SYNTHESIS REPORT

FOR PUBLICATION

CONTRACT N° : BRE2-CT92-0337

PROJECT N° : ~~0337~~ BE-5974

TITLE : PURIFICATION OF OPTICAL ISOMERS WITH CONTINUOUS CHROMATOGRAPHY << ENANTIO CHROM »

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STARTING DATE : 01/12/1992 DURATION :36 MONTHS

PROJECT FUNDED BY THE EUROPEAN COMMISSION UNDER THE BRITE/EURAM PROGRAMME

DATE : 31/01/1996

PURIFICATION OF OPTICAL 1SOMERS WITH CONTINUOUS CHROMATOGRAPHY

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ABSTRACT

There is an increasing demand for optically pure molecules especially for the pharmaceutical industry. Different routes already used for the production of optically pure compounds (asymmetric synthesis, enzymatic processes, crystallisation) usually suffer from a lack of generality, require a significant development time and can be very expensive. The idea of this project is to perform the separation of racemic mixtures by chromatography which is of very wide applicability. In order to minimize eluent consumption, to maximise productivity, and to obtain a continuous production, the chromatography is implemented in the Simulated Moving Bed (SMB).

On a chemical engineering point of view, the SMB is a complex process, which is very ensitive to five different internal flowrates and thus require process simulation in order to be operated properly. On a chemical point of view, the implementation of chromatography at large scale is linked to the availability of chiral stationary phases (CSP) leading to an adequate selectivity. CSP of different types (silica grafted with proteins, cyclodextrin polymers or monomers, polyacrylamides, ligand exchange resins) were developed, extensively tested at the lab-scale. The most efficient were then tested on laboratory scale SMB and finally on an industrial scale SMB.

In order to test the process efficiency and stability, the separation of phytol stereoisomers is performed on an industrial high performance liquid SMB, made of eight high performance columns of 200 mm internal diameter. Although the chromatographic selectivity between both isomers is low (α = 1.16) highly purified (>99 %) trans-phytol is produced with a recovery ratio higher than “99 %. Thanks to the simulation software, operating parameters are optimized, which leads to the processing of 20 kg of feed per day.

The unit has then been used in order to perform, the first industrial-scale chiral separation on SMB described: both isomers of 1,1 ‘-hi-naphthol were purified from the racemic mixture, on a Pirkle-type chiral stationary phase. Optical purities superior to 98% were simultaneously reached for both isomers, with a productivity equal to 1.7 kg of racemate per day.

The applicability of SMB chromatography to industrial separations of optical isomers is clearly proven. We would like to stress on the fact that production costs are reasonable and can be as low as 20 $/kg (including depreciation, labour...) for separations of 100 tons per year.

INTRODUCTION

Chiral chromatography is extremely useful and widely used in order to perform analysis of optical isomers [1,2]: a lot of chiral stationary phases are available, and almost 10CI % of the racemates can be separated by chromatography.

As "classical" processes allowing to obtain optically pure products (asymmetric synthesis, enzymatic processes, crystallisation) usually suffer from a lack of generality, require a significant development time and can be very expensive, chromatography is proposed as an alternative technique.

In the recent past, a lot of original chromatographic modes have been investigated in order to reduce the main drawbacks of classical preparative chromatography, a discontinuous and dilutent process [3,4,5,6]. Among them the Simulated Moving Bed (SMB) was developed in the late 50's by the American engineering company UOP for the separation of oil derivatives (p-xylene purification) [7]. The theory of SMB has been described in previous articles [8,9]. More than 100 very big plants have been built for the separation of oil derivatives and sugars (fructose-glucose), but SMB separations of fine chemicals were not investigated until the late 80's, due to the lack of models and efficient numerical methods and computers for the process simulation.

The study is aimed at the development of CSP and adaptation of SMB in order to perform enantioseparations.

MODELING

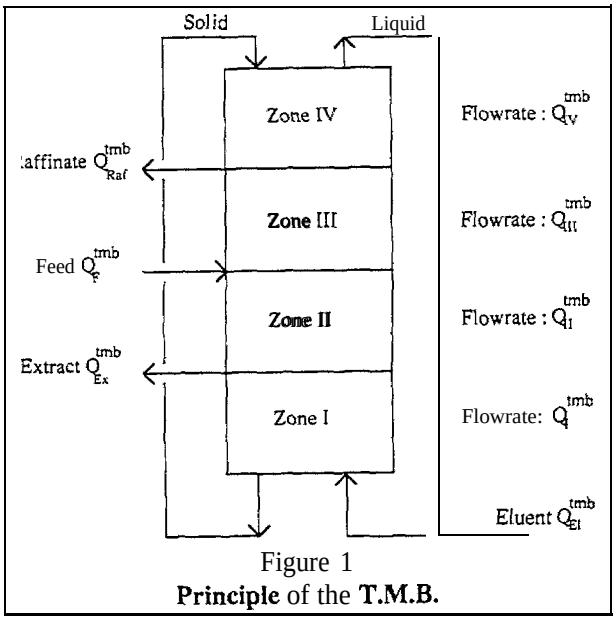


Figure 1
Principle of the **T.M.B.**

Different configurations of counter - current adsorption processes have been described in the literature [10]. However, the four - zone cascade of the " Sorbex" type [11] has been proven to be the most efficient [12]. Figure 1 shows a true moving bed (TMB) made of four zones, "true" referring to an actual circulation of solid.

