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SEPARATION OF ORGANIC COMPOUNDS BY GRADIENT SIMULATED MOVING BED CHROMATOGRAPHY

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A promising solution for the separation of organic compounds in pharmaceutical industry is the gradient simulated moving bed chromatography (SMB). The above mentioned process can be used for the production of high purity materials (isomers, optical isomers, biomolecules).

We assumed isotherm, isochor equilibrium adsorption (competitive multicomponent Langmuir-adsorption equilibrium) in the mathematical model and neglected the effects of axial dispersion. In our present work we extended the mathematical model with solvent adsorption-desorption processes (acetone-dichloromethane eluent, steroid compounds, silicagel). The mathematical model was solved by finite differences numerical mathematical method using PC. The gradient SMB separations were carried out with a laboratory scale four column equipment in open loop system at 1:1:2:0 column configuration. The SMB equipment (L=25 cm, I.D.=1 cm) was planned and constructed for separation of a steroid mixture using YMC S-50 silica gel as adsorbent (specific surface=798.63 m^2 g^{-1}). The effect of switching time change (5.5 min, 9 min, 11.5 min, 22.5 min) on component separation was examined. During our measurements the amount of acetone in dichloromethane was 55 % v/v in the fresh eluent and pure dichloromethane in the feed. The process variables of the gradient SMB (product purity, yield, productivity, specific solvent consumption) are very favourable. Our conclusion is that the measured and the calculated data agree well and we have produced more than 99.9 %m/m purity and 90 % yield , productivity 1300-3000 g steroid kg^{-1} adsorbent day at 0.1-0.3 m^3 fresh eluent kg^{-1} steroid eluent consumption.

Keywords: Preparative liquid chromatography, Simulated moving bed chromatography, Solvent gradient SMB

Introduction

The SMB process was developed in the early 1960s by Brougthon and Gerhold [1] and has been used for many years in the petrochemical and sugar industries for large scale separation [2]. Recently, the separation of enantiomers due to the demand for high purity products has become necessary [3]. The SMB *(Fig. 2.)* is a continuous unit operated in cyclic mode which reproduces the performance of the equivalent true moving bed (TMB) unit *(Fig. 1.)*.

The SMB is divided into four sections, each constituted of a counter current adsorption column which plays a specific role in the separation. Let us consider a feed mixture consisting of more retained species (A) and a less retained one (B) dissolved in the eluent. The separation is obtained in the two central sections, where B is carried by the mobile phase to the raffinate outlet. The fresh eluent is fed to the bottom of the section I, so as to desorb A and regenerate the adsorbent solid, before it is recycled to section IV. On the other hand B is retained in section IV and the pure eluent is recycled to section I. In practice the movement of the solid is not feasible and the TMB is replaced by the SMB configuration where the adsorption beds are fixed and the counter-current solid-liquid movement is simulated by periodical switching the inlet and outlet ports of the unit [4].

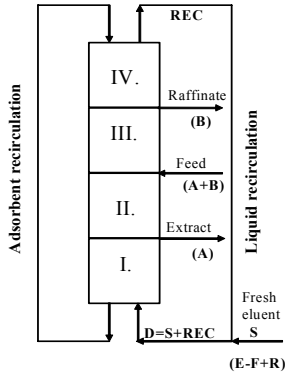

Fig. 1.: True moving bed (TMB) adsorber – I, II, III, IV – zones; S – desorbent (solvent, eluent); Rec – recirculated eluent; E – extract stream with the better adsorbed component A; F – feed stream with the components A and B; R – raffinate (liquid outlet) stream with the less adsorbed component B

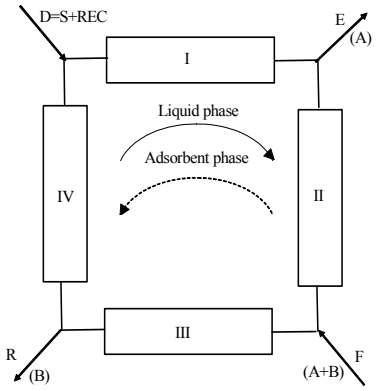

Fig. 2.: Simulated moving bed (SMB) adsorber – I, II, III, IV – zones, respectively HPLC columns

Use of gradient elution is recommended, if conditions must be changed during separation. The applied gradient can be the pressure, temperature or solution composition.

