Recent Achievements in Simulated Moving Bed (SMB) Technology. Part II.

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Progress in the method of simulated moving bed (SMB) technology and some important achievements in separation of specific classes of racemic compounds of therapeutic interest are reported in the Part I of this review. Part II describes novel methods of SMB technology. Complex technologies, such as the combination of SMB and biocatalytic reactions, and SMB with crystallization process, are presented. VariCol variant of SMB, and its application in the separation of the racemic mixtures of commercial and academic interest are discussed. In the conclusive section, comments are given concerning the economic dimension and the market of enantiomerically pure compounds.

Key words: *Simulated moving bed (SMB), SMB-biocatalytic reactors, SMB-crystallizers, VariCol technology*

1. Introduction

The huge success of "classic" SMB in the separation of commercially important racemic mixtures has prompted even more effective resolution methods in the continuous mode and on the large scale. First, the separation capacity has been improved by introducing the VariCol process, a variant of SMB, then improvements of in-process monitoring of SMB that enable its coupling to crystallization process, and to parallel chemical transformations, biocatalytic processes in particular.

2. Examples of complex variants of SMB technology

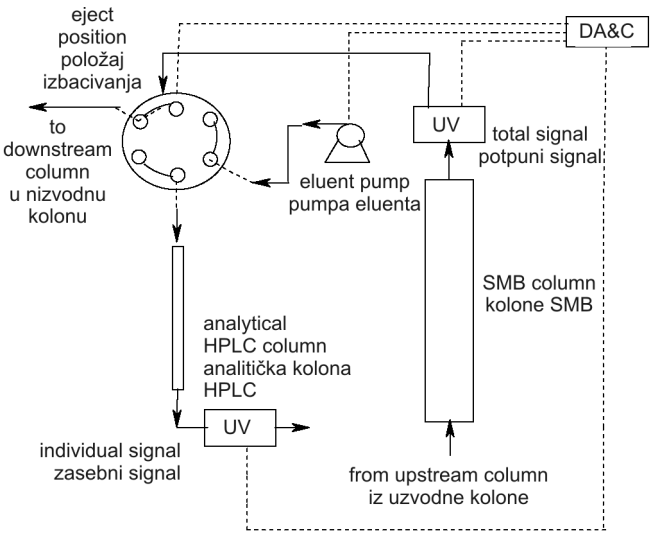
2.1. In-process control of SMB separation

This aspect of SMB technology, recently improved by an automated *on-line* enantiomeric analysis system comprising an analytical HPLC set-up with two UV detectors sharing the same light source, has been employed to monitor the internal composition profile, Fig. 1.[1]

The feasibility and effectiveness of this *on-line* enantiomeric monitoring scheme were assessed experimentally on the separation of racemic Troger's base (**1**), Fig. 2. Complete separation was achieved on Chiralpak AD as stationary phase and methanol as eluent.

Using a sampling interface placed between two SMB columns, effluent samples are directed into a high-efficiency analytical column at a sampling rate faster than the overall dynamics of the preparative unit to complete *on-line* enantiomeric analysis of the composition profile. The other UV detector is placed in the SMB loop before the fraction collector to provide instantaneous measurement of the total enantiomeric concentration, Fig. 1. It was found that robust monitoring of the concentration profiles of the individual enantiomers is best achieved when the enantiomeric purity obtained from the peak areas of the *on-line* enantiomer analysis chromatograms is combined with the *on-line* UV measurement of total enantiomeric concentration. The accuracy and robustness of the proposed *on-line* enantiomeric monitoring system open up promising perspectives for in-process control and dynamic optimization of the SMB.

As for any SMB process, in this case the adsorbtion isotherms were first determined. As already discussed in Part I, *the operating conditions of chiral SMB process cannot be*



F i g. 1 – *Schematic diagram of the on-line chiral monitoring system. The main equipment comprises six-port two-position valve, an analytical HPLC column, one HPLC pump, and two UV detectors. The set-up is fully automated*

S l i k a 2 – *Shematski dijagram nadzornog sustava "on-line". Glavna oprema sastoji se od šest ulaza, dva ventila, analitičke HPLC-kolone, HPLC-pumpe i dva UV-detektora. Postrojenje je potpuno automatizirano*

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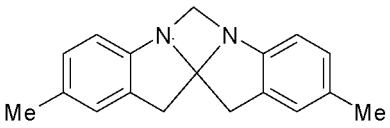
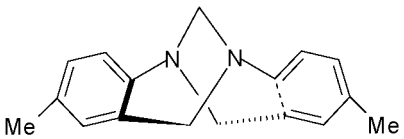


(±)-Troger's base **1**
(presented as planar, energetically unavailable conformation)
(±)-Trogerova baza **1**
(predstavljena kao planarna, energetski nedostupna konformacija)



(+)-enantiomer **1**
(+)-enentiomer **1**

F i g. 2 – *Racemic and (+)-form of Troger's base (**1**)*
S l i k a 2 – *Racemični i (+)-oblik Trogerove baze (**1**)*

properly determined without knowledge of the competitive isotherms of the two enantiomers.[2–6] The isotherms of the enantiomers of Troger's base were estimated by implying *the inverse method* to the band profiles of the racemic mixture obtained both in linear and overloaded eluation modes,[7] without measuring single component chromatograms. This last condition allows development of the SMB process without having standards of the pure enantiomers, an important condition in developing separation method of novel racemates, previously unresolved by any available technique.

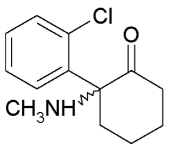
The inversed method of isotherm determination[7] is becoming popular as a quick procedure for the estimation of the competitive isotherms necessary for designing SMB separations.[8–10]

above that of the eutectic formed by the two enantiomers.[11] In the crystallizers the pure enantiomers are precipitated, typically by evaporative crystallization, and withdrawn, whereas the mother liquors that contain still both enantiomers are recycled back to SMB together with the evaporated solvent. The key idea behind this concept is that, as the purity in the SMB decreases, the performance parameters such as productivity and solvent consumption improve, *i. e.* there is a net positive effect.

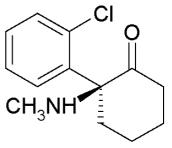
A multi-objective optimization study on the separation of Troger's base enantiomers in a combined process was carried out based on experimental data on the absorption isotherms, the solubility of two enantiomers in ethanol, on a detailed SMB model, and on a simplified model of the crystallizers.[11] With the aim of achieving maximum throughput and minimum solvent evaporation, it was shown that the optimal purity reached in the SMB in this case was about 97 %, as lower purities would imply an excessively large mother liquor recycling.