In fact, it is extremely difficult to operate a TMB because it involves circulation of a solid adsorbent [10], this is why a simulated moving bed [11] is suitable. Most of the benefit of a true counter-current operation can be achieved by using several fixed-bed columns in series and an appropriate shift of injection and collection points [10].

The procedure described is based on the modeling of non - linear chromatography, an experimental procedure being likely to fail unless adsorption isotherms are linear (which is very uncommon in fact or imply to work at very low concentrations).

Parameters we want to evaluate are : Feed concentrations, Number of columns per zone, Column length, Column diameter, Particle size, Recycling (i.e. flowrate occurring in zone I according to an arbitrary definition chosen in this paper) and Inlet/Outlet flowrates.

TMB and SMB concepts are similar. In fact, it has been shown that a SMB and its hypothetical corresponding TMB have very close performances [13]. Knowing that optimum operating conditions can be found directly for a TMB and simulate this kind of process leads to much shorter computation times, it is in our interest to take advantage of this similitude when designing a SMB. Consequently, a study of an hypothetical TMB is performed first.

Table I gives the relation between a SMB and its corresponding TMB [10]. V_c is the volume of one SMB column. Inlet/outlet flowrates of a SMB and its corresponding TMB are identical. A SMB does not exactly work in steady state but in periodic steady state : during a given period, internal concentration profiles vary, but internal profiles examined at the same time of two successive periods are identical (except for a one-column translation).

TMB	SMB
Steady state	Periodic steady sate
Solid flowrate $\dot{M}$	Periodic shift of injection/collection lines $AT = \frac{(1-\varepsilon)\cdot V_c}{M}$
Internal flowrates Q_k^{tmb} k =1, II, III or IV	Internal flowrates $Q_k^{smb} = Q_k^{tmb} + \frac{\varepsilon}{1-\varepsilon}\cdot\dot{M}$
Eluent, extract, feed, raffinate flowrates	Eluent, extract, feed, raffinate flowrates

Table I : Relation between a SMB and its corresponding TMB

The rules used to calculate SMB flowrates from TMB flowrates just mean that the velocity of the liquid relatively to the solid is kept constant.

Adsorption Isotherm

In the case of a single component system, the adsorption isotherm gives the concentration in the stationary phase $\overline{C}$ versus the mobile phase concentration C when the equilibrium is reached, at a given temperature. Even if it can sometimes be linear in a wide concentration range, the relation $\overline{C}$ Vs C is usually not linear and is expressed as: $\overline{C}_i = \overline{C}_i(C_1, C_2, \cdots)$.
Among different isotherm equations described in the literature [14,15], the competitive Langmuir isotherm is flexible enough to be used for process design:

$$\overline{C}_i = \lambda . C_i + \frac{\overline{N}\cdot\tilde{K}_i\cdot C_i}{1+\sum_j \tilde{K}_j\cdot C_j} \qquad (4)$$

where $\overline{N}$ is the saturation capacity assumed here to be equal for all components and $\tilde{K}_i$ a numerical coefficient quantifying the affinity of the solute towards the solid.

Under inear conditions, the retention time of a product on a column is directly inked to the "zero retention time of the system and to the adsorption isotherm initial slope:

$$t_{Ri} = t_o \cdot \left(1 + \frac{1-\varepsilon}{\varepsilon} \overline{K}_i\right) \qquad \overline{K}_i = \lambda + \overline{N}.\tilde{K}_i \tag{5}$$

The determination of adsorption isotherms may be achieved by saturations and desaturations of a column with solutions of the racemic mixture at different concentrations. A numerical method based on the IAS (ideal adsorbed solution) theory has also been applied to allow multicomponent adsorption isotherm determinations from experiments performed with single components.

Equilibrium stage model

Many different models have been applied to the modeling of chromatographic processes [16]. The equilibrium stage model has been proven to be suitable under usual conditions of high performance preparative chromatography [17].
The column is considered as an association of cells in series. The adsorption equilibrium is supposed to be reached in each cell, called equilibrium stage or plate. Broadening effects, linked to the transfer kinetics and hydrodynamics, are lumped together and are quantified by the number of theoretical plates N which can be derived from an "analytical" pulse injection.
In the case of fixed - bed operations (elution chromatography, SMB...), the mass balance equation of a component i over a plate k is :

$$C_{i,k-1} = C_{i,k} + \tau \cdot \frac{dC_{i,k}}{dt} + \tau \cdot \frac{1-\varepsilon}{E} \cdot \frac{d\overline{C}_{i,k}}{dt} \tag{6}$$

where τ is the mean residence time of the mobile phase in a plate and ε the external porosity which is usually in the range 0.35-0.45.
The equilibrium stage concept can also be applied to true moving bed adsorbers [18]. The mass balance equation of a component i over a plate k is :

$$C_{i,k-1} + \frac{M}{Q} \cdot \overline{C}_{i,k+1} = C_{i,k} + \frac{M}{Q} \cdot \overline{C}_{i,k} + \tau \cdot \frac{dC_{i,k}}{dt} + \frac{(1-\varepsilon)}{E} \cdot \tau \cdot \frac{d\overline{C}_{i,k}}{dt} \tag{7}$$

where Q and M are the fluid and solid flowrates.

Equations (6) and (7) are first order ordinary differential equations and can be solved with classical numerical methods [19] when associated to a set of boundary and initial conditions.
The steady state of a TMB can be calculated directly without solving equations (6), but when solving a set of non - linear algebraic equations obtained after having cancelled accumulation terms in (7) [18]. Calculating a TMB steady state without simulating the corresponding transient regime is attractive because it leads to much shorter computation times.

