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

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Simulated moving bed (SMB) technology is over half a century known in continuous chromatographic separation of binary mixtures. Invented and developed in the petrochemical and sugar industries, it was recognized by organic chemists in the pharmaceutical industry as a powerful tool in separation of racemic mixtures. Over the years, it was developed into a standard laboratory, then pilot-plant and finally large-scale method for production of chiral compounds in the optically pure form. Final products of this technology are enantiopure drugs, other biologically active compounds and their intermediates. In Part I of this review, the basic principles and selected examples of recent SMB technology applications are presented.

Key words: *Simulated moving bed, continuous chromatography, triangle theory, enantioseparation*

1. Introduction

In view of the fact that most research chemists in Croatia, both in academy and industry, are engaged in research projects aimed at the synthesis of compounds with potential biological activity, many of them chiral in the racemic form, this review is expected to promote their interest in the application of enantioseparation in general, and SMB technology in particular.

In 1961, Broughton and Gerhold from Universal Oil Products (UOP) introduced the concept of simulated moving bed (SMB).[1] SMB technology was first applied by UOP for large scale separations in the petrochemical industry. For nearly half a century SMB was used for separation of xylene from other C_8 aromatics, and separation of *n*-paraffins from branched and cyclic hydrocarbons. After successful application in separation of glucose from fructose, two structurally isomeric aldohexoses, this method was applied in separation of enantiomers in racemic mixtures. The main difference between chromatographic conditions in separation of structurally similar compounds like structural isomers and diastereomers on one side, and enantiomers on the other, lies in the fact that the former can be separated on achiral stationary phases, typically on silica gel, whereas the latter require chiral stationary phases (CSPs) in the chromatographic columns to achieve enantioseparation.

For separations in the sugar industry, the columns of the SMB unit are typically filled with cheap ion-exchange resins with a large particle diameter (200–500 μm). Twelve to twenty-four columns are commonly used with a bed length of 1 m. For chiral applications, the situation is quite different. The CSPs are expensive materials, the cost being mainly related to the chemical complexity of the chiral selector (CS). Optimization of the process usually leads to the reduction of the packing particle size and selection of the optimal number of the columns in order to minimize the separation cost. Furthermore, for chiral applications, the consumption, usually single organic solvent or mixture thereof, typically stays between 100 and 1000 L kg^{-1} of feed (racemic material). Of course, recycling is greatly simplified if a one-component eluent is used in SMB.

The SMB process, originally developed to replace conventional, less effective techniques such as distillation or batch chromatography, has found widespread application and more than 130 units have been licensed by UOP.[2,3] The first examples of the SMB for enantiomer separations appeared in the early 1990s.[4–6] The interest in the development of the SMB technology grew once its potential to perform chiral separations was realized.[7,8] Within five years of the first chiral separation demonstrations, UCB Pharma, in 1997, installed a multi-ton SMB unit for large-scale manufacturing.[9] Further in 2002, Lundbeck's single enantiomer drug Lexapro became the first US Food and Drug Administration's (FDA) approved drug to be manufactured using SMB technology.[10] Although it is hard to assess the full reach of the technology, due to confidentiality issues, several key active pharmaceutical ingredients (APIs) are manufactured using this technology and several installations are being operated around the world.[11,12]

Preparing this review, we found over 1700 papers and patents, related to the development and application of SMB technology, cited in the electronic databases. Approx. 1100 citations appear after the year 2000, and in the last five years nearly 500 citations on SMB were found. Mostly, the results on the progress of SMB technology in the last decade were therefore covered by this review, since previous achievements were covered by the chapters in the former monographs[13–19] and review articles.[20–23] Emphasis is given to the recent successful application in enantioseparation of racemates of definite commercial interest, either intermediates or target compounds with specific biological activity.

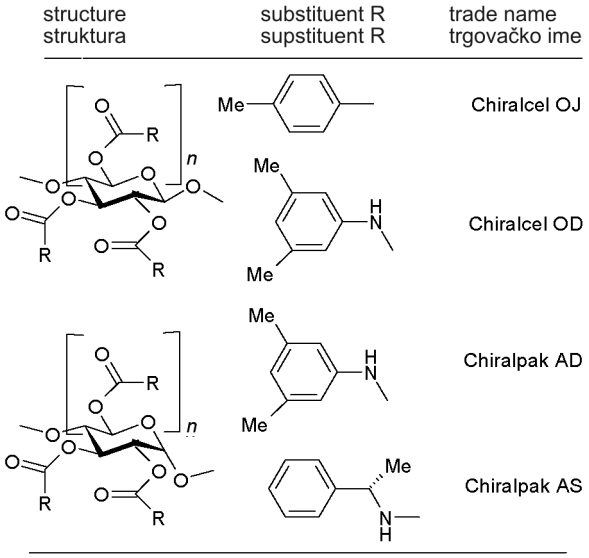
2. Discontinuous and continuous chiral chromatography

2.1. Discontinuous chromatographic separation of enantiomers

Chromatographic separation on various CSPs is discussed in detail in the recent monographs and reviews.[24–28] We have published an author-review related to our research on novel CSPs,[29] and informative overviews in this technology-oriented journal.[30,31] For easier following of the discussion in this section, only two aspects of chiral chromatography are briefly commented; *the main types of chiral selectors (CS)* nowadays in common use, and *elementary thermodynamics of chromatographic enantioseparation*.

Two important elements distinguish the two main types of CS; molar mass and type of binding to silica. According to mol. mass, CS are either derived from chiral polymers, usually from polysaccharides or proteins, or they are small chiral molecules, often designed on purpose for separation of specific racemate, and named "brush-type" or "Pirkle type", according to the inventor of such CSPs.[32] Polysaccharide-based chiral selectors represent over 90 % of the market, and in even a higher percentage if the number of reported separation of racemates were considered. Repeatedly cited in this review, Fig. 1,[33] are four of them, called "the golden four", which practically cover this market – two of them are based on cellulose (Chiralcel), and the other two on amylose (Chiralpak). The financial dimension of the world market of chiral technologies was cca. $5 billion in 1999, and is expected to more than triple in 2009.[34]

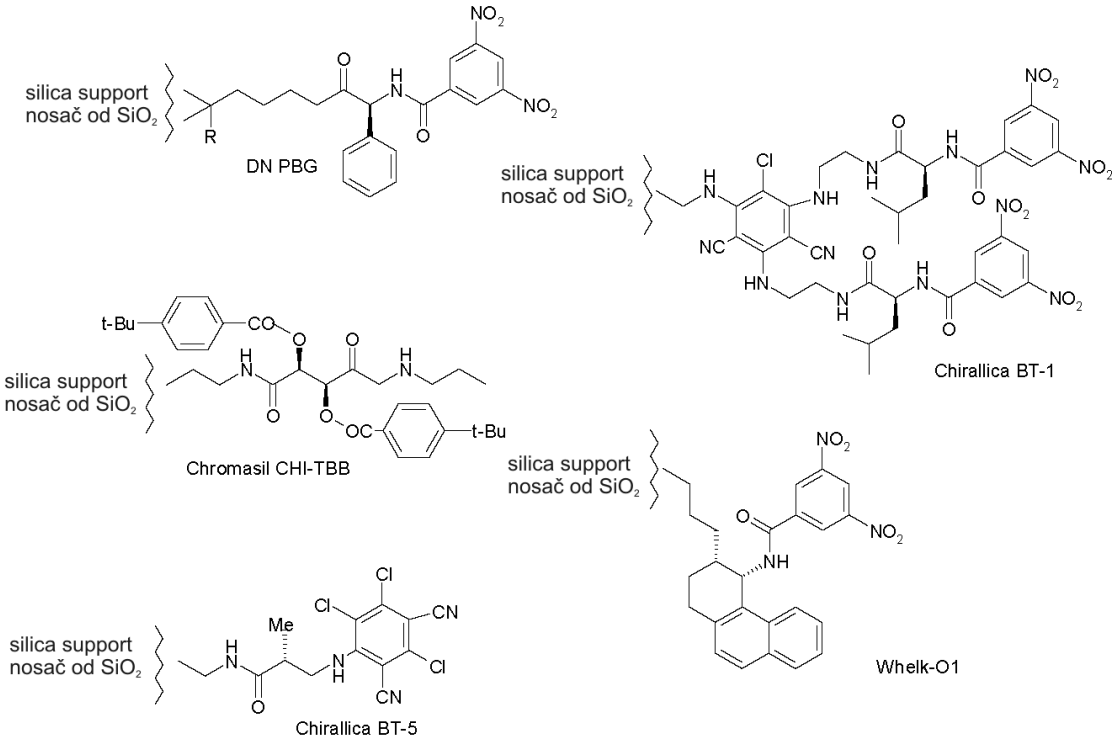
According to the type of binding, CS can be either non-covalently adsorbed, as is usual for polymer-based CS, or covalently bound to the activated surface of silica gel. However, there is still a need for new covalent binding modes of both, polymer-based and small-molecule, or "brush-type" CSPs. Fig. 2 presents the structures of five selected, commercial "brush-type" selectors.



