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STUDY OF OPEN–LOOPED SIMULATED MOVING BED (SMB) CHROMATOGRAPHIC PROCESS

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In this experimental work laboratory scale four-column simulating moving bed (SMB) equipment (L=25 cm, ID=1 cm) was planned and constructed for separation of a steroid mixture [1] using YMC S-50 silica gel as adsorbent, with the co-operation of Central Mechanical Workshop, University of Veszprém. 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. Product purity and other specifications (yield, productivity, eluent consumption) were measured by gas chromatography. An equilibrium mathematical model of the SMB process for open and closed eluent loops was constructed by means of a computer program [2, 3]. Adsorption equilibrium, and kinetic data, theoretical plate number measurement, frontal and elution adsorption-desorption measurements for determination of the optimum conditions for the SMB process and for construction of the mathematical model were measured by means of laboratory experiments. Finally results coming from simulation program were compared to measurement results. Our conclusion is that the measured and the calculated data agreed well and we have produced more than 99.9 % m/m purity and 90 % yield, at productivity 1300-3000 g "B" component/ kg adsorbent within a day using 60 g dm^{-3} inlet steroid composition in case of 1:1:2:0 column configuration.

Keywords: SMB, preparative liquid chromatography, simulated moving bed chromatography,

Introduction

The most recent developments in preparative chromatographic processes are the simulated moving bed processes; these will probably be widely used, mostly for the production of high purity materials or materials otherwise difficult to isolate in pharmaceutical industry, fine chemical and biotechnological separation tasks. If materials are difficult to separate ($\alpha \approx 1$), the process efficiency is disadvantageous, as in case of a component of a mixture being strongly adsorbed (k'»). The process becomes uneconomical when a large volume of eluent must be used.

The SMB process was developed in the early 1960s by Brougthon and Gerhold [4] and has been used for many years in the petrochemical and sugar industries for large scale separation. Recently, the separation of enantiomers due to the demand for high purity products becomes necessary [5]. The SMB (*Fig.2.*) is a continuous unit operated mode in cyclic 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 a 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

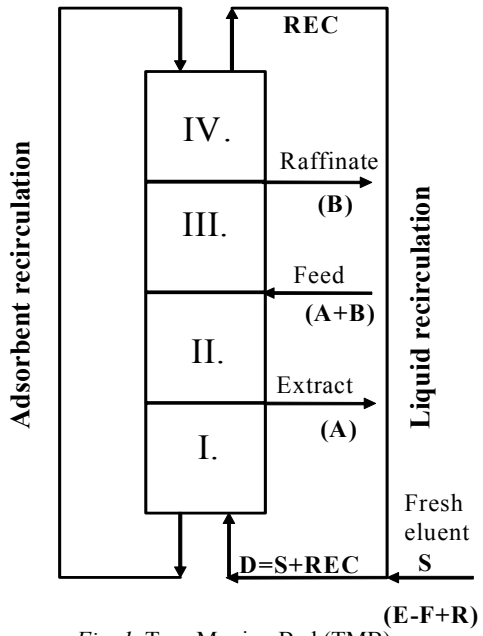

Fig. 1. True Moving Bed (TMB)

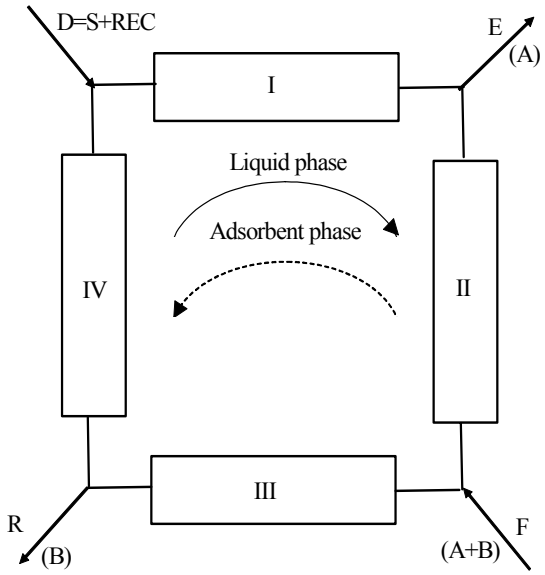

Fig. 2. Simulated Moving Bed (SMB)

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 [6].

