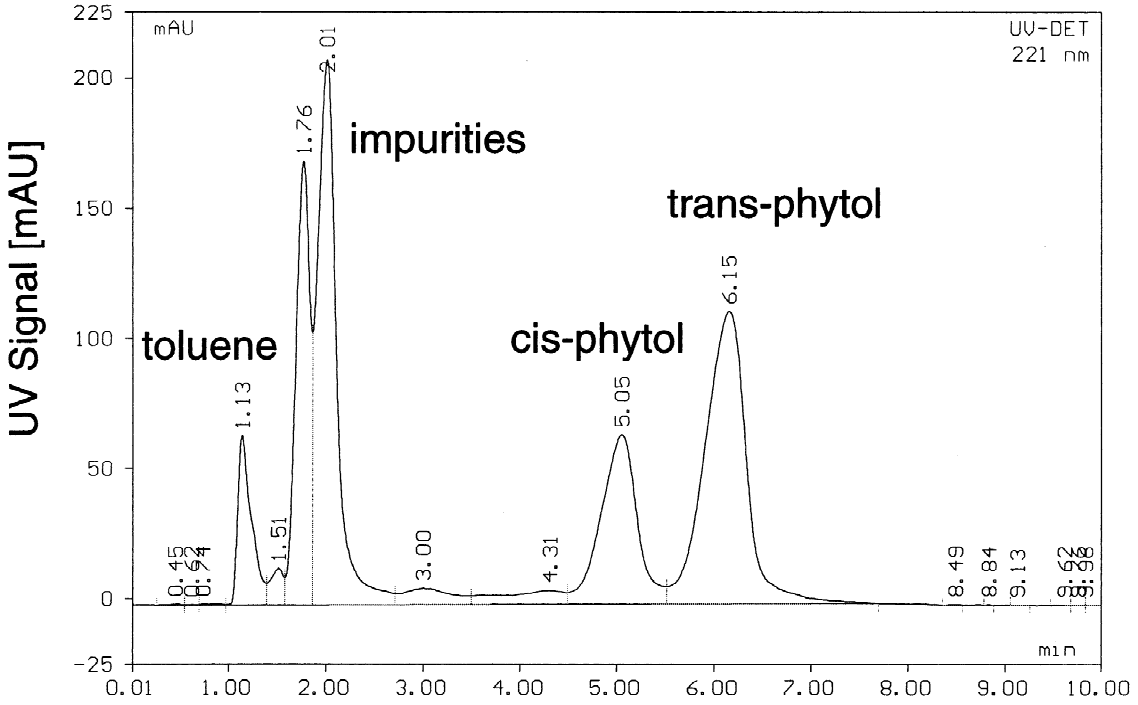

Fig. 6. Chromatogram of the toluene–phytol mixture.

columns in the SMB system the packing is compressed and the carbon dioxide is pumped through the packing. The compression pressure is increased in steps of about 5 MPa, until the needed pressure is reached. Then all columns are tested individually in elution mode by using a mixture of toluene and phytol in hexane (1 and 7.5 g, respectively, per 100 ml hexene).

The operating conditions were: flow rate of the mobile phase 54 g/min, IPA flow 2.4 g/min, pressure 23 MPa, temperature 313 K, injection of 100 μl sample and detection at 221 nm using a UV detector (SPD-10 AV, Shimadzu, Japan) equipped with a high-pressure cell. The dead volume of the apparatus was determined by mounting an unpacked column with piston driven to the bottom into the system and recording the residence time of toluene for several flows. Fig. 6 shows the chromatographic separation of phytol. Column lengths, mean retention times and the number of plates are reported in Table 1. Using Eq. (1) the linear adsorption parameter K is calculated for *cis*-phytol to 13.34 and for *trans*-phytol to 16.97. The selectivity is the ratio of these two: $\alpha_{trans/cis} = 1.27$. For the separation of a diluted phytol

Table 1
Column lengths, mean retention times and number of plates of the SMB columns