F i g. 1 – *Four most important polysaccharide-based chiral selectors ("the golden four")*[33]

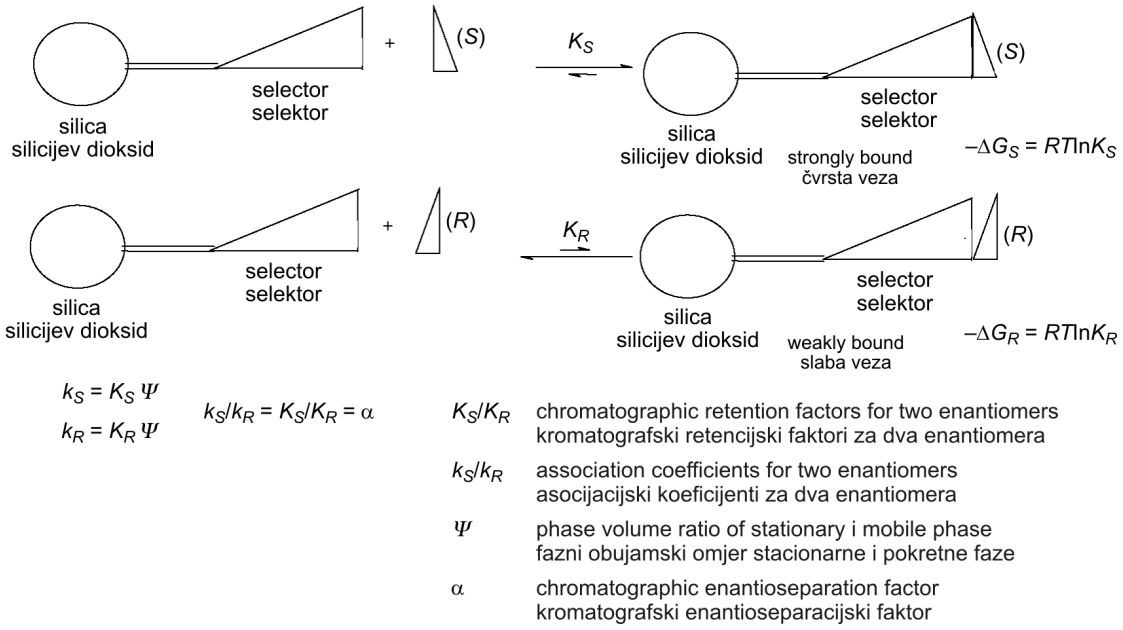
S l i k a 1 – *Četiri najvažnija kiralna selektora ("četiri zlatna") zasnovana na polisaharidima*[33]

Thermodynamics of enantioseparation is based on the simple model of equilibrium between free and bound analyte, *i.e.* two enantiomers to be separated, Fig. 3.



F i g. 2 – *Five selected commercial brush-type CSPs*[33]

S l i k a 2 – *Pet odabranih komercijalnih CSP-a četkolikog tipa*[33]



F i g. 3 – *Model of chromatographic enantioseparation and thermodynamics that describes the process*
S l i k a 3 – *Model kromatografske enantioseparacije i termodinamika koja opisuje proces*

It is important to note that α is an experimentally easily available parameter from k_S/k_R and K_S/K_R values. This parameter is usually used as comparison for efficacy of enantioseparation, whereas k_S and k_R values are similar or same variables as the Henry constants H_A and H_B. These values, along with binding constants and retention times, are the key parameters for design of the SMB process, see section 2.4.

2.2. Simulated moving bed chromatography

Unlike other unit operations for separation, such as distillation, membrane permeation, or extraction, the SMB is not a steady process but a *steady periodic process*. This means that SMB is not operated under stead-state conditions, but under *cyclic steady-state conditions*, also known as *steady periodic conditions*.[35,36] While the batch or elution chromatography mode has found the largest number of applications up to now, SMB chromatography as a steady periodic process is gaining more attention due to its advantages in terms of productivity, and eluent or desorbent consumption. This concept is based on true moving bed chromatography (TMB), represented schematically in Fig 4a. TMB envisages countercurrent movement of the *solid and liquid*, a concept difficult to reproduce in practice. In contrast, in the SMB variant the adsorbent is distributed over a number of *fixed columns*, 4–24 in standard equipment.

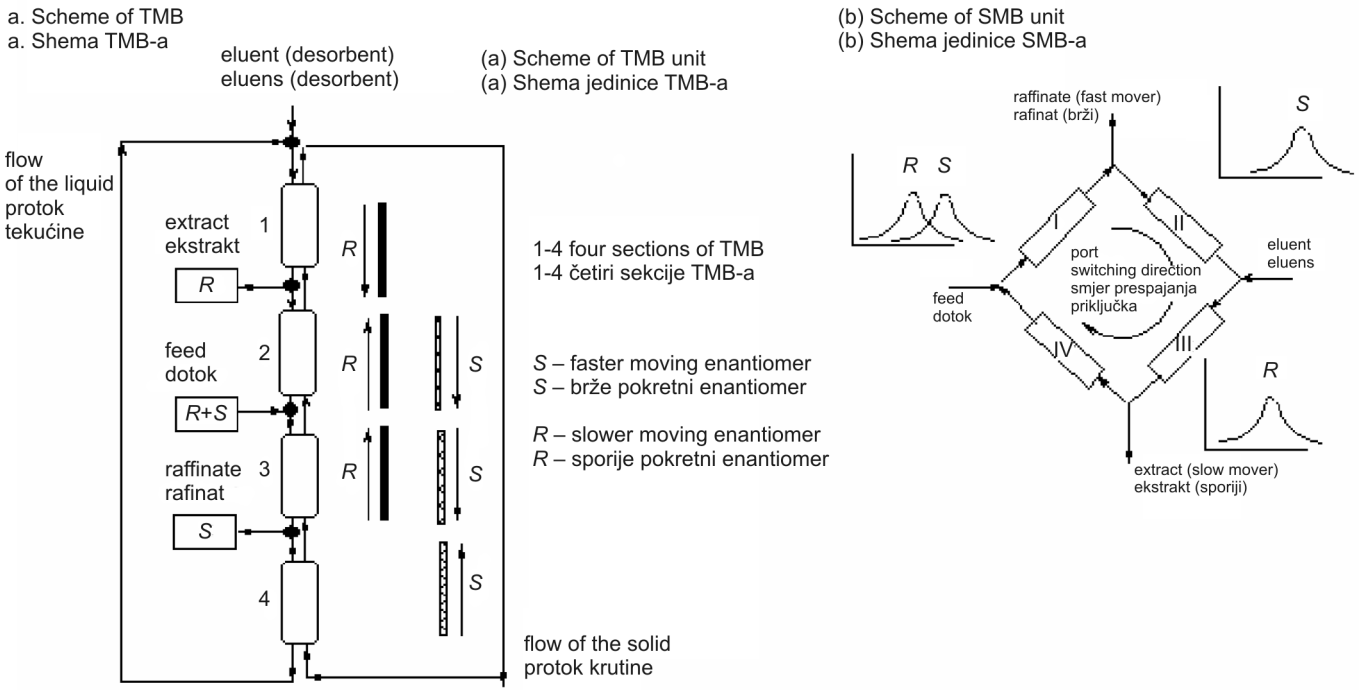
Eluent and feed streams enter the process continuously. A counter-current solid stream is nearly reproduced by shifting the inlet ports periodically in the direction of the internal recycle flow as shown in Fig. 4b, thus the solid stream is "simulated". This leads to the desired separation of the feed components that can be withdrawn at the extract and raffinate ports, which are shifted in the same manner as the inlets.[37]