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

The third out of theses is usually chosen, and the process is known as solution composition changing gradient SMB. The literature reveals that four scientific „schools" study this subject, the Kluyer Laboratory for Biotechnology at Delft University of Technology in the Netherlands [7-9], ETH Zürich, Inst. Verfahrenstechnik in Switzerland [10,11], the MPI Magdeburg Inst. Dyn. Komplex Techn. System in Germany [12,13] and there are significant scientific results in France, too.

We calculated the initial parameters with the method of Morbidelli et al. [14]. After the authors in a two components system can be determined a 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 determined 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.

Experiments

Equilibria Measurements

Adsorption equilibria data for acetone (*Fig. 3.*) and for steroids "A" and "B" (*Fig. 4.*) were determined on YMC S-50 silica gel with 1:1 (v/v) acetone-dichloromethane at 293 K at Richter Rt, Department of Preparative Chromatography. Monitoring happened by analytical HPLC with a multistepped frontal saturating method.

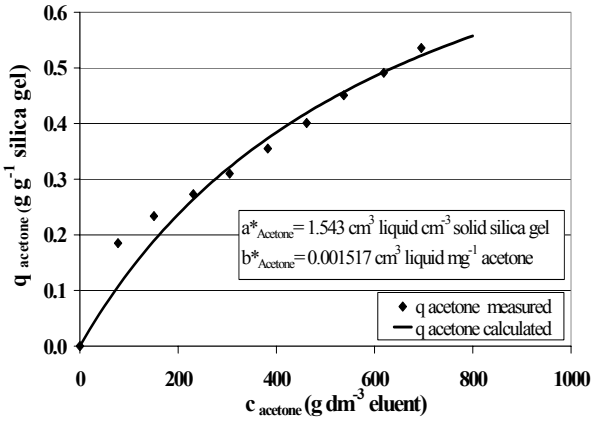

Fig. 3. Adsorption equilibria measurement of acetone
Acetone in Dichloromethane
YMC S-50 silica gel, 20°C, measurements of G. R.

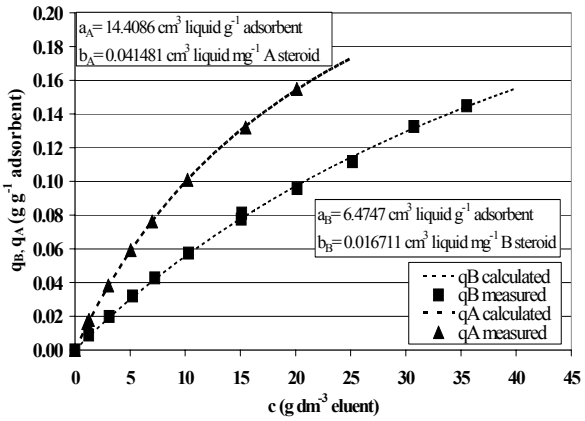

Fig. 4. Adsorption equilibria measurement of „A" and „B" components
Steroid A, B adsorption, YMC S - 50 silica gel
in 1:1 (v/v) acetone-dichloromethane, 20°C, measurements of G. R.

