Pais, L.S., Loureiro, J.M., and Rodrigues, A.E.

Chiral Separation by SMB Chromatography

in *ISCD'98 10th International Symposium on Chiral Discrimination*, Vienna, Austria, August 30 - September 2, 1998. *(poster)*

10th International Symposium on
Chiral Discrimination

Vienna Hilton
August 30 - September 2, 1998

ISCD '98

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10th International Symposium on Chiral Discrimination, ISCD'98

August 30 - September 2 1998 in Vienna (Austria)

[Topics] [[History]] [Program] [Exhibition]

Scientific Program - Posters Session II

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POSTER SESSION I

Topics

A1 Fundamental Aspects of Chirality, Molecular Recognition and Molecular Modelling, Suprastructural Phenomena, Chiral Polymers

B Novel Developments in Asymmetric Synthesis Including Chemocatalysis

C Asymmetric Synthesis using Biocatalysis and Enzymatic Methods

D1 Gas- and Liquid Phase Separation Techniques (LC, CE, CEC, MEKC, GC)

E Enantioseparation via Crystallographic Techniques

POSTER SESSION II

Topics

A2 Fundamental Aspects of Chirality, Molecular Recognition and Molecular Modelling, Suprastructural Phenomena, Chiral Polymer

D2 Gas- and Liquid Phase Separation Techniques (LC, CE, CEC, MEKC, GC)

F Preparative Enantiomer Separation Techniques including Chromatography (LC, GC, CCC) and Membrane Technology

G Chiral Aspects in Pharmacology, Pharmacokinetics, Pharmacodynamics, Drug Binding, etc.

H Chiroptical Spectroscopy, NMR, Instrumentation, etc.

POSTER SESSION II

Tuesday/Wednesday, September 1/September 2, 1998

HIGH PERFORMANCE LIQUID CHROMATOGRAPHY OF BINAPHTHYL DERIVATIVES ENANTIOMERS ON NEW CHOLIC ACID-BASED STATIONARY PHASES. APPROACH OF THE CHIRAL RECOGNITION MECHANISM
Vaton-Chanvrier L., Combret Y. and Combret J.C.; Mt. St. Aignan (France)

BISBENZYLISOQUINOLINE ALKALOIDS AS COMPLEXATION AGENTS
Millership J.; Belfast (Northern Ireland)

RESOLUTION OF THE DIASTEREOMERS OF SB-238592-DB BY CAPILLARY ELECTROPHORESIS USING NONIONIC SURFACTANTS
Hadley M.R. and Gilges M.; Tonbridge (UK)

ENANTIOSEPARATION OF SOTALOL ON A CBH-I BASED CHIRAL PHASE: EFFECT OF COLUMN TEMPERATURE
Fulde K. and Frahm A.W.; Freiburg (Germany)

SELECTIVITY TUNING IN CHIRAL GAS CHROMATOGRAPHY
Krupcik J., Spanik I. and Sandra P.; Bratislava (Slovak Republik)

ON THE USAGE OF CYCLODEXTRINS IN GC AND CE.
Koppenhoefer B., Wuerthner S., Jakob A., Juvanecz Z. and Szeitli G.; Budapest (Hungary)

CHIRAL KBS: A KNOWLEDGE-BASED SYSTEM FOR CHIRAL SEPARATIONS
Torres-Lapasio J.R., Maftouh M., Vander Heyden Y., Vargas M.G. and Massart D.L.; Brussels (Belgium)

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F Preparative Enantiomer Separation Techniques including Chromatography (LC, GC, CCC) and Membrane Technology

DEVELOPMENT OF ENANTIOSELECTIVE LARGE SCALE PREPARATIVE SEPARATIONS
Cox G., Dapremont O., Suteu C. and Murakami T.; Illkirch (France)

OPTIMISATION OF THE PREPARATIVE ENANTIOMERIC SEPARATION OF AN ALPHA-HYDROXYACID BY LIQUID CHROMATOGRAPHY ON TWO DERIVATISED POLYSACCHARIDE (DAICEL TYPE) STATIONARY PHASES
Suteu C., Cox G. and Amberg W.; Illkirch (France)

