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SEPARATION OF A TWO-COMPONENT STEROID MIXTURE BY SIMULATED MOVING BED CHROMATOGRAPHY

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A method, combining laboratory scale equilibrium and elution experiments, simplified model based heuristic rules, as well as sophisticated dynamic simulation, was applied to design the separation of a two-component steroid crude mixture in a given laboratory-scale Simulated Moving Bed unit. The adsorption equilibrium isotherms of the pure components were determined by Frontal Analysis method. Langmuir isotherm model was fitted to the measured isotherm data. With the knowledge of these a priori data, elution chromatograms of the pure components were measured for the identification of the hydrodynamic and kinetic parameters in the SMB columns. The process simulation was made by the new method, based on the Direct Computer Mapping of the Generic, Bi-layered Net model. The first estimations of the SMB parameters were derived by means of the Morbidelli's triangle theory. Starting from a feasible solution, stepwise improvement of the SMB process was carried out by the detailed dynamic simulation, according to a strategy, based on the role of the design parameters. Simultaneously, laboratory-scale SMB experiments were carried out. Good agreement of the measured and calculated data was found. In the next step, the dynamic simulation has been applied for the improvement of the SMB separation (production rate, solvent consumption, recovery). In comparison with simple elution chromatographic separation method, considerable improvement of specific capacity parameters was obtained.

Keywords: Simulated Moving Bed, Direct Computer Mapping, Generic Bi-layered Net model, dynamic simulation, process design

Introduction

In our recently published papers [1-2] a methodology, combining laboratory scale equilibrium and elution experiments, simplified model based and heuristic rules, as well as sophisticated dynamic simulation was introduced to design the separation of a two-component steroid crude mixture in a given laboratory-scale Simulated Moving Bed unit.

The adsorption equilibrium isotherms of the pure components were determined by Frontal Analysis method. [3-6] Langmuir isotherm model was fitted to the measured isotherm data (see Table 1).

With the knowledge of Langmuir constants, elution chromatograms of the pure components were measured for the identification of the hydrodynamic and kinetic parameters in the SMB columns. The elution experiments were carried out in one of the columns of the SMB unit. Two elution experiments were carried out for each compound. One of them was used for the identification and the other for the validation of the obtained parameters.

Table 1: Parameters of Langmuir adsorption isotherms of component A and B

Compounds	a (l/g)	b (l/g)
A	5.859	0.029676
B	13.3	0.050386

For the identification we combined the dynamic simulator with a genetic algorithm [7] that changed the parameters to be identified within the prescribed

ranges, and evaluated the simulation with the integrated (summarized) quadratic difference of the calculated and the measured values. Finally, the suggested solution was refined by a few manually evaluated simulation trials. The fixed hydrodynamic and kinetic parameters of the models were the following:

Number of compartments (N) = 200; mixing coefficient (w) = 0; kinetic constant for both components (k) = 0.2 1/s

These hydrodynamic and kinetic parameters were used for all SMB simulations. [1-2]

The process simulation was made by the new method, based on the Direct Computer Mapping of the Generic, Bi-layered Net model. [8-10]

Table 2: Parameters of the laboratory scale SMB experiments

Process parameters	SMB-1	SMB-2	SMB-3	SMB-4	SMB-5	SMB-7	SMB-8	SMB-9	SMB-10	SMB-11
Column connection	2-2-2-2	2-2-2-2	2-2-2-2	2-2-2-2	2-2-2-2	2-6-6-2	2-6-6-2	3-4-7-2	3-4-7-2	3-5-8-0
Feed (ml/s)	0.025	0.025	0.0125	0.025	0.025	0.05	0.05	0.05	0.05	0.05
Conc. B (mg/ml)	1	1	6	9	9	9	9	9	9	12
Conc. A (mg/ml)	4	4	24	36	36	36	36	36	36	48
Eluent (ml/s)	0.1253	0.1217	0.1317	0.1567	0.1767	0.3633	0.37	0.2534	0.28	0.39
Extract (ml/s)	0.1083	0.1083	0.1183	0.1484	0.1683	0.3233	0.35	0.2148	0.255	0.255
Raffinate (ml/s)	0.042	0.0384	0.0259	0.0333	0.0334	0.09	0.07	0.0886	0.075	0.185
Column switching time step (s)	1350	1350	1200	600	750	360	360	360	360	360
Liquid recycle (ml/s)	0.0367	0.0367	0.037	0.06	0.055	0.11	0.11	0.11	0.11	-

To find a feasible parameter set for the first SMB experiments, the Morbidelli's triangle theory [11-14] was applied and a few simulation experiments were made. The input/output interface of the Generic Bi-layered Net model based dynamic simulator is described in an EXCEL workbook, where, with the knowledge of the filled input data, a macro generates the nonlinear Morbidelli diagram, and shows the point characterizing the proposed design to be tried.