Another example of the combined SMB-crystallization process is found in production of optically pure ketamine.

S-Ketamine (**2**), 2-methylamino-2-(2′-chlorophenyl)-cyclohexanone. Ketamine (Ketaset(R)) is commercially available as a racemate. It is a dissociate anesthetic agent that has been widely used in clinical practice.[15,16]



(±)-Ketamine **2**
(±)-Ketamin **2**

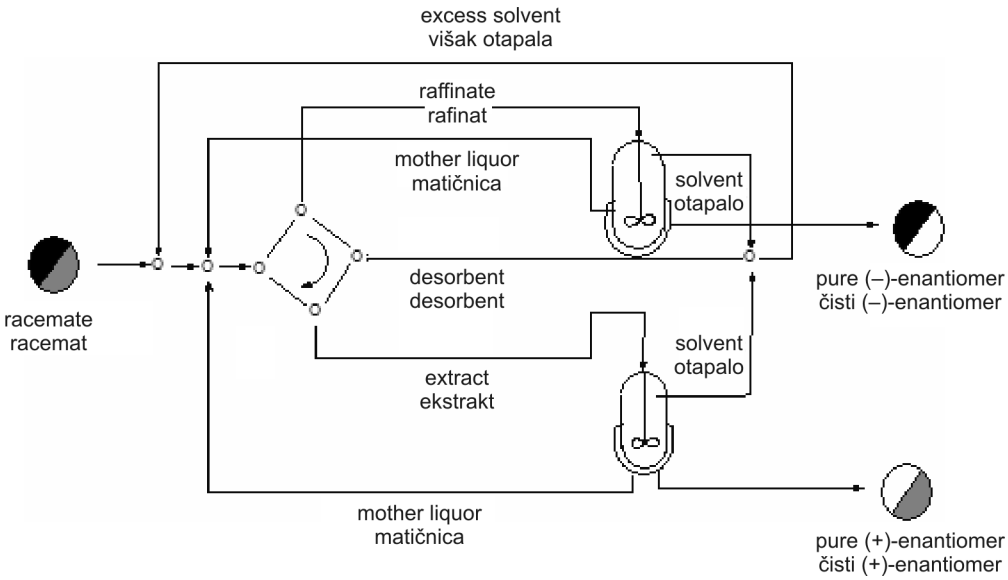


S-(+)-Ketamine **2**
S-(+)-Ketamin **2**

2.2. The combined SMB-crystallization process

Most often enantiomers have to be delivered as a powder after SMB separation and evaporation of the solvent. In some cases, the downstream crystallization step may be viewed as a final polishing step where the purity achieved in the SMB is further enriched.

Crystallization can be effectively exploited by coupling SMB and crystallization, as proposed by several researchers in the last few years.[11–14] A schematic diagram of the combined process is shown in Fig. 3, where the SMB unit is followed by two crystallizers for the extract and the raffinate streams, which are at a purity below process specifications but



F i g. 3 – *The combined SMB-crystallization process, where racemates as well as the pure enantiomers are fed and withdrawn, respectively, as solid material*
S l i k a 3 – *Kombinirani SMB i kristalizacijski proces, u kojem se racemat dodaje i čisti enantiomeri odvode kao krutina*

S-Ketamine is four times more potent in analgesia than *R*-ketamine.[16] Ketamine resolution has been reached in commercial applications *via* diastereomeric salts,[17,18] which is one of the most traditional and least effective techniques in the field of enantioseparation. A paper by *Santos et al.*,[19] describes the continuous enantioseparation of ketamine in a semipreparative scale SMB unit, using microcrystalline cellulose triacetate (MCTA) as a chiral filling, providing a suitable separation of the two enantiomers with virtually 100 % optical purity. A limitation, however, is the low productivity of the process in the laboratory unit, around 0.15 to 0.5 g d^{-1}.

Recent study has enabled the introduction of a hybrid process consisting of continuous chromatography and crystallization to acquire high purity enantiomers with high productivity.[20] In this work, the theoretical behavior of SMB units in separation of racemic Ketamine was analyzed taking into account the non-linearity of adsorption isotherms, and non-homogeneity of packing columns. Experimental operating points were selected aiming at the higher purity of the *S*-enantiomer in the raffinate stream. The results obtained showed purities above 99.5 % for *S*-ketamine in the raffinate stream and above 97.7 % for *R*-ketamine in the extract stream.

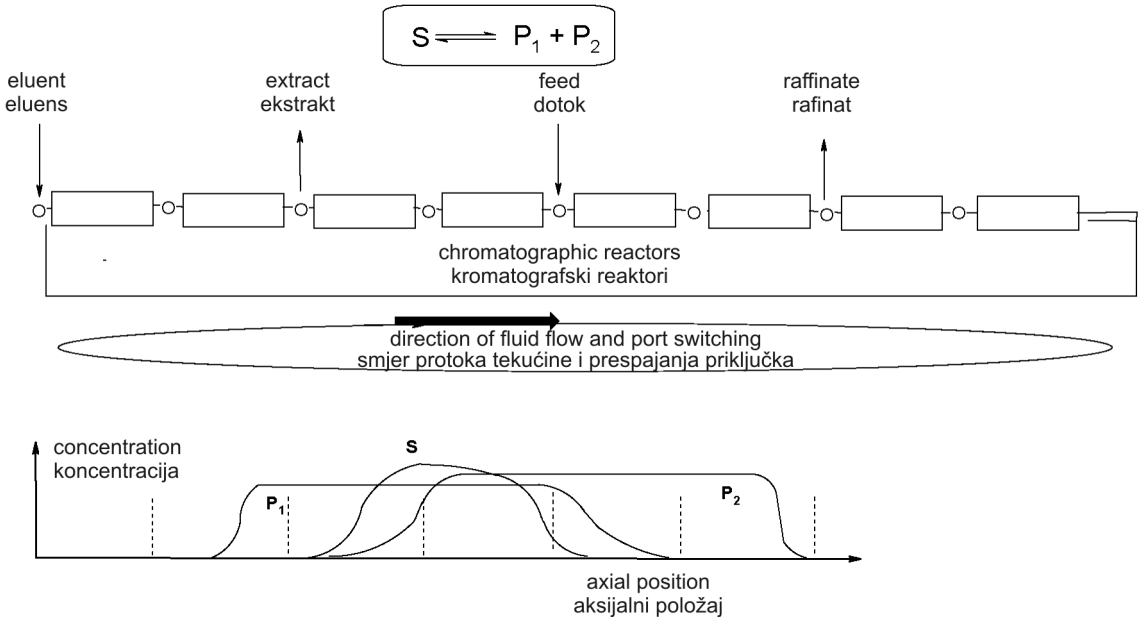
2.3. Simulated moving bed reactor (SMBR)