Column No.	1	2	3	4	5	6	7	8	Mean
Length (cm)	11.50	10.60	11.70	11.10	11.50	11.10	11.50	11.30	11.29
t_R of toluene (min)	1.27	1.15	1.30	1.19	1.26	1.22	1.22	1.21	1.23
n_{th} of toluene	539.00	181.00	377.00	206.00	329.00	220.00	337.00	158.00	293.38
t_R of *cis*-phytol (min)	5.54	4.87	5.27	4.88	5.5.00	5.28	5.39	4.97	5.25
n_{th} of *cis*-phytol	1578.00	487.00	893.00	501.00	563.00	500.00	729.00	392.00	736.57
t_R of *trans*-phytol (min)	6.73	5.84	6.35	5.87	6.67	6.38	6.55	5.99	6.34
n_{th} of *trans*-phytol	1604.00	286.00	1043.00	541.00	631.00	547.00	671.00	465.00	723.50

Table 2
Flow rates (g/min) for the separation of phytol under linear conditions

Recycling	Eluent	Extract	Feed	Raffinate
70.7	23.0	16.5	7.1	20.0

feed under linear conditions the operating flow rates are listed in Table 2.

The switching time for the valves is 324 s. The pressure drop in the system was 12.1 MPa (23.2 MPa in the first and 11.1 MPa in the last column).

3. Results

In a first experimental run we pumped phytol (111 g added to 1000 g IPA) into the carbon dioxide feed stream. After ten cycles we obtained fraction purities of 99% *trans*-phytol in the extract and 99% *cis*-phytol in the raffinate stream, setting the area of the two isomers to 100%. Fig. 7 shows the analytical chromatograms of the feed, the raffinate, extract and the recycling fraction. The analytical operating conditions were: flow rate of the mobile phase 6 g/min, inlet pressure 23 MPa, temperature 313 K, injection of 100 μl sample, detection at 221 nm using a UV detector (SPD-10 AV, Shimadzu, Japan) equipped with a high-pressure cell.

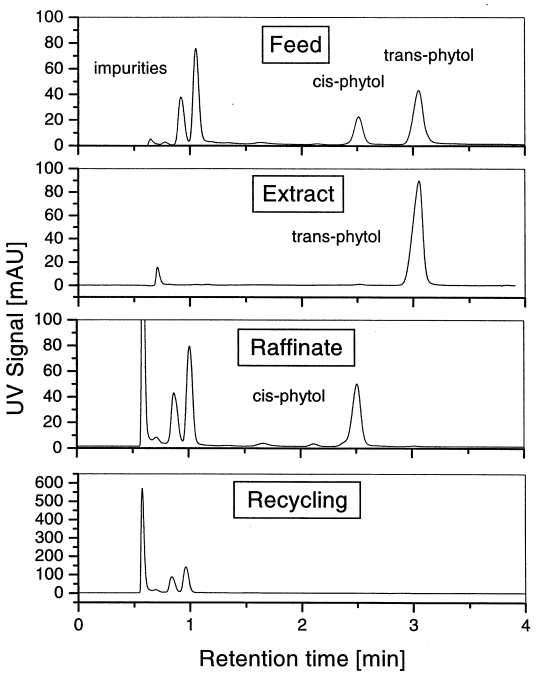

Fig. 7. Analytical chromatograms of the solvent free fractions of the SMB. Impurities in the feed are less than 5% (GC Area).

The internal concentration profile for cycle 10 is shown in Fig. 8. Concentrations are determined 20 s after switching of the valves. The feed concentration of phytol was 0.38% (w/w) in carbon dioxide.

3.1. Determination of adsorption isotherms for phytol

The apparatus for the determination of the adsorption isotherms is shown in Fig. 9. Liquid carbon dioxide is compressed up to the desired pressure by a pneumatically driven pump. The flow of liquefied gas is lowered to operating pressure by a pressure reducing valve. This process is carried out in a modified PM-101 module (NWA, Lörrach, Germany). With a double head HPLC pump (type 420, Kontron) IPA as the modifier is pumped into the system. Operating temperature is achieved with a heating cabinet (Binder, Germany) containing the column and five 6-port Rheodyne valves. A supercritical mixture of carbon dioxide and phytol is filled into a syringe pump (260 D, Isco, Lincoln, NE, USA) to serve as feed. For adsorption a 250×4 mm column filled with LiChrospher Si 60 from Merck is used. After detection with a UV detector (SPD-10A, Shimadzu) at $\lambda = 221$ nm the pressure is reduced in a two stage expansion module (PE-103, NWA) to ambient pressure. The gas flow is measured with a gas meter.