In other words, conventional fixed bed chromatographic columns can be used, and the inlet and outlet ports to the unit are switched periodically in the direction of the fluid flow to simulate, in a discontinuous manner, the continuous countercurrent movement of the solid phase, Fig. 5. Continuous movement is simulated better when the four SMB sections consist of a large number of fixed bed columns, 12 in Fig. 5, and the port switch occurs at high frequency.

Design methods have been developed for robust operation and scale-up, using data obtained from analytical experiments. In the last few years, rapid developments have been made in the areas of design, improved process schemes, optimization and robust control. This review addresses these developments, as well as both the fundamentals of the SMB science and technology, and some practical issues concerning the operation of SMB units.

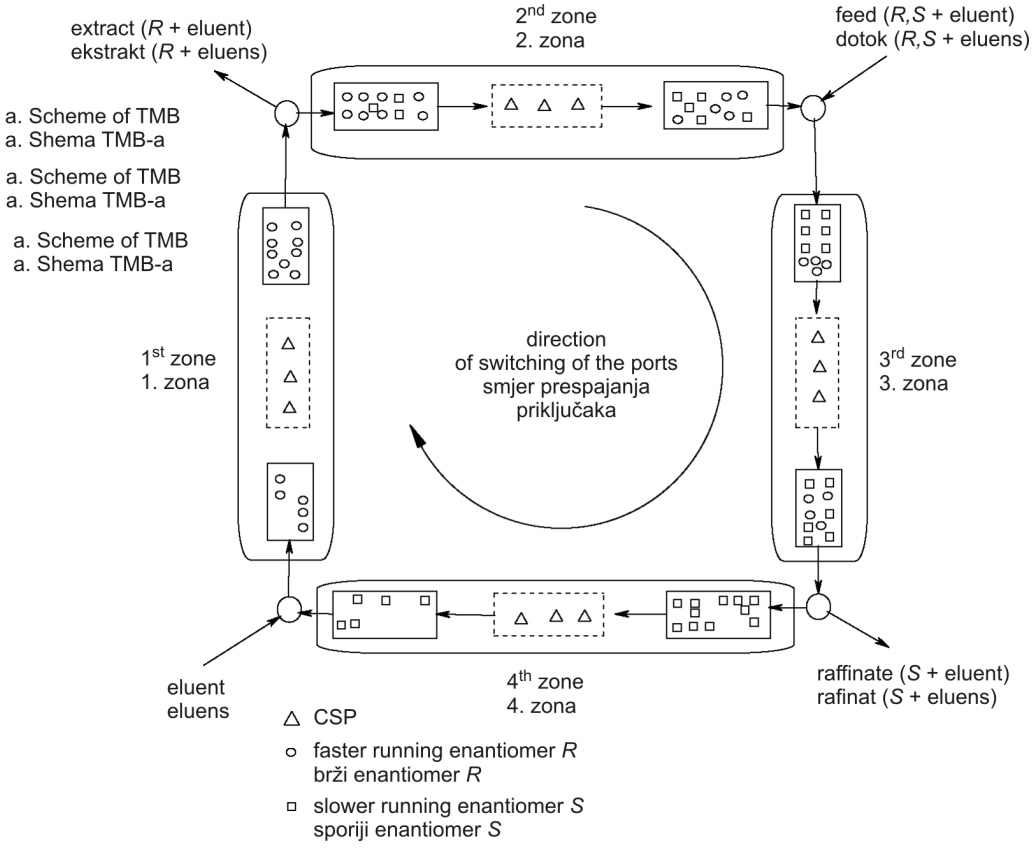
Design and optimization of operating conditions for SMB are computer-based processes, which use experimental data from classic chromatography as the first input, and simulate SMB conditions by specific programs, based on separation theories of different sophistication degree. In other words, SMB is based on the standard principles of chromatography, but uses specific chromatographic set-ups composed of a given number of chromatographic columns. In comparison with preparative HPLC, chromatographic separations using SMB units show several distinct advantages, especially lower solvent consumption, lower requirement for CSP, and, of course, continuity.

Application and function of SMB cannot be understood, however, without some basic knowledge of the theory, *i.e.* of the guidelines and mathematic formalism for designing and optimizing the results of classic chromatographic separation. SMB units are complex systems, whose operations require the choice of several parameters, *e.g.* flow rates in the sections (columns), the periods between switching inlet and outlet ports (valves), and the composition of the feed (solvent plus racemate).



F i g. 4 – *Schematic presentation of: (a) four-section true moving bed (TMB) and (b) simulated moving bed (SMB) units separating a racemic mixture (R, S). The arrows in the TMB scheme indicate the direction of the species fluxes in each section of the unit working under complete separation conditions.*

S l i k a 4 – *Shematski prikaz: (a) četiri sekcije pravog pokretnog ležaja (TMB) i (b) jedinice simuliranog pokretnog ležaja koje razdvajaju racemičnu smjesu (R, S). Strelice u shemi TMB označavaju smjer toka pojedinih faza u svakoj sekciji postrojenja kada radi u uvjetima potpunog odjeljivanja.*



F i g. 5 – *Principle of the simulated moving bed process with 12 columns*

S l i k a 5 – *Princip procesa simulirajućeg pokretnog ležaja (SMB) s 12 kolona*

In the SMB model, the transport of a solute *i* along the axial coordinate *z* of a chromatographic column in section *j* of the SMB unit can be described by the following material balance:

$$V_j \frac{\partial c_{i,j}}{\partial z} + \frac{\partial}{\partial t}\left[c_{ij} + \frac{1-\varepsilon}{\varepsilon} n_{ij}\right] = D_{L,i,j} \frac{\partial^2 c_{i,j}}{\partial z^2} \qquad (1)$$

where $c_{i,j}$ and $n_{i,j}$ are the concentrations of the solute in the fluid and solid phases respectively, ε is the void fraction of the column, and $D_{L,i,j}$ is the axial dispersion coefficient, which to a good approximation may be linearly dependent on the fluid velocity. The interstitial fluid velocity in section *j*, v_j, is related to the volumetric flow rate, Q_j as $v_j = Q_j/(A\,\varepsilon)$, where *A* denotes the cross sectional area of the column. This equation is coupled to the mass balance in the solid phase:

$$\frac{\partial n_{i,j}}{\partial t} = k_{i,j}(n^*_{i,j} - n_{i,j}) \qquad (2)$$