According to the literature of solution composition changing gradient SMB, where the solution composition is chosen, four scientific „schools" exist; the MPI Magdeburg Inst. Dyn. Komplex Techn. System in Germany [5,6,7], the Kluyer Laboratory for Biotechnology at Delft University of Technology in the Netherlands [8,9,10]. ETH Zürich, Inst. Verfahrenstechnik in Switzerland [4, 11] and there are significant scientific results in France [12], too.

We calculated the initial parameters with the method of Morbidelli et al. [13]. After the authors in a two component system can be determined a the m_{II}-m_{III} area from the geometric data of the SMB equipment, the volumetric velocities, the parameters of Langmuir-type isotherms and the concentrations of the mixture to be separated. The actual operating conditions determine a point on the m_{II}-m_{III} diagram. The variable operating conditions are: fresh eluent, recirculated eluent, feed, extract and raffinate flow rates, switching time. Mathematical models and joined computer programmes published in our earlier papers [14,15] have been developed and applied for the calculation of SMB.

Experiments

All necessary additional information for this project, like the adsorption equilibrium data, the Number of Theoretical Plates (NTP) and Height of Equivalent Theoretical Plate (HETP), the frontal adsorption - elution measurement was published earlier [16].

Parameters of SMB-LC Measurements

We applied an 1-1-2-0 column configuration in the SMB system. This way the steroid B has "bigger space" along the length of the columns. In this case we did not use the raffinate pump, we adjusted the flow rate in segment III so that the steroid B appeared in the LROUT flow in the open-looped SMB system.

The function of segment I is the regeneration of the adsorbent and the production of the steroid A in the extract. As fresh eluent in the segment I we used 1.2:1 (v/v) acetone - dichloromethane (gradient). The function of segment II is the separation of steroid A and B and the extraction of the steroid A in this segment. The function of segment III is to separate steroid A and B and to produce steroid B in the LROUT flow.

We fed the mixture of steroid A and B into the third segment, the steroids were soluted in pure dichloromethane because this improved the solution of the steroids and helped us to use gradient SMB.

Each of the columns in the four-column SMB equipment were previously equilibrated with pure dichloromethane at 293 K, we wanted to separate the dichloromethane mixture of 42 g dm^{-3} steroid B and 18 g dm^{-3} steroid A.

The fresh eluent 1.2:1 v/v acetone-dichloromethane volumetric ratio was 4.25 cm^3min^{-1}. The feed flow rate of the steroid sample was 0.8 cm^3 min^{-1}. Steroid A was extracted with 2.2 cm^3 min^{-1} parameter, so the LROUT flow was 2.85 cm^3min^{-1} and the switching time was 22.5 min. Process parameters were determined by Morbidelli method *(Fig. 3.* and *Table 1).*

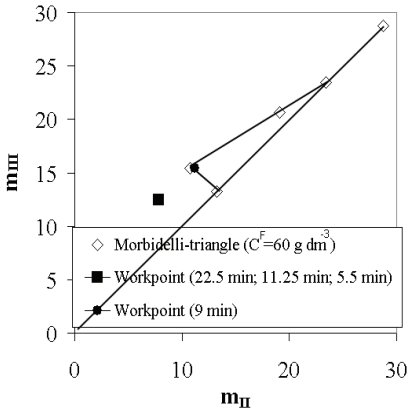

Fig. 3.: The measurement points placed in the Morbidelli triangle at different switching times

When we decreased the switching time to 11.25 min, we doubled the original flow rates. When we used 5.5 min for switching time, we doubled once again the flow rates. In case of 9 min as switching time, we used computer simulation to optimize the work point to get as close to the points of Morbidelli triangle as it was possible (F= 1.8 cm^3min^-1, D= 14.4 cm^3min^{-1}, E=7.8 cm^3min^{-1}, LROUT= 8.4 cm^3min^{-1}).