CHIRAL SEPARATION BY SMB CHROMATOGRAPHY
Pais L.S., Loureiro J.M. and Rodrigues A.E.; Porto Codex (Portugal)

PRODUCTIVITY OF DIFFERENT CHIRAL STATIONARY PHASES FOR PREPARATIVE ENANTIOSEPARATION BY SIMULATED MOVING BED (SMB)-CHROMATOGRAPHY
Schulte M. and Ludemann-Homburger O.; Darmstadt (Germany)

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Introduction

- Concept of Simulated Moving Bed:
  1st *UOP* patent (1961)
  Sorbex processes.

- Applications:

  Petroleum refining and petrochemicals
  (*Parex* and *Molex* processes)

  Carbohydrate industry
  (production of fructose from corn syrup)
  (Sarex process)

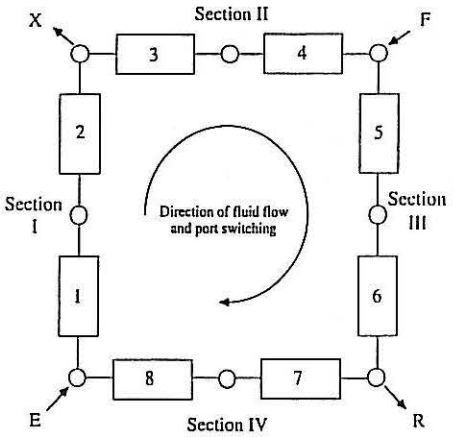
- The SMB technology has recently found new applications in the areas of biotechnology, pharmaceuticals and fine chemistry.

SMB Principle

- Flow scheme that takes advantages of continuous and countercurrent movement of liquid and solid without actual movement of the adsorbent.

- The adsorbent bed is divided into a number of fixed-bed columns, while the inlet and outlet lines move simultaneously one column at fixed time intervals in the direction of the liquid phase flow.

- Advantages of SMB chromatography:
  It is a continuous process;
  Can perform low selectivity separations;
  Reduction in eluent consumption and adsorbent requirements.



Schematic diagram of a Simulated Moving Bed

Objectives

- Modeling strategies of a Simulated Moving Bed unit

- SMB simulation and study of the influence of operating parameters on the SMB performance

- Optimization of the SMB operation conditions

- Experimental operation of a SMB pilot unit
  (Licosep 12-26, NOVASEP, France)

Modeling

- Two main strategies:

  The SMB model: considers the real shift of the injection and collection points.

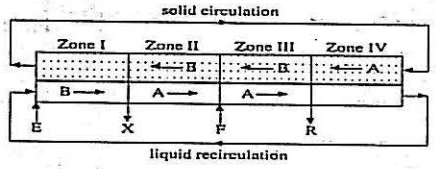
  The TMB (true moving bed) model: considers liquid and solid flow in opposite directions.

- For practical purposes, optimization and choice of SMB configuration (length of each section) can be safely carried out on the basis of analogy with TMB modeling.

Reference: Pais, Loureiro and Rodrigues, "Modeling Strategies for Enantiomers Separation by SMB Chromatography", *AIChE J.*, 44, 561-569 (1998).

The TMB model considers:

- Axial dispersion flow for the bulk fluid phase
- Intraparticle mass transfer rate described by the linear driving force approximation
- The model can handle any kind of adsorption isotherm



Schematic diagram of a True Moving Bed

Model equations for the steady-state TMB model

Mass balance in a volume element of the bed j:

$$D_{L_j}\frac{d^2c_{ij}}{dz^2}-v_j\frac{dc_{ij}}{dz}-\frac{(1-\varepsilon)}{\varepsilon}k(q_{ij}^{*}-q_{ij})=0$$

Mass balance in the particle:

$$u_s\frac{dq_{ij}}{dz}+k(q_{ij}^{*}-q_{ij})=0$$

Boundary conditions for section j:

$z=0$: $\quad c_{ij}-\frac{D_{L_j}}{v_j}\frac{dc_{ij}}{dz}=c_{ij,0}$

$z=L_j$: $\quad c_{ij}=c_{ij+1,0}$ extract, raffinate nodes

$$c_{ij}=\frac{v_I}{v_{IV}}c_{ij+1,0}$$ eluent node

$$c_{ij}=\frac{v_{III}}{v_{II}}c_{ij+1,0}-\frac{v_F}{v_{II}}c_i^F$$ feed node

and $\quad q_{ij}=q_{ij+1,0}$

Global balances:

$v_I = v_{IV} + v_E$ eluent node

$v_{II} = v_I - v_X$ extract node

$v_{III} = v_{II} + v_F$ feed node

$v_{IV} = v_{III} - v_R$ raffinate node

Multicomponent adsorption equilibrium isotherm:

$$q_{Aj}^{*}=f_A(c_{Aj},c_{Bj}) \text{ and } q_{Bj}^{*}=f_B(c_{Aj},c_{Bj})$$

Model parameters

$\frac{1-\varepsilon}{\varepsilon}$ Ratio between solid and fluid volumes

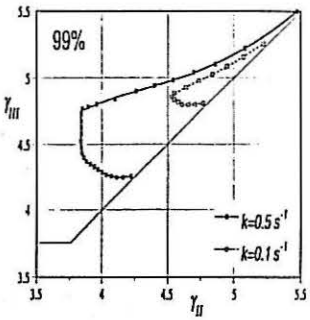
$\gamma_j=\frac{v_j}{u_s}$ Ratio between fluid and solid velocities

$Pe_j=\frac{v_jL_j}{D_{Lj}}$ Peclet number

$\alpha_j=\frac{k\,L_j}{u_s}$ Number of mass transfer units

Adsorption equilibrium parameters have to be added to the list above.

Simulation results



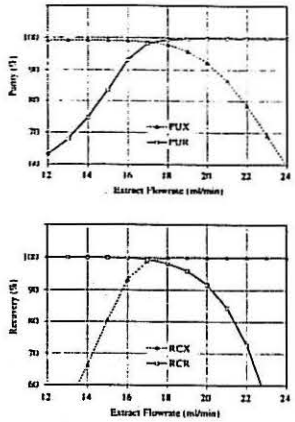
Influence of the mass transfer resistance on the separation region (target 99%)

Optimum operation conditions (99% vertex)

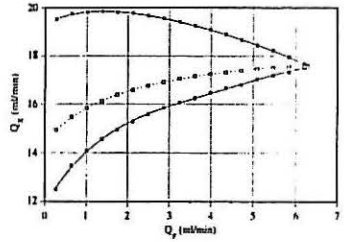
k (s-1)	Q_E	Q_X	Q_F	Q_R
0.5	18.29	17.62	6.80	7.47
0.1	22.70	16.90	2.39	8.19

System: bi-naphthol enantiomers
SMB Operation conditions:
C_{feed} = 2.9 g/l each enantiomer
$V_{adsorbent\ bed}$: 446 ml
$Q_F+Q_E=Q_X+Q_R$=25.09 ml/min
Switch time interval: 3 min
Recycling flow rate: 35.38 ml/min

Effect of the extract flow-rate on the SMB performance



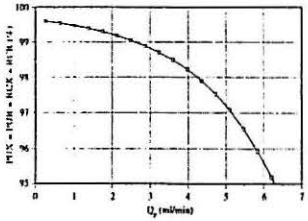
- The deviation of the extract flow-rate from its optimum value drastically affects the performance of one or the other enantiomer, depending on which direction Qx is changed.



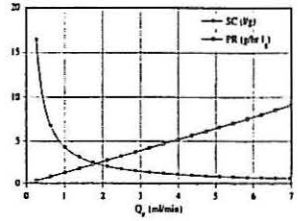
Separation region in a Q_X versus Q_F plot.