where $k_{i,j}$ is the mass transfer coefficient which is usually weakly dependent on the fluid velocity, while $n^*_{i,j}$ is the solid phase concentration in equilibrium with the fluid phase, which is given by a proper adsorption isotherm:

$$n^*_{i,j} = f_i(c_{A,j}, c_{B,j}) \qquad (3)$$

For the classical SMB process, these node balances relate the internal flow rates Q_j, ($j = 1, \ldots, 4$) to the external flow rates Q_D, Q_E, Q_F, Q_R, that denote the flow rates of the desorbent, eluent, extract, feed and the raffinate streams, respectively:

$$Q_1 = Q_4 + Q_D \qquad (4a)$$

$$Q_2 = Q_1 - Q_E \qquad (4b)$$

$$Q_3 = Q_2 + Q_F \qquad (4c)$$

$$Q_4 = Q_3 - Q_R \qquad (4d)$$

Similarly, component node balances can be written as:

$$c^{in}_{i,1} = \frac{(Q_4 c^{out}_{i,4} + Q_D c_{i,D})}{Q_1} \qquad (5a)$$

$$c^{in}_{i,2} = c^{out}_{i,1} \qquad (5b)$$

$$c^{in}_{i,3} = \frac{(Q_2 c^{out}_{i,2} + Q_D c_{i,F})}{Q_3} \qquad (5c)$$

$$c^{in}_{i,4} = c^{out}_{i,4} \qquad (5d)$$

where the superscripts "in" and "out" refer to the inlet and outlet streams, respectively. Equations (5a)–(5d) along with suitable initial and boundary conditions can be solved numerically to obtain the transient behaviour of the SMB unit. In addition, the switching mechanism is explicitly implemented by assuming that the internal concentration profiles are conserved within each physical column when the inlet and outlet ports are switched (every t^* time units). The transport of solutes in chromatographic columns can lead to shock fronts, and hence it is important to use high resolution schemes to solve the set of algebraic-partial differential equations described above.[38,39] Importantly, it is possible to obtain pure components at the exit ports of the unit by ensuring that the concentration fronts approaching the outlet ports are pure. This is a characteristic feature of the SMB that enhances its performance, compared to elution chromatography, especially when using columns that have low efficiency.

2.3. Triangle theory of linear adsorption isotherms

The triangle theory allows an easy graphical description of the internal flow-rates and the switch time, both of which determine the flow-rate ratios ψ_j in SMB unit. Flow-ratios are defined by the eq. (6):

$$\psi_j = \frac{Q_j t^* - V\varepsilon^*}{V(1-\varepsilon)} \qquad (j = 1 - 4) \qquad (6)$$

where Q_j (for $j = 1 - 4$) are the volumetric flow rates in sections 1–4 of the SMB, ε^* is the overall void volume, *i.e.* void fractions of the columns. This parameter influences separation in small columns much more than for the large columns. Parameter t^* defines the switch time and *V* the single column volume.

These isotherm parameters allow definition of the regions in an "operating parameter plane" in the triangle presented in Fig. 6. In this plane, the linear adsorption behaviour is reflected in the span of the flow-rate ratios ψ_2 and ψ_3, in the central sections of the SMB unit. In this triangle, various areas can be distinguished. A triangular region describes an area where the flow-rates in sections 2 and 3 of the SMB lead to complete separation. This triangle is determined through adsorption isotherms, the concentrations of the two species to be separated, and the two Henry constants H_A and H_B of the two enantiomers. Detailed explanation of these parameters is given in the literature.[40]

The triangle diagram on "the ψ_2, ψ_3 plane" in Fig. 6 needs a brief comment. It represents the operating point (w or q; .), resulting from the internal flow-rates and the switch times. Various areas in this plane describe different separation regimes in terms of purity of the outlet streams. These points are calculated according to equation (6).[41] It is important to note two regions above the central triangle; in the region on the right, only the extract stream with more retained compound is pure, while region on the left is where only the raffinate stream with less adsorbed compound is pure.

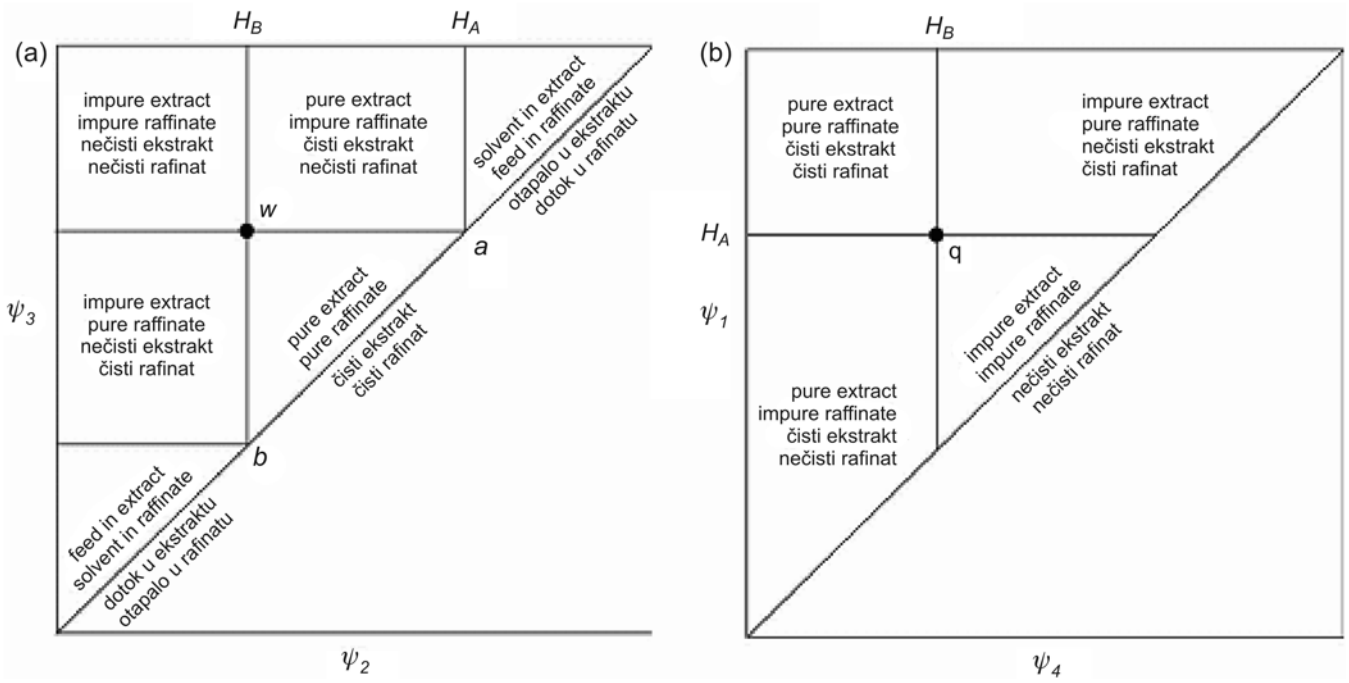
This approach paves the way for rapid scale-up based on the Henry constants H_A and H_B of the two enantiomers, which can be easily measured analytically. The constraints given by equations (7a–7d) define a region in the four dimensional space represented enclosed by the coordinates ψ_j, ($j = 1, \ldots, 4$), that ensures the complete separation of the binary mixture along with complete regeneration of both the stationary and mobile phases.

$$H_A \le \psi_1 \qquad (7a)$$

$$H_B < \psi_2 < H_A \qquad (7b)$$

$$H_B \le \psi_3 < H_A \qquad (7c)$$

$$\psi_4 \le H_B \qquad (7d)$$



F i g. 6 – *Complete separation region and SMB operating regimes on (a) (ψ_2, ψ_3) plane and (b) (ψ_1, ψ_4) plane for the binary separation of species A and B, with linear adsorption isotherm*