Starting from a feasible solution, stepwise improvement of the SMB process was carried out by the detailed dynamic simulation, according to a strategy, based on the role of the design parameters. Simultaneously, some laboratory-scale SMB experiments were carried out. Good agreement of the measured and calculated data was found. It was shown, that the applied simulation model is suitable for prediction of SMB processes. Consequently in the following work, based on extensive computer simulations, we tried to improve the specific capacity parameters of the SMB separation (higher production rate and recovery and less solvent consumption), while we allowed a limited amount of the less retained compound (A) in the extract.

Experimental

Chemicals

The problem under investigation was the separation of a two-component non-isomer steroid crude mixture, produced by Gedeon Richter Ltd. The goal was to produce pure raffinate (maximum 0.3% strongly retained compound is allowed) and optionally slightly contaminated extract (maximum 5% weakly retained compound is allowed) products.

For the isotherm measurements and elution experiments the pure compounds with a purity of > 99% *m/m* were used. The pure compounds were produced by preparative elution chromatography. For the SMB investigations model mixtures of pure compounds were prepared with a composition, similar to the real crude mixture. The less retained compound is steroid A with k'=3.082, while the more retained one is steroid B with k'=8.046, (α=2.61).

YMC GEL Silica 6 nm S-50 μm was used as stationary phase, it was purchased from YMC, Europe GmbH (Schermbeck/Weselerwald, Germany).

The mobile phase was methylene-chloride-acetone 50:50% *v/v*. Solvents were purchased from Merck KgaA (Darmstadt, Germany).

Simulated Moving Bed Experiments

A laboratory-scale SMB unit (KNAUER CSEP 9116) was used for the SMB experiments. The number of columns in the four zones was changed between 8 and 16, respectively. In case of eight-column configuration two columns were in each zone. When sixteen columns were applied, different column configurations were used (2-6-6-2, 3-4-7-2). In one case a special open loop three-zone configuration was also examined (3-5-8-0 column configuration). The columns were packed by dry-packing method, using vibration (column dimension was I.D.=10 mm L=250 mm). The uniformity of columns was tested by elution experiments, injecting pure A compounds on the columns and eluting it with the eluent.

The parameters of the laboratory scale SMB experiments are summarized in *Table 2*.

Analytical Method for Measurement of SMB Samples

The samples of SMB experiments were examined by analytical HPLC which consisted of a gradient pump (SpectraSYSTEM P2000), a controller (SpectraSYSTEM SN4000), a light scattering detector (Polymer Laboratories PL-ELS 2100), a thermostat (JET-STREAM Plus) and an injection valve (Rheodyne, 20 µL loop). The system was operated by Windows NT/ChromQuest software.

A normal phase HPLC system was applied for measurements. The column was Merck, Lichrospher Si 60, particle size 5 µm, I.D.=4mm L=250mm
The eluent was acetone-methylene-chloride-methanol 40:50:10% *v/v*.

The injected sample volume was 20 µl, the volumetric flow rate of eluent was 1 ml/min. The experiments were carried out at 25°C column temperature. The nebulization and evaporation temperature was 32°C and the volumetric flow rate of the nebulizer gas was 0.8 SLM Nitrogen.

Process Design of Simulated Moving Bed Separation of the Given Compounds

The Simulated Moving Bed (SMB) process is the up-to-date solution for the continuous, counter current preparative chromatography. The principle of the technique has been described in numerous publications [15-16]. The essence of the process is that instead of the impossible continuous transportation of the particulate solid phase, the packed columns are changed stepwise, cyclically. This cyclic change is solved either by switching of valves or by the real rotation of the columns, connected to special distributing valves (as it is shown in Fig. 1).