The basic operating concept of an SMBR is analogous to that of an SMB, Fig. 4. The enzyme is simply added throughout the SMB unit, either to the solid phase (SP) in immobilized form or to the mobile phase in soluble form. Consequently, the starting materials can be continuously converted in all sections of the SMBR. Consider a thermodynamically limited reaction of the substrate S to the products P_1 and P_2. Species S is added to the SMBR in the feed flow and is enzymatically converted to P_1 and P_2. Species P_1 and P_2 are separated from each other due to their different adsorption behavior. This separation prevents the backward reaction and enables complete conversion of S. Products P_1 and P_2 can be collected at the extract and raffinate port, respectively, in high purity. Ideally, the retention of S should be between that of P_1 and P_2.

2.4. Integrated operation of SMB and biotransformations

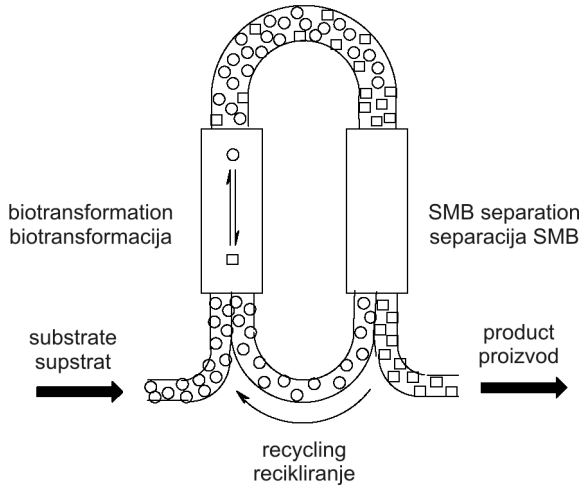
This approach represents one of the most recent technological achievements for the high yield production of generics and fine chemicals. The rapid progress in biocatalysis, identification and development of enzymes over the last decade has enormously enlarged the chemical reaction space that can be addressed not only in research applications, but also on industrial scale. Prominent examples stem from the aldolase-catalyzed enantioselective carbon-carbon bond forming reactions, reactions catalyzed by isomerising enzymes, and reactions that are kinetically controlled. On the other hand, continuous chromatography concepts such as the SMB technology have matured and are increasingly realized on industrial scale for the efficient separation of difficult compound mixtures – including enantiomers – with unprecedented efficiency. It was recently proposed[21] that coupling of the enzyme reactor and continuous chromatography is a very suitable and potentially generic process concept to address the thermodynamic limitations of promising biotransformations. This way, it should be possible to establish novel *in situ* product recovery processes of unprecedented efficiency and selectivity that represent a feasible way to recruit novel biocatalysts to the industrial portfolio.

The question is posed whether by smartly coupling biocatalytic and process engineering steps we can design generic processes that extend our arsenal of industrial biocatalysis. One such area could be, for example, reactions whose yield is limited by thermodynamic constraints, which might re-



F i g. 4 – *Simulated moving bed reactor (SMBR) with axial concentration profile of racemic substrate S and products P_1 and P_2*

S l i k a 4 – *Reaktor sa simuliranim pokretnim ležajem (SMBR), s aksijalnim koncentracijskim profilom za racemični supstrat S i produkte P_1 i P_2*



F i g. 5 – *Concept of an on-line coupling of continuous chromatography and biotransformation*

S l i k a 5 – *Koncept povezivanja kontinuirane kromatografije i biotransformacije "on-line"*

quire carrying out biocatalysis and product removal in one unit. A prominent example is isomerase catalyzed reactions. Usually, in such reactions the operator is left with a potentially difficult process mixture of starting materials and products. In order to achieve decent yields on an expensive starting material, in reactions involving at least two starting materials, the cheaper starting material is often applied in large excess, adding to the difficulty of purification. Consequently, such reactions have remained largely unexplored on the preparative level.

Removal of the product from the reactor immediately or shortly after its formation can be achieved by separating the compound mixture in a continuous chromatograph, removing the product, and returning the remainder of the starting material to the reactor, Fig. 5. Depending on the type of reaction, both operations could be carried out in one reactor. Chromatography's high resolution power provides a unique opportunity to accommodate the fact that biocatalysts frequently do not change the physico-chemical properties of a molecule by much, usually rendering work-up of mixtures difficult. Furthermore, continuous chromatography considerably reduces eluent consumption and product dilution compared to traditional batch chromatography schemes, making it a much more attractive procedure.[22–26]

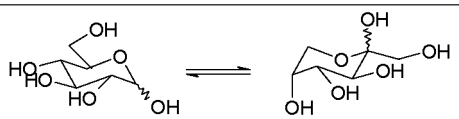
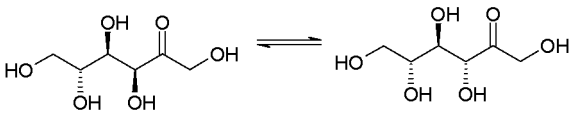
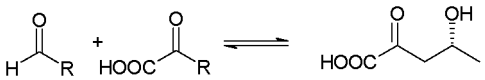
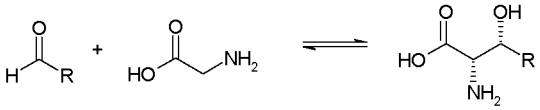
The few realized model processes combining biotransformation and SMB technology are almost exclusively based on the SMBR concept, with enzymatic reactions leading to at least two species, unreacted substrate and product, Table 1.[27] In earlier works, the SMBR was investigated as a two zone SMBR without the zones for regenerating eluent and solid phase.[28–30] Regeneration of the solid phase was accomplished by decoupling the last column of the extract zone and eluting the strongly adsorbed compound with fresh eluent. It was shown that the applied concept required only 34–72 % of the amount of enzyme needed in a corresponding conventional batch reactor of the same productivity.[30] This concept was further developed into a closed-loop four zone SMBR by *Azevedo et al*.[31]

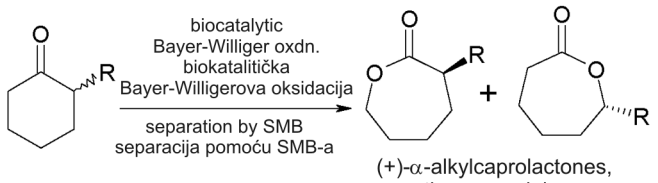
α-Alkylcaprolactones. *P. Keiser et al*.[32] have recently reported preparative-scale SMB separation of *biocatalytically produced* regioisomeric α-alkylcaprolactones, Scheme 1.