S l i k a 6 – *Regije potpunog odjeljivanja i radni režim SMB-a na (a) (ψ_2, ψ_3)-ravnini i (b) (ψ_1, ψ_4)-ravnini za razdvajanje binarne smjese A i B, uz linearne adsorpcijske izoterme*

The projection of these separation regions on the (ψ_2, ψ_3) and (ψ_1, ψ_4) planes, as shown in Fig. 6a and 6b is worth considering. The constraints, given by eqs. (7b) and (7c), delimit a triangular region in the upper half of the (ψ_2, ψ_3) plane, which corresponds to operating conditions that will result in incomplete separation. Other regions can also be identified on the (ψ_2, ψ_3) plane as indicated in the figure. Similarly, the constraints given by equations (7a) and (7d), delimit a rectangular region in the upper half of the (ψ_1, ψ_4) plane that corresponds to the combination of ψ_1 and ψ_4 values that will result in a complete separation, provided the constraints on ψ_2 and ψ_3 are satisfied. These diagrams show that by proper choice of ψ_j values, different separation performances can be realized. This representation not only gives explicit design equations, but also provides a methodology to rationalize the operation of the SMB process in terms of ψ_j values. Owing to the triangular nature of the region denoting the complete separation on the (ψ_2, ψ_3) plane, this method of designing SMB has been termed as the "triangle theory".[42,43] In spite of their applicability, equations a and 7b are not necessarily followed by the major part of industrial applications where operational conditions are developed for concentrated mixtures because they are in the nonlinear regime. Nonlinear conditions design is recently developed by the same authors.[44,45]

2.4. Design of the SMB process

Due to the cyclic steady state nature of the SMB process and the rather complex dynamics of such a multi-column chromatographic process, the detailed models presented in the previous section are suitable for SMB simulations and SMB optimization, *but are not convenient as a basis to develop criteria for SMB process design*. Over the last twenty years, the use of the equilibrium theory of linear and nonlinear chromatography extended to multi-column processes has been proven an extraordinarily useful tool for process design. *The triangle theory for linear adsorption isotherms* proved particularly useful in deriving the design and operating criteria for the complete separation of a binary mixture of A (more retained solute), and B in a non-retained solvent. To this aim, the design criteria for the SMB consider the model of a chromatographic column within the frame of the equilibrium theory, where axial dispersion is neglected and local equilibrium between the fluid and the solid phase is assumed, *i.e.* mass transfer resistances are considered negligible. Under these assumptions, eq. (8) can be recast as:

$$V_j \frac{\partial c_{i,j}}{\partial z} + \frac{\partial}{\partial t}\left[c_{i,j} + \frac{1-\varepsilon}{\varepsilon} n^*_{i,j}\right] = 0 \qquad (8)$$

Provided the isotherm relationship, initial and boundary conditions are available, it is possible to work towards the solution of these equations analytically using the method of characteristics.[46,47] Let us assume that the adsorption isotherm is linear, *i.e.*:

$$n^*_i = H_i c_i \qquad (9)$$

where H_i is the Henry constant, and $H_A > H_B$. Under these conditions, eq. (8) for *R* and *S* is decoupled and can be solved easily for each species. The retention time of a solute, $t_{Ri,j}$, injected at the inlet of an SMB column located in section *j* at time $t = 0$ is therefore:

$$t^R_{i,j} = \frac{V\varepsilon}{Q_{j,\mathrm{SMB}}}\left(1 + \frac{1-\varepsilon}{\varepsilon} H_i\right) \qquad (10)$$

The criteria for achieving complete separation of the binary mixture in the linear case can be derived by considering the specific role of the different sections in the SMB unit, Fig. 5. Sections 2 and 3 perform the separation and hence it is worth considering them first. The operation of section 3 should be designed in such a way that the switch time should be larger than the retention time of component *S* in section 3, and smaller than that of *R*. This will ensure that component *S* reaches the raffinate port, whereas component *R* does not contaminate it. In a similar fashion, section 2 should be designed in such away that the switch time should be larger than the retention time of component *S* in section 2, and smaller than that of *R*. This will ensure that *S* is completely removed from the column and does not pollute the extract after the next port switch, whereas *R* is still present and can be collected in the extract. The role of section 1 is to ensure that component *R* is completely removed, or eluted before the next switch, so that stationary phase is completely regenerated. Finally, the role of section 4 is to ensure that the fluid phase leaving is pure, *i.e.* solvent free of component *S*.

2.5. Operational aspects of SMB technology

Before discussing some exciting examples of SMB separation of important chiral compounds, here are indicated some key practical aspects of this technology. Nowadays, SMB is the choice technology for industrial separation of larger quantities of racemates, motivated by the following benefits:

– easy scale up of the separation process

– short times required for implementation of production process under good manufacturing practice (GMP) requirements

– reduced production costs

– broad productivity range, typically between 0.2 and 3 kg kg^{-1} d^{-1} CSP.

Figure 7a shows the lab-scale SMB equipment at Chirallica Ltd, which capacity can be extended from 1 g to 100 g d^{-1} of separated pure enantiomer. This equipment can adopt columns from d_i = 4 mm to 16 mm, which have an approx. filling capacity between 3–30 g of CSP. Figure 7b shows the analytical and semi-preparative columns filled at Chirallica Ltd, with CSPs produced and tested in this spin-off company.

The following are key practical steps in the development of SMB technology;

– screening of CSPs by standard HPLC methods

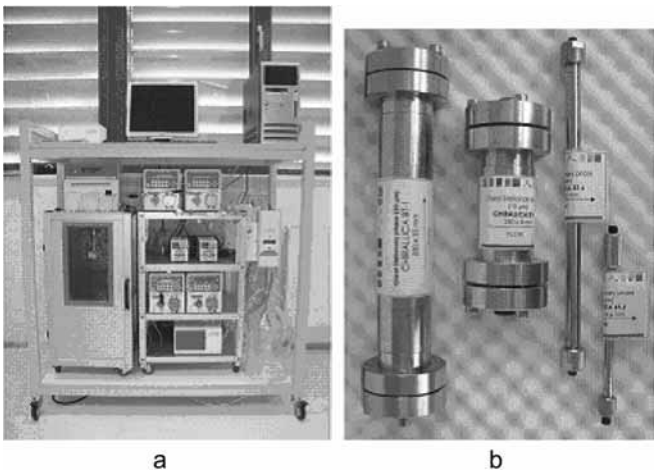
– determination of the most effective couple CSP/eluent system

– determination of loading capacity and adsorption isotherms for the most effective system

– identification of the system with highest productivity and lowest solvent consumption.

3. Recent examples of industrial application of SMB technology

SMB technology is best presented by examples of its successful application in enantioseparation of racemates of either structurally interesting or commercially important compounds. This section should inform the reader about the versatility of the method. Part II of this review presents some inventive solutions related to SMB capacity to be integrated in other (related) technological processes, such as crystallization operating or enzyme catalyzed reactions. The characteristic operative, technological parameters are given for any presented separation, in order to illustrate the vast spectrum of conditions developed for separations on multigram to multi-kilo scales of important pharmaceutical products. Many of them are high-volume drugs on the world market, as presented in Part II of this review.