The height equivalent to a theoretical plate H is (defined as L/N) can be related to experimental system parameters through the Van - Deemter [20] or Knox [21] equations, which especially give H as a function of the interstitial mobile phase velocity **u.** In the case of preparative chromatography, where relatively high velocities are used, these equations can very often be simplified into a linear relation [22,23].
The pressure drop is estimated with the Kozeny-Carman equation.

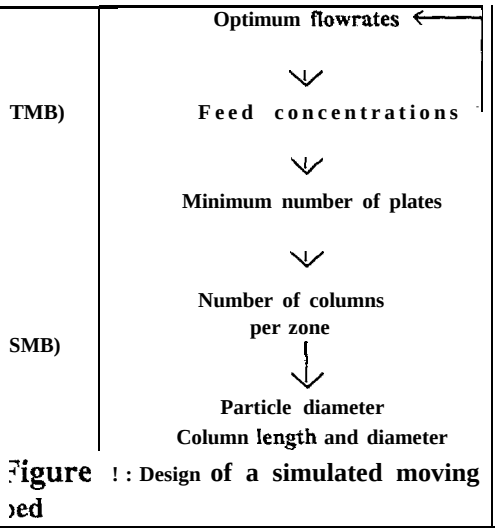


Figure ! : Design of a simulated moving bed

The general procedure we use to design a SMB is described in figure 2. It widely resorts to the equivalence between a SMB and its hypothetical corresponding TMB as explained previously.

A complete and more precise chromatographic model has also been developed, which includes hydrodynamic and kinetic effects (axial dispersion and intraparticle diffusion and convection) occuring in the columns.

TMB optimum flowrates

For a given feed composition, optimum flowrates, i.e. giving the highest productivity and the lowest eluent consumption, are estimated first for an "ideal system" which mainly means that kinetic and hydrodynamic dispersive effects are assumed to be negligible.
The conditions to be applied to a TMB internal flowrates have been broadly described in the literature [10]. In preparative chromatography, high feed concentrations are suitable and lead to non - linear adsorption behaviors. Non-1 inear (and related competitive) effects must absolutely be taken into account when evaluating the flowrates. This issue has been barely addressed in the literature [24,25]. It is under the scope of this paper to describe exactly the calculation procedure.

Feed concentration

Feed concentrations have a strong influence on SMB performances and must be well chosen. Productivity and eluent consumption are two main economic criteria involved in chromatographic processes [26]. Their variations versus feed concentrations can be checked in order to choose an appropriate feed composition.

The productivity increases and the eluent consumption decreases when C_i^F increases : variations are usually rather steep in the low concentration range and very smooth otherwise. As a consequence low injection concentrations will have to be avoided. However, even if achievable, very high concentrations will not be suitable because they can lead to a very low feed flowrate which might be difficult to control.

Number ofplates requirement

Flowrates derived previously lead to 100 % purities in the case of art "ideal" TMB. The approach used here is to keep these flowrates and to seek the minimum number of plates N_m required to reach purities as high as 99 %.
This procedure is sensible because it has been proven that a TMB or SMB performances are only slightly sensitive to the number of plates [13]. In most of cases, the number of plates requirement can easily be achieved and optimum flowrates are then available.
The steady state of a TMB is calculated, as explained in the theoretical part of this paper, for different numbers of theoretical plates, an identical number of plates in each zone being assumed. Extract and raffinate purities are derived from each numerical simulation.

The only way to estimate the number of columns per zone NC is to perform numerical simulations of a SMB including the shift of injection and collection points at regular time intervals. This kind of calculations can be performed using dummy values of the column volume and TMB solid flowrate (to estimate the period AT). SMB flowrates are derived from TMB flowrates according to the rules summarized in table I.

For most of the situations, it was found out that an 8-column configuration (2 columns per *zone)* was suitable.

For a given particle size, the optimum choice of column length L and average mobile phase velocity u_m is given if the constraints connected to the minimum plate number requirement and to a maximum pressure are taken into account. Very often, we derive an optimum column length of about 5-10 cm when particle sizes of 20 to 30 microns are used.

EQUIPMENT

Analytical scale:

For the sake of simplicity, all the analytical equipment used by all the partners involved in this work cannot be listed here.

Laboratory scale SMB:

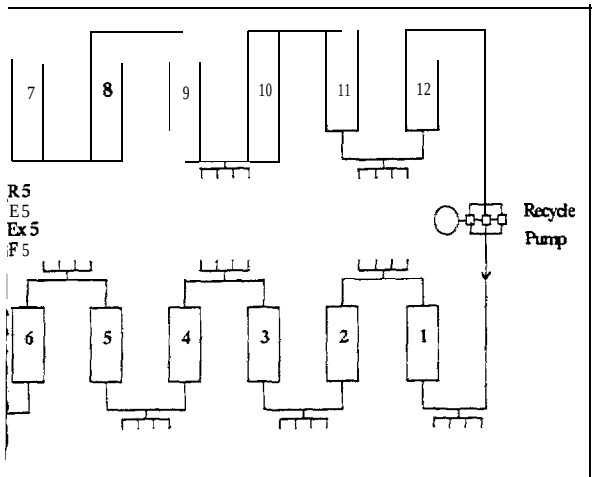


figure 3
F[ow sheet of the laboratory scale SMB

The flow sheet of the laboratory scale SMB is given in the figure 3. The main features of the SMB are the following:

- 12 glass columns (Superformance®) of 26 mm internal diameter and up to 150 mm long. The maximal operating pressure is 60 bar.
- five pumps :
- recycling: one triplex membrane pump of 12 l/h maximal flow-rate. This pump is controlled by a frequency variator.
- feed and raffinate : one Merck-Hitachi L6000 HPLC pump of 0.6 l/h maximal flow-rate
- eluent and extract : one Merck-Hitachi L6200 HPLC pump of 0.6 l/h maximal flow-rate.