Generally, the separation of enantiomerically pure, but regioisomeric compounds by SMB is attractive if the process leads to high-purity products in high yield with excellent throughput and reduced solvent use. The main factors influencing method optimization were identified and the parameters of temperature, pressure, weak adsorption, separation factor and robustness were examined with the aim to resolve bottlenecks. Under optimized conditions, the

T a b l e 1 – *Enzymatic transformations in combination with SMB separation*[21]

T a b l i c a 1 – *Enzimska transformacija u kombinaciji s odjeljivanjem SMB*[21]

Enzyme Enzim	Enzymatic reaction Enzimska reakcija	EC number EC-broj
D-xylose isomerase D-ksiloza-izomeraza		5.3.1.5
D-tagatose-3-epimerase D-tagatoza-3-epimeraza		5.1.3.X
amino acid racemase aminokiselinska racemaza		5.1.1.10
pyruvat-dependent aldolase aldolaza ovisna o piruvatu		4.1.3.3.
glycin-dependent aldolase aldolaza ovisna o glicinu		4.1.2.5.



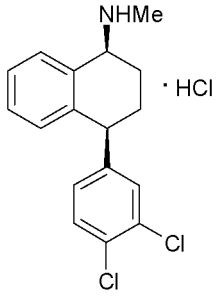
S c h e m e 1 – *SMB separation of regioisomiric lactones*[32]
S h e m a 1 – *SMB-razdvajanje regioizomernih laktona*[32]

productivity of the process in Scheme 1 was 260 g kg^{-1} stationary phase/day) of pure regioisomers and the solvent consumption was 36.3 L kg^{-1} feed.

2.5. SMB combined with racemization of the "wrong enantiomer"

The following example belongs to one of the most thoroughly investigated applications of SMB technology on the large-scale.

Sertralin (**3**), (1*S*,4*S*)-1-methylamino-4-(3′,4′-dichlorophenyl)tetrahydronaphthalene. Sertralin hydrochloride (Zoloft®) is an inhibitor of serotonine reuptake, and is an important pharmaceutical agent for the treatment of depression as well as dependency- and other anxiety-related disorders.[26,33]



sertralin hydrochloride **3**
sertralin hidroklorid **3**

The structure of Sertralin is characterized by two stereogenic centers with absolute 1*S*,4*S*-configuration, and relative *cis* configuration. Due to two stereogenic centers *cis* and *trans* racemates are conceivable, often named *syn*- and *anti* diastereomers, and therefore diastereo- and enantioselectivity are required in the specific synthetic steps.

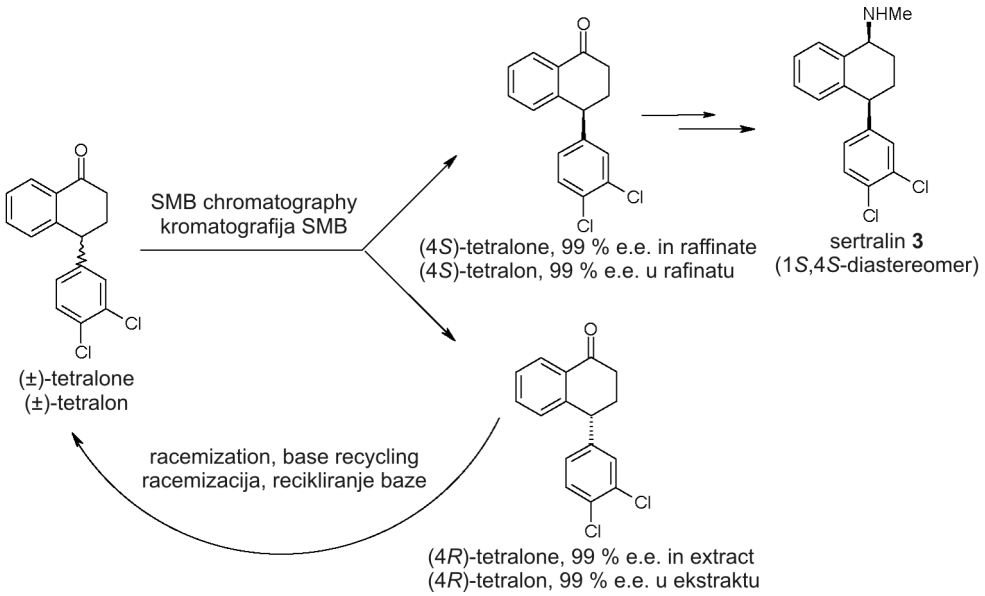
The research of a technology for cost-effective production of 4*S*-tetralone, Scheme 2, the key intermediate on the route to Sertralin was shifted to a continuous chromatographic separation of enantiomers based on SMB technology.[27,28,34,35] Investment in SMB technology led to a commercial route to Sertralin that increased throughput by eliminating the processing of the "wrong" 4*R*-tetralone through the entire process.[29,36] This is in accord with the general rule for the synthesis of chiral compounds in the enantiomerically pure form; if you have to undertake separation of enantiomers on the route, then do it as early as possible. Research at Pfizer Inc. culminated in the process depicted in Scheme 2. Crucial for the success of this process proved fast, base-catalyzed racemization of the "wrong" 4*R*-enantiomer in the extract, and feed of racemtae back to SMB unit. Most important operating parameters for pilot scale performance are given in Table 1; impressive is the almost 100 % recovery of the target 4*S*-enantiomer.