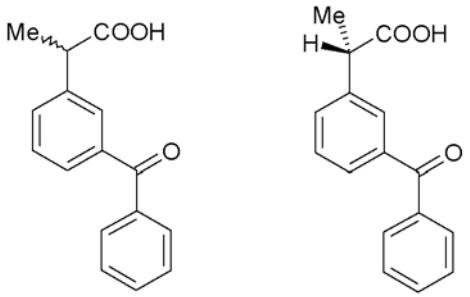
F i g. 7 – *(a) Simulated moving bed system (Knauer SMB Production System C9812) at Chirallica Ltd. (b) Analytical and preparative columns filled with original Chirallica CSPs.*

S l i k a 7 – *(a) Sustav simulirajućeg pokretnog ležaja u Chirallica d. o. o. (b) Analitičke i preparativne kolone napunjene originalnim kiralnim stacionarnim fazama (CSP) iz Chirallica d. o. o.*

3.1. Separation of nonsteroidal antifinflamatorics

This section presents the examples of industrially developed processes for SMB separation of the representative *profenes*, α-arylpropionic acid derivatives, a group of antiinflmatory drugs with multibillion-dollar value on the world market. For this group of drugs, it is well established that *S*-enantiomers possess significantly better therapeutic index.[48,49]

S-Ketoprofen (**1**), 2-(3′-benzoil)phenylpropionic acid. Racemic ketoprofen (Ketofen®) belongs to the well-known group of non-steroidal anti-inflammatory agents.

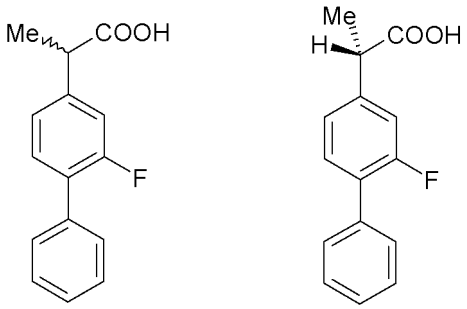


(±)-Ketoprofen **1** S-(+)-Ketoprofen **1**

Recent study on the preparative chromatographic separation of ketoprofen enantiomers evaluated the choice of mobile phase composition and measurement of competitive adsorption isotherms.[50] Best separation conditions were obtained with amylose-based chiral stationary phase (Chiralpak AD). Three mobile phase compositions were studied: the usual 20 % ethanol/80 % hexane mixture, and two pure mobile phases: methanol and ethanol. The results obtained show that, for preparative separations, pure ethanol is a better mobile phase than the usual 20 % ethanol/80 % *n*-hexane mixture; it allows higher solubility of the racemate, lower retention times, and also a higher selectivity at high enantiomer concentrations.

It is interesting to mention, however, that Ketoprofen was never introduced into therapy in the optically pure *S*-form, since it was observed that specific group of enzymes, called *racemazes*, converts *in vivo S* into *R*-enantiomer.[51]

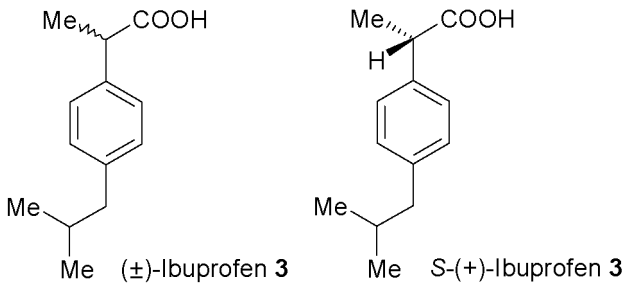
S-Flurbiprofen (**2**), 2-(3′-fluoro-4′-phenyl)phenylpropionic acid. SMB separation of racemic Flurbiprofen (Ansaid) is specifically claimed among other separations of racemic carboxylic acids.[52]



(±)-Flurbiprofen **2** *S*-(+)-Flurbiprofen **2**

Large-scale separation is achieved using binary solvent mixture consisting of low-boiling hydrocarbons and *tert*-butanol, and Chiralpak AD (20 μm) as the most effective CSP. The analysis determined that the enantiomeric purity of -*R*-enantiomer in the extract was 99 %, and enantiomeric purity of S-enantiomer in the raffinate was 98 %.

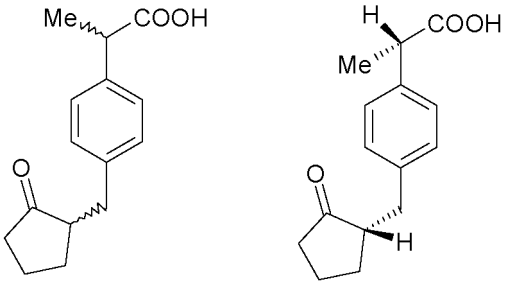
S-Ibuprofen (**3**), 2-(4′-isobutyl)phenylpropionic acid. Ibuprofen racemate (Advil) was separated in a SMB system with 4 columns packed with TBB gels.[53]



(±)-Ibuprofen **3** *S*-(+)-Ibuprofen **3**

TBB is a protein present in the mixture of TB proteins in buckwheat (*Fagopyrum*), an annual melliferous crop grown in many countries worldwide.[54] Retention times of *R*- and *S*-enantiomers of ibuprofen were measured in batch chromatographic experiments with hexane/TBME/AcOH mixed solvent. Isotherm parameters of SMB were calculated from the batch chromatographic data, and operation flow parameters obtained from ψ_2 and ψ_3 plane of Morbidelli and coworkers.[47]

Loxoprofen (**4**), 2-(4′-(cyclopentanon-2′′-yl)-methyl)phenylpropionic acid.



(±)-Loxoprofen **4** (1′*S*,2*S*)-(+)-Loxoprofen **4**
(±)-loksoprofen **4** (1′*S*,2*S*)-(+)-loksoprofen **4**

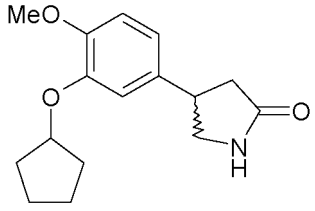
Since Loxoprofen racemate (Loxonin) has four enantiomers owing to its two chiral centers, gaining a pure enantiomer is impossible with only one step. To apply enrichment of Loxoprofen using SMB, the extract and raffinate should be separated as a binary mixture.

The enrichment of Loxoprofen (1′*S*,2*S*)-enantiomer was completed by 6-columns SMB chromatography.[55] To enrich Loxoprofen racemate as a binary mixture, and to characterize its enantiomer, the authors performed experiments with various types of columns. When TBB column, CSP based on the protein from buckwheat (Fagopyrum) was used, the mixture of (1′*R*,2*S*) and (1′*S*,2*S*) forms was eluted as a raffinate, while that of (1′*R*,2*R*) and (1′*S*,2*R*) forms was discharged as an extract under linear adsorption isotherm range. When the feed flow rates were 0.1 and 0.3 mL min^{-1}, the purities of the raffinate and extract were 98 % and 95 %, resp. In this case, the productivity of raffinate was 7.81 g g^{-1} h^{-1} CSP, and that of the extract was 6.95 g g^{-1} h^{-1} CSP. These results enabled preparation of multigram quantities of (1′*S*,2*S*)-**4**, required for *in vivo* tests on anti-inflammatory activity.

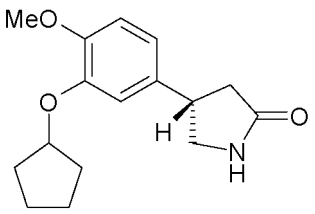
3.2. Additional examples of SMB separation of commercially important, biologically active compounds and their intermediates

In this section are selected the most recent examples from the scientific and patent literature on SMB separation of commercially important racemates, either drugs or biologically active compounds of general interest, and their key intermediates.