Table 1: Input data of the software SMB-KROM-N

<table>
<tr><td>Number of components</td><td>k = 3</td></tr>
<tr><td>Column inner diameter</td><td>ID.=1 cm</td></tr>
<tr><td>Column length</td><td>L=25 cm</td></tr>
<tr><td>Number of columns</td><td>N=4</td></tr>
<tr><td>Free volume coefficient</td><td>EPS= 0.8018 cm^3 liquid free volume cm^{-3} column</td></tr>
<tr><td>Bulk density</td><td>ROH= 0.4045 g silica gel cm^{-3} column</td></tr>
<tr><td>Langmuir constants</td><td>(same as on page)</td></tr>
<tr><td>Feed concentration</td><td>$c^F_{acetone}$ = 0 mg acetone cm^{-3} liquid
c^F_B = 42 mg B component cm^{-3} liquid
c^F_A =18 mg A component cm^{-3} liquid</td></tr>
<tr><td>Flow rates</td><td>
<table>
<tr><td>Simulation</td><td>SMB 8/41</td><td>SMB 8/42</td><td>SMB 8/46*</td><td>SMB 8/44</td></tr>
<tr><td>Switching time(min)</td><td>22.5</td><td>11.25</td><td>9</td><td>5.5</td></tr>
<tr><td>F (cm^3 min^{-1})</td><td>0.8</td><td>1.6</td><td>1.8</td><td>3.2</td></tr>
<tr><td>D (cm^3 min^{-1})</td><td>4.25</td><td>8.5</td><td>14.4</td><td>17.0</td></tr>
<tr><td>E (cm^3 min^{-1})</td><td>2.2</td><td>4.4</td><td>7.8</td><td>8.8</td></tr>
<tr><td>R (cm^3 min^{-1})</td><td>0</td><td>0</td><td>0</td><td>0</td></tr>
</table>
* Optimized by simulation
$c^S_B = c^S_A = 0$ mg B or A component cm^{-3} liquid
</td></tr>
<tr><td>Fresh eluent</td><td>$c^F_{acetone}$ = 435.6 mg acetone cm^{-3} liquid</td></tr>
<tr><td>Number of Theoretical Plates</td><td>NTP=200 / 25 cm column</td></tr>
<tr><td>Calculation time</td><td>585 min</td></tr>
</table>

Simulation Data of 1:1:2:0 Column Configuration SMB

Simulation was done by SMB-KROM-N software. The input data are summarized in Table III. The software takes into account the solvent adsorption-desorption phenomena, too.

Fig. 4 shows the profile of A and B component along the length of columns and *Fig. 5* shows the acetone gradient along the length of columns, at quasi-stationary state in case of RG SMB8/46 simulation.

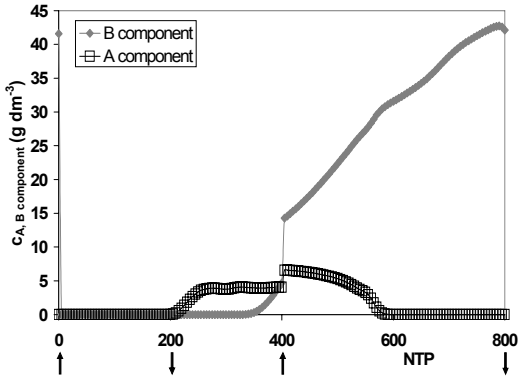

Fig. 4.: Profile of A and B components at quasi-stationary state

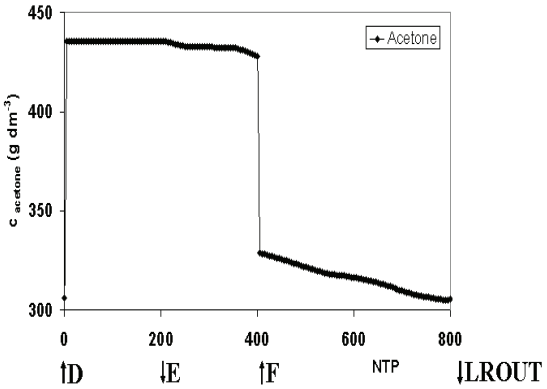

Fig. 5.: Profile of acetone at quasi-stationary state

Fig. 6 and *7* shows the acetone concentration change in the raffinate and extract outlet versus simulation time in case of RG SMB8/46 simulation.

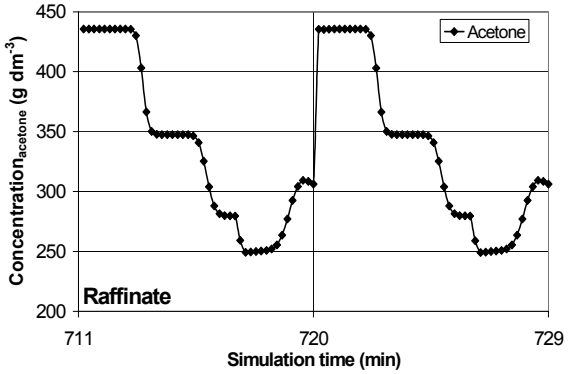

Fig. 6.: Acetone concentration versus two period of simulation time in the raffinate outlet