Region limited by closed squares:
separation region for a 95% purity criteria.
Open squares: path of equal raffinate and extract purities.
(mass transfer coefficient: k=0.1 s-1)

- Since the objective of the SMB operation is to obtain the two pure enantiomers, the path of equal purities is the optimum trajectory that must be followed.
- The optimum will result from a trade-off between solvent consumption and productivity, purity and recovery requirements, and system robustness.



Optimum purities and recoveries as a function of the feed flow rate.

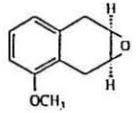


Solvent consumption and adsorbent productivity as a function of the feed flow rate.

References: Pais, Loureiro and Rodrigues
Chem. Engng Sci., **52**, 245-257 (1997).
J. Chromatog. A, **769**, 25-35 (1997).
J. Chromatog. A, submitted (1998).

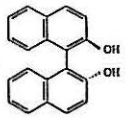
Systems studied

Separation of chiral epoxide enantiomers



(*Sandoz Pharma , Basel, Switzerland*)

Stationary phase: microcrystalline cellulose triacetate (dp=45 μm)
Mobile phase: methanol
Temperature: 25 °C



Separation of bi-naphthol enantiomers

(*Aldrich, USA, Cat. No. 10,465-5*)

Stationary phase: Pirkle type, DNBPG-Silica (dp=25-40 μm)
Mobile phase: heptane-isopropanol (72:28)
Temperature: 25 °C

Operation

SMB pilot unit:

LICOSEP 12-26 (Novasep, France)

Experimental performance parameters.

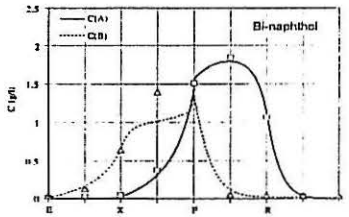
System	PUX (%)	PUR (%)	RCX (%)	RCR (%)
Chiral epoxide	90.0	92.0	94.0	91.1
Bi-naphthol	93.0	96.2	97.3	91.6

System	SC (ml/g) $\frac{(Q_E+Q_F)}{Q_F(C_A^F+C_B^F)}$	PR (g/day lbed) $\frac{Q_F(C_A^F+C_B^F)}{V_{bed}}$
Chiral epoxide	400	52
Bi-naphthol	1200	68

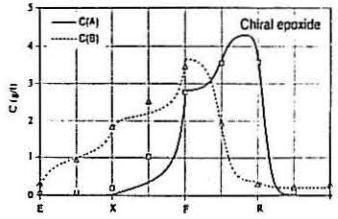
SMB pilot operation conditions.

Parameter	Chiral epoxide	Bi-naphthol
Column diameter (cm)	2.6	2.6
Column length (cm)	9.9	10.5
Number of columns	8	8
Configuration	2-2-2-2	2-2-2-2
Temperature (°C)	25	25
Pressure drop (bar)	10 (22 ml/min)	20 (40 ml/min)
Feed conc (g/l each)	5	2.9
Switch time interval (min)	3.30	2.75
Recycling (ml/min)	23.20	35.38
Eluent (ml/min)	4.53	21.45
Extract (ml/min)	4.00	16.00
Feed (ml/min)	1.52	3.64
Raffinate (ml/min)	2.05	9.09

Comparison between experimental and model results



bi-naphthol enantiomers



chiral epoxide enantiomers

Conclusions

- The SMB/TMB packages are important learning and training tools used to predict the effect of operating variables on the process performance, and so the choice of the best conditions for the SMB operation.
- The regions for enantiomer separation can be numerically predicted, considering non-linear competitive adsorption isotherms, dispersion and mass transfer resistances phenomena. The mass transfer resistance phenomenon affects (reduces) the separation region of both enantiomers.
- Q_X versus Q_F plot provides a practical tool for choosing the better SMB operating conditions. The optimum will result from a trade-off between solvent consumption and productivity, purity and recovery requirements, and system robustness.