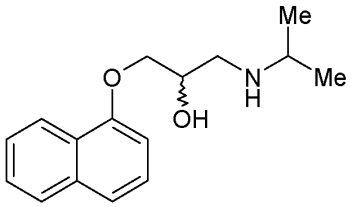
Rolipram (**5**), 4-(3-(cyclopentyloxy)-4-methoxyphenyl)pyrrolidin-2-one. Rolipram (Adeo) is an antidepressant with significant pharmacological properties. Although Rolipram is often used as a racemate in biological experiments, the biological activity of the enantiomers proved widely divergent and *R*-Rolipram tends to be more potent than *S*-Rolipram.[56,57] Therefore, it is desirable to use this compound routinely as a single enantiomer for both *in vitro* and *in vivo* studies.[58,59]



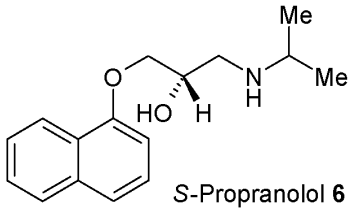
(±)-Rolipram **5**



R-(+)-Rolipram **5**



(±)-Propranolol **6**



S-Propranolol **6**

Separation of the intermediary *N*-Boc-Rolipram racemate has been completed on cellulose tris-(3,5-dimethylphenylcarbamate) CSP coated on silica by SMB chromatography.[60] The experiments were carried out under diluted conditions. The operating condition was defined using the point chosen in the triangle-shaped diagram, as shown in Table 1. Chosen were a switch time (t^*) of 20 min, and a feed mass concentration of 2.5 g L^{-1} (linear condition). Henry's constants were determined and the system revealed selectivity close to 1.26.

T a b l e 1 – *Operating conditions based on the triangle approach (switch time of 20 min and feed mass concentration of 2.5 g* L^{-1}*)*[60]

T a b l i c a 1 – *Radni uvjeti zasnovani na pristupu trokutom (vrijeme okreta 20 min i masena koncentracija dotoka 2,5 g* L^{-1}*)*[60]

Flow rate ratios of each section of SMB unit Omjeri protoka svake sekcije jedinice SMB				Fluid flow rates of the inlet and outlet streams of SMB unit (mL min^{-1}) Protoci fluida ulaznih i izlaznih struja jedinice SMB (mL min^{-1})				
ψ_1	ψ_2	ψ_3	ψ_4	D_{in}	D_{out}	F	Ex	Raf
3.25	2.56	2.64	1.40	1.06	0.64	0.10	0.24	0.28

Purity, the enantiomeric excess of the extract and raffinate, and other performance parameters of the studied system were determined, Table 2. Results showed reasonable performance of the SMB unit to separate the *N*-Boc-Rolipram enantiomers.

T a b l e 2 – *Analyses of purity and enantiomeric excess (e.e.) of the extract and raffinate streams*[60]

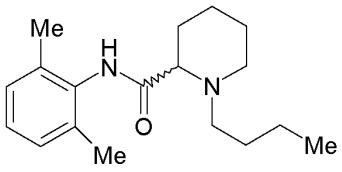
T a b l i c a 2 – *Analiza čistoće i enantiomernog viška (e.e.) u struji ekstrakta i rafinata*[60]

Cycle Ciklus	Analysis of the raffinate stream Analiza struje rafinata		Analysis of the extract stream Analiza struje ekstrakta	
	purity (%) čistoća (%)	e.e. (%)	purity (%) čistoća (%)	e.e. (%)
1	-	-	-	-
2	-	-	58.72	17.44
3	-	-	76.87	53.74
4	70.45	40.90	77.30	54.60
5	89.91	79.82	76.77	53.54
6	91.43	82.86	75.75	51.50

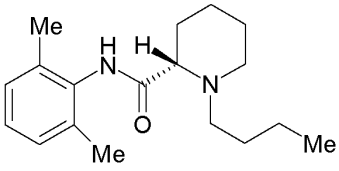
Propranolol (**6**), 1-(α-naphthyloxy)-2-hydroxy-3-dimethylaminopropane. Resolution of Propranolol hydrochloride (Inderal) was studied in self-packed columns of perphenyl carbamoylated β-cyclodextrin (β-CD).[61]

Both bed void volume and linear equilibrium constants were evaluated from linear elution chromatograms by moment analysis. A modified *H*-root method was used to determine competitive Langmuir isotherm of Propranolol hydrochloride in the nonlinear region. Continuous separation of the target enantiomer from its racemic mixture was studied by SMB in both linear and nonlinear region. Desired *S*-Propranolol hydrochloride was produced in the raffinate at a high purity. SMB productivity was further increased at the expense of decreasing product purity. The obtained solution was further purified by the crystallization process.

Bupivacaine (**7**), 1-butyl-*N*-(2,6-dimethylphenyl)pypecolinamide. Bupivacaine (Marcaine) belongs to long-lasting local anesthetics, drugs that block nerve conduction when they are applied locally to nerve tissue at appropriate concentrations.[62] The compound is historically marketed as a racemate but clinical studies have shown that *S*-enantiomer (levobupivacaine) is less cardiotoxic and also exhibits a weaker CNS toxicity in men, making its application significantly safer than that of racemate.[63] Although the racemate is used more often in medicine,[64] the *S*-enantiomer (marketed under the trade name Chirocaine) is recommended in place of bupivacaine.[65]



(±)-Bupivacaine **7**
(±)-bupivakain **7**

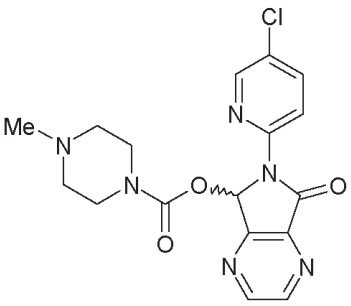


S-Bupivacaine **7**
S-bupivakain **7**

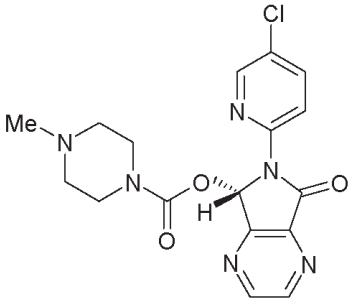
Utilizing SMB, the conditions for separation of Bupivacaine enantiomers were determined by the triangle theory and simulations using the gPROMS software and the Aspen Chromat. package.[66] The SMB model in this study assumed an axial dispersion flow for the liquid phase, and the intraparticle mass transfer was described in terms of a simple linear driving force (LDF) approximation. The parameters *a* and *b* of the Langmuir adsorption isotherm (LAI) were determined using a dynamic method. In the optimal condition, the calculated concentrations were confirmed by the

experimental results. Values projected by the gPROMS software more closely matched experimental values than those projected by the Aspen Chromat. package.

Zopiclone (**8**), *N,N*-6-trimethyl-2-(4-methylphenyl)imidazo[1,2-a]pyridine-3-acetamide, hemitartarate. Zopiclone (Sepracor®), a cyclopyrrolone sharing activity with benzodiazepines in the CNS, is a short-acting sedative being developed by Sepracorfor for potential treatment of sleeping disorders. Sepracor was granted US-05786357 in August 1998 covering methods and compositions of *S*-zopiclone in the treatment of sleeping disorders. In August 2000, Merrill Lynch predicted *S*-zopiclone sales of US $30 million in 2002, rising to US $150 million in 2004.[67] Racemic form of Zopiclone (Zolpidem) or salt thereof are presently used for the treatment of anxiety or insomnia.[68] In view of favorable pharmacodynamic properties of *S*-enantiomer, an efficient resolution method was desirable.