- each column is connected to the four inlet and outlet pumps through four electro-pneumatic high pressure valves.
- all the materials coming in contact with the products and the eluent are made of stainless steel, glass, PTFE or PVDF).
- the temperature control of the recycling and both inlet flows is achieved a thermostatic bath.

Industrial scale SMB:

The industrial high performance SMB unit, called the LICOSEP 8-200, includes an 8-column SMB connected to an on-line unit for the evaporation of outlet flows (extract and raffinate) under low pressure and the automatic recycling of the eluent. The general flow sheet is shown in the figure 4. All the electrical equipment are explosion proof or low voltage ones (e.g. intrinsically secure).

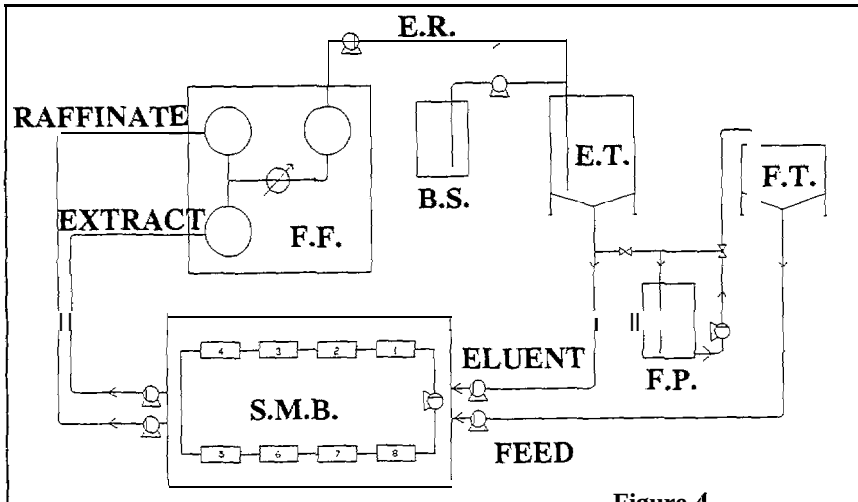


Figure 4
Flow sheet of the industrial scale SMB

The SMB flow sheet is given in the figure 4. The main features of the SMB are the following :

- 8 axial compression columns of '200 mm internal diameter and up to 400 mm long. Maximal operating pressure is 40 bar.
- a hydraulic group
- five pumps :
- recycling : one triplex membrane pump of 400 l/h maximal flow-rate
- feed and raffinate : one duplex membrane pump of 30 l/h maximal flow-rate
- eluent and extract: one duplex membrane pump of 60 l/h maximal flow-rate
- Each pump is controlled by a frequency variator.
- each column is connected to the four inlet and outlet pumps through four electro-pneumatic high pressure valves.
- all the materials coming in contact with the products and the eluent are made of stainless steel or PTFE).
- the temperature control of the recycling and both inlet flows is achieved by heat exchangers.

The extract and the raffinate purified in the SMB are pumped in the solvent recycling unit:

- Each outlet line is processed by a falling fiIm evaporator composed of up to twelve 3 m tubes of 10 mm (id.).
- The eluent vaporized under reduced pressure in the falling film evaporators is separated from the extract and the raffinate in two glass cyclona and condensed in a 50-liter glass vessel. This vessel is periodically emptied by a pump servo-controlled by two level probes located in the vessel. The eluent is stored in a 1000-liter tank.
- When a binary mixture of solvent is used as eluent, due to the difference of physical properties of solvents the evaporation yields of the two components are different. Thus the ratio of both solvents in the eluent recycled is changed. This change is continuously analyzed in the eluent tank and the actual composition is compared to the programmed one by the control software, and automatically adjusted thanks to a back-up solvent pump.

CSP DEVELOPMENT

In order to develop a complete family of CSP and thus to be in position to solve a wide range of problems, different routes have been investigated.

1. Synthesis of protein-silica CSP :

Since their introduction as enantioselective high performance liquid chromatography (HPLC) supports, protein based stationary phases have been extensively used in the development of analytical methods for chiral compounds. They are generally considered to allow a limited loading and thus not suitable for preparative purposes. As no quantitative results were available, we decided to prepare Bovine Serum Albumine (BSA) and *Human Serum* Albumine (HSA) based CSP in order to check this point.

HSA and BSA were covalently bonded on a spherical experimental Kromasil (EKA-NOBEL, BOHUS, SWEDEN). The silica gel has a nominal pore size of 200 Å, a particle size of 10 µm and a specific surface of 200 m^2/g. The quantity of immobilized protein was about 100 mg per g of silica. The method developed is an « in situ>> grafting of the protein by percolation in a column, pre-packed with epoxide activated silica.

2. Synthesis of cyclodextrin polymer-silica CSP :

CSP obtained from the coating of β-cyclodextrins ((3-CD) polymers on silica are commercially available at least for analytical purposes. It is known that chemical modification of the (3-CD can strongly affect the chiral recognition and sometimes allow a separation which is not achieved with standard β-CD.