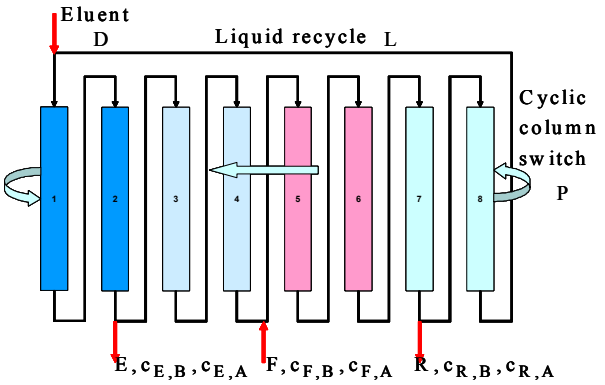

Figure 1: The main parameters of the SMB unit

In the SMB the strong (more retained, B) and weak (less retained, A) components of the feed (F) of concentration $c_{F,B}$ and $c_{F,A}$ are separated into two outlet flows. In the extract (E, $c_{E,B}$, $c_{E,A}$) the better adsorbing strong, while in the raffinate (R, $c_{R,B}$, $c_{R,A}$) the less adsorbing weak components are enriched, respectively. The process parameters to be controlled are the liquid recycle (L), the recycle of the packing (P), the flow rate of the fresh solvent (D) and the ratio E/(E+R) of the outlet flows. The process is characterized by the very slow transient of the fluctuating concentrations, converging toward the (optionally multiple and sometimes impossible) steady state. The simulation needs the solution of systems of nonlinear, coupled IPDAE (Integer Partial Differencial Algebraic Equations) under cyclically changing initial and boundary conditions.

The conventional SMB unit consists of four zones, containing a number of columns that can be changed.

In our last paper [1] three eight-column configuration SMB experiments were described. (2 columns were in each section of the SMB unit.) It was shown that the applied simulation model is

suitable for prediction of SMB processes. Consequently in the following work, based on computer simulations, we tried to improve the specific capacity parameters of the SMB separation (higher production rate and recovery and less solvent consumption) while we allowed a limited amount of the less retained compound (A) in the extract.

In Fig. 2 the eight-column (2-2-2-2) configuration experiments are compared with preparative elution chromatographic separation of the respective compounds. It can be seen, that applying only eight columns in the SMB unit, considerable improvement of specific capacity parameters was obtained. It is worth mentioning that in case of eight columns (2-2-2-2 connection) the impurity level of the extract was a little bit higher than five percent, but there was no option to change the number of columns in the zones, freely. The other feasible 1-3-3-1 connection would not be appropriate for safe separation, because in the first and fourth zones two columns are required for cleaning the recycling streams.

The next step was to increase the number of columns in the SMB unit from eight columns to sixteen. The improvement of the specific capacity parameters and purity of both products were examined.

It was apparent from computer simulations, that increasing the number of columns from 2-2-2-2 connection to 4-4-4-4 connection, i.e. the proportional scaling-up of the respective streams, did not improve the specific capacity parameters and the purity of products, either.

Consequently, we examined the effect of the different column configurations of the four-zone SMB on the more effective separation of compounds.

Accordingly in the next SMB experiment (SMB-7) the column connection was 2-6-6-2. The feed flow rate was doubled, compared to the eight column configuration (2-2-2-2 connection) system. The recycling streams were proportionally increased. The eluent flow rate proportionally increased, but for the appropriate extract quality, the eluent excess was distributed among the two outlets. Carrying out an SMB experiment with the above described experimental conditions, the more retained compound B appeared in the raffinate after sixteen cycles (see Figs. 3a-3d and Table 3).

