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Simulated Moving Bed Technology for the Industrial Small and Mid Scale Separation of Racemates

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Abstract: Over the last decade in the fine chemical and pharmaceutical industry, simulated moving bed technology has become an import chromatographic method for the separation of racemates. In this report we describe the SMB principle along with its application for the small and mid scale separation of binary mixtures. A practical approach to method development is presented with highlights on the factors that are critical for the design of a robust separation process and its expected productivity. An example of process optimization is also given in regard to the separation of racemic Z-β-homo-alanine.

Keywords: Chromatography · Enantioseparation · Simulated Moving Bed · SMB · Z-β-homo-alanine

Introduction

In the past decade, automation and high-throughput techniques have led to a dramatic increase in the number of new intermediates and potential candidates for the development of pharmaceuticals. In the evaluation and commercialization of processes, it is essential that these compounds are available in high purity. Consequently, isolation and purification methods applied in process development and scale-up are of the utmost importance. If the compounds of interest are single enantiomers resulting from the resolution of racemates or diastereomers isolated from isomeric mixtures, the most established industrial processes, *e.g.* crystallization, extraction and distillation may require extensive development effort.

In such cases, batch chromatographic methods are valuable tools for early stage purification/isolation of compounds. A broad choice of commercially available solid phase materials for preparative chromatographic devices, like HPLC, allows the rapid development of suitable methods to solve almost any given separation problem. The principal drawbacks of these conventional techniques are the high costs for the stationary phase and the consumption of eluant, especially on larger scale. Only discrete amounts of a mixture can be separated in a 'discontinuous' way. A continuous process, on the other hand, would increase the productivity and reduce costs [1].

Simulated Moving Bed (SMB) Chromatography

A continuous separation process is realized in the Simulated Moving Bed (SMB) technology. The characteristic feature is the simulation of a counter-current between the liquid and solid phases in a loop of chromatographic columns (beds). This allows a continuous injection of a binary substrate mixture and a continuous withdrawal of product streams. Besides simulated moving bed, also true moving bed (TMB) processes are known. The application of TMB technology, however, is hindered by technical problems in realizing the flow of the solid phase.

The first industrial SMB process was developed in the 1960s by Universal Oil Products (UOP) for the separation of C8-hydrocarbons [2]. In the following decades the application of SMB technology was extended, for instance, to the separation of sugars and petrochemical products on a multi-ton scale.

In the 1990s the first SMB separations of enantiomers were reported [3]. Since then, SMB processes have become an increasingly attractive alternative to enzymatic or batch chromatographic methods.

Principles of Moving Bed Chromatography

In a conventional preparative chromatographic separation, a defined sample of the mixture is injected into the column (Fig. 1a). The components of the mixture will exhibit different migration velocities due to their different adsorption interactions with the solid phase. Therefore, a separation during the elution process will take place.

In a counter-current chromatographic process, like TMB, the solid phase flows in the opposite direction to the eluant (moving bed). With a proper choice of velocities, the components will migrate in different directions and will be separated completely (Fig. 1b).

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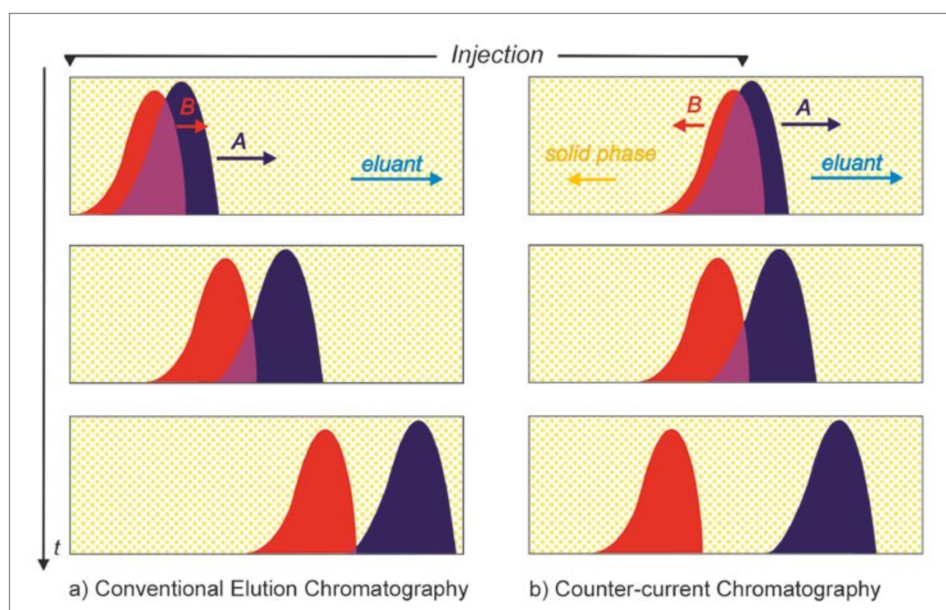