Three different types of packing were proposed :

. Polymer modification by alkylation :

A support obtained by adsorption of β CDEPN$^+$ (βCD-epichlorydrin polymer) on LICHROSPHER (100 Å pore, 5 µm diameter) is reacted by acetyl chloride or benroyl chloride.

. Polymer rnodeification by methylation :

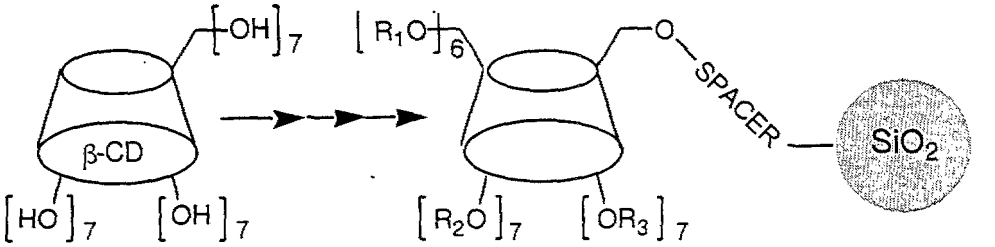
The methylation of the βCDEPN$^+$ polymer is achieved in DMSO in the presence of NaOH.

. Preparation of β-CD carbonates derivatives :

The preparation of (3-CD acyl carbonate is achieved by reaction of silica impregnated with polyvinylimidazole β-CD (PVI CD) in pyridine. The PVI CD is prepared by reaction in water of 1 g of polymer PVI and 2 g of monochloro β-CD.

3. Synthesis of cyclodextrin monomer-silica CSP :

Important works have been undertaken to find a synthetic pathway able to give monofunctionalized derivative of β-cyclodextrin in a reproducible and economic way. Indeed this functionalization is possible in three positions (2-, 3- or 6-OH) with taking care to avoid polysubstitution (β–cyclodextrins possess twenty-one hydroxy groups!).
The synthesis performed exhibit good potential to obtain a high diversity of modified persubstituted mono-2-0- or 6-O-n-alkenyl-b-cy clodextrins (methyl, propyl and acetyl) able to give chiral selectors for liquid-chromatography.
In order to prepare chiral bonded-phases, the approach consists in the chemical binding of substituted cyclodextrin via a spacer to a silica support. Coverages of 0.12 to 0.30 μmol/m^2 silica have been achieved, depending on the chiral selector.
Both linkage and modified cyclodextrin are hydrolytically stable under standard liquid chromatographic conditions.



4. Synthesis of Pirkle type packing :

Some PIRKLE type CSP made of dinitrobenzoyl-phenylglycine (DNPBG) was produced in order to obtain a relatively cleap CSP suited for preparative purposes.
The CSP is prepared by condensation at about -10°C of DNPBG on aminopropyl silica by use of EEDCl (Ethyl-2-ethoxy-1.2-dihydrochinolin-1-carboxylate).
The aminopropyl silica is obtained by reaction of 3-aminopropyl trimethoxysilane on dried silica.

5. Synthesis of polyacrylamide packings :

These new CSP are based on the experience of MERCK in the preparation of polyacrylamide/diol silica composite by radical initiated grafting polymerization of (S)-phenyl alanine ethyl ester. A diol silica based on LICHROSPHER Si100 carrying 3.0 μmol/m² diol groups was used as starting material.

6. Synthesis of ligand exchange packings :

Proline based ligand exchange resins were available for separations of D,L aminoacids at the beginning of this project. Other systems are now efficient : pipecolic acid and (S)-porretine based Ligand Exchange CSP. Proline basal CSP still give the best results.
New (pentadentated) supports based on silica have been synthetised for the chiral separations of monoamine, aminoalcohols and monoacids. The procedure involves the grafting on silica of a monomer obtained by reaction of bis-epoxypropylaminopropyl trimethoxysilane and (S)-(+)-2-aminobutane.

A new chromatographic method has been developed : chiral separations of amino-acids are now performed in 0.2 M NH_3. The main advantage is the increase of the amino-acid volubility in the eluent.

EXPERIMENTAL

CSP evaluations for preparative purposes

Two new CSP have been tested in the scope of preparative chiral separations on SMB : a HSA-silica and a βCDEPN$^+$-silica. The chiral test compound is warfarine, a coumarine derivative.

The operating conditions have been optimized :

- column HSA 5pm (25 x 4.6cm). Mobile phase: KH_2PO_4 (0.008M) pH= 7 / CH_3CN / iPrOH (72.55/25.5/1.95). Temperature 21 °C +/- 1 °C
- column βCDEPN 5pm (25*4.6 cm). Mobile phase : KH_2PO_4 (0.05M) pH= 4 / Methanol (80/20 v/v). Temperature : 200C

The methodology is the following:

1. Injections of increasing amounts of a test racemic mixture on an analytical column, until overlapping appears
2. Determination of adsorption isotherms by a numerical method
3. Calculation of purities and productivities achievable on a pilot plant SMB by numerical simulation

SMB separations

Phytol:

The phytol (3,7,11, 15-tetramethyl-2hexadecen-1 -01, $C_{20}H_{40}O$) is a fatty alcohol. Synthetic phytol is a 33 % / 67 % mixture of its cis and trans stereoisomers. The latter one is used in perfumery as a fixer.