T a b l e 2 – *Pilot-scale operating parameters and performance for SMB separation of rac-Tetralone*[36]
T a b l i c a 2 – *Operacijski parametri na pilotnoj skali i radni učinak SMB odjeljivanja rac-Tetralona*[36]

column kolona	amylose (3-chloro-4-methylphenylcarbamate) amiloza (3-klor-4-metilfenilkarbamat)
mobile phase, ψ pokretna faza, ψ	$\psi_{MeCN/MeOH} = 9 : 1$
number of columns, *N* broj kolona, *N*	6
column length, *l* duljina kolone, *l*	9.9 cm
column diameter, *d* promjer kolone, *d*	4.8 cm
feed mass concentration, γ masena koncentracija dotoka, γ	30 g L^{-1}
volume flow rate, *Q* obujamski protok, *Q*	37 mL min^{-1}
pressure, *p* tlak, *p*	25 bar
(4*S*) tetralone, e.e. (4*S*) tetralon, e.e.	99.7 %
(4*S*) tetralone recovery, *Y* (4*S*) obnavljanje tetralona, *Y*	98.4 %
productivity, *P* produktivnost, *P*	371 kg kg^{-1} a^{-1}

2.6. VariCol variant of SMB technology

VariCol represents simulated moving beds with non-constant operating conditions. The main benefit of the VariCol operation mode is that it allows reducing the number of columns with respect to the standard SMB operation without sacrificing throughput and process specifications. In the operation of the classical SMB unit, the column configuration, *i.e.* the number of sections and the number of columns per section is fixed prior to start-up. Once the unit is started, the inlet and outlet ports are switched simultaneously, i.e. a synchronous switch is implemented. Hence, in this mode of operation, at any time the unit configuration is the one chosen prior to start-up, where only an integer number of columns per section can be assigned. Let us consider as an example a 6-column SMB unit. It is worth noting that using six columns, with the limitation that a minimum of one column is present in each section, ten different configurations are possible, *i.e.* 1/2/2/1, 3/1/1/1… . In the case of an SMB unit for the entire duration of the switch period the unit configuration and the position of the inlet and outlet ports remain the same. More freedom in choosing the unit configuration is offered by the VariCol process, where each port is switched independently of the others, *i.e.* port switching is performed asynchronously as shown in Fig. 6.[37]



S c h e m e 2 – *Production scheme for enantiomerically pure (1S,4S)-Sertralin*
S h e m a 2 – *Proizvodna shema za enantiomerno čisti (1S,4S)-Sertralin*

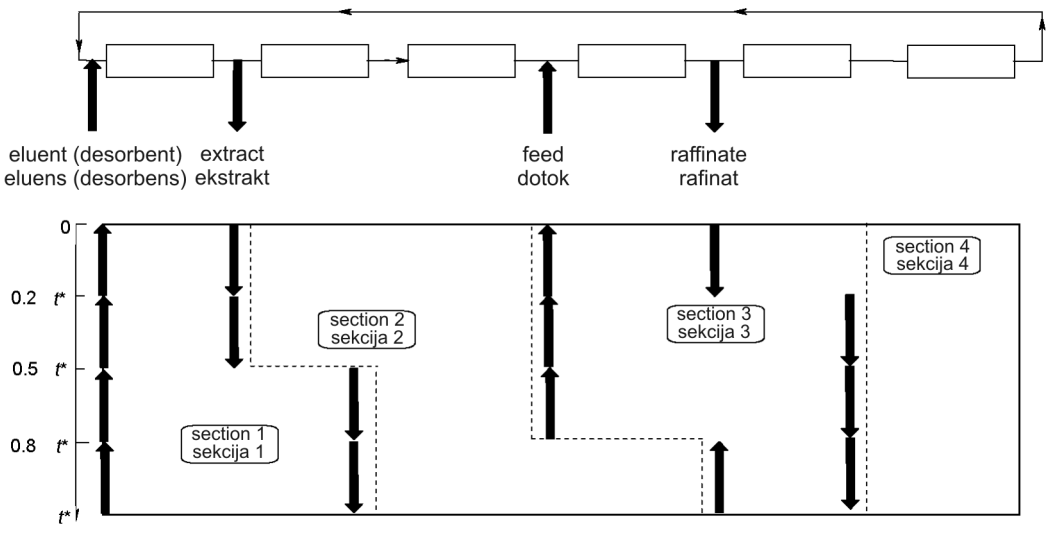
As readily observed, the switching period is subdivided into four sub-intervals of duration 20 % or 30 % of the switch time, and only one port is switched at the end of each subinterval. Therefore, during the four subintervals of the example the unit configuration is first 1–2–1–2, then 1–2–2–1, then 2–1–2–1, finally 2–2–1–1, and then again 1–2–1–2 after exactly *t*. The average unit configuration can be calculated, and turns out to be in this case 1.5–1.7–1.6–1.2, *i.e.* by asynchronously switching the ports, the number of columns per section attains non-integer values. This operation mode allows in principle for infinite unit configurations and hence gives the possibility to make the best use of the column for separation. The VariCol has been experimentally demonstrated[38,39] and commercialized.[40] Several theoretical and experimental studies have shown that VariCol provides improved performance compared to the classical SMB.[41,42] VariCol, due to asynchronous switching, is fairly complex to design and there exist various methodologies discussed in the specialized articles and chapters.[43–45]

Beside the VariCol process, there are ulterior modifications of the original SMB process. Here we will be mentioned two most promising variants;

– time-variable manipulation of flow rates, known as PowerFeed process,[46,47] and

– modulation of the feed mass concentration, known as *ModiCon* process.[48,49]

PowerFeed process is characterized by the exchange of internal and external liquid flow-rates during the switching period. This operation mode is referred to as PowerFeed.



F i g. 6 – *Example of a VariCol switching strategy*[37]
S l i k a 6 – *Primjer strategije prespajanja VariCol*[37]

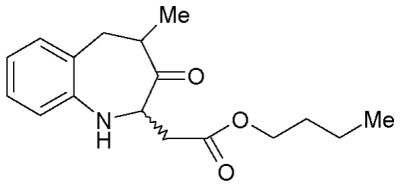
Similar to theVaricol process, which allows for the asynchronous movement of the ports, the PowerFeed process exhibits more degrees of freedom than the classical SMB process, and therefore allows more room for optimization. Using an optimization technique based on a genetic algorithm, three processes have been optimized for a few case studies in order to determine their relative potentials. It is found that PowerFeed and Varicol provide substantially equivalent performances, which are however significantly superior to those of the classical SMB process.[46]

The *ModiCon* process, instead, is based on the cyclic modulation of the feed concentration. It is demonstrated that such a feed concentration gradient during the shifting cycle can improve the performance of SMB process significantly.[49] The productivity and the product concentrations can be increased while simultaneously the solvent consumption can be decreased compared to the conventional SMB process with constant feed parameters. This new concept of modulation of feed mass concentration is based on exploitation of thermodynamic equilibria, and requires, as it is the case with VariCol and PoweFeed processes, a combined approach to software development and experimental control of separation.

2.6.1. Recent separations by VariCol technology

In this section, examples of successful application of the VariCol process will be presented.