Langmuir constants used for calculations are given below (*Table 1.*):

Calculation for the three-component mixture:

Adsorption isotherm of acetone:

$$q_{\text{acetone}} = \frac{a_{\text{acetone}}\ c_{\text{acetone}}}{1 + b_{\text{acetone}}\ c_{\text{acetone}}} = \frac{1.543\ c_{\text{acetone}}}{1 + 0.001517\ c_{\text{acetone}}} \quad \text{mg g}^{-1} \qquad (1)$$

Adsorption isotherm for steroid B in 1:1 (v/v) acetone-dichloromethane:

$$q_{\text{B}} = \frac{6.474\ c_{\text{B}}}{1 + 0.001671 c_{\text{B}}} \quad \text{mg g}^{-1} \qquad (2)$$

For the competitive Langmuir:

$$q_{\text{B}} = \frac{a_{\text{B}}\, c_{\text{B}}}{1 + b_{\text{acetone}}\, c_{\text{acetone}} + b_{\text{B}}\, c_{\text{B}}} \qquad (3)$$

If $c_B \approx 0$, the first derivative of the isotherm is:

$$\frac{\mathrm{d}\, q_{\text{B}}}{\mathrm{d}\, c_{\text{B}}} = \frac{a_{\text{B}}}{1 + b_{\text{acetone}}\, c_{\text{acetone}}} \qquad (4)$$

We obtained new Langmuir constants when the acetone-dichloromethane volume is additive and $c_{acetone}$=396 g dm^{-3} :

$$6.474 = \frac{a_{\text{B}}^*}{1 + 0.001517 \cdot 396} \qquad a_{\text{B}}^* = 10.36\ cm^3\ \text{g}^{-1} \qquad (5)$$

$$0.01671 = \frac{b_{\text{B}}^*}{1 + 0.001517 \cdot 396} \quad b_{\text{B}}^* = 0.02675\, cm^3\ \text{mg}^{-1} \qquad (6)$$

Calculation method for steroid A is similar.

Table 1. Adsorption isotherms on YMC-S-50 silica gel

Langmuir constants for acetone in dichloromethane
$a^*_{\text{Acetone}} = 1.543 \dfrac{cm^3 \ \text{liquid free volume}}{\text{g silicagel}}$
$b^*_{\text{Acetone}} = 0.001517 \dfrac{cm^3 \ \text{liquid free volume}}{\text{mg acetone}}$
Langmuir constants for steroids 1: 1 (v/v) acetone -dichloromethane
$a_{\text{B}} = 6.474 \dfrac{cm^3 \ \text{liquid free volume}}{\text{g silicagel}}$
$b_{\text{B}} = 0.01671 \dfrac{cm^3 \ \text{liquid free volume}}{\text{mg B component}}$
$a_{\text{A}} = 14.086 \dfrac{cm^3 \ \text{liquid free volume}}{\text{g silicagel}}$
$b_{\text{A}} = 0.04148 \dfrac{cm^3 \ \text{liquid free volume}}{\text{mg A component}}$
Langmuir constants of three-component compound
$a^*_{\text{Acetone}} = 1.543 \dfrac{cm^3 \ \text{liquid free volume}}{\text{g silicagel}}$
$b^*_{\text{Acetone}} = 0.001517 \dfrac{cm^3 \ \text{liquid free volume}}{\text{mg acetone}}$
$a^*_{\text{B}} = 10.36 \dfrac{cm^3 \ \text{liquid free volume}}{\text{g silicagel}}$
$b^*_{\text{B}} = 0.02675 \dfrac{cm^3 \ \text{liquid free volume}}{\text{mg B component}}$
$a^*_{\text{A}} = 22.55 \dfrac{cm^3 \ \text{liquid free volume}}{\text{g silicagel}}$
$b^*_{\text{A}} = 0.06640 \dfrac{cm^3 \ \text{liquid free volume}}{\text{mg A component}}$

*Determination of Number of Theoretical Plates (NTP) – Height of Equivalent Theoretical Plate (HETP***)**

A Supelco chromatographic column (ID=1 cm, L=25 cm) was filled with YMC S-50 silica gel (8 g) with the aid of a column-packing vibrator. Air was removed from the column by means of 1:1

(v/v) acetone-dichloromethane and an LMIM D-167 pump. A Rheodyne injection valve with 100 μL loop was connected to the column inlet and a Waters UV detector to the outlet, where we monitored the signal from 0.2 % (v/v) acetophenone in eluent on 300 nm wavelength. We evaluated the retention time density function with the triangle method.