Fig. 1. Basic chromatographic principles

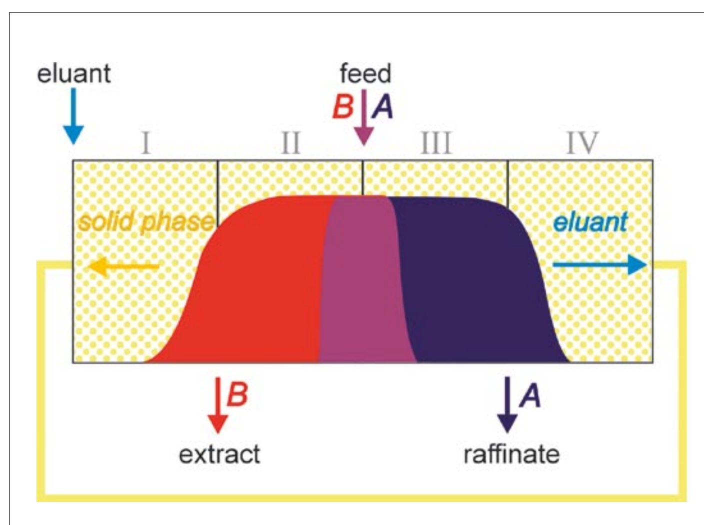

Fig. 2. True moving bed principle

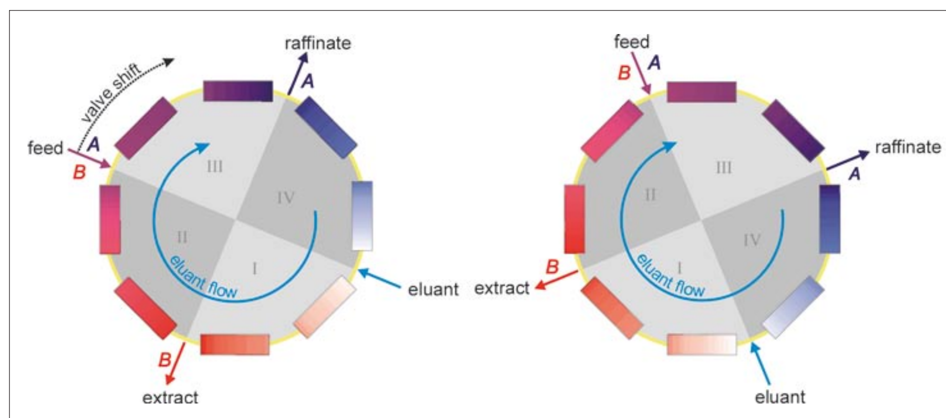

Fig. 3. Simulated moving bed principle

This concept is realized in the true moving bed (TMB) process. The setup of a true moving bed device consists of four sections forming a loop (Fig. 2), two separation sections (II, III), and two desorbing sections (I, IV). Each section comprises one or more chromatographic columns.

The substrate mixture, or feed, is introduced continuously into the device between sections II and III. The components are separated in the sections II and III and are withdrawn by the raffinate and the extract streams. The solvent loss is compensated by an eluant inlet between section I and section IV. Due to differences in the net flow between section I and II, and section III and IV, respectively, the components are desorbed totally from the solid phase material and transported from section I to IV.

The total flow in each section can be adjusted to reach a dynamic steady state, so that the concentration profiles do not change with time. The components are separated continuously; high feed concentration and high overloading of the solid phase leads to high productivity. A general limitation of this method is that only two components (or fractions) can be separated at a time.