SB-553261 racemate (**4**). The biological profile of this compound is not cited in the available literature, still its separation on the multigram scale indicates preclinical or first--time-in-human (FTIH) trials with the preferred enantiomer.[50,51]

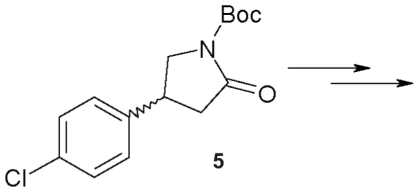


SB 553261 (**4**)

Under optimized conditions, the VariCol method proved superior to SMB technology by 50 % in throughput and by 30 % in reduction of desorbent consumption, which is a vast improvement.[52]

N-Boc-4-[p-chlorophenyl]-2-pyrrolidone (**5**). This compound is a key racemic intermediate on the route to (*S*)-Baclofen), 4-amino-3-(4-chlorophenyl)butanoic acid. Racemic Baclofen (Lioresal, Kemstro) is well known oral medication that relaxes skeletal muscles. Chemically, baclofen is related to γ-aminobutyric acid (GABA), a naturally occurring neurotransmitter in the brain. It is an agonist specific to mammalian GABAB receptors.[52,53] Baclofen is used for the treatment of spastic movement, especially in instances of spinal cord injury, spastic diplegia, and multiple sclerosis. Baclofen has been shown to be as effective as diazepam in uncomplicated alcohol withdrawal syndrome.[54] A study showed that it was effective in promoting alcohol abstinence in patients with severe liver cirrhosis.

Using adsorption equilibrium data, determination of the optimal operational conditions for SMB separation of the *N*-Boc-4-[*p*-chlorophenyl]-2-pyrrolidone enantiomers in a semi-preparative scale VariCol unit is reported.[55]



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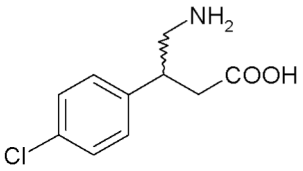
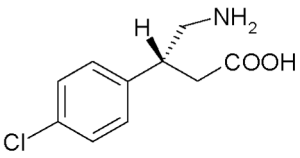


(±)-baclofen
(±)-baklofen

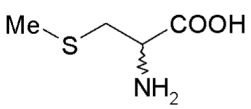


S-(–)-baclofen
S-(–)-baklofen

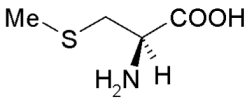
This SMB unit was used to obtain high purity enantiomers on a scale of 1 g d^{-1}. The outlet streams were analyzed by an online system that consisted of a UV-vis spectrophotometric unit, a polarimeter, and HPLC. Enantiomeric purities of up to 97 % were obtained for the raffinate stream and up to 90 % for the extract stream.

SMB technology is claimed as the method of choice for separation of protected amino acids.[56] In view of their simple conversion to amino alcohols, and incorporation of the latter in the mono- and bidentate ligands, this technology opens the route to novel organometallic catalytic complexes.

L-Methionine (**6**). L-Methionine is an important sulfur amino acid in controlling nutrient metabolism and cell functions,[57] and also prevents diabetes and diabetic complications.[58]



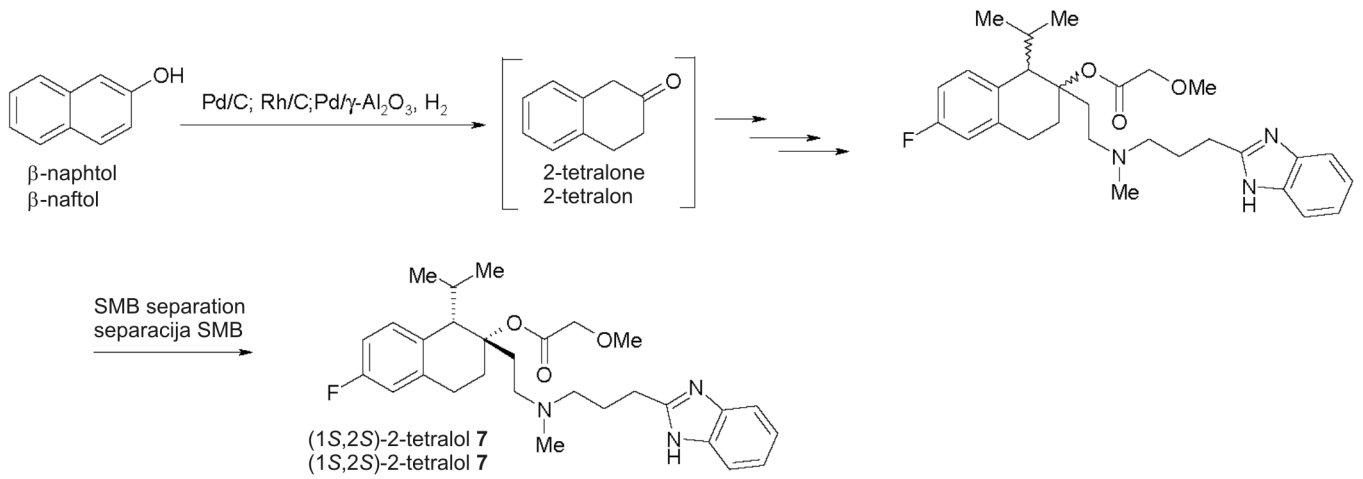
(±)-methionin **6**
(±)-metionin **6**



L(+)-methionin **6**
L(+)-metionin **6**

Particularly instructive application of SMB technology in separation of racemic methionine uses an eremomycin based-chiral stationary phase.[59] This new CSP is based on the macrocyclic glycopeptide eremomycin immobilized on epoxy-activated silica. ψ_{MeOH/H_2O} = 20:80 (0.1 mol L^{-1} NaH_2PO_4) was used as the mobile phase. Separation was realized under nonlinear conditions providing productivities around 15 g product per l g CSP per h for both enantiomers of **6**. Column to column fluctuations were negligible and long-term stability of the preparative stationary phase was satisfactory according to the results of perturbation experiments performed before and after long-term SMB runs.