Analysis

The solvents used for the HPLC analysis are HPLC grade n-heptane and ethyl acetate (LABOSI, France). The analytical HPLC separations of cis- and trans-phytol are performed in the following conditions :

- Column : LICHROSPHER Si 1005 pm, 25*0.46 cm (E. MERCK, Germany)
- Temperature : 20°C
- Eluent : n-heptane/ethyl acetate 80/20 v/v
- Flow-rate :1 ml/min
- Injection :20 µl (full loop) of phytol solutions (O to 105 g/l in the SMB eluent)

SMB consumables

The solvents used are technical grade heptane and ethyl acetate (LAMBERT RIVIERE, France) evaporated twice on falling film evaporators (F.F.) before use. The selected eluent is a 80/20 v/v mixture of n-heptane/ethyl acetate. The silica is a normal silica Si 60 (25-40 pm) supplied by E. MERCK (Germany).

Binaphtol:

Binaphtol enantiomers are used as chiral catalysts in numerous asymmetric synthesis.

Analysis

The solvents used for the HPLC analysis are HPLC grade heptane and isopropanol (LABOSI, France). The analytical HPLC separations of the isomers are performed in the following conditions :

- Column: 3,5-dinitrobenzoyl phenylglycine/Lichrospher 5pm, 25*0.46 cm (E. MERCK, Germany)
- Temperature : 20"C
- Eluent : heptane/isopropanol 75/25 v/v
- Flow-rate: 1 ml/min
- Injection: 20 µl (full loop) of binaphthol solutions (0 to 7 g/l in the SMB eluent)

SMB consumables

The solvents used are technical grade heptane and isopropanol (LAMBERT RIVIERE, France) evaporated twice on falling film evaporators (F.F.) before use. The selected eluent is a 72/28 v/v mixture of heptane and isopropanol. The CSP is a DNPBG silica (25-40 µm) produced in the frame of this project.

RESULTS

CSP evaluations

1. Chiral screening on analytical columns

The table II summarizes (only the main families of compounds are listed) positive results obtained by partners involved in the development of new CSP, in the scope of analytical chiral chromatography.:

racemate	type of CSP	eluent
native amino acids	Proline-Cu Ligand Exchange CSP	0.2 NH_3 in water
N-benzoyl derivatives (amino acids)	BSA and HSA / silica	Phosphate buffer pH 7 / acetonitrile
Dansyl derivatives (amino acids)	BSA and HSA / silica PVI-βCD and βCDEPN$^+$ / silica	Phosphate buffer pH 7 / acetonitrile Sodium acetate pH 4 / methanol
benzodiazepins	BSA and HSA / silica methylated βCDEPN$^+$ / silica	phosphate buffer pH 7/ isopropanol Sodium acetate pH 4 / methanol
profens	BSA / silica	phosphate pH 7 / acetonitrile / octanoïc acid
coumarin derivatives	native and methylated βCDEPN$^+$ / silica	phosphate buffer pH 7 / methanol
quinin derivatives	native, benzoylated and methylated βCDEPN$^+$ / silica	phosphate buffer pH 7 / methanol
barbiturates	native and methylated βCDEPN$^+$ / silica methylated βCD monomers / silica	phosphate buffer pH 7 / methanol heptane/isopropanol
mandelic acid derivatives	βCDEPN$^+$ / silica	Sodium acetate pH 4 / methanol

Table II : main families of chiral compounds separated on our new CSP

2. Evaluation of CSP potential for chiral separations on SMB

The potential of two CSP newly synthesized have been estimated :

1. HSA-silica CSP :
Adsorption isotherms of warfarine enantiomers were numerically calculated :

$$\overline{C}_1 = 1,056 C_1 + \frac{1,729\, C_1}{1 + 3,29 C_1 + 10,72 C_2}$$

$$\overline{C}_2 = 1,056 C_2 + \frac{5,633\, C_2}{1 + 3,29 C_1 + 10,72 C_2}$$

After modeling the isotherms, the maximum productivity for this separation with the LICOSEP 12-26 has been estimated thanks to our simulation software.

Feed concentration :	2 g/1
Total number of theoretical plates:	200
Particle diameter:	20 µm
Column length:	5 *cm*
Theoretical purity;	Extract: 99.6$10 Raffinat : 99.9%

Theorical Productivity	3.74 g of racemate per day

2.. βCDEPN$^+$ / silica CSP :
The adsorption isotherms in the operating conditions described were :

$$\overline{C_R} = 3,95\ C_R + \frac{0,85\ C_R}{1 + 0.43\ C_R + 0.51\ C_S}$$

$$\overline{C_S} = 3,95\ C_S + \frac{205\ C_S}{1 + 0.43\ C_R + 0.51\ C_S}$$

Feed concentration :	0.6 g/1
Total number of theoretical plates:	200
Particle diameter:	20 µm
Column length:	5 cm
Theoretical purity:	Extract: 99.7 % Raffinat : 99.8%

Theorical Productivity	6.9 g of racemate per day

Although cyclodextrin and protein based CSP are known to have a poor capacity (and thus a poor preparative potential), the present results show that their implementation in a SMB can lead to acceptable productivities, when compared to « classical » CSP (see the results obtained for the binaphthol on the Pirkle phase, hereafter).

SMB separations

Phytol

Laboratory scale:

Pulse test injections of different volumes and concentrations have been performed on an analytical column packed with the silica used for SM13 and eluted with the eluent retained for SMB.