As mentioned above, practical application of TMB is limited by the transport of the solid phase. To resolve this problem, the SMB process simulates the counter-current stream by switching the positions of the inlet and outlet valves to match the advancing concentration profiles (Fig. 3).

In an SMB set up of *n* columns, after *n* switches (tacts) one cycle is completed and the valves are back in their starting positions. Due to the discontinuous valve movement, the product concentrations in the outlet streams oscillate with a period of the tact time. Like in a TMB process, the components are separated continuously with high productivity and low solvent consumption.

For the hypothetical case that the bed consists of a large number of very short columns, the switching time becomes very small and the movement almost continuous and the SMB process equal to a TMB process.

SMB Design and Setup

In standard small-scale SMB devices 4, 8, 12, or 16 preparative HPLC columns are used. Four or five conventional HPLC pumps control the flow rates through the columns. An off-line analytical HPLC monitors the purity of the product streams. In Fig. 4, the Knauer CSEP 916 SMB unit with four pumps for small-scale production installed at Sigma-Aldrich, Buchs, is shown. In the CSEP 916 SMB, the counter current is realized by physically moving the columns attached to a 64-port rotor valve relative to the inlet and outlet valves (Fig. 5). This construction principle reduces the dead volume of the system compared to other instruments, where each column is linked to all inlet and outlet valves and a couple of multi port switches direct the flow path, as found in the Novasep system and most large scale units. A disadvantage of the Knauer system is that no Varicol [4] operation (asynchronous switching of single columns) with an increased productivity is possible. On the other hand, similar productivity increase can be obtained under ModiCon [5] (modulation of the feed concentration during a tact) or PowerFeed

[6] (modulation of the feed flow during a tact) operation modes. More detailed information about the different operation modes can be found in the literature cited.

SMB processes are generally sensitive to variations of the retention times of the compounds. Therefore, the variance of the resolution of the preparative columns forming the bed, expressed *e.g.* by the theoretical number of plates, should be as low as possible in order to prevent losses in the separation performance. Furthermore, the column temperature along with the composition and the temperature of the eluant must be kept within tight limits [7].

The Knauer CSEP 916 is equipped with an oven which allows the columns to be heated from 10 degrees above the ambient temperature to 60 °C. To broaden the temperature range to temperatures below 35 °C, we installed a liquid-cooled heat sink inside the oven. An accuracy of +/- 0.05 °C can be applied to temperatures as low as 15 °C, achieving a high resolution and stable separation process.

To avoid problems with different compositions from batch to batch, the solvent for a separation campaign (duration 3–4 weeks) is mixed on a 200 l scale and stored. Additional measures were taken to fulfill safety regulations. The solvent, product stream containers and SMB unit were physically separated as the SMB unit is not suitable for use in an area where large solvent quantities are openly handled.

Productivity of a SMB Process

SMB processes are more productive per time and solid phase unit compared to batch-chromatographic separations. Additionally, the solvent consumption per separation is comparatively low.

Besides the above mentioned limitation that only two compounds or fractions can be separated at any one time, there are several other limiting factors which should be taken into account:

- The separation factor of compounds has a major impact on process productivity, with values higher than 1.3 being typically obtained for optimal separation. It should be noted that we were able to separate a diastereomeric mixture of lactones (separation factor 1.15) with a productivity of 15.8 g/d on 12 silica columns (2 × 25 cm).
- If the separation factor exceeds a value of 2, the flow difference between the cleaning zones I and IV becomes very high, resulting in increased solvent consumption. It is therefore preferable to maintain the value of the separation factor between 1.3 and 2.0.
- The solubility of compounds in the eluant can also be a limiting factor. Feed concentrations between 5 and 25 g/l are generally applied in an SMB process, depending on the separation factor and 'loadability' of the solid phase material. The drop in performance observed with low solubility and feed concentration can be partially compensated for by reducing tact time and proportionally increasing the flows, as shown below in the separation of the Z-β-homo-alanine.
- In most cases, the pressure limit of the system determines the maximal flow rate and therefore the maximal productivity per unit time. In spite of this, higher productivities can be achieved by increasing the column diameter, on the condition that the maximal flow rate of the pumps are taken into account.
- In our enantiomeric separation projects we have so far obtained productivities of *ca*. 8–16 g/d using a bed of eight 3 × 15 cm columns. These values do not represent the upper limit; because of the low solubilities we had to apply feed concentrations of only 5 g/l. In an optimal case, productivities of 25 g/d should be feasible.
- The low feed concentrations also negatively affected the solvent consumption; 950 to 1190 ml/g of racemate was necessary for our enantioseparation. In the case of the diastereomeric lactone separation on silica (12 columns, 2 × 25 cm, feed concentration of 10 g/l) only 360 ml/g was necessary to effect the separation.