(1S,2S)-Tetralol (**7**). (1*S*,2*S*)-1-isopropyl-2-(2′-methoxyacetyloxy)-2-(2″-(3″-benzimidazol-2″-yl)-propionylamino-6-fluorotetrahydronaphthalene. (1*S*,2*S*)-Tetralol (Mibefradil) is the first Ca-channel blocker antagonist to appreciably antago-



S c h e m e 3 – *Production scheme for enantiomerically pure (1S,2S)-tetralol*
S h e m a 3 – *Proizvodna shema za enantiomerno čisti (1S,2S)-tetralol*

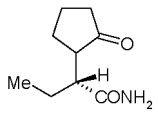
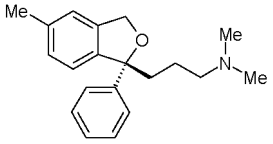
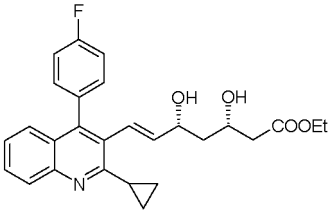
nize T-type Ca-channels, and one of the most effective antihypertensive compounds.[60] Due to easy availability of diastereomeric racemates from β-naphthol,[61] industrial separation of biologically active (1*S*,2*S*)-enantiomer has gained on importance, Scheme 3.

Chiral separation of racemic Tetralol by SMB was completed using a standard simulation package to predict the effect of the operating variables on the process performance. The experimental operation of the pilot plant SMB unit Licosep 12–26 (Novasep, France) is carried out using the chiral adsorbent Chiralpak AD with particle diameter d_p = 20 nm.[62] To obtain real insight into operation of the SMB unit Licosep 12-26 the mathematical model accounts for all dead volumes inside of the SMB unit and time delay in shifting of injection and withdrawal points. Experimental and theoretical results based on the SMB model are compared in terms of process performance parameters and internal concentration profiles.

More recently, the basic data necessary for further development of the production-scale processes using Chiralpak IA columns were acquired.[63] A broad range of solvents used as components of mobile phases were tested and their influence on the separations evaluated. A satisfactory separation considering further utilization of SMB was found for Propranolol, Guaifenesin, and β-Tetralol using the following mobile phases $\psi_{n\text{-heptane/MeOH/EtOH}}$ (5:95:0.1) vol/vol), $\psi_{n\text{-heptane/EtOH}}$ and $\psi_{n\text{-heptane/DCM}}$ (both in volume ratio 85:15), respectively. Inverse size exclusion chromatography was implemented to measure the porosity of the column using the set of polystyrene standards. The multicomponent adsorption equilibrium was characterized by linear Langmuir model for Tetralol due to its limited solubility in selected mobile phases.

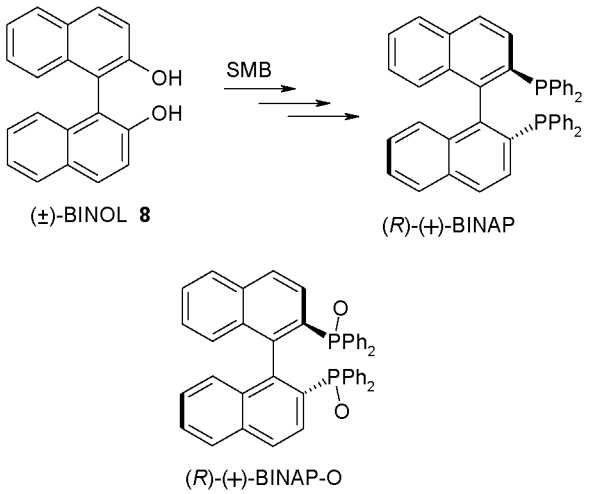
Table 3 gives a short, informative list of some active pharmaceutical ingredients (APIs), which are not discussed in more detail in this review, but separated in large quantities for commercial purpose.

T a b l e 3 – *Commercial APIs separated by SMB technology*
T a b l i c a 3 – *Komercijalni API razdvojeni tehnologijom SMB*

Structure Struktura	Trade name Trgovačko ime	CSP/solvent CSP/otapalo	Column ID ID kolone	Production/year Proizvodnja/godina
	Levetiracetam, Leppra	Chiralpak AD *n*-hexane/EtOH	35–45 cm	> 12 t/a
	Citalopram, Lexapro	Chiralpak AD, and others MeCN/EtOH	80 cm	> 50 t/a
	DOLE	Chiralcel OF *n*-hexane/2-propanol	10 cm	130 kg

2.7. SMB separation of axially chiral compounds

Axially chiral compounds in optically pure form have gained enormous importance as bidentate ligands in organometallic catalytic complexes.[64,65] Their separation from racemates by crystallization of their salts is often hampered by the absence of strong basic or acidic groups, or pure crystallization properties. Therefore, chromatographic separations, in particular SMB became methods of choice for production of catalytic ligands in optically pure form. Outstanding examples of effective SMB separation are BINOL (**8**), the key intermediate on the route to BINAP, chiral ligand with broad application in industrial processes,[66,67] and BINAP-O, another precursor of BINAP and useful ligand in enantioselective alkylations of arylaldehides.[68]



(±)-BINOL **8**

(*R*)-(+)-BINAP

(*R*)-(+)-BINAP-O

SMB technology is developed for separation of *rac*. BINOL, on the route to enantiomerically pure (*R*)-(+)–BINAP, and patents are claimed by Merck[69] and GreatLakes/Monsanto[70] companies.

We have recently claimed separation of BINAP-O on the original, "Brush type" CSP, using SMB technology.[71] This technology enabled us to produce approx. 100 g of both enantiomers with 99.9 % and 100 % e.e., respectively, Table 4.

It is important to emphasize that after intensive screening of the solvents, this process uses MeOH, one-component, cheap and easily recyclable eluent.

Table 4 – *SMB parameters for separation of BINAPO*[71]
Tablica 4 – *Parametri SMB za separaciju BINAPO*[71]

8 Columns (g of CSP) 8 kolona (g od CSP)	48	48
feed flow (mL min^{-1}) protok dotoka (mL min^{-1})	0.5	0.5
feed mass concentration (g L^{-1}) masena koncentracija dotoka (g L^{-1})	12.5	12.5
solid flow rate (mL min^{-1}) protok krutine (mL min^{-1})	0.63	0.66
raffinate flow rate (mL min^{-1}) protok rafinata (mL min^{-1})	1.04	1.07
extract flow rate (mL min^{-1}) protok ekstrakta (mL min^{-1})	1.02	1.17
zone I flow rate (mL min^{-1}) protok zone I (mL min^{-1})	5.91	6.22
zone II flow rate (mL min^{-1}) protok zone II (mL min^{-1})	4.90	5.06
zone III flow rate (mL min^{-1}) protok zone III (mL min^{-1})	5.40	5.56
zone IV flow rate (mL min^{-1}) protok zone IV (mL min^{-1})	4.36	4.49
eluent flow rate (mL min^{-1}) protok eluensa (mL min^{-1})	1.56	1.74
switch time (tact) (min) vrijeme prespajanja (takt) (min)	2.53	2.41
extract purity (% ee) čistoća ekstrakta (% ee)	100	100
extract concentration (g L^{-1}) koncetracija ekstrakta (g L^{-1})	4.26	7.72
raffinate purity (% ee) čistoća rafinata (% ee)	99.9	100
raffinate mass concentration (g L^{-1}) masena koncetracija rafinata (g L^{-1})	3.05	7.05
productivity (mg L^{-1} h^{-1}) produktivnost (mg L^{-1} h^{-1})	$2.96 \cdot 10^4$	$3.91 \cdot 10^4$
eluent consumption (L g^{-1}) potrošak eluenta (L g^{-1})	0.48	0.27