From dilute injections, we obtained: $\overline{K}_{cis}$ = 1.30 $\overline{K}_{cis}$ = 1.51 and thus a selectivity of 1.16, which is low.

From the information obtained at higher concentrations, we derived the complete adsorption isotherm:

$\lambda = 0.5$ $\overline{N}$ = 100 g / 1 $\tilde{K}_{cis}$ = 0.00792 $\tilde{K}_{trans}$ = 0.00983

Pressure drop and plate number were measured at different flowrates, and we obtained:

HETP = 0.1 5.u m u = m / s

$\Delta P / L$ = 53000 .u bar / m

pilot-scale:

Using the previous information, we determined the flowrates to be used in the laboratory scale SMB packed with 8 columns of 10 cm length. The columns were packed according to a procedure described in [26].

For a feed concentration of 50 g/l, in very close agreement with the prediction, significant purities (greater than 97%) were obtained for the following set of parameters:

$Q_{Recycling}$ = 49.21 ml / min Q_{Feed} = 1.66 ml / min

$Q_{Extract}$ = 5.48 ml / min Q_{Eluent} = 6,82 ml / min

$Q_{Raffinate}$ = 3.00 ml/ min switching period = 1.5 min

With these first results, we have proven the efficiency of the pilot plant and its ability to solve difficult separation problems.

Industrial scale:

Each of the eight columns is vacuum-packed with 3 kg of Lichroprep Si 6025-40 µm silica (E. MERCK, Germany) suspended in about 5 liters of eluent. The top flange of the column is then screwed and the lower piston moved upwards thanks to the hydraulic group until the pressure applied is 40 bar. All the columns were tested and they led to identical retention times with a precision of 1.1910.

The system was successfully operated with different feed concentrations up to 105 g/l. At 105 g/l, a suitable set of parameters was:

Q_{Recycl} = 226 l/h Q_{Feed} = 7.8 l / h $Q_{Extract}$ = 32411 h

Q_{Eluent} = 36 l/h $Q_{Raffinate}$ = 11.4 l / h switching period = 0.0341 h

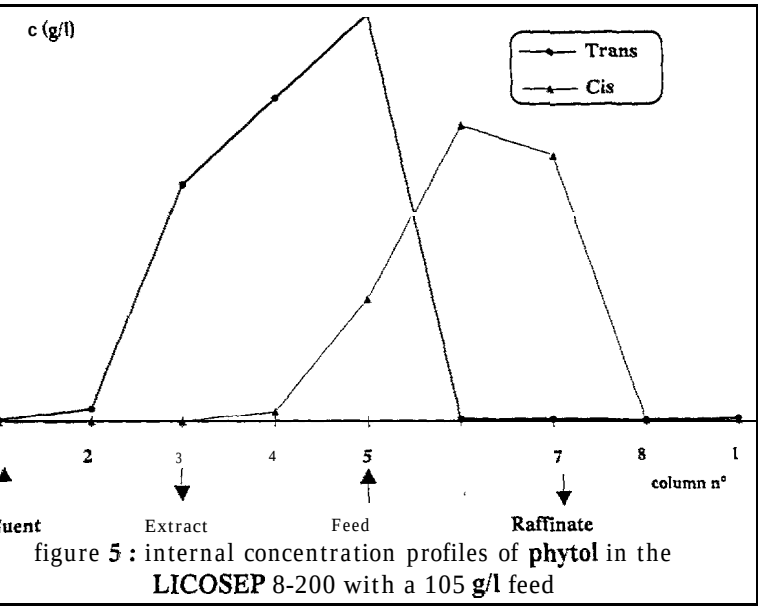


figure 5 : internal concentration profiles of phytol in the LICOSEP 8-200 with a 105 g/l feed

purities (determined by GC analysis) are respectively 99.6 % and 99.5 % for the extract and the raffinate. The figure 5 shows experimental concentration profiles obtained. These ones clearly confirm that the two outlet lines essentially contain one isomer. The total pressure drop in the system with this set of flow-rates is 26 bar.

The previous operating parameters are applied to the SMB for the production of purified trans-phytol. The system is run continuously and automatically (including the eluent composition adjustment). The noticeable features of the results are the constant purity (> 99.2 % for the trans-phytol produced) and high recovery ratio (> 99 % of the initial trans-phytol recovered at this purity) that are reached.

The production rate reaches nearly 20 kg/day with an operating pressure of 26 bar which is already significant for fine chemistry. Provided the system is designed to withstand operating pressures up to 40 bar, the throughput could be improved by a 50910 factor (by a 50 % increase of all the flow-rates and a l/3rd decrease of the period time). Moreover the total efficiency in the system is much higher than the minimal theoretical efficiency required for getting similar results. This means that the bed length could be reduced and the internal flow-rates increased, resulting in a tremendous enhancement of the specific productivity.

Binapthol

Laboratory scale:

Using the method described for the phytol example, we obtained: $\overline{K}_+ = 2.63$ $\overline{K}_- = 3.86$ and thus a selectivity of 1.47.

We derived the complete adsorption isotherms:

$\lambda =$ 0 $\overline{N} =$ 53.6 g / l $\tilde{K}_+ =$ 0.049 $\tilde{K}_- = 0.072$

As expected, the saturation capacity of a CSP is significantly lower than the saturation capacity of classical silica.

The pressure drop and plate number were measured at different flowrates, and we obtained:

HETP = 2.65. u m $u = m / s$

$\Delta P / L =$ 49160 . u bar / m

pilot-scale:

The Laboratory scale SMB was packed with 8 columns of 10 cm length.

