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Less common applications of simulated moving bed chromatography in the pharmaceutical industry☆

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Abstract

Simulated moving bed (SMB) chromatography is often perceived in the pharmaceutical industry as chromatographic method for separating binary mixtures, like racemates. However, SMB can also be used for unbalanced separations, i.e. binary mixtures of varying compositions and multi-component mixtures. These less common application modes of isocratic SMB chromatography are exemplified for four different compounds (racemates and diastereomers) and discussed in view of the so-called 'triangle theory' from an industrial perspective.

Keywords: Simulated moving bed chromatography; Preparative HPLC; Chiral separation; Enantiomer separation; Chiral discrimination

1. Introduction

In the recent years simulated moving bed (SMB) chromatography on chiral stationary phases (CSPs), especially helical homochiral polymers derived from naturally occurring macromolecules, such as cellulose or amylose, has become an essential tool for the chromatographic resolution of racemates on a preparative scale [1]. The technology has shown in some cases distinct advantages over synthetic routes involving chiral or prochiral precursors and "classical" resolutions. The impact of enantioselective chromatography on the development of pharmaceuticals has been reviewed recently by Francotte [2,3] and others [4,5].

Efficient criteria for the optimal design of SMB systems have been developed, which allow one to account for the non-linear character of the involved adsorption equilibria and to optimize the productivity per kg CSP easily [6]. Following the so-called 'triangle theory' constraints on these criteria have been derived which allow for complete separation of a binary mixture following the Langmuir and the modified Langmuir isotherm [7] and the most general case of a bi-Langmuir multi-component adsorption isotherm [8]. Today, development, scale-up and optimization of SMB separations follow a straightforward protocol and can be performed within a few days.

In comparison to preparative HPLC chromatographic separations using SMB units show several distinct advantages, especially a lower solvent consumption and a lower inventory of chiral stationary phase. These time and cost-saving advantages prompted us to study possibilities to use SMB units not only for racemate resolutions, but also for more complex separation problems such as "unbalanced" (i.e. not 1:1 ratio of binary substrates) and multi-component mixtures. It should be emphasized that multi-component separations using the SMB technology are common practice in the petrochemical industry and that the Molex process pioneered by UOP as described by the first patent filed on SMB [9] in 1961 by Broughton and Gerhold is intended for the separation of linear and branched hydrocarbons. Today a number of industrial scale processes similar to the Molex are used on a 100,000 t/a scale. However, all of them use either zeolithes or ion-exchangers as stationary phases and do not employ high pressure liquid chromatography [10].

Various examples for pharmaceutical applications will be given for such less-common application modes, paying

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special attention to benefits to be gained in comparison to more conventional *modi operandi*. All purifications, about which we will report in the following paragraphs, are performed for investigational new drugs, which have not yet been submitted for patent application. Thus presently the structural information cannot be disclosed. However, we aim to present scenarios, which can be generalized and can easily be transferred to other chromatographic purifications.

2. Experimental

2.1. Equipment

The analytical HPLC unit used was an Agilent HP1090 system (Basel, Switzerland) consisting of a quaternary pump, auto sampler and a diode array detector.

Two Licosep 10 × 50 units, produced by Novasep (Pompey, France) were used for the pilot runs. A detailed description of the unit layout has been given recently [11]. It was equipped with eight NW-50 (non-jacketed) columns produced by Merck (Darmstadt, Germany) with a measured internal diameter of 48 mm. The column length can be adjusted up to a maximum of 120 mm. The columns can be self-packed easily.

2.2. Materials

The chiral stationary phases (CSPs) were obtained from Chiral Technologies Europe (Illkirch, France) as 20 μm bulk packing. All compounds submitted for purification were synthesized in the laboratories of CarboGen AG (Aarau, Switzerland). The solvents used as eluents were reagent grade or better quality and obtained from SDS, Peypin, France. Analytical in process control of extract and raffinate stream was performed employing the same stationary phase and eluent as for the preparative separation. Dilution with the eluent was employed when necessary.

2.3. Column packing and testing

Bulk CSPs were packed into eight NW-50 columns purchased from Merck (Darmstadt, Germany). Each column contained exactly 110.0 g dry mass of the stationary phase. The column volume was determined individually for all columns, which were tested with a preparative HPLC system provided by Knauer (Berlin, Germany), which consisted of a K-1800 pump with a 1000 mL/min pump head, a HPLC-Box and a K-2500 UV detector.

2.4. Determination of adsorption isotherms, Henry constants and start parameters for the separations

Analytical HPLC columns, containing various lots of Chiralpak AD or Chiralcel OD were installed into a HP1090 system (cf. Section 2.1) equipped with a Jasco CO-1560 oven (Omnilab, Mettmenstetten, Switzerland) and thermostated at the operating temperature of the SMB unit ±0.1 °C.

A simulation software called “softSMB” is supplied with the SMB and allows one to approximate the adsorption isotherms of binary mixtures and to optimize the operating parameters before starting the unit itself. Based on a few injections at increasing volume of a concentrated product solution on analytical HPLC columns filled with Chiralpak AD or Chiralcel OD the Novasep software package “softSMB” correlates through a curve-fitting procedure the equilibrium experimental results with a postulated modified Langmuir competitive isotherm (cf. Eq. (1)), which takes the form:

$$n_i = \lambda c_i + \frac{\bar{N}_i K_i c_i}{1 + \sum_{k=1}^{2} K_k c_k} \quad (1)$$

In this equation n_i and c_i are the adsorbed and the fluid phase concentration, respectively; λ is a dimensionless coefficient; K_i the equilibrium constant of the ith component, which accounts for the overload effects; the upper limit of n_i is given by the saturation capacity $\bar{N}_i$.

The Henry constants give the slope of a component’s adsorption isotherm under linear conditions, i.e. at infinitely small concentration:

$$n_i = H_i c_i \quad (2)$$

At low concentrations the modified Langmuir isotherm (cf. Eq. (1)) allows a calculation of the Henry constants:

$$H_i = \bar{N}_i K_i + \lambda \quad (3)$$

The ratio of the Henry constants is equal to the enantioselectivity α. It should be noted that the constants, which can be determined independently from simple experiments [12], are affected by variations in bed density and the resulting overall porosity ε^*.

2.5. SMB hardware and control software

Two different SMB units of identical layout were used for the separations. The Licosep 10 × 50 SMB units from Novasep (Pompey, France) are controlled by a central system composed of a Siemens PLC (type S7-300) and a personal computer as the user interface. The supervision software works under DOS or Windows 2000 and allows the full control of the unit parameters (valves, pumps, flow rates, pressures) when the unit is running or under test. All relevant parameters and data are continuously stored in files for quality control. The software allows an easy access to real time curves (flow rates, temperature, pressure). All measurements are transmitted from the Licosep 10 × 50 through a control board, containing the PLC and all required interfaces and supplies.