The apparatus allows the measurement of adsorption isotherms with frontal analysis and a perturbation method. The following data are determined with frontal analysis. Due to the anti-Langmuir behavior of the isotherms at lower concentrations the desorption fronts are integrated. The experimental data are correlated with a quadratic isotherm equation [Eq. (2)], because both isotherms have a point of inflection (Figs. 10 and 11).

$$q = q_s \cdot \frac{c(b_1 + 2b_2c)}{1 + b_1c + b_2c^2} \quad (2)$$

The measured data correspond well to the correla-

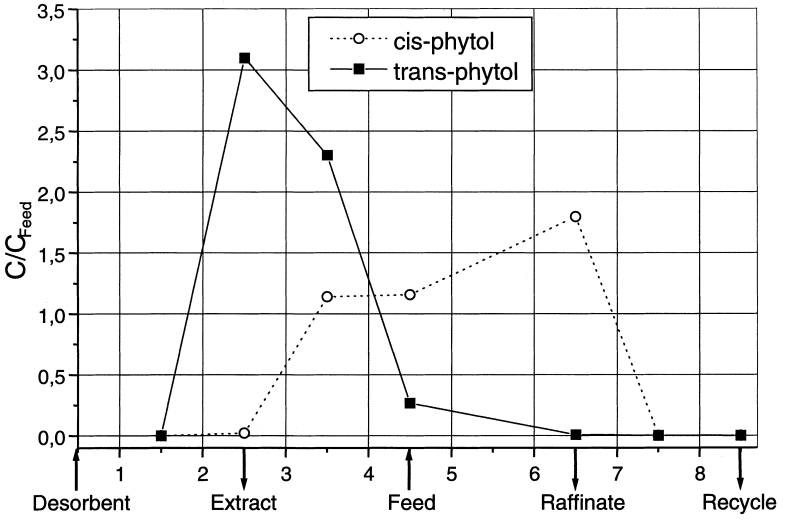

Fig. 8. Internal concentration profile for cycle 10. Concentrations are determined 20 s after switching of the valves. Open symbols/dotted line: *cis*-phytol, filled symbols/solid line: *trans*-phytol. C = Fluid phase concentration.

tion. The derivative of the correlation is shown to demonstrate the point of inflection. The presented isotherms are isotherms of the mixture because the data are determined directly from the binary phytol mixture and not from the pure isomers.

3.2. Simulation of batch chromatograms

For the simulation of batch chromatograms a plug flow model with axial dispersion and a linear mass transfer resistance is used. The solution of the

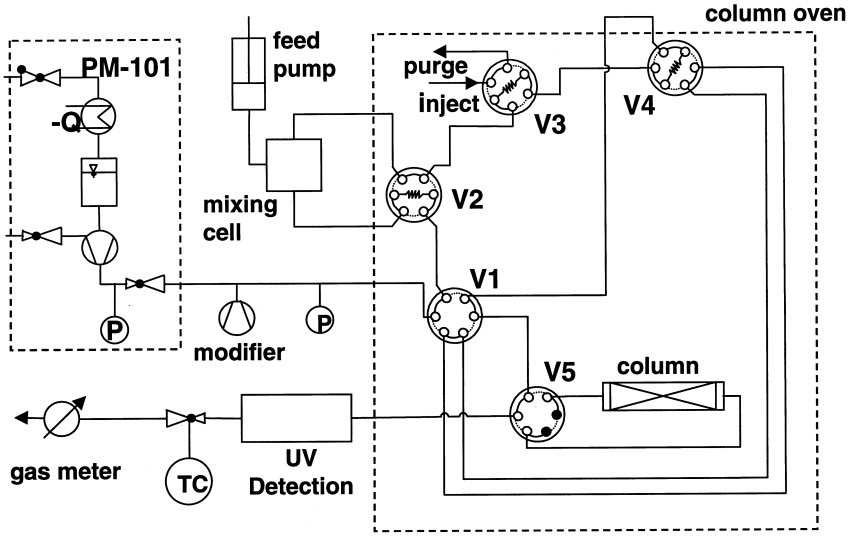

Fig. 9. Apparatus for determination of isotherms.