For a feed concentration of 5.8 g/l, in very close agreement with the prediction, significant purities (respectively 97.3 % and 99.2 % for the extract and the raffinate) were obtained for the following set of parameters:

Q_{Recycl} = 35.38 ml / min Q_{Feed} = 3,64 ml/ min

$Q_{Extract}$ = 17.98 ml / min Q_{Eluent} = 21.45 ml / min

$Q_{Raffinate}$ = 7.1 1 ml / min switch period = 287 min

Even if the selectivity between these two isomers is higher, the productivity is smaller than the productivity obtained for the phytol because of the lower saturation capacity and solubility.

Industrial scale:

Each of the eight columns is vacuum-packed with 2 kg of DNPBG 25-40 µm silica (E. MERCK, Germany) suspended in about 4 liters of eluent. The top flange of the column is then screwed and the lower piston moved upwards thanks to the hydraulic group until the pressure applied is about 40 bar. All the columns were tested and they led to identical retention times with a precision of 1.5 %.

The system was successfully operated with different feed concentrations up to 7 g/l. At 7 g/l, a suitable set of parameters was:

Q_{Recycl} = 114 l / h Q_{Feed} = 10.0 l/h $Q_{Extract}$ = 45 l/h

Q_{Eluent} = 52 1 / h $Q_{Raffinate}$ = 17 l / h switching period = 0.096 h

In order to improve the results, the number of columns per zone of the SMB was modified as follows :

- zones I and III :2 columns
- zone II :3 columns
- zone IV :1 column

The concentration profiles obtained in the LICOSEP 8-200 are shown in the figure 6

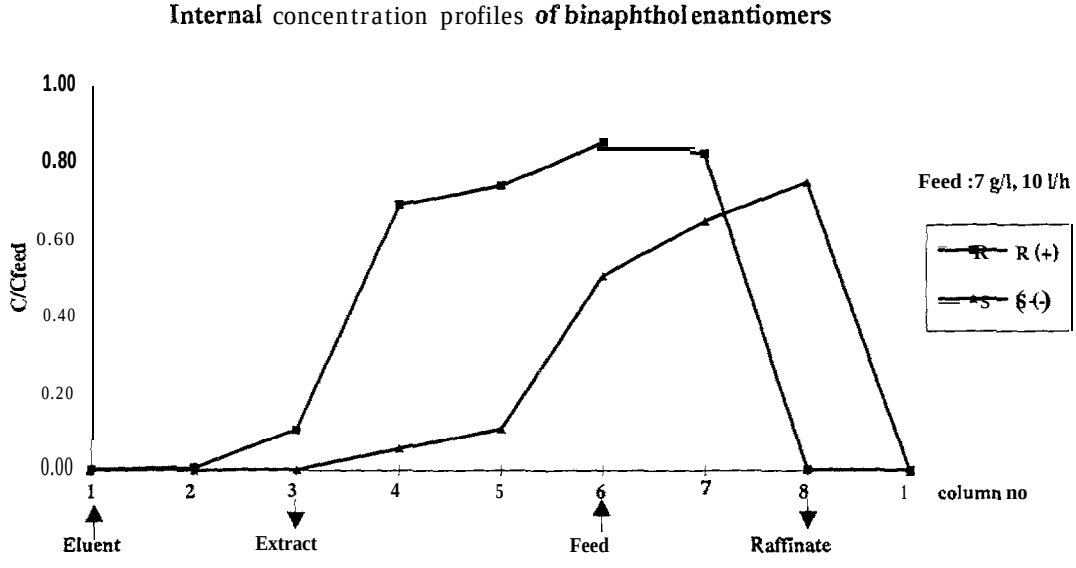


Figure 6: internal concentration profiles of binaphthol enantiomers in the industrial SMB

The productivity, limited by the feed volubility limit in the eluent, reached 1.7 kg/day, Extract and raffinate purities were respectively 97.7 % and 97.2 %. They even reached 99.5 % and 98.170 (resp. extract and raffinate purities) with a productivity equal to 1.2 kg/day.

CONCLUSION

A number of new chiral stationary phases have been developed, which are able to solve a lot of chiral separations at the analytical scale. Although they are generally considered as purely analytical tools, a protein and a cyclodextrin based CSPS have been tested in the scope of preparative enantioseparations. The results are positive, and show that these phases could be used in a SMB for specific chiral applications.

Difficult separations of synthetic stereoisomers and enantiomers are achieved by an automated industrial high performance SMB on different silicas (classical or chiral). A few kg/day of a feed is processed, yielding highly purified products (> 99 %) with a recovery ratio superior to 98%. The separation is optimized thanks to the numerical simulation.

The possibility to consider preparative chromatography (in the simulated moving bed mode) as a real production tool for performing optical isomers separation is thus completely proven.

Contrary to classical separations, which are performed on very efficient packings (normal and reversed phase silica), it must be pointed out that chiral separations are performed on polymer gels and monomer- or polymer-coated silica, which are in general much less efficient than classical silica packings. This means that the comparison between elution and SMB is more favorable to the latter process in these cases [7], because the high number of plates required by elution chromatography in order to reach a good resolution implies a low flow-rate, hence a low productivity.

ACKNOWLEDGEMENTS

We gratefully thank the European Commission for its financial contribution to the development of SMB devoted to separations of optical isomers (project BRE2CT2-0337).

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