The flow rates during the measurements were in the range of 1-13 cm^3 min^{-1}. The equation of the trendline is $NTP/25(cm) = 1522.4v_0(cm^3\ min^{-1})^{-0,707}$, the regression value is $R^2 = 0.9639$.

Frontal Adsorption - Elution Measurement

Measurement was performed with a chromatographic column (*ID*=0.735 cm, *L*=42 cm) packed with YMC S-50 silica gel. Air was removed from the column by means of 1:1 (v/v) acetone-dichloromethane at 293 K, directed upwards by means of an LMIM-D167 piston pump.

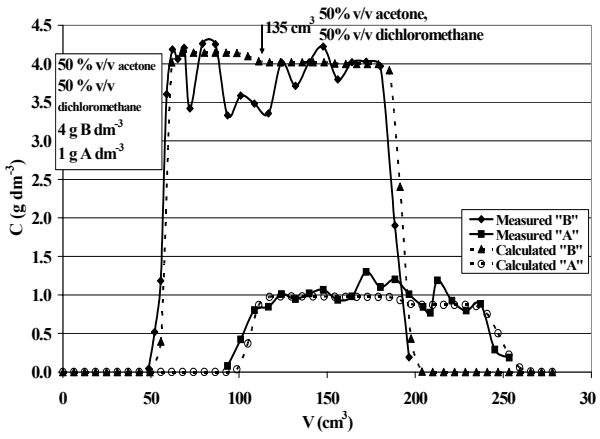

Fig. 5. Frontal adsorption-desorption measurement of steroids

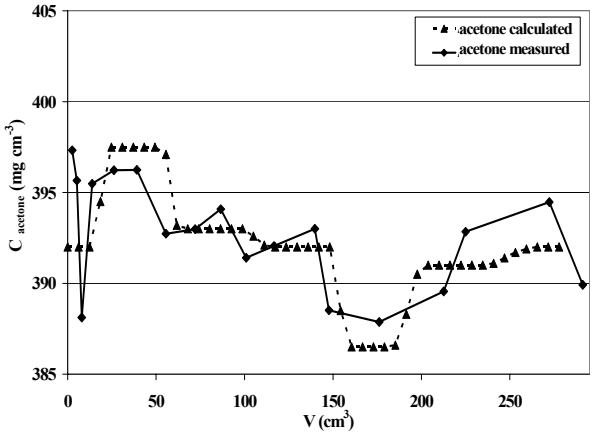

Fig. 6. Frontal adsorption-desorption measurement of acetone

During frontal adsorption an 80:20 % (m/m) mixture of steroids B+A (total concentration 5 g dm^{-3}) was applied downwards to the column at a flow of 2.47 cm^3 min^{-1} at 293 K. Application of the mixture of A and B was stopped after 55 min (135 cm^3 liquid) and pure eluent (1:1 (v/v) acetone-dichloromethane) was let to the column at a flow rate 2.85 cm^3 min^{-1} (*Fig. 5.* and *Fig. 6.*). The outlet liquid was collected in cooled (273 K) sample collectors and the concentration was measured by analytical gas chromatography.

Frontal Adsorption - Desorption Simulation Data

Parameters in KROM-N software with solvent adsorption-desorption (*Table 2.*).