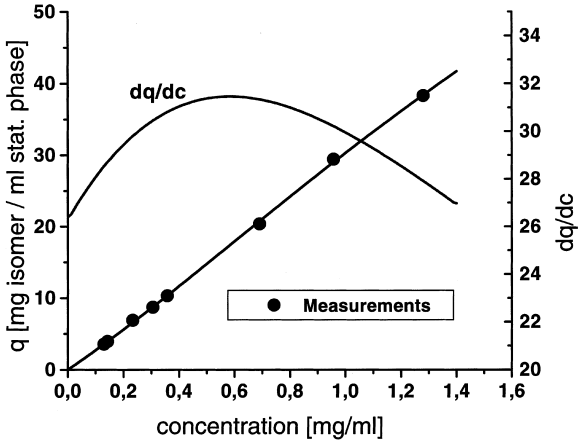

Fig. 10. Adsorption isotherm of *cis*-phytol at 23 MPa, 313 K, 1.8% (w/w) IPA. q = Absorbed phase concentration.

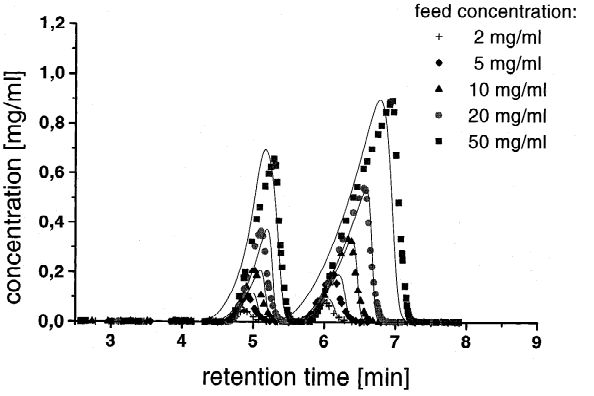

Fig. 12. Experimental and simulated phytol chromatograms at 23 MPa, 313 K, 1.8% (w/w) IPA, column: 250×4 mm, LiChrospher Si 100.

resulting mass balance equations is performed with a finite difference method [43]. Interactions between the two isomers are neglected for simulation of the chromatograms. The pressure drop of about 3 MPa in the column leads to a decrease in density of 3% under experimental conditions. This small change in density is taken into account by using a mean density. Only minor differences between a more detailed model for the pressure drop and this simplification have been found. Although, interaction between the isomers are neglected, the simulated chromatograms agree well with experimental data (Fig. 12). For other applications or the higher concentration region a more detailed model like IAS theory is necessary.

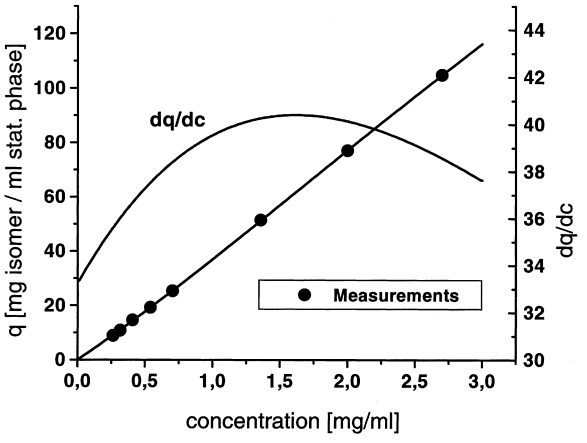

Fig. 11. Adsorption isotherm of *trans*-phytol at 23 MPa, 313 K, 1.8% (w/w) IPA.