Fig. 4. Knauer CSEP 916 pilot SMB installed at Sigma-Aldrich

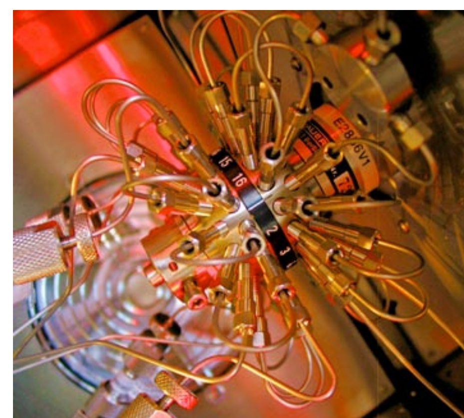

Fig. 5. 64 Port rotor valve

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Practical Approach for the Development of a SMB Separation Method

The first step to design a SMB method is to determine the optimal isocratic separation conditions (solid phase material, eluant, temperature) on an analytical HPLC. These data are then verified using a representative preparative SMB column. Linear isotherms – basic thermodynamic parameters describing the distribution of compounds between the solid and liquid phase – can be calculated from the retention times [8]. These parameters allow the computational simulation of the SMB separation using a simple linear Langmuir model. The simulation gives acceptable results for low feed concentrations. For higher concentrations, as generally applied in practical separations, the non-linear behavior of the compounds in the simulation gives only a rough idea of the optimal parameters [9].

More complex models containing non-linear parameters allow a more precise simulation and determination of the optimal flows, feed concentration and switching time, but further thermodynamic data has to be collected *via* time-consuming HPLC experiments [10]. Even if the data are accurately collected, there is no guarantee that the mathematical model describes correctly the behavior of the compounds of interest.

For our first two projects we chose to determine the non-linear isotherms using the 'elution by characteristic point method' (ECP) [11]. In both cases the fit of the mathematical model to the experimental data was unsatisfactory. The values of the starting parameters obtained from the computational simulation deviated by more than 30% from the ones optimized during the SMB separation, resulting in a loss of recovered material and time.

In the following projects we simply measured the retention times of the compounds on the preparative columns by HPLC and compared them with the retention times from the first projects, where we had already optimized values for the SMB flows and the tact time. The new starting values were then calculated by the 'rule of three', where an unknown fourth parameter can be calculated from two known and one given value. In all cases, the parameters were already very close to the optimum, and after one day of fine-tuning the purities of both product streams were higher than 99%. This method also worked very well when the solid phase material, the temperature, the feed concentration or class of compounds was different to the optimized project.

Table. Separation of D/L-Z-β-homo-alanine

Parameters	1st campaign		2nd campaign	
	initial values	optimised	adapted	optimised
tact time	10.0 min	10.0 min	9.4 min	7.0 min
zone 1	17.0 ml/min	17.9 ml/min	21.8 ml/min	34.5 ml/min
zone 2 (extract pump)	14.7 ml/min	14.9 ml/min	17.3 ml/min	27.4 ml/min
zone 3	15.9 ml/min	16.1 ml/min	18.7 ml/min	29.6 ml/min
zone 4 (raffinate pump)	13.4 ml/min	13.4 ml/min	15.6 ml/min	24.7 ml/min
feed (feed pump)	1.2 ml/min	1.2 ml/min	1.4 ml/min	2.2 ml/min
eluant (eluant pump)	3.6 ml/min	4.5 ml/min	6.2 ml/min	9.8 ml/min
raffinate stream	2.5 ml/min (1.2 g/l)	2.5 ml/min (1.2 g/l)	3.1 ml/min (1.1 g/l)	4.9 ml/min (1.1 g/l)
extract stream	2.3 ml/min (1.3 g/l)	3.2 ml/min (0.9 g/l)	4.5 ml/min (0.8 g/l)	7.1 ml/min (0.8 g/l)
max. pressure	18 bar	18 bar	18 bar	38 bar
productivity (99% purity)	8.6 g/d	8.6 g/d	10.1 g/d	15.8 g/d
eluant consumption	0.8 l/g racemate	0.95 l/g racemate	1.09 l/g racemate	1.09 l/g racemate