Table 2. Input data of the software

Number of components:	$k = 3$
Column inner diameter:	ID=0.735 cm
Column length:	L=42 cm
Free volume coefficient:	EPS= 0.8018 cm^3 liquid free volume cm^{-3} column
Feed:	B=2.47 cm^3 min^{-1}
Bulk density:	ROH= 0.4045 g silica gel cm^{-3}column
Langmuir constants:	(same as in Table 1)
Sample feeding time:	55 min (135.85 cm^3)
Sample concentration:	$c_{Acetone}$=396 mg cm^{-3}
	c_B=4 mg cm^{-3}
	c_A=1 mg cm^{-3}
Eluent concentration:	$c_{Acetone}$=396 mg cm^{-3}
	c_B=c_A=0 mg cm^{-3}
Number of Theoretical Plates	NTP=400
End of elution time:	112 min

SMB Equipment Planning, Construction and Installation

The SMB preparative liquid chromatographic equipment with four columns, four sectors and open eluent loops were constructed in the Central Mechanical Workshop of University of Veszprém (*Fig. 7.*).

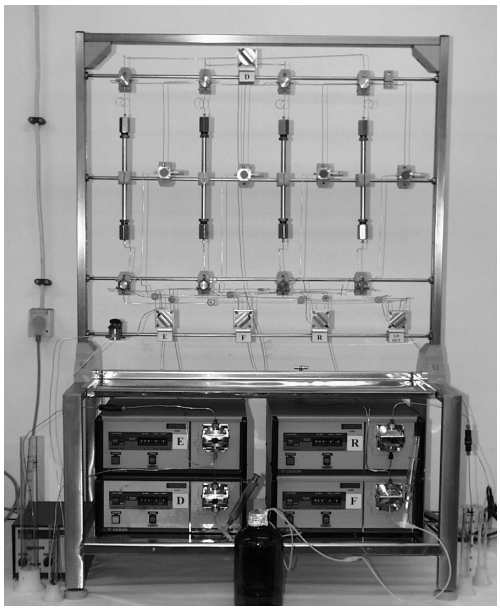

Fig. 7. SMB equipment photo

During installation the four preparative liquid chromatographic columns were filled with YMC S-50 silica gel applying vibration method (~ 60 min filling time). The column packing density was 0.405 g cm^{-3}, the free volume factor was 0.8018. Each column was filled with approximately 7.95 g silicagel. Stainless steel fritts (2 μm) were placed at the top and bottom of each column. Before measurements air was removed with dichloromethane.

Parameters of SMB-LC Measurements

We applied an 1-1-2-0 column configuration in 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. We used 1,2:1 (v/v) acetone - dichloromethane (gradient) like fresh eluent in the segment I. 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 mixture of 42 g dm^{-3} steroid B and 18 g dm^{-3} steroid A in the same solvent.

The flow rate of the steroid sample input was 0.8 cm^3 min^{-1}. Steroid A was extracted with 2.2 cm^3 min^{-1} parameter, so the LROUT flow was 4.25 cm^3 min^{-1} and the switching time was 22.5 min. Process parameters have been determined by Morbidelli method (*Fig. 8.*).

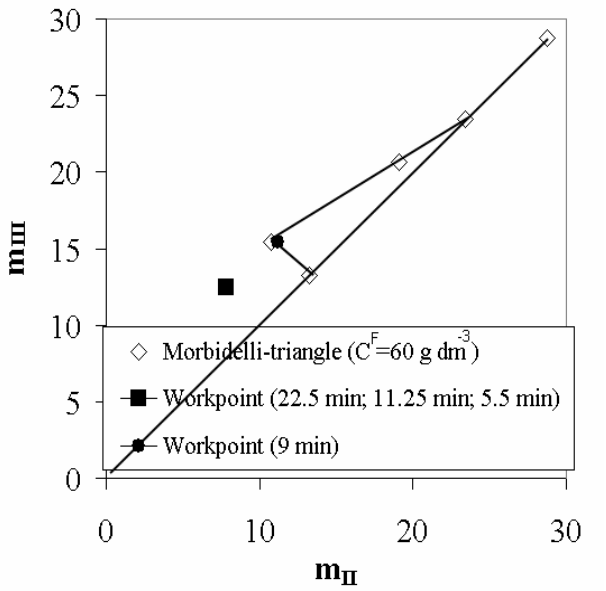

Fig. 8. The measurements points placed in the Morbidelli triangle at different switching times

When we decreased the switching time to 11.25 min, we doubled the original flow rates. When we used 5.5 min for switch time, we doubled once again the flow rates. In case of 9 min 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.