3.3. Simulation of the SMB process

Because of its significantly shorter computation time, a simpler equilibrium axial dispersed plug flow model is used for the simulation of the SMB process. All kinetic effects are lumped into the apparent dispersion coefficient, D_{ap}. The pressure drop in the columns is calculated with the Ergun equation. Perrut [32] showed that the Ergun equation, in combination with an equation of state, predicts the pressure drop in chromatographic columns with good accuracy. The equation of state from Span and Wagner [44] is used to calculate the mobile phase density. Unlike with the simulations of batch chromatograms, the mobile phase velocity for the SMB simulations is considered variable. The numerical solution of the mass balance equations [Eq. (3)] is done with a finite difference method first developed by Rouchon [45] for the simulation of a single bed and adapted to the conditions of the SMB process by Kniep et al. [46].

$$0 = \frac{\partial c_i}{\partial t} + u \cdot \frac{\partial c_i}{\partial z} + c_i \cdot \frac{\partial u}{\partial z} - D_{ap} \cdot \frac{\partial^2 c_i}{\partial z^2} + \frac{1 - \epsilon_{total}}{\epsilon_{total}} \cdot \frac{\partial q_i}{\partial t} \quad (3)$$

Following the ideas of Ruthven [41] and Storti [42] one can describe the TMB process as well as the SMB process with four key parameters: the net flow ratios m_j [Eq. (4)]:

$$\frac{Q_{TMB\ zone} - Q_s \epsilon_p}{Q_s(1 - \epsilon_p)} = \frac{Q_{SMB\ zone} t_{shift} - V_{column} \epsilon_{total}}{V_{column}(1 - \epsilon_{total})} \quad (4)$$

j = Zone I to Zone IV.

Using these parameters the region of complete separation of a binary mixture can be shown in a (m_2, m_3) plane. The pressure drop in the columns leads to variable volume flow in the different sections of the SMB. Therefore a new parameter m_j^* (constant for each zone) has to be defined that is based on the mass flows in the different SMB sections:

$$m^*_j = \frac{Q_{SMB\ zone} \rho_{mobile\ phase} t_{shift} - V_{column} \epsilon_{total} \rho_{ref}}{V_{column}(1 - \epsilon_{total}) \rho_{ref}} \quad (5)$$

j = Zone I to Zone IV.

For the most common adsorption isotherm equations i.e. Langmuir and bi-Langmuir multicomponent isotherms analytical solutions exist for the complete separation region. These analytical solutions are based on equilibrium theory and, therefore, neglecting mass transfer resistance and axial dispersion. In addition, the number of columns the SMB process consists of is not taken into account by the analytical solution, because it is based on the TMB process. The mentioned algorithm is fast and robust enough to calculate the region of complete separation in the (m_2^*, m_3^*) plane numerically considering the effects of axial dispersion and a discrete number of columns in a SMB process.

3.3.1. Influence of column configuration

To show the influence of column configuration on the separation of the two phytol isomers the region of complete separation (purity > 99.9%) in the (m_2^*, m_3^*) plane is calculated for an eight (Fig. 13) and a four (Fig. 14) column configuration. For both calculations the same amount of stationary phase material is assumed. The overall number of theoretical plates is identical for both simulations. For these calculations a pressure drop of 0 MPa is assumed to show the influence of column configuration separately from the effect of pressure drop.

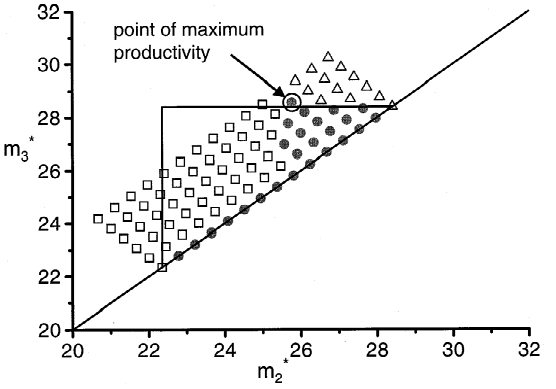

Fig. 13. (m_2^*, m_3^*) plane for C_{feed} = 5.0 mg/ml phytol (23 MPa, 313 K, 1.8% (w/w) IPA) compared to infinite dilution situation and an infinite number of theoretical plates (black triangle); column configuration: 2/2/2/2; 500 theoretical plates per column; calculations without pressure drop; □ *cis*-phytol purity > 99.9%, △ *trans*-phytol purity > 99.9%, · both isomers > 99.9% pure.