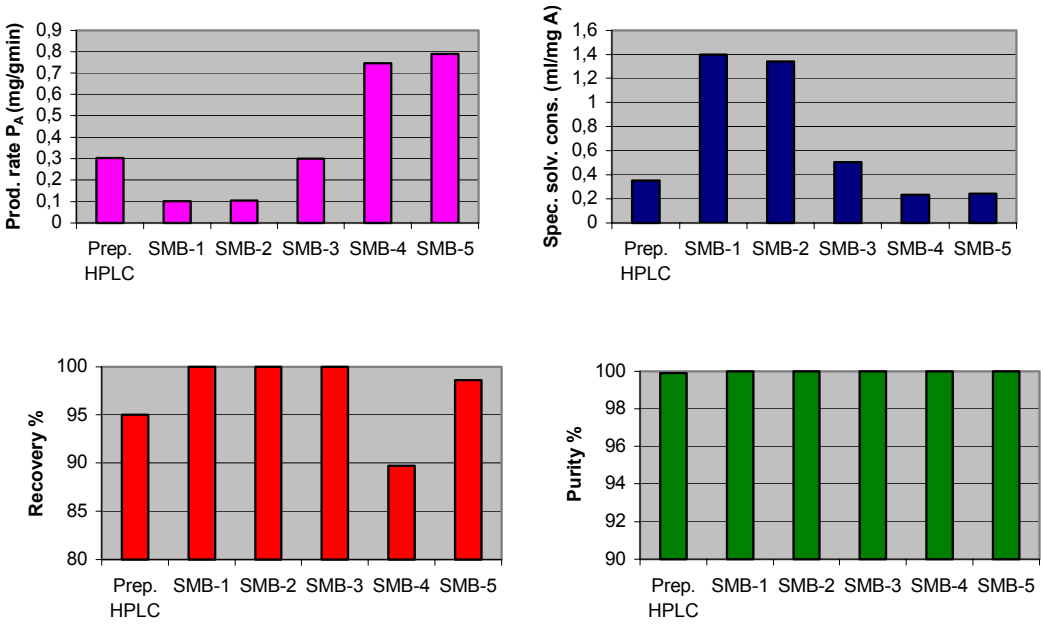

Figure 2: Comparison of the eight-column SMB experiments with the simple preparative elution data

Fig. 3d shows the long term simulation results in a logarithmic scale. It can be seen, that the contamination of the raffinate is the result of a very slow transient process which could be avoided by deep investigation of long term simulation data. Contamination of the raffinate can be prevented by using more fresh eluent and higher extract/raffinate ratio.

In the SMB-8 experiment only the amount of fresh eluent and the extract/raffinate ratio were increased, compared to experiment SMB-7. (See *Table 2*.) In this way we were able to produce pure raffinate and only slightly contaminated extract, but the specific solvent consumption was a little bit higher, than in case of the best eight-column (SMB-5) experiment. (See *Table 3*.)

Table 3: Specific capacity parameters of SMB experiments

SMB experiments	Feed A:B (g/l)	Production rate P_A [mg/(g min)]	Specific solvent consumption (ml/mg A)	Recovery (%)	Purity (%)
Isocratic, 8 columns, 4 zones, column connection: 2-2-2-2					
SMB-5	36:9	0.7891	0.2429	98.62	100
Isocratic, 16 columns, 4 zones					
SMB-7 2-6-6-2	36:9	0.8114	0.2376	100	97.46
SMB-8 2-6-6-2	36:9	0.7920	0.2471	99.31	100
SMB-10 3-4-7-2	36:9	0.8065	0.1907	99.25	100
Gradient, 16 columns, 3 zones					
SMB-11 3-5-8	48:12	1.0175	0.2015	99.86	100

Therefore in the following the main goal was to decrease the specific solvent consumption by changing the column distribution in the four zones of the SMB unit.

Based on computer simulations, this objective can be reached by changing the column connection for 3-4-7-2, while leaving the recycle and feed streams unchanged. (See *Table 2*.) This asymmetrical column connection can be explained by the actual separation task, because the separation of the less retained compound A (which is present in a much higher amount than compound B) and the more retained compound B occured in the third and second zones. The first zone had an important role too, in which there were three columns, because the desorption of the more retained compound B accomplished here.

As it can be seen from Figs. 4a-4c and from *Table 3*, using the above described experimental conditions the specific solvent consumption could be decreased.

Finally, we tried also a three-zone (open-loop) SMB configuration, where there was no liquid recycle at all. In this case the steroid mixture was solved in pure methylene-chloride. In this way the solubility of the compounds could be considerable increased, that is why the specific capacity parameters of the SMB 11 separation could be improved further (see Figs 5a-5c and *Table 3*).