Setup: 8 Chiracel OD 20 μm columns (3 × 15 cm) in a 2:2:2:2 configuration at 20 °C, eluant & feed heptane/2-propanol/trifluoro acetic acid (800:200:1 v:v.v), feed concentration 5.0 g/l

Application of the SMB Technology for the Separation of D/L-Z-β-Homo-alanine

β-Homo-alanine as a non-natural amino acid is an interesting building block and a promising candidate for enantioseparation on the SMB. To facilitate the detection *via* HPLC for the method development and the in-process controls we needed to incorporate a chromophore into the compound. After screening we chose the benzylcarbamate derivative (Fig. 6) due to the good separation factor of 1.37 on a Chiracel OD 20 μm at 20 °C with a heptane/2-propanol/trifluoro acetic acid (800:200:1 v:v.v) mixture. We used eight columns (3 × 15 cm) in a symmetric 2:2:2:2 setup. The quite low solubility (*ca.* 6 g/l) of the Z-β-homo-alanine in the eluant was a limitation for the feed concentration; however, a feed concentration of 5.0 g/l was applied.

The initial parameters (Table, column 1) for the SMB separation estimated from the HPLC retention times gave almost pure product, only the flow in zone 1 had to be increased to prevent a breakthrough of the extract product into zone 4. Using the optimized parameters (column 2) both products could be obtained with an enantiopurity higher than 99%, although the productivity of 8.6 g/day was relatively low.

In a second production campaign these optimized parameters were used as starting values. Due to changes of the column properties on storage and the slightly different eluant properties, the flows and the tact time had to be adapted to obtain pure products (column 3). In a further step, the productivity was increased to 15.8 g/day by reducing the tact time and proportionally increasing the flow rates (column 4). Remarkably, no fine tuning of the flow rates was necessary to maintain the enantiopurity above 99%. The productivity obtained for the given column configuration was the highest to date, with the eluant flow approaching the maximum pump flow rate of 9.9 ml/min.

During the second campaign, an incident highlighted the importance of an accurate temperature control of the SMB columns. An oven fan failure led to an increase of the temperature of a few degrees, resulting in a breakdown of the separation process and a drop of enantiopurity down to 70%.

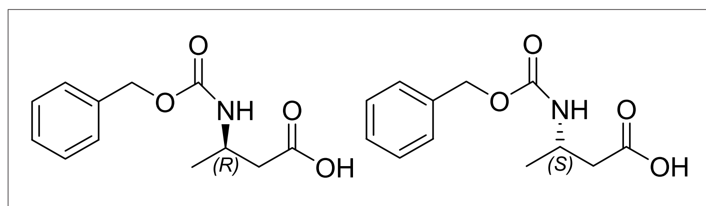

Fig. 6. D- and L-Z-β-homo-alanine

Conclusion and Outlook

The separation of racemic Z-β-homo-alanine demonstrates that SMB is the technology of choice for the chromatographic enantioseparation on both medium and large scales. A practical and time efficient

approach to separation was obtained by correlating HPLC retention times with known SMB flows and tact times, then estimating the initial parameters from which the method would be developed. This approach held across all separations, not only those examples that have been presented.

Productivities of 10–15 g/day (or more with the given set-up of eight 3 × 15 cm columns) can be achieved with a straightforward optimization of the SMB process. During the development and optimization phase little to no pure product may be produced, however recycling of these 'development fractions' is generally not a problem. Our experience also showed that the strict control of the column temperature, eluant and feed composition is crucial to achieve a robust and reproducible separation. Once the SMB process is established, the separation can be conducted in a very cost efficient manner and with little required maintenance.

In the near future, we will expand the abilities of our SMB unit to operate in ModiCon mode to further expand the productivity.

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