Using only four separation columns leads to a much smaller region of complete separation. The point of maximum productivity for the eight column

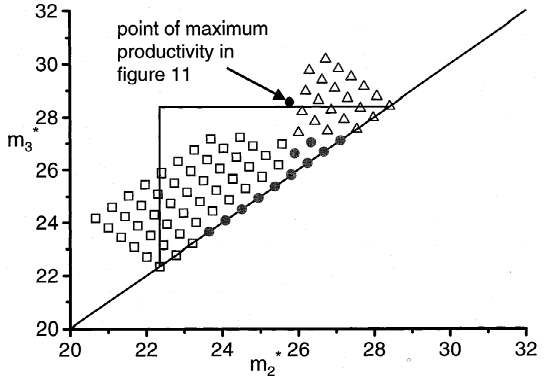

Fig. 14. (m_2^*, m_3^*) plane for the same parameters as in Fig. 11 but column configuration: 1/1/1/1; 1000 theoretical plates per column, same amount of stationary phase as in Fig. 11; calculations without pressure drop, □ *cis*-phytol purity > 99.9%, △ *trans*-phytol purity > 99.9%, · both isomers > 99.9% pure.

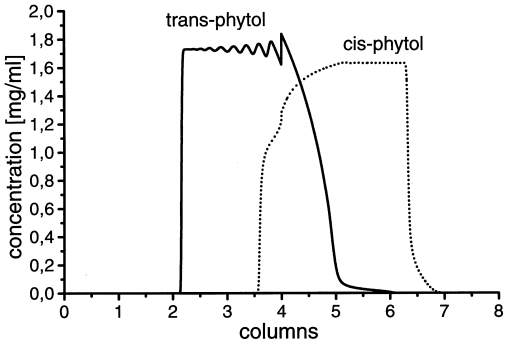

Fig. 15. SMB concentration profile just before switching for the point of maximum productivity in Fig. 11; *cis*-phytol purity > 99.9%, *trans*-phytol purity > 99.9%.

configuration ($m_2^* = 25.76$, $m_3^* = 28.57$, shown in Fig. 13) is simulated with the dynamic SMB model for eight and four columns (Figs. 15 and 16). The use of only four columns while keeping the same productivity as with eight columns results in product streams that are slightly contaminated. The decrease of purity is about 1% in this example.

3.3.2. Influence of pressure drop

Taking the pressure drop into account (Fig. 17) leads to a shift of the complete separation region to smaller values of m_2^* and m_3^* compared to the calculations without pressure drop.

As shown in Fig. 18 simulations for columns with 300 theoretical plates per column for an eight column configuration has only a small influence on the complete separation region compared to the

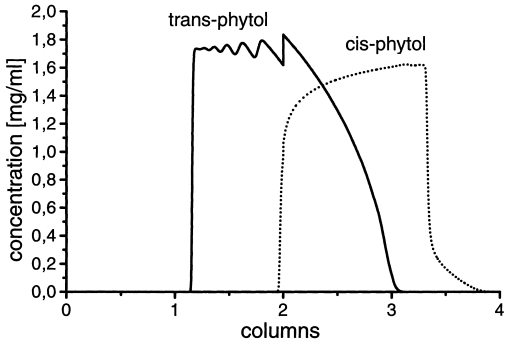

Fig. 16. SMB concentration profile just before switching for the same set of operating parameters as in Fig. 13 but column configuration: 1/1/1/1; each column 1000 theoretical plates; *cis*-phytol purity > 99.0%, *trans*-phytol purity > 99.1%.