3. Conclusive remarks, commercial aspects of chiral drugs

New FDA regulations have had a major impact on the pharmaceutical industry. The percentage of single-enantiomeric drugs in the market increased from 10 % before the 1990s to about 37 % in 2005, when the sale of single-enantiomeric pharmaceutical products amounted to US$ 225 billion (2005 prices).[72]

Table 5 evidences the importance of chiral drugs in the optically pure form for the global economy. In relation to the volume of chiral drugs, it is interesting to consider the current financial environment of the pharmaceutical industry in terms of costs and R&D productivity. In 2006, only 18 new medical entities (NME) were approved by FDA, the same number as in 2005; the decrease of approvals is a direct result of reduced number of new drug applications.[73]

Analyses of the cost of an approved NME by the Boston Consulting Group resulted in a figure of $881 million, in good agreement with *DiMasi et al.* estimate of approx. $800 million.[74] The "Blockbuster business model" introduced by pharmaceutical companies a few decades ago, was focused on the development of high market-volume drugs. However, the potential for the withdrawal of blockbuster drugs from the market due to safety reasons has became a key vulnerability of this model.[75]

Considering all these data, the present delay in delivery and marketing of NMEs is not surprising. Inventive biotech com-

panies are therefore introducing new concepts and technologies in R&D of new biologically active molecules, and SMB technology to speed up the chemical part of these projects.

Table 5 – *Chiral leaders; nine of the top-10 drugs have chiral active substance*

Tablica 5 – *Kiralni vođe; devet od 10 vrhunskih lijekova posjeduju kiralnu aktivnu tvar*

Drug Lijek	Global 2004 drug sale ($ billions) Svjetska prodaja lijekova u 2004. (milijarde $)	Active substance Aktivna tvar	Form of active substance Oblik aktivne tvari	Therapeutic class Terapijska skupina
Lipitor	12.0	atorvastatin	single enant. jedini enantiomer	cholesterol reducer snizuje kolesterol
Zocor	5.9	simvastatin	single enant. jedini enantiomer	cholesterol reducer snizuje kolesterol
Plavix	5.0	clopidogrel klopidogrel	single enant. jedini enantiomer	antithrombotic antitrombotik
Nexium	4.8	esomeprazole esomeprazol	single enant. jedini enantiomer	antiulcerant antiulcerant
Zyprexa	4.8	olanzapin	achiral akiral	antipsychotic antipsihotik
Norvasc	4.8	amlodipin	racemate racemat	antihypertensive antihipertenziv
Seretide	4.7	salmeterol	racemate racemat	bronchodilator bronhodilator
		fluticasone flutikazon	single enant. jedini enantiomer	antiinflammatory protuupalni
Eripo	4.0	epoetin alpha epoetin alfa	protein protein	red blood cell stim. stimulator crvenih krvnih stanica
Ogastro	3.8	lansoprazol	racemate racemat	antiulcerant antiulcerant
Effexor	3.7	venflaxin venflaksin	racemate racemat	antidepressant antidepresiv
Total Ukupno	53.5			

Note: Sales figures from IMS Health

4. Conclusion

This Part II of the review on SMB technology presents some examples of the complex modification of the basic methodology, *i. e.* its combination with crystallization and biosynthetic processes, and its modification into Varicol process, characterized by continuous, virtual movement of both ports and sections. The final section gives some numeric data that reflect the high commercial importance of this technology, in particular for development of new chiral drugs in the pharmaceutical industry.

Finally, the intention of the authors was to familiarize the interested reader with the characteristics of modern chemical technology. First, SMB is characterized by intensive use of specific software packages. Their development in the expert companies or modifications by users, as well as their use in commercial form requires specific knowledge of the chemist and chemical engineers. Beside, understanding of sterochemical processes and characteristics of chiral molecules are indispensable, as well as the knowledge of chromatographic processes and materials used in chiral chromatography. From all said, it is obvious that successful use of SMB technology is a team enterprise, where all the members, synthetic chemists, chromatographic experts and process engineers, are expected to have up-dated knowledge in the indicated fields of computational chemistry, stereochemistry, chiral chromatography and chemical technology.

List of symbols
Popis smbola

d – diameter, cm
– promjer, cm

d_i – inside diameter, cm
– unutarnji promjer, cm

d_p – particle diameter, nm
– promjer čestice, nm

l – length, cm
– duljina, cm

N – number of columns
– broj kolona

P – productivity, $m_{e.e}\, m_{CSP}^{-1}\, t^{-1}$, kg kg^{-1}h^{-1}
– produktivnost, $m_{e.e}\, m_{CSP}^{-1}\, t^{-1}$, kg kg^{-1}h^{-1}

p – pressure, bar
– tlak, bar

Q – volume flow rate, mL min^{-1}
– obujamski protok, mL min^{-1}

t – time, min, h, a
– vrijeme, min, h, a

Y – yield, %
– iskorištenje, %

γ – mass concentration, g L^{-1}
– masena koncentracija, g L^{-1}

ψ – volume ratio, mL min^{-1}
– obujamski omjer, mL min^{-1}

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SAŽETAK

Novija dostignuća tehnologije simuliranog pokretnog ležaja. II. Dio.

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U prvom dijelu ovog pregleda prikazan je napredak metode simuliranog pokretnog ležaja (SMB) i neka važnija dostignuća u separaciji specifičnih skupina racemičnih spojeva od terapeutskog značenja. U drugom dijelu ovog pregleda opisane su neke nove SMB tehnologije. Prikazane su kompleksne tehnologije, kao što su kombinacija SMB-a i biokatalitičkih reakcija te kombinacija SMB-a i procesa kristalizacije. Raspravlja se varijanta VariCol SMB-a i njezina primjena u separaciji racemičnih smjesa od komercijalnog i akademskog interesa. U zaključnom dijelu komentira se značenje ekonomske dimenzije i tržišta enantiomerno čistih spojeva.

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