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 3.* The software takes into account the solvent adsorption-desorption phenomena, too.

Table 3. Input data of the software

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

Results

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

In the *Figs. 9. 10. 11. 12.* 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.

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. Numerically describe 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.

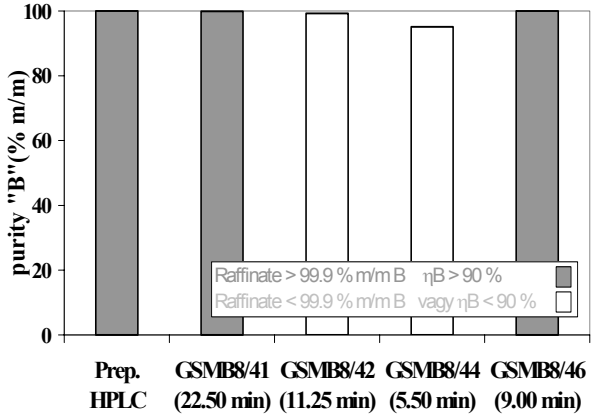

Fig. 9. Comparing the purity of steroid B in different measurements

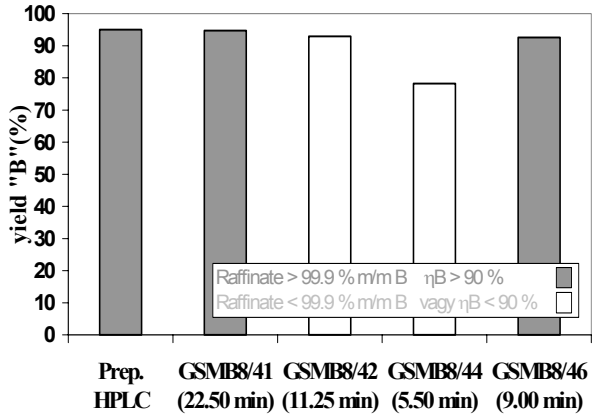

Fig. 10. Comparing the yield of steroid B in different measurements

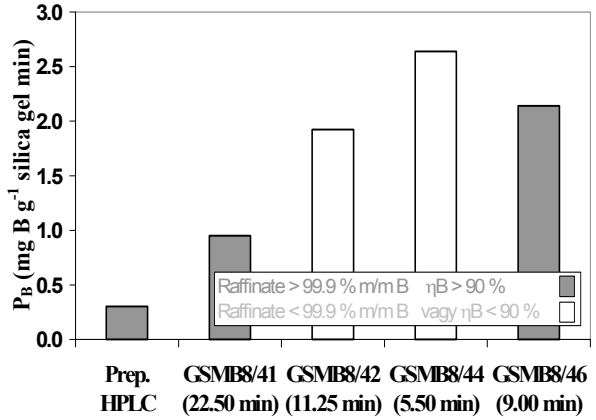

Fig. 11. Comparing the productivity of steroid B in different measurements

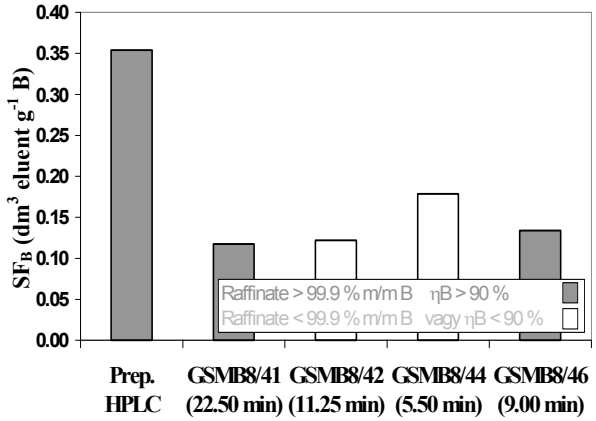

Fig.12. Comparing the eluent consumption of steroid B in different measurements

We achieved the best favourable result in the RG-1040-GSMB 8/46 measurement at 9 min switching time. In this case calculated values of measurement were compared to data given in *Table 4.* 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.