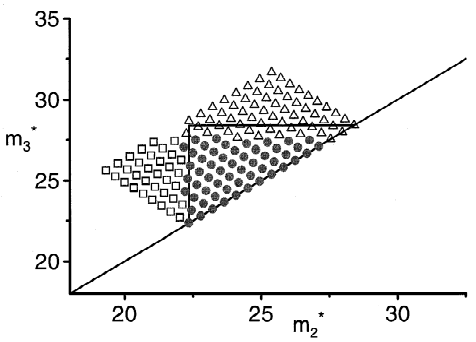

Fig. 17. (m_2^*, m_3^*) plane for a phytol isomer separation under linear conditions (23 MPa, 313 K, 1.8% (w/w) IPA) compared to infinite dilution situation and an infinite number of theoretical plates (black triangle); column configuration: 2/2/2/2; 300 theoretical plates per column; calculations *with* pressure drop, □ *cis*-phytol purity > 99.9%, △ *trans*-phytol purity > 99.9%, ● both isomers > 99.9% pure.

results of the equilibrium theory that assumes an infinite number of theoretical plates (black triangle).

4. Conclusions

A SMB-SFC plant has been build and tested. The columns show good separations of the phytol isomers. The packing technique allows packing of all columns within a day with good reproducibility. The system is started in the linear mode with a diluted

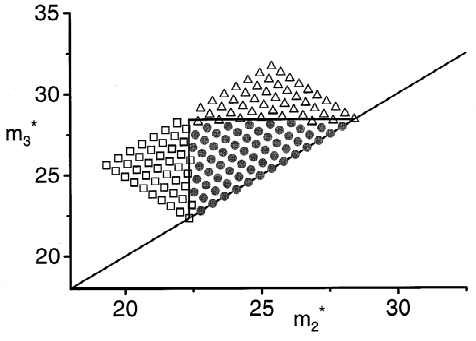

Fig. 18. (m_2^*, m_3^*) plane for a phytol isomer separation under linear conditions (23 MPa, 313 K, 1.8% (w/w) IPA) compared to infinite dilution situation and an infinite number of theoretical plates (black triangle); column configuration: 2/2/2/2; 300 theoretical plates per column; calculations *without* pressure drop, □ *cis*-phytol purity > 99.9%, △ *trans*-phytol purity > 99.9%, ● both isomers > 99.9% pure.

feed. Fraction purities of 99% were reached. For separations at higher feed concentrations the measured adsorption isotherms are needed. The experimental chromatograms under supercritical conditions can be described well, with a correlated quadratic isotherm equation based on measured adsorption data. To describe the SMB-SFC separations a new parameter m_j^* similar to the net flow ratios from Ruthven [41] and Storti [42] has been defined. Taking a finite number of theoretical plates, the column configuration and the pressure drop into account the (m_2^*, m_3^*) plane can be calculated. The optimal operating points and the resulting concentration profiles for an eight and four column configuration are shown. The influence of pressure drop on the separation is demonstrated.