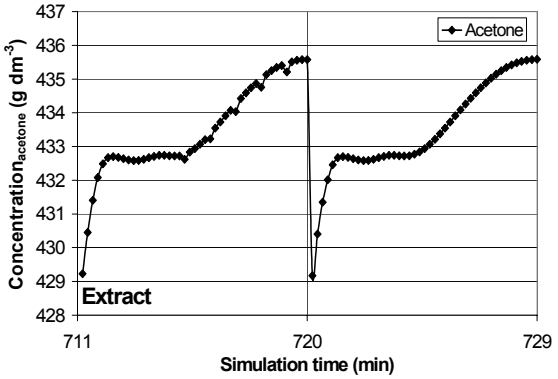

Fig. 7.: Acetone concentration versus two period of simulation time in the extract outlet

Results

Measurement Results of 1:1:2:0 Column Configuration SMB Compared to Simulation

On the Fig. 8, 9, 10 and 11 those measurements are marked with grey colour where the desired results can be seen, with white colours the measurements which are out of our requirements.

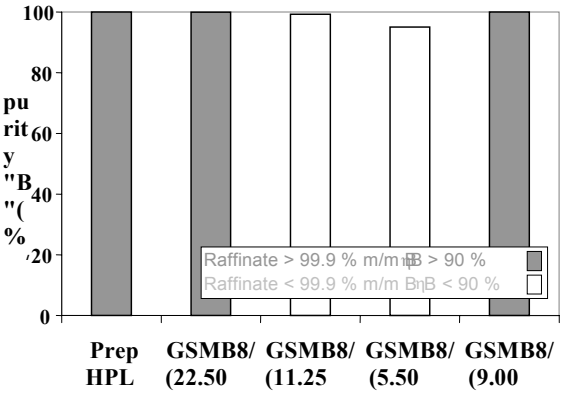

Fig. 8.: Comparing the purity of steroid B in different measurements

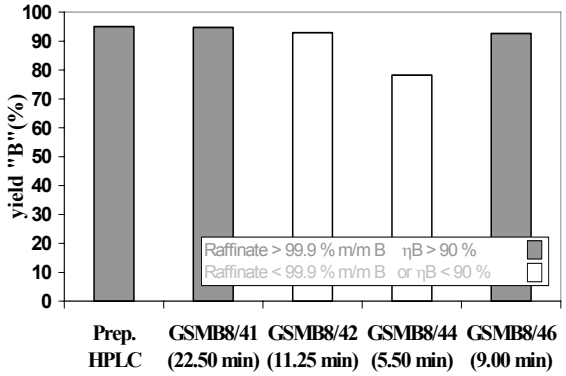

Fig. 9.: Comparing the yield of steroid B in different measurements

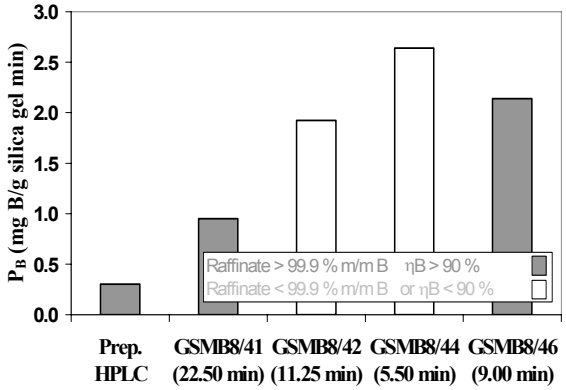

Fig. 10.: Comparing the productivity of steroid B in different measurements

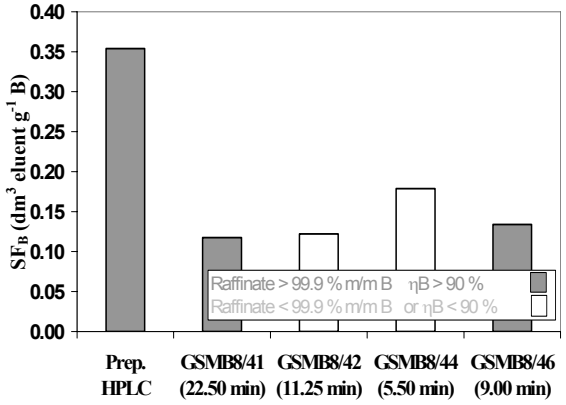

Fig. 11.: Comparing the eluent consumption of steroid B in different measurements

The result of the experiments shows that the decrease of the switching time highly improves the productivity, especially at the optimized 9 min switching time experiment. In this case the eluent consumption is also properly low. To describe numerically the above GSMB 8/41 and GSMB 8/46 the productivity was increased from 0.95 mg steroid B g^{-1} adsorbent min^{-1} to 2.64 mg steroid B g^{-1} adsorbent min^{-1}. The eluent consumption was changed from 0.12 cm^3 eluent mg^{-1} steroid B to 0.18 cm^3 eluent mg^{-1} steroid B.