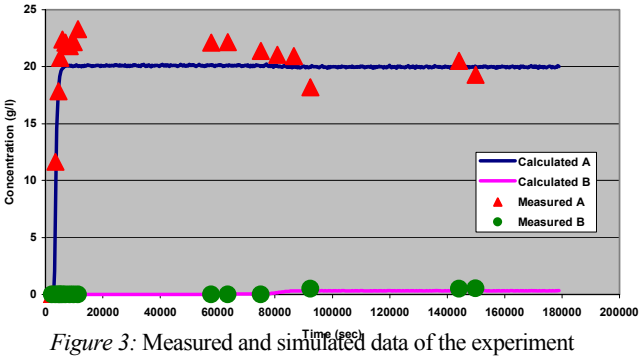

Figure 3: Measured and simulated data of the experiment SMB-7
3a) Average concentration of the raffinate

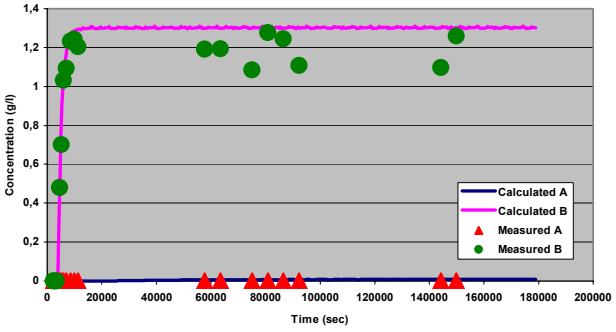

Figure 3: Measured and simulated data of the experiment SMB-7
3b) Average concentration of the extract

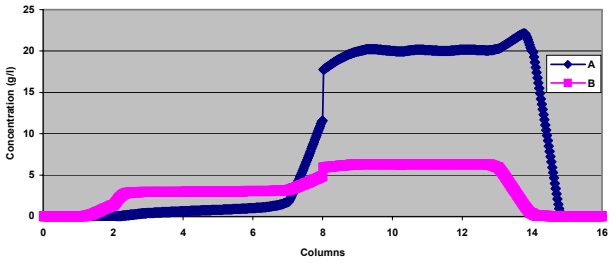

Figure 3: Measured and simulated data of the experiment SMB-7
3c) Average concentration profiles in the liquid phase

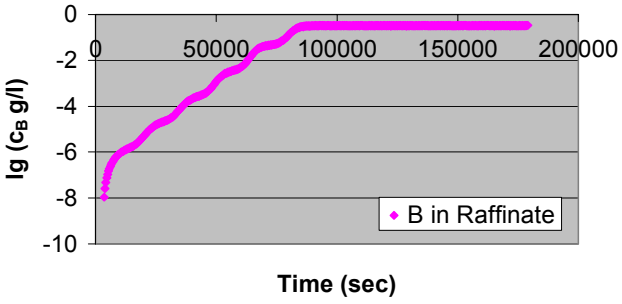

Figure 3: Measured and simulated data of the experiment SMB-7
3d) Illustration of the slow transient in logarithmic scale

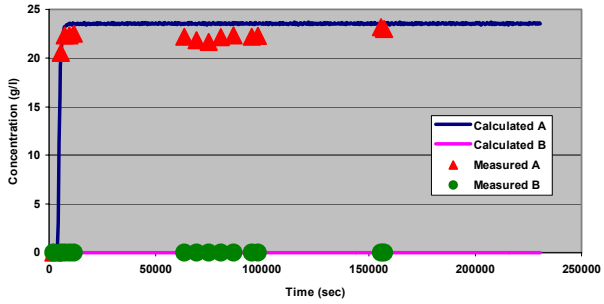

Figure 4: Measured and simulated data of the experiment SMB-10
4a) Average concentration of the raffinate

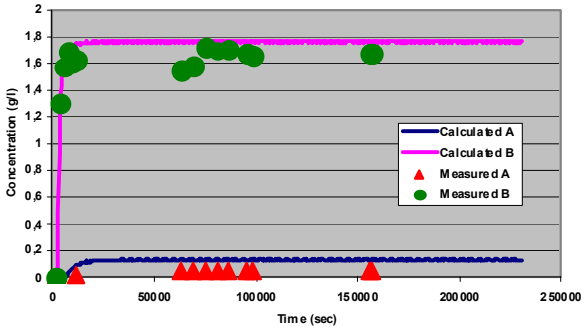

Figure 4: Measured and simulated dataof the experiment SMB-10
4b) Average concentration of the extract