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References

[1] K. Gottschall, paper presented on PREP 1995, Washington, DC, 12–14 June 1995.
[2] J. Strube, Chem. Eng. Tech. 70 (1998) 1271.
[3] D.B. Broughton, US Pat. 3 291 726 (1966).
[4] R.M. Nicoud, LC·GC Int. 5 (1992) 43–47.
[5] P. Deckert, Chem. Eng. Tech. 69 (1997) 115.
[6] M. Schulte, R. Ditz, R.M. Devant, J.N. Kinkel, F. Charton, J. Chromatogr. A 769 (1997) 93.
[7] S. Nagamatsu, J. Chromatogr. A 832 (1999) 55.
[8] E. Küsters et al., Chromatographia 40 (1995) 387.
[9] L.S. Pais et al., J. Chromatogr. A 769 (1997) 25.
[10] M. Negawa, F. Shoji, J. Chromatogr. 590 (1992) 113.
[11] D.W. Guest, J. Chromatogr. A 760 (1997) 159.
[12] G. Fuchs, L. Doguet, D. Barth, M. Perrut, J. Chromatogr. 623 (1992) 329.
[13] E.R. Francotte, P. Richert, J. Chromatogr. A 769 (1997) 101.
[14] M.J. Gattuso, B. McCulloch, J.W. Priegnitz, in: Symp. on Chiral Europe, 1994.
[15] J. Blehaut, F. Charton, R.-M. Nicoud et al., LC·GC Int. 9 (1996) 226.
[16] N. Gottschlich, S. Weidgen, J. Kasche, J. Chromatogr. A 719 (1996) 267.
[17] N. Gottschlich, V. Kasche, J. Chromatogr. A 765 (1997) 201.
[18] J.Y. Clavier, in: 7th Int. Symposium on Supercritical Fluid Chromatography and Extraction, Indianapolis, 31 March–4 April 1996.
[19] P. Jusforgues, M. Shaimi, H. Colin, D. Colopi, in: D. Tondeur (Ed.), Proceedings of Spica, Strasbourg, 23–25 September 1998.
[20] J. Blehaut, F. Charton, R.-M. Nicoud, LC·GC Int. 9 (1996) 228.
[21] E. Klesper, A.H. Corwin, D.A. Turner, J. Org. Chem. 27 (1962) 700.
[22] C. Berger, M. Perrut, J. Chromatogr. 505 (1980) 37.
[23] T.A. Berger, J. Chromatogr. A 785 (1997) 3.
[24] A.L. Blilie, T. Greibrokk, Anal. Chem. 57 (1985) 2239.
[25] J.G.M. Janssen, P.J. Schoenmakers, C.A. Cramers, J. High Resolut. Chromatogr. 12 (1989) 645.
[26] K.L. Williams, L.C. Sander, J. Chromatogr. A 785 (1997) 149.
[27] P. Lembke, in: 7th Int. Symposium on Supercritical Fluid Chromatography and Extraction, Indianapolis, 31 March–4 April 1996, abstract L-38.
[28] P. Lembke, in: K. Anton, C. Berger (Eds.), Supercritical Fluid Chromatography with Packed Columns, Marcel Dekker, New York, 1998.
[29] M. Perrut, C. Berger, P. Jusforgues, 1st Int. Symposium on Supercritical Fluids, Nice, 1988, p. 397.
[30] L. Doguet, D. Barth, M. Perrut, in: 2ème Colloque sur Les Fluides Supercritiques, Paris, October 1991, p. 219.
[31] F. Reichmann, A. Depta, G. Brunner, in: PREP, Basle, 1–4 September 1996, abstract 04.
[32] M. Perrut, J. Chromatogr. A 658 (1994) 293.
[33] O. Aaltonen, M. Alkio, J. Lundell, S. Ruohonen, L. Parvinen, V. Suoninen, BioPharm Europe 8 (1998) 42.
[34] G. Fuchs, L. Doguet, D. Barth, M. Perrut, J. Chromatogr. A 623 (1992) 329.
[35] A.M. Blum, K.G. Lynam, E.C. Nicolas, Chirality 6 (1994) 302.
[36] K.D. Bartle, J. Chromatogr. A 697 (1995) 579.
[37] T. Yu, S.-E. Li, Y.-H. Chen, H.P. Wang, J. Chromatogr. A 724 (1996) 91.
[38] T. Yu, Y.-H. Chen, J. Chromatogr. A 790 (1997) 31.
[39] M. Mazzotti, G. Storti, M. Morbeidelli, J. Chromatogr. A 786 (1997) 309.
[40] D.M. Ruthven, C.B. Ching, Chem. Eng. Sci. 44 (1989) 1011.
[41] G. Storti, M. Mazzotti, M. Morbidelli, S. Carra, AIChE J. 39 (1999) 471.
[42] M. Mazzotti, G. Storti, M. Morbidelli, J. Chromatogr. A 769 (1997) 3.
[43] K. Kaczmarski, D. Antos, J. Chromatogr. A 756 (1996) 73.
[44] R. Span, W. Wagner, J. Phy. Chem. Ref. Data 25 (1996) 1509.
[45] P. Rouchon, M. Schnauer, P. Valentin, G. Guiochon, Sep. Sci. Technol. 22 (1987) 1793.
[46] H. Kniep, T. Falk, A. Seidel-Morgenstern, in: PREP, Basle, 1–4 September 1996.