We achieved the best favourable result in the RG-1040-GSMB 8/46 measurement at 9 min switching time. In this case the calculated values of measurement were compared to data given in *Table 2.* We note that the LROUT 1, 2 are given by halving the LROUT liquid stream for 0-4,5 min and 4,5-9 min fractions.

Table 2: Results of the RG 1040 GSMB 8/46 measurement compared to result of the simulation

	Measurement	Simulation
Purity of raffinate (LROUT)	LROUT1 96.96 %m/m B LROUT2 > 99.9 %m/m B	LROUT 1 +LROUT 2 > 99.9 %m/m B
Purity of extract (E)	88.89 %m/m A	93.5 %m/m A
Yield	LROUT1 6.46 %B LROUT2 92.6 %B Extract 68.1 %A	LROUT 1 +LROUT 2 > 99.99 % 98.3 %
Productivity	LROUT 2 2.14 $\frac{mg\ B}{g\ silica\ gel\ \min}$ Extract 0.54 $\frac{mg\ A}{g\ silica\ gel\ \min}$	LROUT 1 +LROUT 2 2.16 $\frac{mg\ B}{g\ silica\ gel\ \min}$ Extract 0.69 $\frac{mg\ A}{g\ silica\ gel\ \min}$
Eluent consumption	LROUT 2 0.134 $\frac{cm^3\ fresh\ eluent}{mg\ B}$ Extract 0.403 $\frac{cm^3\ fresh\ eluent}{mg\ A}$	LROUT 1 +LROUT 2 0.197 $\frac{cm^3\ fresh\ eluent}{mg\ B}$ Extract 0.61 $\frac{cm^3\ fresh\ eluent}{mg\ A}$

Discussion

Our conclusion on the basis of laboratory gradient, 1:1:2:0 column configuration, open loop SMB measurements is that varying the switching time of SMB process results big changes in productivity. In our case we get the highest productivity at 9 min switching time. We significantly increased the operation results according to the preparative HPLC measurement *(Table 3).*

Table 3: Results of the RG 1040 GSMB 8/46 measurement compared to preparative HPLC measurement

	Preparative HPLC	RG1040 SMB8/46 measurement (9 min)
Purity of raffinate (LROUT 2)	>99.9 % m/m B	>99.9 % m/m B
Yield (LROUT 2)	~ 95 % B	>92.6 % B
Productivity (LROUT 2)	0.303 $\frac{mg\ B}{g\ silica\ gel\ \min}$	2.14 $\frac{mg\ B}{g\ silica\ gel\ \min}$
Eluent consumption (LROUT 2)	0.354 $\frac{cm^3\ fresh\ eluent}{mg\ B}$	0.134 $\frac{cm^3\ fresh\ eluent}{mg\ B}$

We achieved 700% productivity increase and 50 % eluent consumption decrease beside more than 99.9 % m/m B purity and 90 % B yield. It could be seen, that the developed SMB process was outstandingly economic, the value of the productivity was successfully increased to 3.082 kg B/ kg silica gel within a day, at 0.134 m^3 fresh eluent/kg B steroid eluent consumption.

SYMBOLS

$c_{Acetone}$	concentration of acetone, g dm^{-3}
c_B	concentration of steroid B, g dm^{-3}
c_A	concentration of steroid A, g dm^{-3}
k	number of components
k’	capacity factor
ID	column inner diameter, cm
L	column length, cm
F	flow rate of feed, cm^3 min^{-1}
D	flow rate of fresh eluent, cm^3 min^{-1}
E	flow rate of extract, cm^3 min^{-1}
R	flow rate of raffinate, cm^3 min^{-1}
LROUT	outlet liquid at 1:1:2:0 column configuration at R=0
T	switching time, min
ε	free volume coefficient, cm^3 liquid free volume cm^{-3} column
ROH	bulk density, g silica gel cm^{-3}column
NTP	Number of Theoretical Plates
N	Number of columns

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