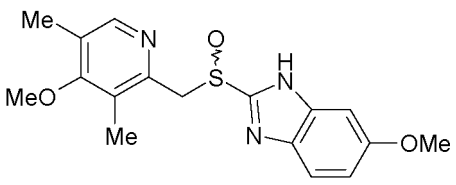
(±)-Zopiclone **8**
(±)-zopiklon **8**



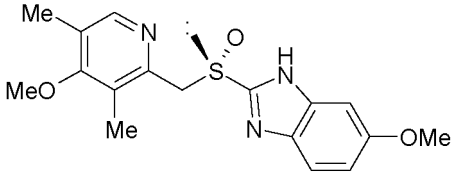
S-Zopiclone **8**
S-zopiklon **8**

To this end, a SMB process for enantiomeric separation of zopiclone was claimed by the group from Merck Development Center Ltd, UK.[69] The authors claimed stationary phase used in the SMB process that comprised amylose or cellulose derivatives of *tris*-(3,5-dimethylphenyl carbamate), or an amylose derivatives of *tris*-(*p*-methylbenzyl carbamate). The process can be carried out on industrial scale, and provides *S*-Zopiclone of >99 % e.e., and a pharmaceutically acceptable salt thereof.

Omeprazol (**9**), 5-methoxy-2-(4-methoxy-3,5-dimethyl-2--pyridyl)methylsulfinyl-1*H*-benzimidazole. Omeprazole (Prilosec) is a proton pump inhibitor drug in widespread use for the reduction of gastric acid secretion. It is effective in the treatment of gastro-esophageal reflux disease, gastric ulcer or, together with antibiotic therapy, in the eradication of *Helicobacter pylori* infections.[70]



(±)-Omeprazol **9**

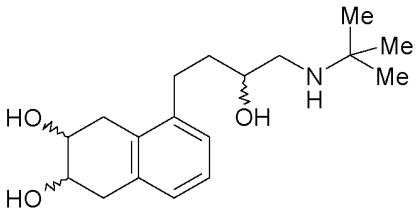


S-Omeprazol **9**

This compound possess a stereogenic center at the sulphur atom, and due its configurational stability is amenable to chromatographic enantioseparation and application in the enantiomerically pure form. The application of the pure *S*-enantiomer (Nexium®) avoids undesired metabolic pathway, and it is reported that it may lead to overall higher success rates in the treatment of various acid secretion related diseases.[71]

Favorable pharmacological properties of *S*-Omeprazole prompted various teams in industry[72,73] and academy[74] to develop chromatographic methods for the large-scale separation of racemate. Thus, a Chinese team has claimed SMB system with chiral fixed phase of cellulose tri-phenylcarbamate and eluens (desorbent) consisting of a mixture of ethanol, *n*-hexane and diethylamine. Racemic mixture of Omeprazole is separated to obtain high purity *S*-Omeprazole. The separation process is a continuous process, has high automation, high production efficiency, low solvent consumption and no toxic solvent.

Nadolol (**10**), (2*R*,3*S*)-5-{(2*R*-3-(*tert*-butylamino)-2-hydroxypropyloxy}-1,2,3,4-tetrahydronaphthalene-2,3-diol. Nadolol (Corgard, Corzide) is a well known β-blocker drug used in the management of hypertension and angina pectoris.[75,76] It has also been proved in pharmacologic treatment of portal hypertension in the prevention of community--acquired spontaneous bacterial peritonitis.[77]



Nadolol **10**
(eight stereoisomers possible)
(moguće je osam stereoizomera)

It has three chiral centers, *i.e.* eight (2^3) stereoisomers. It is currently marketed as an equal mixture of 4 stereoisomers, two diastereomeric racemates with *cis*-hydoxy groups in the cyclohexane unit.

In the preliminary experiments for SMB separation, resolution of 3 of the 4 racemic mixtures of Nadolol was obtained by HPLC, with a complete separation of the most active enantiomer (*R,S,R*)-Nadolol, on a column packed with perphenyl carbamoylated β-cyclodextrin (β-CD) immobilized onto silica gel. Continuous separation of enantiomer (*R,S,R*)--Nadolol from its racemate, in both 2-raffinate and 2--extract configuration of 5-zone SMB was achieved.[78] Experimental setup was applied to both configurations by modifying SMB controlling program accordingly. Separation performances of the 5-zone SMB were investigated for both 2-raffinate and 2-extract configurations and the same safety factors were applied to systematically investigate the effect of $\psi_3 - \psi_2$ (or $\psi_4 - \psi_3$) on the separation performance. The desired enantiomer of Nadolol was obtained with a high purity and yield in 2-raffinate configuration.

4. Conclusion

Modeling of continuous chromatographic separation, based on experimental chromatographic parameters, has enabled development of SMB technology. Part I of this review presents the elementary principles of SMB process modeling, and recent applications of SMB in separation of commercially important, optically pure compounds. These target compounds are mostly drugs in development or in therapeutic use, and therefore represent huge potential or already achieved market value. Due to the importance of these compounds, some details of their biological and medical profile are given, as well as characteristic parameters of the SMB separation process.

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List of symbols
Popis simbola

- A – cross sectional area, mm^2
  – presjek, mm^2
- c – concentration of solute in fluid, mol L^{-1}
  – koncentracija tvari u fluidu, mol L^{-1}
- D – dispersion coefficient, $m^2\ s^{-1}$
  – disperzni koeficijent, $m^2\ s^{-1}$
- d_i – inner diameter of column, mm
  – unutarnji promjer kolone, mm
- e.e. – enantiometric excess, %
  – enantiomerni višak, %
- H – Henry constant
  – Henryjeva konstanta
- K – chromatographic constant
  – kromatografska konstanta
- k – mass transfer coefficient, m s^{-1}
  – koeficijent prijenosa mase, m s^{-1}
- n – concentration of solute in solid phases, mol L^{-1}
  – koncentracija otopljene tvari u čvrstoj fazi, mol L^{-1}
- n^* – solid phase concentration in equilibrium with fluid phase, mol L^{-1}
  – koncentracija čvrste faze u ravnoteži s tekućom fazom, mol L^{-1}
- P – productivity, $m_{e.e}\ t^{-1}$, g $g^{-1}h^{-1}$
  – produktivnost, $m_{e.e}\ t^{-1}$, g $g^{-1}h^{-1}$
- Q – volume flow rate, mL min^{-1}
  – obujamski protok, mL min^{-1}
- t – time, min, h
  – vrijeme, min, h
- V – volume, mL, L
  – obujam, mL, L
- z – axial coordinate, m
  – aksijalna koordinata, m
- α – chromatographic enantioseparation factor
  – kromatografski enantioseparacijski faktor
- ε – void fraction of the column
  – nepopunjen udjel u koloni
- ε^* – overall void volume
  – sveukupan nepopunjen obujam
- ψ – volume ratio, mL min^{-1}
  – obujamski omjer, mL min^{-1}

SAŽETAK

Novija dostignuća tehnologije simuliranog pokretnog ležaja. I. Dio.

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Tehnologija simuliranog pokretnog ležaja poznata je više od pola stoljeća na području kontinuirane kromatografske separacije binarnih smjesa. Otkrivena i razvijena u petrokemijskoj i industriji šećera, ova tehnologija je prepoznata od strane organskih kemičara u farmaceutskoj industriji kao moćno oruđe za separaciju racemičnih smjesa. Niz godina razvijana je kao standardna laboratorijska metoda, zatim kao postupak za pilotna postrojenja, i konačno kao industrijska metoda za dobivanje kiralnih spojeva u optički čistom obliku. Konačni produkti ove tehnologije su enantiomerno čisti lijekovi te drugi biološki aktivni spojevi i njihovi intermedijari. U prvom dijelu ovog pregleda prikazani su osnovni principi i odabrani primjeri nedavne primjene tehnologije SMB.

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