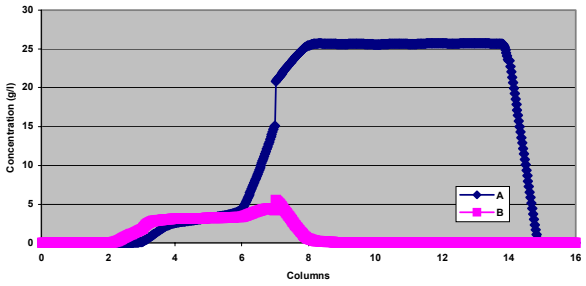

Figure 4: Measured and simulated data of the experiment SMB-10
4c) Average concentration profiles in the liquid phase

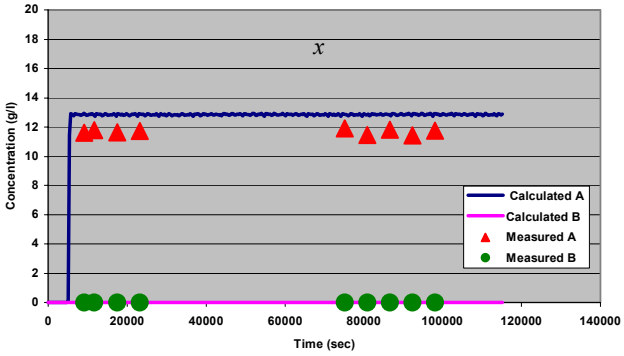

Figure 5. Measured and simulated data of the experiment SMB-11
5b) Average concentration of the extract

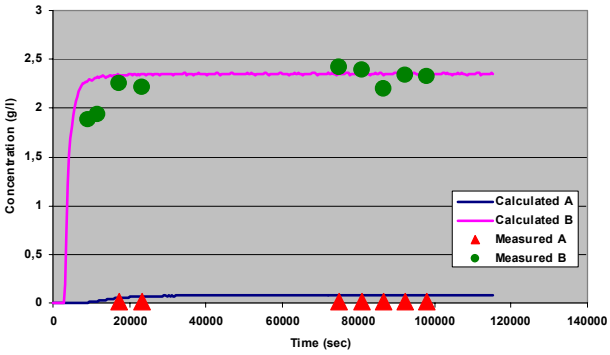

Figure 5. Measured and simulated data of the experiment SMB-11
5b) Average concentration of the extract

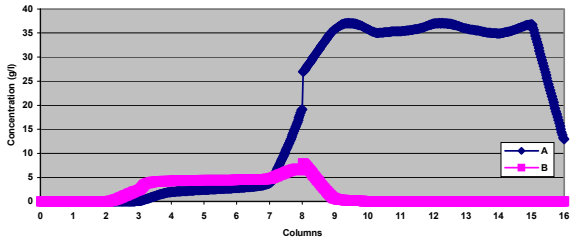

Figure 5. Measured and simulated data of the experiment SMB-11
5c) Average concentration profiles in the liquid phase

Conclusions

1. The application of the Generic Bi-layered Net based Direct Computer Mapping makes possible to develop an appropriate tool for the detailed dynamic simulation of the Simulated Moving Bed process. The measured and calculated results agree with each other.
2. We have elaborated a methodology, combining
   – experimental determination of the Langmuir isotherms for the individual components,
   – use of the competitive Langmuir equation for the calculation of the driving force in the kinetic model,
   – simulation based identification of the kinetic and hydrodynamic parameters from elution chromatograms,
   – application of the Morbidelli's triangle theory to find feasible initial solutions, and
   – simulation based improvement and optimization of the SMB process.
   The method has been proved to be applicable for the solution of the detailed process design of the SMB separation.
3. Based on the new design methodology, involving the Generic Bi-layered Net model we solved an actual, industrial separation problem successfully. The specific capacity parameters of the SMB separation (production rate, specific solvent consumption, recovery) considerably improved compared to simple preparative elution chromatographic separation of the given compounds.

SYMBOLS

A	Less retained compound
B	More retained compound
a_i, b_i	Langmuir parameters
N	Number of cell
w	Mixing coefficient
k	Kinetic constant
k'	Capacity factor
SLM	Standard Litre Per Minute (Gas flow rate)
I.D.	Internal diameter
v/v	volumetric ratio
m/m	mass ratio
F	Feed
c	Concentration of the compounds
R	Raffinate
E	Extract
L	Liquid recycle
D	Fresh solvent
P	"Recycle of the packing", column switching time

GREEK LETTER

α	Selectivity

INDICES

i	Identifier of the components
A	Less retained compound
B	More retained compound
F	Feed
R	Raffinate
E	Extract

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