Conclusion

Our conclusion on the basis of laboratory 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 5.*).

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.

Acknowledgement

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Table 4. 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 $\frac{mg\ A}{g\ silic\ gel\ \min}$	LROUT 1 +LROUT 2 2.16 $\frac{mg\ B}{g\ silica\ gel\ \min}$ Extract 0.69 $\frac{mg\ A}{g\ silic\ gel\ \min}$
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 $\frac{cm^3\ fresh\ eluent}{mg\ A}$

Table 5. 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 $\frac{cm^3\ fresh\ eluent}{mg\ B}$

SYMBOLS

$q_{Acetone}$ adsorbent concentration of acetone, mg g-1

$a_{Acetone}$ Langmuir constant of acetone, cm^3 liquid free volume g^{-1} silica gel

$b_{Acetone}$ Langmuir constant of acetone, cm^3 liquid free volume mg^{-1} acetone

$c_{Acetone}$ concentration of acetone, g dm^{-3}

q_B adsorbent concentration of steroid B, mg g-1

a_B Langmuir constant of steroid B, cm^3 liquid free volume g^{-1} silica gel

b_B Langmuir constant of steroid B, cm^3 liquid free volume mg^{-1} B component

c_B concentration of steroid B, g dm^{-3}

q_A adsorbent concentration of steroid A, mg g-1

a_A Langmuir constant of steroid A, cm^3 liquid free volume g^{-1} silica gel

b_A Langmuir constant of steroid A, cm^3 liquid free volume mg^{-1} A component

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

REFERENCES

1. SZANYA T., ARGYELAN J., KOVATS S. and HANAK L.: J. Chromatogr. A, 2001, 908:265-272
2. MIRON M., SZANYA T., HANAK L., ARGYELAN J. and MARTON GY.: Hung. J. Ind.Chem. 1995, 23:293-298.
3. KOVATS S., CSUKAS B., ARANYI A. and POZNA E.: Hung. J. Ind.Chem. 1998, 26: 44-53.
4. BROUGHTON D. B. and GERHOLD C. G.: US Pat. 2 985589, 1961.
5. JUPKE A., EPPING A. and SCHMIDT-TRAUB H.: J. Chromatogr. A, 2002 944:93-117
6. GIOVANNI O., MAZZOTTI M., MORBIDELLI M., DENET F., HAUCK W. and NICOUD R.: J. Chromatogr. A, 2001, 919:1-12
7. JENSEN T., REIJNS T., BILLIET H. and WIELEN L.: J. Chromatogr A, 2000, 873:149-162
8. HOUWING J., BILLIET H. and WIELEN L.: J. Chromatogr A, 2002, 944:189-201
9. HOUWING J., HATEREN S., BILLIET H. and WIELEN L.: J. Chromatogr A, 2002, 952:85-98
10. ABEL S., MAZZOTTI M. and MORBIDELLI M.: J. Chromatogr A, 2002, 944:23-29
11. GIOVANNI O., MAZZOTTI M., MORBIDELLI M., DENET F., HAUCK W. and NICOUD R.: J. Chromatogr A, 2001, 919:1-12
12. ANTOS D. and MORGENSTERN A.: J. Chromatogr., 2002, 944:77-91
13. ANTOS D. and MORGENSTERN A.: Chem. Eng. Sci., 2001, 56:6667-6682
14. MIGLIORINI C., MAZZOTTI M. and MORBIDELLI M.: J. Chromatogr. A, 1998, 827:2:161-173